ISSN 1948-9366 (online)

# World Journal of

# *Gastrointestinal Surgery*

*World J Gastrointest Surg* 2022 January 27; 14(1): 1-77

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 14 Number 1 January 27, 2022

## MINIREVIEWS



## ORIGINAL ARTICLE

### Retrospective Cohort Study



### Retrospective Study

*World Journal of Gastrointestinal Surgery*

**Monthly Volume 14 Number 1 January 27, 2022**

# Contents

## ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Ajaz Ahmad Rather, FACS, FICS, FRCS (Ed), MBBS, MS, Professor, Department of Surgery, SKIMS Medical College, Srinagar 190012, Jammu and Kashmir, India. drajazrather@gmail.com

## AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJGS* mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

## INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJGS* as 2.582; IF without journal self cites: 2.564; 5-year IF: 3.378; Journal Citation Indicator: 0.53; Ranking: 97 among 212 journals in surgery; Quartile category: Q2; Ranking: 73 among 92 journals in gastroenterology and hepatology; and Quartile category: Q4.

## RESPONSIBLE EDITORS FOR THIS ISSUE

**Production Editor:** *Rui-Rui Wu*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Ya-Juan Ma.*

**NAME OF JOURNAL**
*World Journal of Gastrointestinal Surgery*

**ISSN**
ISSN 1948-9366 (online)

**LAUNCH DATE**
November 30, 2009

**FREQUENCY**
Monthly

**EDITORS-IN-CHIEF**
Peter Schemmer

**EDITORIAL BOARD MEMBERS**
https://www.wjgnet.com/1948-9366/editorialboard.htm

**PUBLICATION DATE**
January 27, 2022



**INSTRUCTIONS TO AUTHORS**
https://www.wjgnet.com/bpg/gerinfo/204

**GUIDELINES FOR ETHICS DOCUMENTS**
https://www.wjgnet.com/bpg/GerInfo/287

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**
https://www.wjgnet.com/bpg/gerinfo/240

**PUBLICATION ETHICS**
https://www.wjgnet.com/bpg/GerInfo/288

**PUBLICATION MISCONDUCT**
https://www.wjgnet.com/bpg/gerinfo/208

**ARTICLE PROCESSING CHARGE**
https://www.wjgnet.com/bpg/gerinfo/242

**STEPS FOR SUBMITTING MANUSCRIPTS**
https://www.wjgnet.com/bpg/GerInfo/239

**ONLINE SUBMISSION**
https://www.f6publishing.com

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 January 27; 14(1): 1-11

DOI: 10.4240/wjgs.v14.i1.1

ISSN 1948-9366 (online)

*MINIREVIEWS*

# Current status of liver transplantation for cholangiocarcinoma

Patrick Twohig, Thoetchai Bee Peeraphatdit, Sandeep Mukherjee

**ORCID number:** Patrick Twohig 0000-0002-5423-8749; Thoetchai Bee Peeraphatdit 0000-0001-7254-5016; Sandeep Mukherjee 0000-0002-0538-3253.

**Author contributions:** Twohig P performed a majority of the writing, prepared the figures and tables; Peeraphatdit TB assisted in writing the manuscript, preparing figures and tables, and reviewing the manuscript; Mukherjee S designed the outline of the manuscript, provided input into writing and reviewing the manuscript; all authors approved of the final manuscript.

**Conflict-of-interest statement:** There is no conflict of interest associated with any of the senior author or other coauthors contributed their efforts in this manuscript.

**Country/Territory of origin:** United States

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

**Patrick Twohig, Thoetchai Bee Peeraphatdit,** Department of Internal Medicine, Division of Gastroenterology and Transplant Hepatology, University of Nebraska Medical Center, Omaha, NE 68198, United States

**Sandeep Mukherjee,** Department of Internal Medicine, Division of Gastroenterology, Creighton University, Omaha, NE 68124, United States

**Corresponding author:** Sandeep Mukherjee, FRCP (C), MD, Full Professor, Department of Internal Medicine, Division of Gastroenterology, Creighton University, Suite 401, Education Building, 7710 Mercy Road, Omaha, NE 68124, United States.
sandeep.mukherjee@alegent.org

## Abstract

Cholangiocarcinoma (CCA) is the second most common liver cancer with a median survival of 12-24 mo without treatment. It is further classified based on its location into intrahepatic CCA (iCCA), perihilar CCA (pCCA), and distal CCA. Surgical resection is the mainstay of treatment, but up to 70% of these tumors are inoperable at the time of diagnosis. CCA was previously an absolute contraindication for liver transplantation (LT) due to poor outcomes primary due to early recurrent disease. However, improvement in patient selection criteria and neoadjuvant treatment protocols have improved outcomes for inoperable pCCA patients with recent studies reporting LT may improve survival in iCCA. Future advances in the treatment of CCA should include refining patient selection criteria and organ allocation for all subtypes of CCA, determining effective immunotherapies and the evolving role of personalized medicine in patients ineligible for surgical resection or LT. Our article reviews the current status of LT in CCA, along with future directions in managing patients with CCA.

**Key Words:** Intrahepatic cholangiocarcinoma; Perihilar cholangiocarcinoma; Liver transplantation; Immunotherapy; Chemotherapy; Transplant



**Core Tip:** Perihilar cholangiocarcinoma (pCCA) is an accepted indication for liver transplantation (LT) using a strict selection process and standardized neoadjuvant treatment protocol with pre-operative disease staging. Intrahepatic cholangiocarcinoma (iCCA) has historically been a contraindication for LT due to poor reported outcomes.

Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0



**Received:** April 7, 2021
**Peer-review started:** April 7, 2021
**First decision:** June 23, 2021
**Revised:** July 12, 2022
**Accepted:** December 28, 2021
**Article in press:** December 28, 2021
**Published online:** January 27, 2022

**P-Reviewer:** Zheng H
**S-Editor:** Gao CC
**L-Editor:** A
**P-Editor:** Gao CC

With improved tumor detection, patient selection, and neoadjuvant treatment, recent studies have reported improved survival in iCCA patients with LT. No standardized protocol exists for the treatment of iCCA using LT. Our review analyzes the history and current literature on the treatment of pCCA and iCCA, along with gaps in knowledge and future perspectives.

**Citation:** Twohig P, Peeraphatdit TB, Mukherjee S. Current status of liver transplantation for cholangiocarcinoma. *World J Gastrointest Surg* 2022; 14(1): 1-11
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i1/1.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i1.1

## INTRODUCTION

Cholangiocarcinoma (CCA) is a malignant tumor that arises from the bile duct epithelium[1]. It is further classified based on its location into intrahepatic CCA (iCCA), perihilar CCA (pCCA), and distal CCA (dCCA) with the Whipple procedure the treatment of choice for dCCA[2]. In the past 20 years, liver transplantation (LT) has evolved to become the treatment of choice for carefully selected patients with unresectable pCCA[1]. Since 2009, a standard model for end-stage liver disease (MELD) exception point is available for patients listed for LT for pCCA[3]. In addition, a clinical trial is currently studying if LT is superior to surgical resection for "resectable" pCCA[4]. For iCCA, a recent prospective study incorporating neo-adjuvant chemotherapy *vs* chemoradiation for selected patients with locally advanced iCCA followed by LT reported 5-year survival of 83%[5]. This has increased interest in LT for iCCA and further studies are ongoing. The aim of this article is to review the current role of LT in the management of CCA, specifically pCCA and iCCA.

## SURGICAL RESECTION

Surgical resection is the mainstay of CCA treatment. Predictors of poor outcomes are size, positive margins, multiple lesions, and nodal metastasis[1]. However, resection is not always possible due to either large size or underlying cirrhosis and recurrence is common leaving LT as a possible option.

CCA is diagnosed with a dominant stricture on cholangiography and one or more of the following criteria positive cytology by endoscopic brushing or biopsy, fluorescence in situ hybridization polysomy, or elevated carbohydrate antigen 19-9 > 100 U/mL in the absence of cholangitis[1,6,7]. iCCA is commonly diagnosed with magnetic resonance imaging or computed tomography which demonstrates peripheral rim arterial phase enhancement followed by centripetal hyperenhancement on venous/delayed phase[2,8]. However, controversy exists surrounding the diagnosis of CCA given the frequency of incidentally found CCA that was suspected to be hepatocellular carcinoma (HCC) pre-operatively[8]. Biopsy may be required to differentiate CCA from HCC, but this carries a risk of tumor seeding.

The treatment and prognosis of CCA is dependent on its location along the biliary tree and likelihood of being completely resected with negative margins[9-11]. Surgical resection has been well-established as the standard treatment of CCA. Advances in surgical technique have improved outcomes in CCA patients over the past 20 years due to: (1) Extending the tumor resection to the hepatic parenchyma including caudate lobe, extended R-sided resection; (2) Extending tumor resection to the pancreatic head; (3) Performing vascular resections; (4) Performing lymphadenectomy to remove lymphatic pathways that may disseminate disease; and (5) Preoperative biliary drainage[1]. With complete resection and negative margins, 5-year survival rates are approximately 40%[1]. However, up to 70% of patients with hilar CCA are inoperable because of the extent of disease at presentation, therefore have a 5-year survival of 0%[2].

## LT FOR PCCA

### History of LT for pCCA

Historically, pCCA was a contraindication to LT. In the 1980s and early 1990s, LT was performed for pCCA in both Europe and the United States, but 5-year survival was 25%-30% with recurrence occurring in up to 60%[12]. The Mayo Protocol for pCCA was subsequently developed in 1993 and is outlined in Figure 1. With a 55% 5-year survival with LT, this has become the standard of care for LT in pCCA[13]. Downsides of this protocol were radiation-related injury which could affect surgery and the higher rates of vascular complications resulting in a greater need for vascular grafts [1]. Despite these difficulties, refining surgical and neoadjuvant protocol techniques have led to better long-term outcomes with survival increasing to 65% at 5 years and 59% at 10 years[14-16]. Since the development of the Mayo protocol in 1993, multicenter studies have validated this protocol and reported 5-year survival of 53% [16]. In 2002, Sudan *et al*[17] reported their experience with a neoadjuvant treatment protocol — using brachytherapy and 5-fluorouracil prior to LT for pCCA, this single center study reported a 45% survival over a median follow-up of 7.5 years[17]. Figure 2 illustrates the history of LT for pCCA. Subsequent studies have highlighted the improved overall survival (OS) of patients undergoing LT *vs* surgical resection, with age and comorbidity-matched patients having better outcomes with LT (3 and 5-year survival 72% *vs* 33% and 64% *vs* 18%, respectively)[18,19].

Despite the significant improvement in survival for pCCA with LT, disagreement exists regarding the need for neoadjuvant therapy. A retrospective study of 28 patients in the European Liver Transplant registry from 1990-2010 reported 5-year survival without neoadjuvant therapy was 59%, highlighting the importance of patient selection pre-transplant as opposed to universal neoadjuvant treatment[20]. However, concern was raised about selection bias in this study. Multiple other studies have found poor outcomes in patients who do not receive neoadjuvant treatment[16]. A recent multicenter prospective study found that patients with unresectable pCCA treated with neoadjuvant therapy and LT had superior 5-year survival (64% *vs* 18%) than those patients treated with LT alone[18]. These results remained significant when controlling for tumor size, nodal status, and presence of primary sclerosing cholangitis (PSC).

Negative surgical margins are critically important as the most common cause of death after LT in CCA patients is abdominal tumor recurrence[1]. This is further enhanced by the need for immunosuppression after transplant[21-23]. Additional research has identified risk factors for waitlist dropout and disease recurrence, which has helped validate current selection criteria as well as identify patients who would be good candidates for future investigational therapies.

### Standard MELD exception point

The standard MELD exception point for pCCA is currently set at Median MELD at transplant (MMaT) minus 3 points[3]. To qualify for standard MELD exception points, a patient must have unresectable disease due to either locally advanced tumor with extensive vascular and/or biliary invasion precluding complete resection, or poor hepatic functional reserve from underlying liver disease. It must be a single tumor < 3 cm in diameter with no evidence of intra- or extrahepatic metastasis and patients treated with neoadjuvant therapy at a center with an approved protocol. Further details on the MELD exception for CCA are found in Figure 3. Due to the increased risk of tumor seeding, it is important that transperitoneal aspiration or biopsy (*i.e.*, endoscopic ultrasound-guided biopsy or percutaneous biopsy) of the primary tumor is not performed[24]. Due to these limitations together with the long waitlist for LT, living donor liver transplant (LDLT) provides a timely opportunity for access to transplantation, which reduces the risk of waitlist morbidity and mortality[1,2].

The current protocol for pCCA treatment is external beam radiotherapy plus brachytherapy with a continuous infusion of 5-fluorouracil, followed by oral capecitabine until transplant (Figure 1). Other protocols have reported the use of stereotactic beam radiotherapy with gemcitabine plus cisplatin[25,26]. However, there are no comparative studies between these different regimens.

### Future directions

A prospective multicenter randomized trial in France is currently comparing neoadjuvant therapy + LT *vs* liver and extrahepatic bile duct resection for "resectable" pCCA, with 5 year survival as the primary outcome[4].

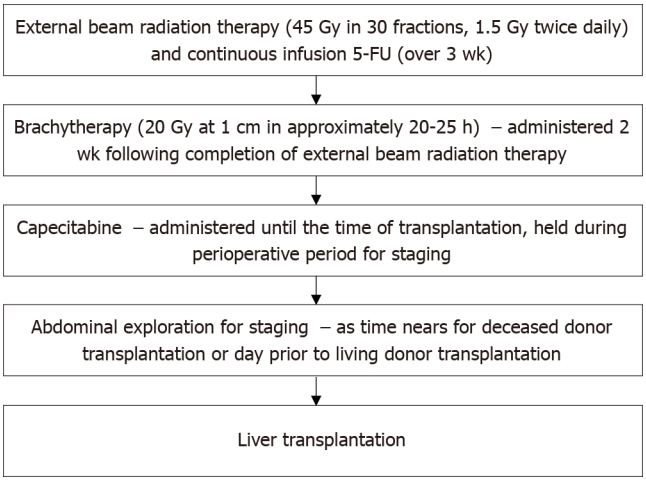



**Figure 1 Mayo clinic protocol for neoadjuvant chemoradiation and staging laparoscopy prior to liver transplantation.** Gy: Gray units of ionizing radiation; 5-FU: 5-Fluorouracil.

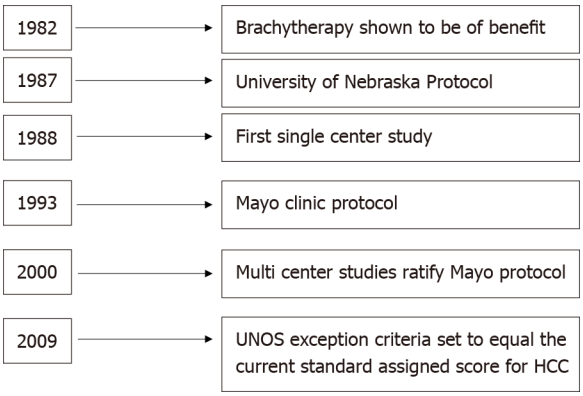



**Figure 2 History of liver transplantation in perihilar cholangiocarcinoma, including the development of the original transplantation protocols, United Network for Organ Sharing approval, and standard exception point for liver transplantation.** UNOS: United Network for Organ Sharing; HCC: Hepatocellular carcinoma.

## LT FOR ICCA

Initial experience regarding LT for iCCA occurred in patient's undergoing LT for suspected HCC which was subsequently diagnosed as iCCA after histologic evaluation of the explant[27]. One- and five-year OS in iCCA patients compared to HCC was shown to be 63.6% *vs* 90% and 63.6% *vs* 70.3% in a retrospective study of 44 patients with iCCA on explant LT for HCC[27]. A review of studies completed on LT in iCCA is reviewed in Table 1.

### *Very-early iCCA in cirrhosis*

Although surgical resection is the ideal treatment for iCCA, up to 70% of iCCA is unresectable at diagnosis with a median survival of 12 mo even with chemoradiation [1,8]. Historically, LT for iCCA carries a high risk of recurrence and thus has not been considered an indication for LT.

In 2014, a Spanish multi-center retrospective trial of 2301 patients undergoing LT for HCC found 8 patients had iCCA in the explant. These patients had a 73% 5-year survival[28]. A single-center retrospective study of LT for HCC from New York of 32 patients found 7 patients had iCCA in the explant. OS of these patients was 57%[29]. An international multi-center retrospective trial of 48 iCCA patients which included 15 patients with tumors < 2 cm and 32 patients with > 2 cm tumors reported that patients with < 2 cm tumors had a 65% 5-year survival, and the > 2 cm tumor group had a 45% 5-year survival[30]. A multi-center retrospective French study of patients examined outcomes of LT *vs* local resection for iCCA or iCCA-HCC for tumors < 2 cm and 2-5 cm. Better outcomes were found for LT in terms of OS and recurrence free survival

**Table 1 Studies assessing patient survival and disease-free survival after receiving a liver transplant for intrahepatic cholangiocarcinoma**

| Ref. | Study type | Number of LT patients | Overall survival (%) | | | DFS at 5-yr (%) | Comments |
|---|---|---|---|---|---|---|---|
| | | | 1-yr | 3-yr | 5-yr | No | |
| **iCCA** | | | | | | | |
| O'Grady *et al*[51], 1988 | Retrospective | 13 | 38 | 10 | 10 | - | |
| Yokoyama *et al*[52], 1990 | Retrospective | 2 | 50 | 0 | - | - | |
| Meyer *et al*[53], 2000 | Retrospective Multicenter | 207 | 72 | 48 | 23 | - | 84% DFS at 25 mo |
| Shimoda *et al*[54], 2001 | Retrospective | 16 | 62 | 39 | - | 35 | |
| Robles *et al*[55], 2004 | Retrospective multicenter | 23 | 77 | 65 | 42 | - | 2 yr DFS 35% |
| Sotiropoulos *et al*[56], 2009 | Retrospective | 10 | 70 | 50 | 33 | - | |
| Fu *et al*[57], 2011 | Retrospective | 11 | 50.5 | 50.5 | | | 3 yr DFS 51.9% |
| Hong *et al*[8], 2011 | Retrospective | 25 | - | 38 | 32 | 33 | |
| Vallin *et al*[58], 2013 | Retrospective multicenter | 10 | 80 | 60 | 24 | - | |
| Facciuto *et al*[29], 2015 | Retrospective | 7 iCCA; 9 iCCA + HCC; 16 iCCA-HCC | 71 | - | 57 | 44 | |
| Vilchez *et al*[59], 2016 | Retrospective multicenter | 440 | 79 | 58 | 47 | - | |
| **Very early iCCA (< 2 cm)** | | | | | | | |
| Sapisochin *et al*[28], 2014 | Retrospective multicenter | 27 | 78 | 66 | 51 | 36 | |
| Sapisochin *et al*[30], 2016 | Retrospective multicenter | 15 single < 2 cm; 33 multiple or > 2 cm | 93; 79 | 84; 50 | 65; 45 | 82; 39 | |
| **Locally advanced iCCA with sustained response to chemotherapy** | | | | | | | |
| Lunsford *et al*[5], 2018 | Prospective single-arm | 6 | 100 | 83.3 | 83.3 | 50 | |

LT: Liver transplant; DFS: Disease free survival; iCCA: Intrahepatic cholangiocarcinoma; HCC: Hepatocellular carcinoma.

[31]. These studies have laid the foundation for a multi-center prospective trial in France which is assessing outcomes for LT in iCCA < 2 cm and 2-5 cm[32].

### *Locally advanced iCCA*

A single center prospective case series analysis at Methodist Houston of 6 patients with large locally advanced unresectable iCCA were treated with neoadjuvant chemotherapy followed by LT[5]. The average total tumor burden was 10 cm in size with 4 lesions. Outcomes were positive with 80% 3-year survival and 50% recurrence free survival[5]. However, as this was only a small single center study, the investigators are developing a multi-center trial to determine if this may be a feasible treatment option for the future.

Similar to neoadjuvant and adjuvant protocols for pCCA, centers that have performed LT for iCCA have used regimens including fluorouracil or capecitabine combined with oxcaliplatin, leucovorin, and gemcitabine[8].

### *Risk factors for recurrent iCCA after LT*

Patients with multifocal tumors, perineural invasion, infiltrative tumor subtypes, and a lack of neoadjuvant and adjuvant therapies have been associated with high risk of recurrence and poor outcomes after LT for iCCA[8]. Interestingly, tumor size did not predict the risk of recurrence.

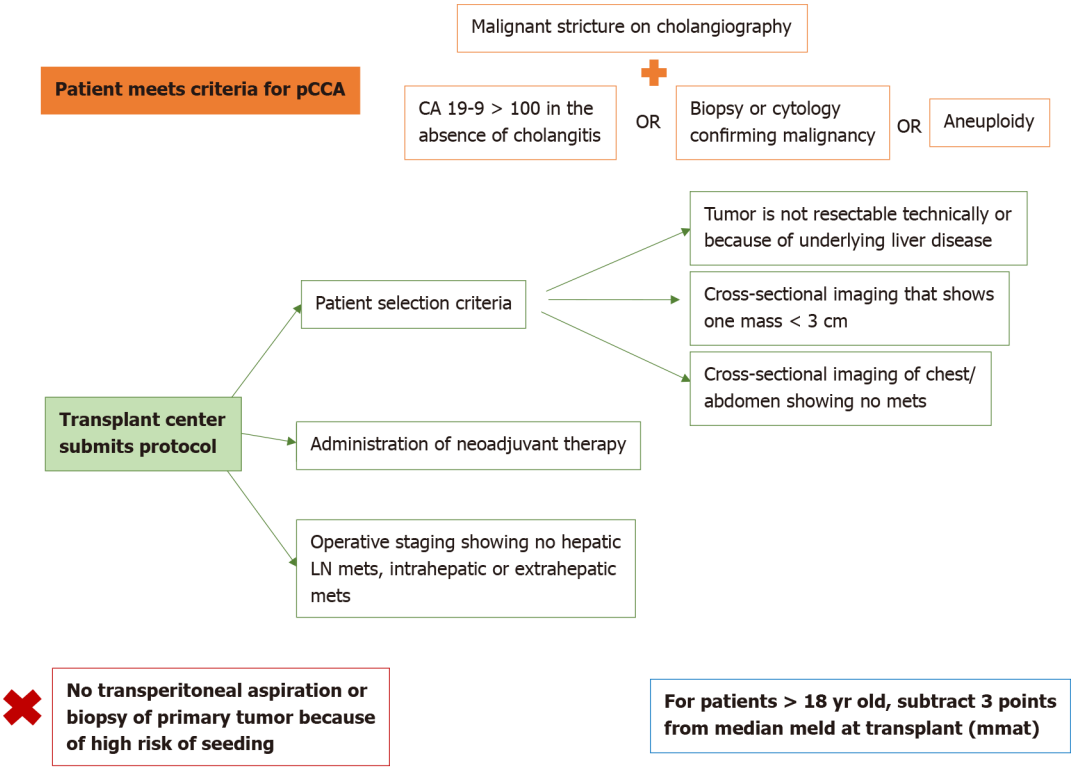



**Figure 3 Model for end-stage liver disease exception point for perihilar cholangiocarcinoma, as developed by the United Network for Organ Sharing.** pCCA: Perihilar cholangiocarcinoma; CA 19-9: Cancer-antigen 19-9; LN: Lymph node.

### *Risks for recurrent iCCA after surgical resection*

Recurrence of iCCA has been shown to occur in approximately 66% of patients who undergo curative resection[33]. Risk factors that increase the likelihood for recurrence include surgical margin < 10 mm, female sex, and presence of liver cirrhosis[33].

Currently, iCCA has no standard MELD exception. The options are to transplant based on calculated MELD score, or to use a LDLT. Although it is possible for a clinician to appeal to the National Liver Review Board (NLRB), there is no current policy or guidance regarding iCCA (unlike what exists for HCC or hCCA), which makes it challenging for NLRB to make decisions on allocation.

### *Future direction*

Until iCCA has an established, suitable indication for MELD exception, surgical resection will remain the standard of care. However, retrospective data suggests patients with small iCCA (< 2 cm) may have good outcomes with LT. The role of neoadjuvant chemoradiotherapy and LT for iCCA > 2 cm in non-cirrhotic patients remains to be defined.

## ALTERNATIVE TREATMENT STRATEGIES

### *Downsizing*

Rayar *et al*[34] treated 45 patients with Yttrium-90 + chemotherapy and were able to downgrade 8 (18%) patients for resection. Given organ scarcity, using chemotherapy to downgrade to resection may be another option to LT[35].

### *Immunotherapy and personalized medicine*

Historically, advanced, unresectable CCA has been treated with gemcitabine-based chemotherapy[1,26]. Recent advances in oncology have focused on the identification of biomarkers and molecular profiles that may be used as novel targets for chemotherapy [36-38]. *In vitro* and *in vivo* studies have suggested significant heterogeneity exists in biomarkers and molecular targets for CCA, especially iCCA[39]. This is further influenced by genetic variation, as well as the etiology for iCCA (*e.g.*, PSC, liver-fluke, viral hepatitis)[38]. Treatments currently under evaluation include T-cells, antibodies,

oncolytic viruses, cancer vaccines, and combinations of traditional chemotherapy with immunotherapy. These treatments are designed to target unique pathobiological pathways involved in CCA[40]. For example, patients with fibroblast growth factor receptor (FGFR) mutations (seen in 30% of patients with iCCA) are diagnosed at a younger age but typically have a more indolent course *vs* those with Kirsten rat sarcoma (KRAS) and p53 mutations which are more aggressive with poorer prognosis [41-46]. These genes are being evaluated as targets for future treatment to inhibit tumor growth[40,41,47,48]. Chemotherapy and immune checkpoint inhibitors have synergistic effects, which may increase tumor cell destruction while also decreasing the dosage of chemotherapy needed which may improve side effect profiles[41]. Radiotherapy is known to increase the sensitivity of the immune system to tumors, which in combination with immunotherapy has been efficacious for CCA. There are ongoing trials assessing the efficacy of immunotherapy, alone or in combination with chemotherapy to treat CCA. Additional promising tumor markers currently being evaluated for CCA include isocitrate dehydrogenase, programmed cell death protein 1, epidermal growth factor receptor, mechanistic target of rapamycin, mitogen-activated protein kinase and breast cancer pathways[41,49]. The identification of novel therapeutic pathways for CCA would provide a promising paradigm shift in the treatment of patients who are not candidates for resection or LT[50].

## CONCLUSION

CCA is becoming increasingly prevalent worldwide. Typically presenting at advanced stages that are inoperable, there has been a rapid evolution of treatments for unresectable CCA, including LT and new immunotherapies. Future research will evaluate the efficacy of novel pharmacotherapies in treating advanced CCA. Continuing to refine patient selection criteria for LT in CCA as well as optimizing neoadjuvant treatment regimens will be helpful. If LT is established as an acceptable therapy for iCCA, determining universal criteria for referral as well as organ allocation such as MELD exceptions will be crucial. Additionally, given the presence of iCCA in explanted livers suspected to be HCC, refining pre-transplant tumor staging and radiologic identification of iCCA will be helpful.

## REFERENCES


1 **Sapisochin G**, Javle M, Lerut J, Ohtsuka M, Ghobrial M, Hibi T, Kwan NM, Heimbach J. Liver Transplantation for Cholangiocarcinoma and Mixed Hepatocellular Cholangiocarcinoma: Working Group Report From the ILTS Transplant Oncology Consensus Conference. *Transplantation* 2020; **104**: 1125-1130 [PMID: 32217937 DOI: 10.1097/TP.0000000000003212]

2 **Zamora-Valdes D**, Heimbach JK. Liver Transplant for Cholangiocarcinoma. *Gastroenterol Clin North Am* 2018; **47**: 267-280 [PMID: 29735023 DOI: 10.1016/j.gtc.2018.01.002]

3 **Organ Procurement and Transplantation Network Policy**. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, Rockville, MD. 2021. [cited 25 Jan 2021]. In: Organ Procurement and Transplantation Network Policy [Internet]. Available from: https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf

4 **Vibert E**. Liver Resection Versus Radio-chemotherapy-Transplantation for Hilar Cholangiocarcinoma (TRANSPHIL). [accessed 2021 Jan 25]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT02232932 ClinicalTrials.gov Identifier: NCT02232932

5 **Lunsford KE**, Javle M, Heyne K, Shroff RT, Abdel-Wahab R, Gupta N, Mobley CM, Saharia A, Victor DW, Nguyen DT, Graviss EA, Kaseb AO, McFadden RS, Aloia TA, Conrad C, Li XC, Monsour HP, Gaber AO, Vauthey JN, Ghobrial RM; Methodist–MD Anderson Joint Cholangiocarcinoma Collaborative Committee (MMAJCCC). Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: a prospective case-series. *Lancet Gastroenterol Hepatol* 2018; **3**: 337-348 [PMID: 29548617 DOI: 10.1016/S2468-1253(18)30045-1]

6 **Rizvi S**, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. *Gastroenterology* 2013; **145**: 1215-1229 [PMID: 24140396 DOI: 10.1053/j.gastro.2013.10.013]

7 **Saha SK**, Zhu AX, Fuchs CS, Brooks GA. Forty-Year Trends in Cholangiocarcinoma Incidence in the U.S.: Intrahepatic Disease on the Rise. *Oncologist* 2016; **21**: 594-599 [PMID: 27000463 DOI: 10.1634/theoncologist.2015-0446]

8 **Hong JC**, Jones CM, Duffy JP, Petrowsky H, Farmer DG, French S, Finn R, Durazo FA, Saab S, Tong MJ, Hiatt JR, Busuttil RW. Comparative analysis of resection and liver transplantation for

intrahepatic and hilar cholangiocarcinoma: a 24-year experience in a single center. *Arch Surg* 2011; **146**: 683-689 [PMID: 21690444 DOI: 10.1001/archsurg.2011.116]

9 **Burke EC**, Jarnagin WR, Hochwald SN, Pisters PW, Fong Y, Blumgart LH. Hilar Cholangiocarcinoma: patterns of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system. *Ann Surg* 1998; **228**: 385-394 [PMID: 9742921 DOI: 10.1097/00000658-199809000-00011]

10 **Klempnauer J**, Ridder GJ, von Wasielewski R, Werner M, Weimann A, Pichlmayr R. Resectional surgery of hilar cholangiocarcinoma: a multivariate analysis of prognostic factors. *J Clin Oncol* 1997; **15**: 947-954 [PMID: 9060532 DOI: 10.1200/JCO.1997.15.3.947]

11 **Washburn WK**, Lewis WD, Jenkins RL. Aggressive surgical resection for cholangiocarcinoma. *Arch Surg* 1995; **130**: 270-276 [PMID: 7534059 DOI: 10.1001/archsurg.1995.01430030040006]

12 **Rosen CB**, Heimbach JK, Gores GJ. Liver transplantation for cholangiocarcinoma. *Transpl Int* 2010; **23**: 692-697 [PMID: 20497401 DOI: 10.1111/j.1432-2277.2010.01108.x]

13 **Rea DJ**, Heimbach JK, Rosen CB, Haddock MG, Alberts SR, Kremers WK, Gores GJ, Nagorney DM. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. *Ann Surg* 2005; **242**: 451-8; discussion 458 [PMID: 16135931 DOI: 10.1097/01.sla.0000179678.13285.fa]

14 **Coelen RJS**, Gaspersz MP, Labeur TA, van Vugt JLA, van Dieren S, Willemssen FEJA, Nio CY, IJzermans JNM, Klümpen HJ, Groot Koerkamp B, van Gulik TM. Validation of the Mayo Clinic Staging System in Determining Prognoses of Patients With Perihilar Cholangiocarcinoma. *Clin Gastroenterol Hepatol* 2017; **15**: 1930-1939.e3 [PMID: 28532698 DOI: 10.1016/j.cgh.2017.04.044]

15 **Rosen CB**, Darwish Murad S, Heimbach JK, Nyberg SL, Nagorney DM, Gores GJ. Neoadjuvant therapy and liver transplantation for hilar cholangiocarcinoma: is pretreatment pathological confirmation of diagnosis necessary? *J Am Coll Surg* 2012; **215**: 31-8; discussion 38 [PMID: 22621893 DOI: 10.1016/j.jamcollsurg.2012.03.014]

16 **Darwish Murad S**, Kim WR, Harnois DM, Douglas DD, Burton J, Kulik LM, Botha JF, Mezrich JD, Chapman WC, Schwartz JJ, Hong JC, Emond JC, Jeon H, Rosen CB, Gores GJ, Heimbach JK. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. *Gastroenterology* 2012; **143**: 88-98.e3; quiz e14 [PMID: 22504095 DOI: 10.1053/j.gastro.2012.04.008]

17 **Sudan D**, DeRoover A, Chinnakotla S, Fox I, Shaw B Jr, McCashland T, Sorrell M, Tempero M, Langnas A. Radiochemotherapy and transplantation allow long-term survival for nonresectable hilar cholangiocarcinoma. *Am J Transplant* 2002; **2**: 774-779 [PMID: 12243499 DOI: 10.1034/j.1600-6143.2002.20812.x]

18 **Ethun CG**, Lopez-Aguiar AG, Anderson DJ, Adams AB, Fields RC, Doyle MB, Chapman WC, Krasnick BA, Weber SM, Mezrich JD, Salem A, Pawlik TM, Poultsides G, Tran TB, Idrees K, Isom CA, Martin RCG, Scoggins CR, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Cardona K, Maithel SK. Transplantation Versus Resection for Hilar Cholangiocarcinoma: An Argument for Shifting Treatment Paradigms for Resectable Disease. *Ann Surg* 2018; **267**: 797-805 [PMID: 29064885 DOI: 10.1097/SLA.0000000000002574]

19 **Moris D**, Kostakis ID, Machairas N, Prodromidou A, Tsilimigras DI, Ravindra KV, Sudan DL, Knechtle SJ, Barbas AS. Comparison between liver transplantation and resection for hilar cholangiocarcinoma: A systematic review and meta-analysis. *PLoS One* 2019; **14**: e0220527 [PMID: 31365594 DOI: 10.1371/journal.pone.0220527]

20 **Mantel HT**, Westerkamp AC, Adam R, Bennet WF, Seehofer D, Settmacher U, Sánchez-Bueno F, Fabregat Prous J, Boleslawski E, Friman S, Porte RJ; European Liver and Intestine Transplant Association (ELITA). Strict Selection Alone of Patients Undergoing Liver Transplantation for Hilar Cholangiocarcinoma Is Associated with Improved Survival. *PLoS One* 2016; **11**: e0156127 [PMID: 27276221 DOI: 10.1371/journal.pone.0156127]

21 **Iwatsuki S**, Todo S, Marsh JW, Madariaga JR, Lee RG, Dvorchik I, Fung JJ, Starzl TE. Treatment of hilar cholangiocarcinoma (Klatskin tumors) with hepatic resection or transplantation. *J Am Coll Surg* 1998; **187**: 358-364 [PMID: 9783781 DOI: 10.1016/S1072-7515(98)00207-5]

22 **Urego M**, Flickinger JC, Carr BI. Radiotherapy and multimodality management of cholangiocarcinoma. *Int J Radiat Oncol Biol Phys* 1999; **44**: 121-126 [PMID: 10219804 DOI: 10.1016/S0360-3016(98)00509-4]

23 **Flickinger JC**, Epstein AH, Iwatsuki S, Carr BI, Starzl TE. Radiation therapy for primary carcinoma of the extrahepatic biliary system. An analysis of 63 cases. *Cancer* 1991; **68**: 289-294 [PMID: 2070327 DOI: 10.1002/1097-0142(19910715)68:2<289::aid-cncr2820680213>3.0.co;2-2]

24 **Heimbach JK**, Sanchez W, Rosen CB, Gores GJ. Trans-peritoneal fine needle aspiration biopsy of hilar cholangiocarcinoma is associated with disease dissemination. *HPB (Oxford)* 2011; **13**: 356-360 [PMID: 21492336 DOI: 10.1111/j.1477-2574.2011.00298.x]

25 **Loveday BPT**, Knox JJ, Dawson LA, Metser U, Brade A, Horgan AM, Gallinger S, Greig PD, Moulton CA. Neoadjuvant hyperfractionated chemoradiation and liver transplantation for unresectable perihilar cholangiocarcinoma in Canada. *J Surg Oncol* 2018; **117**: 213-219 [PMID: 29480952 DOI: 10.1002/jso.24833]

26 **Valle JW**, Wasan H, Johnson P, Jones E, Dixon L, Swindell R, Baka S, Maraveyas A, Corrie P, Falk S, Gollins S, Lofts F, Evans L, Meyer T, Anthoney A, Iveson T, Highley M, Osborne R, Bridgewater J. Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study - The UK

ABC-01 Study. *Br J Cancer* 2009; **101**: 621-627 [PMID: 19672264 DOI: 10.1038/sj.bjc.6605211]

27 **Lee DD**, Croome KP, Musto KR, Melendez J, Tranesh G, Nakhleh R, Taner CB, Nguyen JH, Patel T, Harnois DM. Liver transplantation for intrahepatic cholangiocarcinoma. *Liver Transpl* 2018; **24**: 634-644 [PMID: 29514406 DOI: 10.1002/lt.25052]

28 **Sapisochin G**, Rodríguez de Lope C, Gastaca M, Ortiz de Urbina J, Suarez MA, Santoyo J, Castroagudín JF, Varo E, López-Andujar R, Palacios F, Sanchez Antolín G, Perez B, Guiberteau A, Blanco G, González-Diéguez ML, Rodriguez M, Varona MA, Barrera MA, Fundora Y, Ferron JA, Ramos E, Fabregat J, Ciria R, Rufian S, Otero A, Vazquez MA, Pons JA, Parrilla P, Zozaya G, Herrero JI, Charco R, Bruix J. "Very early" intrahepatic cholangiocarcinoma in cirrhotic patients: should liver transplantation be reconsidered in these patients? *Am J Transplant* 2014; **14**: 660-667 [PMID: 24410861 DOI: 10.1111/ajt.12591]

29 **Facciuto ME**, Singh MK, Lubezky N, Selim MA, Robinson D, Kim-Schluger L, Florman S, Ward SC, Thung SN, Fiel M, Schiano TD. Tumors with intrahepatic bile duct differentiation in cirrhosis: implications on outcomes after liver transplantation. *Transplantation* 2015; **99**: 151-157 [PMID: 25029385 DOI: 10.1097/TP.0000000000000286]

30 **Sapisochin G**, Facciuto M, Rubbia-Brandt L, Marti J, Mehta N, Yao FY, Vibert E, Cherqui D, Grant DR, Hernandez-Alejandro R, Dale CH, Cucchetti A, Pinna A, Hwang S, Lee SG, Agopian VG, Busuttil RW, Rizvi S, Heimbach JK, Montenovo M, Reyes J, Cesaretti M, Soubrane O, Reichman T, Seal J, Kim PT, Klintmalm G, Sposito C, Mazzaferro V, Dutkowski P, Clavien PA, Toso C, Majno P, Kneteman N, Saunders C, Bruix J; iCCA International Consortium. Liver transplantation for "very early" intrahepatic cholangiocarcinoma: International retrospective study supporting a prospective assessment. *Hepatology* 2016; **64**: 1178-1188 [PMID: 27481548 DOI: 10.1002/hep.28744]

31 **De Martin E**, Rayar M, Golse N, Dupeux M, Gelli M, Gnemmi V, Allard MA, Cherqui D, Sa Cunha A, Adam R, Coilly A, Antonini TM, Guettier C, Samuel D, Boudjema K, Boleslawski E, Vibert E. Analysis of Liver Resection Versus Liver Transplantation on Outcome of Small Intrahepatic Cholangiocarcinoma and Combined Hepatocellular-Cholangiocarcinoma in the Setting of Cirrhosis. *Liver Transpl* 2020; **26**: 785-798 [PMID: 32090444 DOI: 10.1002/lt.25737]

32 **Sapisochin G**, Bruix J. Liver transplantation for early intrahepatic cholangiocarcinoma (LT for iCCA). [accessed 2021 Jan 25]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT02878473?term=sapisochin ClinicalTrials.gov Identifier: NCT02878473

33 **Hu LS**, Zhang XF, Weiss M, Popescu I, Marques HP, Aldrighetti L, Maithel SK, Pulitano C, Bauer TW, Shen F, Poultsides GA, Soubrane O, Martel G, Koerkamp BG, Itaru E, Pawlik TM. Recurrence Patterns and Timing Courses Following Curative-Intent Resection for Intrahepatic Cholangiocarcinoma. *Ann Surg Oncol* 2019; **26**: 2549-2557 [PMID: 31020501 DOI: 10.1245/s10434-019-07353-4]

34 **Rayar M**, Sulpice L, Edeline J, Garin E, Levi Sandri GB, Meunier B, Boucher E, Boudjema K. Intra-arterial yttrium-90 radioembolization combined with systemic chemotherapy is a promising method for downstaging unresectable huge intrahepatic cholangiocarcinoma to surgical treatment. *Ann Surg Oncol* 2015; **22**: 3102-3108 [PMID: 25623598 DOI: 10.1245/s10434-014-4365-3]

35 **Le Roy B**, Gelli M, Pittau G, Allard MA, Pereira B, Serji B, Vibert E, Castaing D, Adam R, Cherqui D, Sa Cunha A. Neoadjuvant chemotherapy for initially unresectable intrahepatic cholangiocarcinoma. *Br J Surg* 2018; **105**: 839-847 [PMID: 28858392 DOI: 10.1002/bjs.10641]

36 **Jiao Y**, Pawlik TM, Anders RA, Selaru FM, Streppel MM, Lucas DJ, Niknafs N, Guthrie VB, Maitra A, Argani P, Offerhaus GJA, Roa JC, Roberts LR, Gores GJ, Popescu I, Alexandrescu ST, Dima S, Fassan M, Simbolo M, Mafficini A, Capelli P, Lawlor RT, Ruzzenente A, Guglielmi A, Tortora G, de Braud F, Scarpa A, Jarnagin W, Klimstra D, Karchin R, Velculescu VE, Hruban RH, Vogelstein B, Kinzler KW, Papadopoulos N, Wood LD. Exome sequencing identifies frequent inactivating mutations in BAP1, ARID1A and PBRM1 in intrahepatic cholangiocarcinomas. *Nat Genet* 2013; **45**: 1470-1473 [PMID: 24185509 DOI: 10.1038/ng.2813]

37 **Chan-On W**, Nairismägi ML, Ong CK, Lim WK, Dima S, Pairojkul C, Lim KH, McPherson JR, Cutcutache I, Heng HL, Ooi L, Chung A, Chow P, Cheow PC, Lee SY, Choo SP, Tan IB, Duda D, Nastase A, Myint SS, Wong BH, Gan A, Rajasegaran V, Ng CC, Nagarajan S, Jusakul A, Zhang S, Vohra P, Yu W, Huang D, Sithithaworn P, Yongvanit P, Wongkham S, Khuntikeo N, Bhudhisawasdi V, Popescu I, Rozen SG, Tan P, Teh BT. Exome sequencing identifies distinct mutational patterns in liver fluke-related and non-infection-related bile duct cancers. *Nat Genet* 2013; **45**: 1474-1478 [PMID: 24185513 DOI: 10.1038/ng.2806]

38 **Ong CK**, Subimerb C, Pairojkul C, Wongkham S, Cutcutache I, Yu W, McPherson JR, Allen GE, Ng CC, Wong BH, Myint SS, Rajasegaran V, Heng HL, Gan A, Zang ZJ, Wu Y, Wu J, Lee MH, Huang D, Ong P, Chan-on W, Cao Y, Qian CN, Lim KH, Ooi A, Dykema K, Furge K, Kukongviriyapan V, Sripa B, Wongkham C, Yongvanit P, Futreal PA, Bhudhisawasdi V, Rozen S, Tan P, Teh BT. Exome sequencing of liver fluke-associated cholangiocarcinoma. *Nat Genet* 2012; **44**: 690-693 [PMID: 22561520 DOI: 10.1038/ng.2273]

39 **Ahn DH**, Javle M, Ahn CW, Jain A, Mikhail S, Noonan AM, Ciombor K, Wu C, Shroff RT, Chen JL, Bekaii-Saab T. Next-generation sequencing survey of biliary tract cancer reveals the association between tumor somatic variants and chemotherapy resistance. *Cancer* 2016; **122**: 3657-3666 [PMID: 27495988 DOI: 10.1002/cncr.30247]

40 **French DM**, Lin BC, Wang M, Adams C, Shek T, Hötzel K, Bolon B, Ferrando R, Blackmore C,

Schroeder K, Rodriguez LA, Hristopoulos M, Venook R, Ashkenazi A, Desnoyers LR. Targeting FGFR4 inhibits hepatocellular carcinoma in preclinical mouse models. *PLoS One* 2012; **7**: e36713 [PMID: 22615798 DOI: 10.1371/journal.pone.0036713]

41 **O'Rourke CJ**, Munoz-Garrido P, Andersen JB. Molecular Targets in Cholangiocarcinoma. *Hepatology* 2021; **73** Suppl 1: 62-74 [PMID: 32304327 DOI: 10.1002/hep.31278]

42 **Javle M**, Lowery M, Shroff RT, Weiss KH, Springfeld C, Borad MJ, Ramanathan RK, Goyal L, Sadeghi S, Macarulla T, El-Khoueiry A, Kelley RK, Borbath I, Choo SP, Oh DY, Philip PA, Chen LT, Reungwetwattana T, Van Cutsem E, Yeh KH, Ciombor K, Finn RS, Patel A, Sen S, Porter D, Isaacs R, Zhu AX, Abou-Alfa GK, Bekaii-Saab T. Phase II Study of BGJ398 in Patients With FGFR-Altered Advanced Cholangiocarcinoma. *J Clin Oncol* 2018; **36**: 276-282 [PMID: 29182496 DOI: 10.1200/JCO.2017.75.5009]

43 **Lowery MA**, Abou-Alfa GK, Burris HA, Janku F, Shroff RT, Cleary JM, Azad NS, Goyal L, Maher EA, Gore L, Hollebecque A, Beeran M, Trent JC, Jiang L, Ishii Y, Auer J, Gliser C, Agresta SV, Pandya SS, Zhu AX. Phase I study of AG-120, an IDH1 mutant enzyme inhibitor: results from the cholangiocarcinoma dose escalation and expansion cohorts. *J Clin Oncol* 2017; **35(Suppl** 15): 4015 [DOI: 10.1200/JCO.2017.35.15_suppl.4015]

44 **Lavingia V**, Fakih M. Impressive response to dual *BRAF* and MEK inhibition in patients with BRAF mutant intrahepatic cholangiocarcinoma-2 case reports and a brief review. *J Gastrointest Oncol* 2016; **7**: E98-E102 [PMID: 28078132 DOI: 10.21037/jgo.2016.09.13]

45 **Jain A**, Borad MJ, Kelley RK, Wang Y, Abdel-Wahab R, Meric-Bernstam F, Baggerly KA, Kaseb AO, Al-shamsi HO, Ahn DH, DeLeon T, Bocobo AG, Bekaii-Saab T, Shroff RT, Javle M. Cholangiocarcinoma with FGFR genetic aberrations: A unique clinical phenotype. *JCO Precis Oncol* 2018; **2**: 1-12 [DOI: 10.1200/PO.17.00080]

46 **Li F**, Peiris MN, Donoghue DJ. Functions of FGFR2 corrupted by translocations in intrahepatic cholangiocarcinoma. *Cytokine Growth Factor Rev* 2020; **52**: 56-67 [PMID: 31899106 DOI: 10.1016/j.cytogfr.2019.12.005]

47 **Goyal L**, Saha SK, Liu LY, Siravegna G, Leshchiner I, Ahronian LG, Lennerz JK, Vu P, Deshpande V, Kambadakone A, Mussolin B, Reyes S, Henderson L, Sun JE, Van Seventer EE, Gurski JM Jr, Baltschukat S, Schacher-Engstler B, Barys L, Stamm C, Furet P, Ryan DP, Stone JR, Iafrate AJ, Getz G, Porta DG, Tiedt R, Bardelli A, Juric D, Corcoran RB, Bardeesy N, Zhu AX. Polyclonal Secondary *FGFR2* Mutations Drive Acquired Resistance to FGFR Inhibition in Patients with FGFR2 Fusion-Positive Cholangiocarcinoma. *Cancer Discov* 2017; **7**: 252-263 [PMID: 28034880 DOI: 10.1158/2159-8290.CD-16-1000]

48 **Hagel M**, Miduturu C, Sheets M, Rubin N, Weng W, Stransky N, Bifulco N, Kim JL, Hodous B, Brooijmans N, Shutes A, Winter C, Lengauer C, Kohl NE, Guzi T. First Selective Small Molecule Inhibitor of FGFR4 for the Treatment of Hepatocellular Carcinomas with an Activated FGFR4 Signaling Pathway. *Cancer Discov* 2015; **5**: 424-437 [PMID: 25776529 DOI: 10.1158/2159-8290.CD-14-1029]

49 **Moeini A**, Sia D, Bardeesy N, Mazzaferro V, Llovet JM. Molecular Pathogenesis and Targeted Therapies for Intrahepatic Cholangiocarcinoma. *Clin Cancer Res* 2016; **22**: 291-300 [PMID: 26405193 DOI: 10.1158/1078-0432.CCR-14-3296]

50 **Fong ZV**, Brownlee SA, Qadan M, Tanabe KK. The Clinical Management of Cholangiocarcinoma in the United States and Europe: A Comprehensive and Evidence-Based Comparison of Guidelines. *Ann Surg Oncol* 2021; **28**: 2660-2674 [PMID: 33646431 DOI: 10.1245/s10434-021-09671-y]

51 **O'Grady JG**, Polson RJ, Rolles K, Calne RY, Williams R. Liver transplantation for malignant disease. Results in 93 consecutive patients. *Ann Surg* 1988; **207**: 373-379 [PMID: 2451484 DOI: 10.1097/00000658-198804000-00002]

52 **Yokoyama I**, Todo S, Iwatsuki S, Starzl TE. Liver transplantation in the treatment of primary liver cancer. *Hepatogastroenterology* 1990; **37**: 188-193 [PMID: 2160421]

53 **Meyer CG**, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. *Transplantation* 2000; **69**: 1633-1637 [PMID: 10836374 DOI: 10.1097/00007890-200004270-00019]

54 **Shimoda M**, Farmer DG, Colquhoun SD, Rosove M, Ghobrial RM, Yersiz H, Chen P, Busuttil RW. Liver transplantation for cholangiocellular carcinoma: analysis of a single-center experience and review of the literature. *Liver Transpl* 2001; **7**: 1023-1033 [PMID: 11753904 DOI: 10.1053/jlts.2001.29419]

55 **Robles R**, Figueras J, Turrión VS, Margarit C, Moya A, Varo E, Calleja J, Valdivieso A, Valdecasas JC, López P, Gómez M, de Vicente E, Loinaz C, Santoyo J, Fleitas M, Bernardos A, Lladó L, Ramírez P, Bueno FS, Jaurrieta E, Parrilla P. Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma. *Ann Surg* 2004; **239**: 265-271 [PMID: 14745336 DOI: 10.1097/01.sla.0000108702.45715.81]

56 **Sotiropoulos GC**, Bockhorn M, Sgourakis G, Brokalaki EI, Molmenti EP, Neuhäuser M, Radtke A, Wohlschlaeger J, Baba HA, Broelsch CE, Lang H. R0 Liver resections for primary malignant liver tumors in the noncirrhotic liver: a diagnosis-related analysis. *Dig Dis Sci* 2009; **54**: 887-894 [PMID: 18712480 DOI: 10.1007/s10620-008-0408-6]

57 **Fu BS**, Zhang T, Li H, Yi SH, Wang GS, Xu C, Yang Y, Cai CJ, Lu MQ, Chen GH. The role of liver transplantation for intrahepatic cholangiocarcinoma: a single-center experience. *Eur Surg Res* 2011; **47**: 218-221 [PMID: 22041581 DOI: 10.1159/000332827]

58 **Vallin M**, Sturm N, Lamblin G, Guillaud O, Hilleret MN, Hervieu V, Joubert J, Abergel A, Leroy V, Boillot O, Dumortier J, Scoazec JY. Unrecognized intrahepatic cholangiocarcinoma: an analysis of

993 adult cirrhotic liver explants. *Clin Transplant* 2013; **27**: 403-409 [PMID: 23438040 DOI: 10.1111/ctr.12108]

59 **Vilchez V**, Shah MB, Daily MF, Pena L, Tzeng CW, Davenport D, Hosein PJ, Gedaly R, Maynard E. Long-term outcome of patients undergoing liver transplantation for mixed hepatocellular carcinoma and cholangiocarcinoma: an analysis of the UNOS database. *HPB (Oxford)* 2016; **18**: 29-34 [PMID: 26776848 DOI: 10.1016/j.hpb.2015.10.001]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 January 27; 14(1): 12-23

DOI: 10.4240/wjgs.v14.i1.12

ISSN 1948-9366 (online)

*MINIREVIEWS*

# Gastric per-oral endoscopic myotomy: Indications, technique, results and comparison with surgical approach

Maria Chiara Verga, Stefano Mazza, Francesco Azzolini, Fabrizio Cereatti, Clara Benedetta Conti, Andrea Drago, Sara Soro, Biagio Elvo, Roberto Grassia

**ORCID number:** Maria Chiara Verga 0000-0001-6871-1229; Stefano Mazza 0000-0002-9068-3209; Francesco Azzolini 0000-0002-6547-5918; Fabrizio Cereatti 0000-0003-0628-4473; Clara Benedetta Conti 0000-0001-9774-2374; Andrea Drago 0000-0002-9777-8665; Sara Soro 0000-0002-4802-8403; Biagio Elvo 0000-0001-5695-0310; Roberto Grassia 0000-0003-4491-4050.

**Author contributions:** All authors contributed to literature search and data collect; Verga MC, Azzolini F and Cereatti F wrote the paper; Mazza S, Conti CB, Drago A, Soro S, Elvo B and Grassia R critically revised the paper and contributed to the final version of the manuscript.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**Country/Territory of origin:** Italy

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

**Maria Chiara Verga, Stefano Mazza, Fabrizio Cereatti, Andrea Drago, Sara Soro, Biagio Elvo, Roberto Grassia,** Gastroenterology and Digestive Endoscopy Unit, ASST Cremona, Cremona 26100, Italy

**Francesco Azzolini,** Gastroenterology and Digestive Endoscopy Unit, Ospedale San Raffaele IRCCS, Milano 20132, Italy

**Clara Benedetta Conti,** Digestive and Interventional Endoscopy Unit, ASST Monza, Monza 20800, Italy

**Corresponding author:** Maria Chiara Verga, MD, Doctor, Gastroenterology and Digestive Endoscopy Unit, ASST Cremona, Viale Concordia, 1, Cremona 26100, Italy.
mariachiara.verga@asst-cremona.it

## Abstract

Gastroparesis is a chronic disease of the stomach that causes a delayed gastric emptying, without the presence of a stenosis. For 30 years the authors identified pylorospasm as one of the most important pathophysiological mechanisms determining gastroparesis. Studies with EndoFLIP, a device that assesses pyloric distensibility, increased the knowledge about pylorospasm. Based on this data, several pyloric-targeted therapies were developed to treat refractory gastroparesis: Surgical pyloroplasty and endoscopic approach, such as pyloric injection of botulinum and pyloric stenting. Notwithstanding, the success of most of these techniques is still not complete. In 2013, the first human gastric per-oral endoscopic myotomy (GPOEM) was performed. It was inspired by the POEM technique, with a similar dissection method, that allows pyloromyotomy. Therapeutical results of GPOEM are similar to surgical approach in term of clinical success, adverse events and post-surgical pain. In the last 8 years GPOEM has gained the attention of the scientific community, as a minimally invasive technique with high rate of clinical success, quickly prevailing as a promising therapy for gastroparesis. Not surprisingly, in referral centers, its technical success rate is 100%. One of the main goals of recent studies is to identify those patients that will respond better to the therapies targeted on pylorus and to choose the better approach for each patient.

**Key Words:** Gastric per-oral endoscopic myotomy; Pyloroplasty; Gastroparesis; EndoFLIP; Pyloromyotomy; Gastroparesis cardinal symptom index

Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0



**Received:** May 2, 2021
**Peer-review started:** May 2, 2021
**First decision:** June 27, 2021
**Revised:** July 20, 2021
**Accepted:** December 22, 2021
**Article in press:** December 22, 2021
**Published online:** January 27, 2022

**P-Reviewer:** Cai Q
**S-Editor:** Fan JR
**L-Editor:** A
**P-Editor:** Fan JR



**Core Tip:** Many studies tried to identify the factors that may predict the response to pyloric targeted therapies in gastroparesis according to etiology, prevalent symptoms, antroduodenal manometric study and EndoFLIP. Unfortunately, it is still difficult to reach an accurate determination of the optimal candidates for each treatment. Currently, surgical and endoscopic approach has been compared in term of safety and the results seem encouraging for endoscopic method. In this review we summarize indications, side effects and outcome of gastric per-oral endoscopic myotomy compared to surgical pyloroplasty.

**Citation:** Verga MC, Mazza S, Azzolini F, Cereatti F, Conti CB, Drago A, Soro S, Elvo B, Grassia R. Gastric per-oral endoscopic myotomy: Indications, technique, results and comparison with surgical approach. *World J Gastrointest Surg* 2022; 14(1): 12-23
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i1/12.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i1.12

## INTRODUCTION

### *Epidemiology and pathophysiology*

**Epidemiology:** Gastric retention > 60% at two hours and/or > 10% after four hours from a meal is considered pathological[1], in absence of organic strictures[2]. Gastroparesis (GP) is a chronic alteration of the gastric motility that leads to a delay in stomach emptying. Mainly, it is an idiopathic condition; however it can be also caused by diabetes and post-surgical conditions, such as fundoplicatio, vagotomy, bariatric surgery and esophagectomy. Less frequent etiologies are: Post-infectious gastroparesis and neurological or autoimmune diseases[3]. The related symptoms are often dyspepsia-like. Thus, gastroparesis is an underdiagnosed condition. The prevalence is estimated around 3% in United States (mean age of 37.7 years, with an F:M ratio of 4:1)[4] and American data showed a large increase in hospitalizations between 1997 and 2013 for gastroparesis, estimating a related increase in costs of 1026%[5].

**Pathophysiology:** The current knowledges of the pathophysiology of GP remain partial[6]. This explains the delay in the diagnosis and the lack of a reference therapy, that is still an open challenge.

Histologically, loss of interstitial cells of Cajal (ICC) is the most important finding. Indeed, these cells show ultrastructural modification such as intracytoplasmatic vacuoles and apoptotic features. However, up to now, no definitive explanations are available[7].

### *Diagnosis*

Gastroparesis may be characterized by two different patterns at antroduodenal manometry study: Waves of contraction of reduced amplitude (< 40 mmHg), suggestive for myopathy, or reduced and disorganized gastric motility. This latter pattern is more frequent, but not exclusive, in neurogenic alterations[8,9]. Moreover, pylorospasm appears to be one of the crucial components[10].

However, antroduodenal manometry is a complex procedure and it is unfortunately little available in daily clinical practice.

The patient with a suspicion of gastroparesis should always undergo a thoroughly evaluation of the previous medical history coupled with a complete physical examination. EGDS is mandatory in order to exclude organic lesions.

The second step consists in calculating a validated score, the gastroparesis cardinal symptoms index (GCSI), that evaluates symptoms in the previous two weeks from the patient evaluation. GCSI has shown to be reliable and reproducible[11]. It is based on three subscales (post-prandial fullness/early satiety-4 items; nausea/vomiting-3 items; bloeating-2 items) and each item ranges from 0 (none) to 5 (severe). GCSI is not a diagnostic tool but it is useful to measure the severity of the disease and the post treatment improvement. Most of the available studies exclude the patients who have GCSI < 2.0 from both endoscopic and surgical therapy (Table 1). Importantly, the psychometric evidence of the GCSI was also found to be consistent with European

**Table 1 Gastroparesis cardinal symptom index**

| Are you suffering of | None | Very mild | Mild | Moderate | Severe | Very severe |
|---|---|---|---|---|---|---|
| Nausea | 0 | 1 | 2 | 3 | 4 | 5 |
| Retching | 0 | 1 | 2 | 3 | 4 | 5 |
| Vomiting | 0 | 1 | 2 | 3 | 4 | 5 |
| Stomach fullness | 0 | 1 | 2 | 3 | 4 | 5 |
| Inability to finish a normal sized meal | 0 | 1 | 2 | 3 | 4 | 5 |
| Feeling excessively full after meals | 0 | 1 | 2 | 3 | 4 | 5 |
| Loss of appetite | 0 | 1 | 2 | 3 | 4 | 5 |
| Bloating | 0 | 1 | 2 | 3 | 4 | 5 |
| Belly visibly larger | 0 | 1 | 2 | 3 | 4 | 5 |

guidelines and the Food and Drugs Administration (FDA)[12,13].

Overall, the severity of GCSI appears to properly correlate with the objective measurements of the gastric emptying time at 2 h, but not at 4 h[14]. This is particular true when considering nausea, vomiting, and premature satiety

Moreover, the patient should undergo to a gastric emptying study by scintigraphy or stable isotope breath test, using for example octanoid acid: This is an easy test and do not expose patient to ionizing radiation.

The study of gastric emptying time and GCSI[11] are the most commonly used tools to define the severity of the disease and evaluate the treatment response.

Nevertheless, the evaluation of pyloric sphincter by means of EndoFLIP seems promising. EndoFLIP is a cylindrical bag placed through the pylorus that uses impedance planimetry to determine cross sectional areas (CSA). It allows the measurement of the intrabag pressure and CSA/pressure response (distensibility) of the pylorus.

A study examined 114 patients, showing that the gastric emptying time correlated better with the reduced pyloric distensibility assessed by EndoFLIP than with the basal pyloric pressure assessed by using manometry[15].

However, not all the studies show the same results. A study evaluated the diagnostic accuracy of the EndoFLIP in 54 patients diagnosed with GP. The pyloric diameter and the CSA resulted inversely proportional to the key symptoms of GCSI. However, the study did not find a direct correlation between the pyloric diameter and the CSA and the gastric emptying at two and four hours[16].

A study published by Fathalizadeh and colleagues in December 2020 investigated the feasibility and the safety of intraprocedural EndoFLIP during gastric per-oral endoscopic myotomy (GPOEM). The authors examined 14 patients. 12 of 14 had pre and post procedure measurement. Median GCSI decreased from pre procedural assessment (3.1), to post procedural one, after one month (2.2); they also found an improvement of pyloric diameter and pyloric distensibility (respectively $P = 0.0012$ and $P = 0.007$). The authors concluded that EndoFLIP during pyloromyotomy (pre procedural and immediately post procedural) can be useful to determine if further myotomy is needed and it may also predict the clinical response to GPOEM[17].

Recently, Conchillo *et al*[18] published a very interesting study with 24 patients (100% technical success rate) to investigate the role of antroduodenal motility pattern and EndoFLIP in predicting the outcome after GPOEM: Clinical response was not correlated with motility pattern, whereas was associated with the pyloric distensibility improvement. However, there are no yet parameters that can surely predict the clinical response after GPOEM[18,19].

The present review aims to present indications, technical aspects, advantages and limitations of GPOEM.

All studies mentioned in this article have been searched by PubMed using key words as 'GPOEM', 'gastro peroral endoscopic myotomy', 'POP', 'gastroparesis', 'refractory gastroparesis', 'pyloromyotomy', 'pyloroplasty', 'GCSI', 'gastroparesis cardinal symptom index' 'EndoFLIP'. Only English papers with available abstract and full text were considered.

In our manuscript we firstly presented the indication and the technical aspects of GPOEM. Secondly, we evaluated the criteria for the ideal candidate for GPOEM procedure, based on GCSI and gastric electrical stimulator (GES) analysis. Then we

highlighted the pros and cons of GPOEM, compared to the other existing techniques to treat GP.

## THERAPY

Patients with mild symptoms can be referred for hygienic and dietary correction coupled with medical therapy with prokinetics, especially metoclopramide. However, response to prokinetics decreases over the time. Moreover, these drugs are burdened with important side effects, such as extrapyramidal symptoms and amenorrhea, in case of long term use[20,21].

On the contrary, patients with severe and persistent symptoms require advanced interventional therapies. The use of pyloric-targeted therapies, such as pyloric myotomy, have recently increased. However, when a severe impairment of antral and or duodenal contractile activity is present, even pyloric myotomy can be ineffective[21, 22].

The available pyloric targeted procedures can be divided in two categories: Surgical and endoscopic ones.

### *Surgical options*

**Surgical pyloroplasty:** This technique is mainly performed by using laparascopic approach and the most famous technique is Heineke Mikulicz, which is characterized by a longitudinal incision of the pyloric ring and transverse suture. Almost 90% of patients reached an improvement or the normalization of the gastric emptying. Also the robotic pyloroplasty has been recently proposed as a safe and effective approach [23].

**Placement of an electrical stimulator:** A small stimulator characterized by high frequency (12 cycles/min) and low stimulation energy can be placed on the greater curvature of the stomach, 10 cm far from pylorus, with a laparoscopic or laparotomic approach.

**Gastrectomy:** Subtotal or total gastrectomy with Roux en y gastric bypass can be proposed as the ultimate surgical option.

### *Endoscopic options other then GPOEM*

**Injection of botulinum toxin:** This approach was firstly described by Pasricha *et al*[19] in 1995 and subsequently adapted by Sharma *et al* in 1998[23]. This is an endoscopic procedure where a small dose of botulinic toxin is injected around the pyloric ring in 4 points with a sclerosis needle. No studies support the efficacy of this technique.

**Pyloric stenting:** Temporary deployment of a fully covered self-expanding metal stents was firstly described in 2013 by Clark[24]. Sometimes the stent can be fixed by using Apollo or clips to avoid its migration, which is the main complication of this technique.

### *GPOEM*

This technique was introduced in 2013 by Khashab[25]. It was developed starting from the technical and physio pathological basis of the already established esophageal POEM, experimented by Inoue[26].

The post procedure results, collected from the available literature, seem particularly promising.

Malik *et al*[27] and Jacques *et al*[28] firstly evaluated EndoFLIP data before and after the treatment. Pyloric distensibility index was found as the only predictive parameter for the outcome of GPOEM in both studies[27,28]. Hedberg *et al*[29] analyzed pre and post procedure EndoFLIP data in 13 out of 17 patients who underwent to GPOEM. This study confirmed an increase in pyloric distensibility from 5.6 (± 1.7) to 10.8 (± 5.0) $cm^2$ post procedure[29]. The association between cross sectional pyloric area after treatment, the clinical response and the gastric emptying was confirmed even in a recent study by Vosoughi *et al*[30], that analyzed the outcome of GPOEM on thirty-seven patients analyzed in 5 centers[30].

To date, it is not clear whether the effectiveness of GPOEM depends on the physical destruction of the pyloric musculature itself or if it triggers further changes in gastric pathophysiology (Table 2).

**Table 2 Surgical and endoscopic options**

| | PRO | CONS |
|---|---|---|
| Surgical options | | |
| Pyloromyotomy | (1) High technical success rate; and (2) Improvement in GCSI and GES | (1) Risk of gastric outlet obstruction and leakage; (2) Invasive; and (3) Time consuming |
| Electrical stimulator | (1) Test response with temporary device; and (2) Predictive features are male sex, diabetic etiology and short duration of disease | High rate of long term complications (infection, erosion, migration, perforation and chronic pain) |
| Endoscopic options | | |
| Botulinum toxin | (1) Easy and tolerable procedure; (2) Repeatable; and (3) Predictive for response to other pyloric techniques | (1) Moot in literature; and (2) Can induce sclerosis and anatomic alteration of pyloric region |
| Pyloric stent placement | (1) Temporized technique; and (2) Predictive for response to other pyloric targeted techniques | Risk of stent migration and duodenal perforation |

GCSI: Gastroparesis cardinal symptoms index; GES: Gastric electrical stimulator.

**General recommendations:** Generally, GPOEM procedure is performed in supine position with the patient under general anesthesia. However, sometimes the patient is placed on the left lateral position, in order to reduce the loop of the endoscope in the gastric cavity.

Major complications of the procedure are: Pneumoperitoneum, intra and postprocedural bleeding, perforation of the mucosa overlying the tunnel and, rarely, gastric ulcers and pyloric stenosis (6.8%)[31] (Table 3).

**Technical aspects of GPOEM:** The procedure follows the same technical steps as an esophageal POEM: (1) Mucosal incision about 5 cm from the pylorus with creation of an access to the submucosal plane after detaching the planes by injection of lifting solution (Figure 1A); (2) Creation of the submucosal tunnel with dissection technique up to the duodenal bulb and exposure of the pylorus (Figure 1B and C); (3) Verification of the integrity of the mucosal surface (Figure 1D); (4) Myotomy (Figure 1E); and (5) Closure of the mucosal flap with multiple endoclips (Figure 1F).

From a technical point of view, the access is generally chosen on the greater gastric curvature, with the endoscope kept in neutral position. Nonetheless, some operators choose the access on the small curvature and rarely on the anterior wall or posterior wall[23,31].

An important step of the procedure is to correctly identify the pyloric muscular ring. Generally it is performed visualizing the muscular ring across the blue dyed submucosa of the pyloric area. Nonetheless, sometimes its identification may be cumbersome. Xue *et al*[32], proposed the use of endoclip to facilitate muscular ring location. The study compared Fluoroscopy-guided G POEM *vs* GPOEM on 14 patients. The authors proved in seven patients that this approach was feasible, safe and not time consuming. However, no statistical differences between the two groups were found [32].

There is no unanimity regarding the proper depth of the myotomy. However, it has been shown that selective circular myotomy, including full-thickness, can be successfully achieved without increasing too much the risk of perforation[25].

The length of the myotomy should be between 2 cm and 3.5 cm[26] and the closure of the mucosal access can be carried out either with hemostatic clips or by endoscopic suture[31,33].

A recent study, from a referral center, suggested a possible superiority of a double myotomy: The authors analyzed two groups of patients (single *vs* double myotomy) showing that the patients who underwent a double pyloromyotomy had higher rate of clinical response (86% *vs* 67% $P = 0.04$). Double myotomy could be an interesting and effective approach in the near future. However, due to the study limitations, such as the prospective single center nature, the short term follow-up and the absence of data on the acquired expertise of operators in the double myotomy group, further studies are required[34].

Regarding the accessories used during the procedure, the choice is entrusted to the operator: Triangle tip knife (KD 640 L Olympus), Hybrid Knife (ERBE), Hook Knife (KD 620 LR) are used according operator's choice.

**Table 3 Gastric per-oral endoscopic myotomy**

| | GPOEM | |
|---|---|---|
| PRO | High clinical success rate (71%-100%) | |
| | High technical success rate (100%) | |
| | Less perioperative morbidity and operating time than surgery pyloromyotomy | |
| | Minimally invasive | |
| | Short hospitalization time | |
| | Positive predictive factors | Lower starting GCSI |
| | | Fewer symptoms |
| | | Idiopathic and post-surgical GP |
| CONS | Limited to tertiary care center and very expert physicians | |
| | Risk of pneumoperitoneum and abdominal pain | |
| | Poorer results for diabetic GP and female | |

GPOEM: Gastric per-oral endoscopic myotomy; GCSI: Gastroparesis cardinal symptoms index.

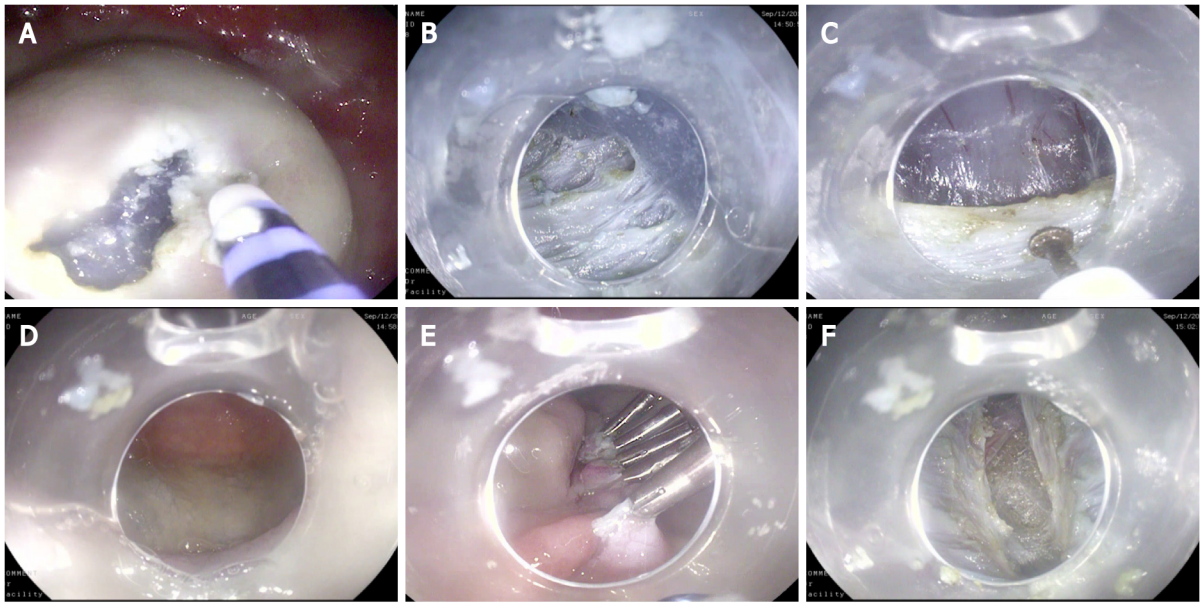



**Figure 1 Technical aspects of gastric per-oral endoscopic myotomy.** A: Making of mucosal incision after lifting; B: Creating of submucosal tunnel with dissection technique; C: Exposure of pyloric ring; D: Study of mucosa of duodenal bulb; E: Execution of myotomy of pyloric ring; F: Endoscopic suture using end clip.

**Technical differences between POEM and GPOEM:** The crucial difference between POEM and GPOEM lies in the in the large knowledge of the pathophysiology of achalasia compared to the little information available regarding the role of gastric motility in GP. There are also some technical and anatomical differences. Although the length of the antral tunnel is shorter than the esophageal one, some anatomical characteristics of the target zone make it more demanding from a technical point of view. The reasons that make GPOEM more difficult than POEM are many. Firstly, the cardial area is not anatomically represented by a real muscle, whereas in GPOEM there is the need to identify the pyloric muscle with the highest precision. Moreover, the curved direction of the submucosal tunnel, the presence of antral contractility, the reduced thickness of the duodenal mucosa increases the difficulty and the risk of perforation [27].

**Post procedural management of the patient undergoing GPOEM:** GPOEM is usually performed in inpatient setting, but no difference in terms of complications was found

in non-hospitalized patients. Moreover, most of the centers use a contrast study after the procedure, before the patient dischargement. However, it has been proposing to avoid the routine post-operative contrast study, unless intraoperative complications occur.

Regarding the antibiotic prophylaxis, the Standards of Practice Committee of the American Society of Gastrointestinal Endoscopy in the 2015 guidelines for antibiotic prophylaxis in endoscopy did not give a precise indications for the procedures of the third space[35]. However, it is routinely performed, even if no high level of evidence is available.

Mostly, prolonged fasting (almost 24 h), and liquid diet are required in the days following the procedure[33].

The use of carbon dioxide for insufflation is mandatory.

Some randomized studies on ESD and POEM did not show statistically significant differences in terms of infections or sepsis in patients who did not undergo antibiotic prophylaxis[36]: To date, however, the vast majority of centers favor the administration of antibiotic prophylaxis. Usually with a single shot of a third generation cephalosporin.

**Outcome of GPOEM:** In 2018, Kahaleh *et al*[37] published a large international multicenter retrospective study on GPOEM. This study was conducted on 33 patients with refractory GP between America and France. The study demonstrated an excellent response to GPOEM, with 85% of patients achieving both symptom improvement, assessed by GCSI, and a reduction of the gastric emptying time.

In 2019, Mekaroonkamol *et al*[38] performed a systematic review on GPOEM. Between January 2013 and September 2018, 13 publications were collected (12 retrospective studies) for a total of 291 patients undergone to endoscopic pyloromyotomy. The three main etiologies of GP were: Diabetes ($n$ = 69), post-surgery ($n$ = 61) and idiopathic ($n$ = 93). Despite that, these studies included heterogeneous populations, with refractory GP as inclusion criterion in almost all of them. Procedural time ranged between 40 and 120', with a technical success rate of 100%. Clinical response rate of GPOEM was very encouraging, with significantly improved symptoms and quality of life, ranging from 73% to 100% after 18-mo of follow-up.

In the largest reported GPOEM published review[39] a 100% technical success was achieved on a total of 325 patients. Major complications were noted in 8.3% of cases. Clinical success ranged from 68% to 90%, with an improvement in GCSI of up to 90% and an improvement in stomach emptying time of up to 66%.

Xu *et al*[40] showed a statistically significant improvement for both GCSI and voiding time, hypothesizing that the former has a negative predictive value (< 30), whereas the second has a positive predictive value (emptying time < 221.6 min and retention at 2 h < 78.6%)

The relationship between gastric emptying time and the clinical manifestations of GP is very controversial. None of the symptoms of GCSI, considered either individually or in the score, correlated well with gastric emptying at baseline. Nonetheless, good responders to any treatment (medical, invasive or minimally invasive) show a linear correlation between symptoms improvement and reduction of gastric emptying time.

One of the main goals of the recent studies is to identify those patients that respond better to the therapies targeted on pylorus. Available knowledge showed that GP related to prior foregut surgery and idiopathic ones respond better to the therapy than the diabetic ones[14].

Another important key factor for clinical success seems to be the disease duration before the treatment. Uemura *et al*[14] demonstrated that the longer duration of the disease is related to a lower reduction in GCSI at 12 mo post procedure, stressing therefore the importance of early intervention to obtain long-term benefits[14].

The overall emptying time alone is therefore not yet an optimal post-procedure evaluation parameter[41]. Malik *et al*[27] showed a significant improvement of symptoms after GPOEM that was not corroborated by a clear reduction of the emptying time: 8 patients had symptoms improvements 6 patients had completed GES post procedure and 4 achieved a normal emptying time, 1 had stable value and 1 reported a worsening of gastric emptying time[27]. This findings were similar to other studies reporting an improvement of gastric emptying time after GPOEM, ranging from 34% to 100%[38].

It could be considered to add the study of the retention pattern with GES to predict the response to GPOEM; the possible role of this test in the pre-procedure diagnostic work up was proposed by Spandorfer *et al*[42]. They used the proximal-to-distal

gastric T1/2 ratio. It found no differences in the pattern between idiopathic and diabetic GP and a correlation between more proximal retention pattern and response to GPOEM. Unfortunately, the sample with complete data before and after GES study was very little[42].

Symptoms that seem to respond better to GPOEM are nausea and vomiting, whereas abdominal pain and swelling responded less to the treatment. One possible explanation is that these latter symptoms are mainly related to visceral individual sensitivity and therefore they are difficult to evaluate.

Strong *et al*[43] reported their experience of GPOEM in 177 patients. 38 patients (21.5%) presented a post-surgical GP. The most frequent procedures were anti-reflux and hiatal hernia surgery. However, other surgical procedures that may induce iatrogenic vagotomy (esophagectomy, heart-lung transplant, excision of bronchial cyst or large hepatic adenoma) were included. This study demonstrated that, in the post-surgical subgroup, GPOEM induced both a clear symptom improvement but also a normalization of emptying time in at least half of the patients. The authors confirmed both the efficacy of GPOEM for post-surgical patients and the role of vagotomy as a suppressor of the propulsive antral component, thus clarifying the pathophysiological reasons for a better response to pyloromyotomy in this subgroup.

Similarly, a case report from John Hopkins University[44] also confirmed the excellent results of the technique in patients undergoing sleeve gastrectomy. Indeed, it is a procedure that may induce important mechanical motility impairment in the proximal stomach. The study highlighted an improvement of symptoms coupled with an enlargement of pylorus diameter and CSA, leading to a better compliance and a reduced pyloric pressure.

A recent systematic review aggregated the results of 10 studies published between 2015 and 2019. A total of 292 patients treated with GPOEM for refractory GP were evaluated[31]. GP etiology was as follow: 26.7% postsurgical, 26.7% diabetes-associated, 5.1% other underlying conditions, 41.5% idiopathic. The mean follow up period was 7.8 ± 5.5 mo Clinical success was achieved in all patients. Significant symptomatic improvement was achieved after 83.9% (95%CI: 78.5–89.3; $I^2$: 0%; $P$ = 0.928) of the procedures. The results of meta-regression analysis showed no significant relationships between clinical success rate and patients characteristics, GP etiology, preprocedural GCSI score, GES evaluation and previous pylorus-directed treatment. The mean post procedural follow up time was 7.8 ± 5.5 mo.

We have limited data concerning long term outcomes: Abdelfatah *et al*[45] in 2020 demonstrated a clinical improvement in 81.1% at initial follow up ( 73/90 patients at 6 mo) while 7.1% had recurrence. One year after procedure, the overall clinical response was 69.1%. The strength of the study is a large size with a very long follow up (until 36 mo): Among 7 patients with follow up of at least three years, 14% had recurrence and 86% of them maintained a clinical response.

Even if few data are available about the long term outcomes, a certain number of patients has been observing to lose clinical response, with a recurrence of refractory symptoms. Therefore, one of the most challenging issues that should be addressed in the future is how to treat them. A recent case report described two patients affected by idiopathic GP. It showed that the redo of GPOEM is feasible and promising, with a good clinical response. However, as underlined by the authors, this procedure needs a very experienced operator, due to the existing fibrosis coming from the first treatment. The main limitation of this interesting case report consists in the short term outcomes (the first loss of response was observed after 18 and 15 mo respectively, but the follow up after redo GPOEM was 6 mo only in one case and unknown in the other)[46].

**Comparison between GPOEM and GES:** GPOEM has also been compared with GES by Shen *et al*[47]. They hypothesize that GPOEM could be superior to GES. They analyzed with a propensity score two groups, 23 patients each, who underwent respectively GES or GPOEM for refractory GP. This study observed a similar clinical response in non-idiopathic GP between the two techniques, but significant better response to GPOEM for idiopathic GP. Moreover, they observed recurrence (with 12 mo. follow up) in 26.1% of patients in GPOEM group and in 56.5% of patients in GES group, without higher adverse events rate in GPOEM group.

**Comparison between GPOEM and surgical pyloroplasty:** A large meta-analysis comparing GPOEM (332 patients) *vs* surgical pyloroplasty (375 patients) showed that the two procedures are comparable in terms of technical success and clinical success [48]. Indeed, the emptying time was reduced to 4 h, the length of hospitalization was reduced, post-procedural pain and complication rate decreased (GES improvement 84% for pyloroplasty and 85% for GPOEM, adverse events 11% each, $P$ = 0.95).

However, GPOEM showed a shorter mean procedural time compared to surgical pyloroplasty. Moreover, idiopathic GP or previous pyloric treatment (botulin toxin and gastric stimulator) seem to be positive predictors to GES improvement after GPOEM

## FUTURE CHALLENGES

One of the most important challenges in the therapeutic scenario of GP is to identify the features of the ideal patient for GPOEM *vs* pyloroplasty, in order to obtain the best clinical result.

The pyloric spasm could be one of the keys to select the patients with the higher probability of being therapy responders. Indeed, it has been widely demonstrated that pylorus motility is only one of the possible factors responsible for GP.

Furthermore, concerning the available tools used to assess GP severity, it would be useful to validate cut-off values to standardize the treatment indications. Up to now, few authors proposed cut offs, such as GCSI baseline of at least 2.0 and emptying time at 4h greater than at least 20% of normal as cut off for proceeding with GPOEM[14] . However, many studies suggest a better response to GPOEM in patients with lower baseline GCSI and little symptoms[14,27].

Interestingly, the literature data show that non-diabetic GP is more responsive to GPOEM and the shorter duration of symptoms seems to be a predictor for the maintenance of the clinical response at 12 mo.

Overall, the studies[7] show that GPOEM seem to reduce more nausea and vomiting than the abdominal pain and the distension. A possible explanation could be that nausea and vomiting are more related to a delayed gastric emptying; whereas, the pain and abdominal distension could be mainly dependent from altered fundic adaptation and individual visceral hypersensitivity[39]. However, it seems that, like the distension of the gastric fundus, also the destruction of the pyloric muscle ring is able to activate the antroduodenal phasic motor activity.

Undoubtedly, the results of GPOEM are promising[14,31] and the experience gained from POEM has made it possible to achieve high technical success with few complications from the first procedures. Indeed, first multicenter study by Khashab *et al*[25] shows a technical success of 100%, with 86% of clinical response and 7% of complication rate.

However, further literature data on GPOEM are needed to standardize the indications and optimize the results.

For both surgical procedures and the endoscopic approach, it would be extremely useful to add informations on the probability of pre-procedural success by stratifying the patients using a score. In this direction, objective and reproducible tests such as the EndoFLIP or electrogastrography with their scores should be routinely used. This would allow to offer to each patient a targeted therapy, based on their clinical condition. Petrov *et al*[49] proposed a decision flowchart, according to both the main symptom pattern and the result of the gastric emptying study. The authors proposed three different therapeutic approaches: Gastric stimulation, gastric stimulation coupled with pyloromyotomy or GPOEM.

## LIMITATIONS

GPOEM is a procedure available only in tertiary endoscopic centers with experienced endoscopist, already trained on “third space” procedures. Indeed, the procedure outcomes are strictly dependent on the operator's experience. Furthermore, importantly, there is a lack of procedural and managerial standardization.

Finally, given its recent introduction, the available follow-up is limited and strong data about the maintenance of benefits are lacking. Indeed, the follow up available in literature ranges from 3 to 24 mo[14,45].

Further studies in larger series with longer follow up are thus needed to corroborate the available results.

## CONCLUSION

GPOEM is a safe and promising technique for the treatment of refractory gastroparesis. Thus, the interest for this procedure is increasing. Nevertheless, further studies are needed to standardize the technique and to create the selection criteria to define the optimal candidates for GPOEM. We propose a diagnostic and therapeutic flowchart (Supplementary Figure 1).

## REFERENCES


1 **Camilleri M**, Parkman HP, Shafi MA, Abell TL, Gerson L; American College of Gastroenterology. Clinical guideline: management of gastroparesis. *Am J Gastroenterol* 2013; **108**: 18-37; quiz 38 [PMID: 23147521 DOI: 10.1038/ajg.2012.373]

2 **Parkman HP**. Idiopathic gastroparesis. *Gastroenterol Clin North Am* 2015; **44**: 59-68 [PMID: 25667023 DOI: 10.1016/j.gtc.2014.11.015]

3 **Usai-Satta P**, Bellini M, Morelli O, Geri F, Lai M, Bassotti G. Gastroparesis: New insights into an old disease. *World J Gastroenterol* 2020; **26**: 2333-2348 [PMID: 32476797 DOI: 10.3748/wjg.v26.i19.2333]

4 **Jung HK**, Choung RS, Locke GR 3rd, Schleck CD, Zinsmeister AR, Szarka LA, Mullan B, Talley NJ. The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006. *Gastroenterology* 2009; **136**: 1225-1233 [PMID: 19249393 DOI: 10.1053/j.gastro.2008.12.047]

5 **Wadhwa V**, Mehta D, Jobanputra Y, Lopez R, Thota PN, Sanaka MR. Healthcare utilization and costs associated with gastroparesis. *World J Gastroenterol* 2017; **23**: 4428-4436 [PMID: 28706426 DOI: 10.3748/wjg.v23.i24.4428]

6 **Camilleri M**, Chedid V, Ford AC, Haruma K, Horowitz M, Jones KL, Low PA, Park SY, Parkman HP, Stanghellini V. Gastroparesis. *Nat Rev Dis Primers* 2018; **4**: 41 [PMID: 30385743 DOI: 10.1038/s41572-018-0038-z]

7 **Grover M**, Farrugia G, Stanghellini V. Gastroparesis: a turning point in understanding and treatment. *Gut* 2019; **68**: 2238-2250 [PMID: 31563877 DOI: 10.1136/gutjnl-2019-318712]

8 **Camilleri M**, Bharucha AE, di Lorenzo C, Hasler WL, Prather CM, Rao SS, Wald A. American Neurogastroenterology and Motility Society consensus statement on intraluminal measurement of gastrointestinal and colonic motility in clinical practice. *Neurogastroenterol Motil* 2008; **20**: 1269-1282 [PMID: 19019032 DOI: 10.1111/j.1365-2982.2008.01230.x]

9 **Desipio J**, Friedenberg FK, Korimilli A, Richter JE, Parkman HP, Fisher RS. High-resolution solid-state manometry of the antropyloroduodenal region. *Neurogastroenterol Motil* 2007; **19**: 188-195 [PMID: 17300288 DOI: 10.1111/j.1365-2982.2006.00866.x]

10 **Mearin F**, Camilleri M, Malagelada JR. Pyloric dysfunction in diabetics with recurrent nausea and vomiting. *Gastroenterology* 1986; **90**: 1919-1925 [PMID: 3699409 DOI: 10.1016/0016-5085(86)90262-3]

11 **Revicki DA**, Rentz AM, Dubois D, Kahrilas P, Stanghellini V, Talley NJ, Tack J. Gastroparesis Cardinal Symptom Index (GCSI): development and validation of a patient reported assessment of severity of gastroparesis symptoms. *Qual Life Res* 2004; **13**: 833-844 [PMID: 15129893 DOI: 10.1023/B:QURE.0000021689.86296.e4]

12 **Chassany O**, Sagnier P, Marquis P, Fullerton S, Aaronson N. Patient-Reported Outcomes: The Example of Health-Related Quality of Life—a European Guidance Document for the Improved Integration of Health-Related Quality of Life Assessment in the Drug Regulatory Process. *Ther Innov Regul Sci* 2002; **36**: 209-238 [DOI: 10.1177/009286150203600127]

13 **Leidy NK**, Revicki DA, Genesté B. Recommendations for evaluating the validity of quality of life claims for labeling and promotion. *Value Health* 1999; **2**: 113-127 [PMID: 16674343 DOI: 10.1046/j.1524-4733.1999.02210.x]

14 **Uemura KL**, Chaves D, Bernardo WM, Uemura RS, de Moura DTH, de Moura EGH. Peroral endoscopic pyloromyotomy for gastroparesis: a systematic review and meta-analysis. *Endosc Int Open* 2020; **8**: E911-E923 [PMID: 32617395 DOI: 10.1055/a-1119-6616]

15 **Snape WJ**, Lin MS, Agarwal N, Shaw RE. Evaluation of the pylorus with concurrent intraluminal pressure and EndoFLIP in patients with nausea and vomiting. *Neurogastroenterol Motil* 2016; **28**: 758-764 [PMID: 26813266 DOI: 10.1111/nmo.12772]

16 **Malik Z**, Sankineni A, Parkman HP. Assessing pyloric sphincter pathophysiology using EndoFLIP in patients with gastroparesis. *Neurogastroenterol Motil* 2015; **27**: 524-531 [DOI: 10.1111/nmo.12522]

17 **Fathalizadeh A**, Klingler M, Landreneau J, Allemang M, Rodriguez J, Ponsky J, El-Hayek K. Real-time intraoperative functioning lumen imaging probe during endoscopic per-oral pyloromyotomy (pop). *Surg Endosc* 2021 [PMID: 33427911 DOI: 10.1007/s00464-020-08237-5]

18 **Conchillo JM**, Straathof JWA, Mujagic Z, Brouns JH, Bouvy ND, Keszthelyi D, Masclee AAM. Gastric peroral endoscopic pyloromyotomy for decompensated gastroparesis: comprehensive motility analysis in relation to treatment outcomes. *Endosc Int Open* 2021; **9**: E137-E144 [PMID: 33532550 DOI: 10.1055/a-1311-0859]

19 **Pasricha PJ**, Colvin R, Yates K, Hasler WL, Abell TL, Unalp-Arida A, Nguyen L, Farrugia G, Koch

KL, Parkman HP, Snape WJ, Lee L, Tonascia J, Hamilton F. Characteristics of patients with chronic unexplained nausea and vomiting and normal gastric emptying. *Clin Gastroenterol Hepatol* 2011; **9**: 567-76.e1 [PMID: 21397732 DOI: 10.1016/j.cgh.2011.03.003]

20 **Rao AS**, Camilleri M. Review article: metoclopramide and tardive dyskinesia. *Aliment Pharmacol Ther* 2010; **31**: 11-19 [PMID: 19886950 DOI: 10.1111/j.1365-2036.2009.04189.x]

21 **Lacy BE**, Parkman HP, Camilleri M. Chronic nausea and vomiting: evaluation and treatment. *Am J Gastroenterol* 2018; **113**: 647-659 [PMID: 29545633 DOI: 10.1038/s41395-018-0039-2]

22 **Bajpai S**, Khan A, Rutledge KM, Stahl RD. Impact of Robotic Versus Laparoscopic Pyloroplasty on Short- and Long-term Outcomes in Patients with Gastroparesis. *J Gastrointest Surg* 2021; **25**: 2679-2680 [PMID: 33772401 DOI: 10.1007/s11605-021-04986-3]

23 **Lacy BE**, Crowell MD, Schettler-Duncan A, Mathis C, Pasricha PJ. The treatment of diabetic gastroparesis with botulinum toxin injection of the pylorus. *Diabetes Care* 2004; **27**: 2341-2347 [PMID: 15451898 DOI: 10.2337/diacare.27.10.2341]

24 **Clarke JO**, Sharaiha RZ, Kord Valeshabad A, Lee LA, Kalloo AN, Khashab MA. Through-the-scope transpyloric stent placement improves symptoms and gastric emptying in patients with gastroparesis. *Endoscopy* 2013; **45** Suppl 2 UCTN: E189-E190 [PMID: 23824975 DOI: 10.1055/s-0032-1326400]

25 **Khashab MA**, Stein E, Clarke JO, Saxena P, Kumbhari V, Chander Roland B, Kalloo AN, Stavropoulos S, Pasricha P, Inoue H. Gastric peroral endoscopic myotomy for refractory gastroparesis: first human endoscopic pyloromyotomy (with video). *Gastrointest Endosc* 2013; **78**: 764-768 [PMID: 24120337 DOI: 10.1016/j.gie.2013.07.019]

26 **Inoue H**, Minami H, Kobayashi Y, Sato Y, Kaga M, Suzuki M, Satodate H, Odaka N, Itoh H, Kudo S. Peroral endoscopic myotomy (POEM) for esophageal achalasia. *Endoscopy* 2010; **42**: 265-271 [PMID: 20354937 DOI: 10.1055/s-0029-1244080]

27 **Malik Z**, Kataria R, Modayil R, Ehrlich AC, Schey R, Parkman HP, Stavropoulos SN. Gastric Per Oral Endoscopic Myotomy (G-POEM) for the Treatment of Refractory Gastroparesis: Early Experience. *Dig Dis Sci* 2018; **63**: 2405-2412 [PMID: 29468376 DOI: 10.1007/s10620-018-4976-9]

28 **Jacques J**, Pagnon L, Hure F, Legros R, Crepin S, Fauchais AL, Palat S, Ducrotté P, Marin B, Fontaine S, Boubaddi NE, Clement MP, Sautereau D, Loustaud-Ratti V, Gourcerol G, Monteil J. Peroral endoscopic pyloromyotomy is efficacious and safe for refractory gastroparesis: prospective trial with assessment of pyloric function. *Endoscopy* 2019; **51**: 40-49 [PMID: 29895073 DOI: 10.1055/a-0628-6639]

29 **Hedberg HM**, Carbray J, Ujiki MB. Initial Experience with Endoscopic Pyloromyotomy, with Description and Video of Technique. *J Gastrointest Surg* 2019; **23**: 1706-1710 [PMID: 31062275 DOI: 10.1007/s11605-019-04237-6]

30 **Vosoughi K**, Ichkhanian Y, Jacques J, Aadam AA, Benias PC, Law R, Hasler WL, Canakis A, Ragi O, Triggs J, Bowers N, Brewer Gutierrez OI, Kumbhari V, Kalloo AN, Bulat RS, Pandolfino JE, Khashab MA. Role of endoscopic functional luminal imaging probe in predicting the outcome of gastric peroral endoscopic pyloromyotomy (with video). *Gastrointest Endosc* 2020; **91**: 1289-1299 [PMID: 32035074 DOI: 10.1016/j.gie.2020.01.044]

31 **Spadaccini M**, Maselli R, Chandrasekar VT, Anderloni A, Carrara S, Galtieri PA, Di Leo M, Fugazza A, Pellegatta G, Colombo M, Palma R, Hassan C, Sethi A, Khashab MA, Sharma P, Repici A. Gastric peroral endoscopic pyloromyotomy for refractory gastroparesis: a systematic review of early outcomes with pooled analysis. *Gastrointest Endosc* 2020; **91**: 746-752.e5 [PMID: 31809720 DOI: 10.1016/j.gie.2019.11.039]

32 **Xue HB**, Fan HZ, Meng XM, Cristofaro S, Mekaroonkamol P, Dacha S, Li LY, Fu XL, Zhan SH, Cai Q. Fluoroscopy-guided gastric peroral endoscopic pyloromyotomy (G-POEM): a more reliable and efficient method for treatment of refractory gastroparesis. *Surg Endosc* 2017; **31**: 4617-4624 [PMID: 28409375 DOI: 10.1007/s00464-017-5524-y]

33 **Tao J**, Patel V, Mekaroonkamol P, Luo H, Li B, Guan Q, Shen S, Chen H, Cai Q. Technical Aspects of Peroral Endoscopic Pyloromyotomy. *Gastrointest Endosc Clin N Am* 2019; **29**: 117-126 [PMID: 30396521 DOI: 10.1016/j.giec.2018.08.012]

34 **Abdelfatah MM**, Li B, Kapil N, Noll A, Li L, Luo H, Chen H, Xia L, Chen X, Patel V, Mekaroonkamol P, Massaad J, Keilin S, Cai Q. Short-term outcomes of double *vs* single pyloromyotomy at peroral endoscopic pyloromyotomy in the treatment of gastroparesis (with video). *Gastrointest Endosc* 2020; **92**: 603-609 [DOI: 10.1016/j.gie.2020.01.016]

35 **ASGE Standards of Practice Committee**, Khashab MA, Chithadi KV, Acosta RD, Bruining DH, Chandrasekhara V, Eloubeidi MA, Fanelli RD, Faulx AL, Fonkalsrud L, Lightdale JR, Muthusamy VR, Pasha SF, Saltzman JR, Shaukat A, Wang A, Cash BD. Antibiotic prophylaxis for GI endoscopy. *Gastrointest Endosc* 2015; **81**: 81-89 [DOI: 10.1016/j.gie.2014.08.008]

36 **Kato M**, Kaise M, Obata T, Yonezawa J, Toyoizumi H, Yoshimura N, Yoshida Y, Kawamura M, Tajiri H. Bacteremia and endotoxemia after endoscopic submucosal dissection for gastric neoplasia: pilot study. *Gastric Cancer* 2012; **15**: 15-20 [PMID: 21559862 DOI: 10.1007/s10120-011-0050-4]

37 **Kahaleh M**, Gonzalez JM, Xu MM, Andalib I, Gaidhane M, Tyberg A, Saumoy M, Baptista Marchena AJ, Barthet M. Gastric peroral endoscopic myotomy for the treatment of refractory gastroparesis: a multicenter international experience. *Endoscopy* 2018; **50**: 1053-1058 [DOI: 10.1055/a-0596-7199]

38 **Mekaroonkamol P**, Shah R, Cai Q. Outcomes of per oral endoscopic pyloromyotomy in gastroparesis worldwide. *World J Gastroenterol* 2019; **25**: 909-922 [PMID: 30833798 DOI: 10.3748/wjg.v25.i8.909]

39 **Podboy A**, Hwang JH, Nguyen LA, Garcia P, Zikos TA, Kamal A, Triadafilopoulos G, Clarke JO. Gastric per-oral endoscopic myotomy: Current status and future directions. *World J Gastroenterol* 2019; **25**: 2581-2590 [PMID: 31210711 DOI: 10.3748/wjg.v25.i21.2581]

40 **Xu J**, Chen T, Elkholy S, Xu M, Zhong Y, Zhang Y, Chen W, Qin W, Cai M, Zhou P. Gastric Peroral Endoscopic Myotomy (G-POEM) as a Treatment for Refractory Gastroparesis: Long-Term Outcomes. *Can J Gastroenterol Hepatol* 2018; **2018**: 6409698 [PMID: 30425974 DOI: 10.1155/2018/6409698]

41 **Janssen P**, Harris MS, Jones M, Masaoka T, Farré R, Törnblom H, Van Oudenhove L, Simrén M, Tack J. The relation between symptom improvement and gastric emptying in the treatment of diabetic and idiopathic gastroparesis. *Am J Gastroenterol* 2013; **108**: 1382-1391 [PMID: 24005344 DOI: 10.1038/ajg.2013.118]

42 **Spandorfer R**, Zhu Y, Abdelfatah MM, Mekaroonkamol P, Dacha S, Galt JR, Halkar R, Cai Q. Proximal and Distal Gastric Retention Patterns in Gastroparesis and the Impact of Gastric Per-Oral Endoscopic Myotomy: A Retrospective Analysis Using Gastric Emptying Scintigraphy. *J Nucl Med Technol* 2020; **48**: 158-162 [PMID: 31811069 DOI: 10.2967/jnmt.119.235630]

43 **Strong AT**, Landreneau JP, Cline M, Kroh MD, Rodriguez JH, Ponsky JL, El-Hayek K. Per-Oral Pyloromyotomy (POP) for Medically Refractory Post-Surgical Gastroparesis. *J Gastrointest Surg* 2019; **23**: 1095-1103 [PMID: 30809781 DOI: 10.1007/s11605-018-04088-7]

44 **Farha J**, Fayad L, Kadhim A, Şimşek C, Badurdeen DS, Ichkhanian Y, Itani MI, Kalloo AN, Khashab MA, Kumbhari V. Gastric Per-Oral Endoscopic Myotomy (G-POEM) for the Treatment of Gastric Stenosis Post-Laparoscopic Sleeve Gastrectomy (LSG). *Obes Surg* 2019; **29**: 2350-2354 [PMID: 31001761 DOI: 10.1007/s11695-019-03893-6]

45 **Abdelfatah MM**, Noll A, Kapil N, Shah R, Li L, Nustas R, Li B, Luo H, Chen H, Xia L, Mekaroonkamol P, Shahnavaz N, Keilin S, Willingham F, Christie J, Cai Q. Long-term Outcome of Gastric Per-Oral Endoscopic Pyloromyotomy in Treatment of Gastroparesis. *Clin Gastroenterol Hepatol* 2021; **19**: 816-824 [PMID: 32450364 DOI: 10.1016/j.cgh.2020.05.039]

46 **Li B**, Calderon, LF, Chen H, Xu J, Cai Q. Redo GPOEM for Refractory Gastroparesis: is it Feasible and Useful? *J Gastroenterol Hepatol Res* 2020; **9**: 3253-3254 [DOI: 10.17554/j.issn.2224-3992.2020.09.922]

47 **Shen S**, Luo H, Vachaparambil C, Mekaroonkamol P, Abdelfatah MM, Xu G, Chen H, Xia L, Shi H, Keilin S, Willingham F, Christie J, Lin E, Cai Q. Gastric peroral endoscopic pyloromyotomy *vs* gastric electrical stimulation in the treatment of refractory gastroparesis: a propensity score-matched analysis of long term outcomes. *Endoscopy* 2020; **52**: 349-358 [DOI: 10.1055/a-1111-8566]

48 **Mohan BP**, Chandan S, Jha LK, Khan SR, Kotagiri R, Kassab LL, Ravikumar NPG, Bhogal N, Chandan OC, Bhat I, Hewlett AT, Jacques J, Ponnada S, Asokkumar R, Adler DG. Clinical efficacy of gastric per-oral endoscopic myotomy (G-POEM) in the treatment of refractory gastroparesis and predictors of outcomes: a systematic review and meta-analysis using surgical pyloroplasty as a comparator group. *Surg Endosc* 2020; **34**: 3352-3367 [PMID: 31583465 DOI: 10.1007/s00464-019-07135-9]

49 **Petrov RV**, Bakhos CT, Abbas AE, Malik Z, Parkman HP. Endoscopic and Surgical Treatments for Gastroparesis: What to Do and Whom to Treat? *Gastroenterol Clin North Am* 2020; **49**: 539-556 [PMID: 32718569 DOI: 10.1016/j.gtc.2020.04.008]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 January 27; 14(1): 24-35

DOI: 10.4240/wjgs.v14.i1.24

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

# Survival after curative pancreaticoduodenectomy for ampullary adenocarcinoma in a South American population: A retrospective cohort study

Ramiro Manuel Fernandez-Placencia, Paola Montenegro, Melvy Guerrero, Mariana Serrano, Emperatriz Ortega, Mercedes Bravo, Lourdes Huanca, Stéphane Bertani, Juan Manuel Trejo, Patricia Webb, Jenny Malca-Vasquez, Luis Taxa, Alberto Lachos-Davila, Juan Celis-Zapata, Carlos Luque-Vasquez, Eduardo Payet, Eloy Ruiz, Francisco Berrospi

**ORCID number:** Ramiro Manuel Fernandez-Placencia 0000-0002-2450-5447; Paola Montenegro 0000-0002-1484-9537; Melvy Guerrero 0000-0002-3555-6338; Mariana Serrano 0000-0001-7830-4475; Emperatriz Ortega 0000-0003-0172-2972; Mercedes Bravo 0000-0002-6965-4841; Lourdes Huanca 0000-0003-0692-3864; Stéphane Bertani 0000-0002-0398-9745; Juan Manuel Trejo 0000-0003-0293-6569; Patricia Webb 0000-0002-8265-7561; Jenny Malca-Vasquez 0000-0003-2258-6113; Luis Taxa 0000-0002-0914-9149; Alberto Lachos-Davila 0000-0002-6190-1959; Juan Celis-Zapata 0000-0001-9687-6637; Carlos Luque-Vasquez 0000-0002-3871-5082; Eduardo Payet 0000-0001-9434-3888; Eloy Ruiz 0000-0001-5561-0752; Francisco Berrospi 0000-0002-0766-2520.

**Author contributions:** Fernandez-Placencia RM was the guarantor and designer of the study and carried out data acquisition, statistical analysis and interpretation, and drafting of the initial manuscript; Montenegro P, Serrano M and Ortega E participated in the acquisition, analysis and interpretation of the data and contributed to the initial

**Ramiro Manuel Fernandez-Placencia, Juan Celis-Zapata, Eloy Ruiz, Francisco Berrospi,** Hepato-Pancreato-Biliary Section, Department of Abdominal Surgery, Instituto Nacional de Enfermedades Neoplasicas, Lima 15038, Peru

**Paola Montenegro, Mariana Serrano, Emperatriz Ortega,** Department of Medical Oncology, Instituto Nacional de Enfermedades Neoplasicas, Lima 15038, Peru

**Melvy Guerrero, Mercedes Bravo, Lourdes Huanca, Patricia Webb, Luis Taxa,** Department of Pathology, Instituto Nacional de Enfermedades Neoplasicas, Lima 15038, Peru

**Stéphane Bertani,** International Joint Laboratory of Molecular Anthopological Oncology, Instituto Nacional de Enfermedades Neoplasicas, Lima 15038, Peru

**Stéphane Bertani,** Unite Pharmacochim & Pharmacol Dev, UMR152, F-31062 Toulouse, France

**Juan Manuel Trejo, Jenny Malca-Vasquez, Alberto Lachos-Davila,** Department of Radiation Oncology, Instituto Nacional de Enfermedades Neoplasicas, Lima 15038, Peru

**Carlos Luque-Vasquez, Eduardo Payet,** Department of Abdominal Surgery, Instituto Nacional de Enfermedades Neoplasicas, Lima 15038, Peru

**Corresponding author:** Ramiro Manuel Fernandez-Placencia, MD, FACS. Surgical Oncologist, Hepato-Pancreato-Biliary Section, Department of Abdominal Surgery, Instituto Nacional de Enfermedades Neoplasicas, 2520 E Angamos Ave. Office 216 Surquillo, Lima 15038, Peru. ramirofp02@gmail.com

## Abstract

*BACKGROUND*

Ampullary adenocarcinoma (AAC) is a rare neoplasm that accounts for only 0.2% of all gastrointestinal cancers. Its incidence rate is lower than 6 cases per million people. Different prognostic factors have been described for AAC and are

draft of the manuscript; Guerrero M and Bravo M participated in the pathological reevaluation and contributed intellectual content; Bertani S participated in the design, data analysis and drafting of the initial manuscript; Huanca L, Trejo JM, Webb P, Taxa L, Lachos-Davila A, Celis-Zapata J, Luque-Vasquez C, Payet E and Ruiz E participated in the data analysis and contributed to the critical review of the manuscript along with important intellectual content; Berrospi F mentored, designed and critically revised the article for relevant intellectual content.

**Institutional review board statement:** Our institutional review board approved this study (Protocol Number 21-17), according to the Declaration of Helsinki19.

**Informed consent statement:** Informed consent was waived by the IRB (IRB No. 21-17).

**Conflict-of-interest statement:** No conflicts of interest to be declared.

**Data sharing statement:** According to the institutional policy, no data from our patients would be shared.

**STROBE statement:** The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

**Country/Territory of origin:** Peru

**Specialty type:** Oncology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0



associated with a wide range of survival rates. However, these studies have been exclusively conducted in patients originating from Asian, European, and North American countries.

***AIM***

To evaluate the histopathologic predictors of overall survival (OS) in South American patients with AAC treated with curative pancreaticoduodenectomy (PD).

***METHODS***

We analyzed retrospective data from 83 AAC patients who underwent curative (R0) PD at the National Cancer Institute of Peru between January 2010 and October 2020 to identify histopathologic predictors of OS.

***RESULTS***

Sixty-nine percent of patients had developed intestinal-type AAC (69%), 23% had pancreatobiliary-type AAC, and 8% had other subtypes. Forty-one percent of patients were classified as Stage I, according to the AJCC 8th Edition. Recurrence occurred primarily in the liver ($n$ = 8), peritoneum ($n$ = 4), and lung ($n$ = 4). Statistical analyses indicated that T3 tumour stage [hazard ratio (HR) of 6.4, 95% confidence interval (CI) of 2.5-16.3, $P$ < 0.001], lymph node metastasis (HR: 4.5, 95%CI: 1.8-11.3, $P$ = 0.001), and pancreatobiliary type (HR: 2.7, 95%CI: 1.2-6.2, $P$ = 0.025) were independent predictors of OS.

***CONCLUSION***

Extended tumour stage (T3), pancreatobiliary type, and positive lymph node metastasis represent independent predictors of a lower OS rate in South American AAC patients who underwent curative PD.

**Key Words:** Gastrointestinal neoplasms; Adenocarcinoma; Ampulla; Pancreaticoduodenectomy; Survival; South America



**Core Tip:** The pancreatobiliary type of ampullary adenocarcinoma, lymph node metastasis and T3 tumour stage (AJCC 8th Ed) are risk factors for lower overall survival in a South American population.

**Citation:** Fernandez-Placencia RM, Montenegro P, Guerrero M, Serrano M, Ortega E, Bravo M, Huanca L, Bertani S, Trejo JM, Webb P, Malca-Vasquez J, Taxa L, Lachos-Davila A, Celis-Zapata J, Luque-Vasquez C, Payet E, Ruiz E, Berrospi F. Survival after curative pancreaticoduodenectomy for ampullary adenocarcinoma in a South American population: A retrospective cohort study. *World J Gastrointest Surg* 2022; 14(1): 24-35
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i1/24.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i1.24

## INTRODUCTION

Ampullary adenocarcinoma (AAC) is a rare neoplasm that represents 0.2% of all gastrointestinal cancers[1,2]. AAC has better prognosis and resection rates than pancreatic ductal adenocarcinoma (PDAC)[3,4]. This may be partly explained by the early symptom of jaundice caused by its location in the ampulla of Vater[5,6]. Nevertheless, three different epithelia (duodenal, biliary, and pancreatic) are present in the ampullary region[7], and their derived malignancies display different clinical behaviours[8]. Kimura and colleagues classified AAC into two histologic subtypes: Pancreatobiliary (PB) and intestinal (INT)[9]. Other features, such as preoperative CA 19-9[7], imaging[10], molecular phenotype[11,12], genetic mutations[13-15], and the diagnosis and classification of AAC[16], have been correlated with overall survival (OS). Consequently, the anatomic paradigm has shifted towards the interaction

**Received:** May 10, 2021
**Peer-review started:** May 10, 2021
**First decision:** August 9, 2021
**Revised:** September 28, 2021
**Accepted:** January 13, 2022
**Article in press:** January 13, 2022
**Published online:** January 27, 2022

**P-Reviewer:** Andrejic-Visnjic B, Mirshahi M, Yamada T
**S-Editor:** Wu YXJ
**L-Editor:** A
**P-Editor:** Wu YXJ

between genetic and epigenetic factors that determine OS and relapse-free survival (RFS)[14,17]. This may explain the wide range of outcomes reported in different centres (5-year OS: 30%-70%)[2].

However, most of these studies have been conducted in European, Asian, and North American countries. To the best of our knowledge, only one study has evaluated the impact of the lymph node ratio in predicting OS among AAC patients in Latin America[18]. Therefore, we evaluated the histopathologic predictors in AAC patients who underwent curative pancreaticoduodenectomy (PD) at the National Cancer Institute of Peru.

## MATERIALS AND METHODS

### Study design and patient selection

We conducted a retrospective cohort study in patients diagnosed with AAC who underwent curative (R0) PD between January 2010 and October 2020 at our tertiary centre. We specifically analysed histopathologic factors that influenced the patients' overall survival. Our institutional review board approved this study (Protocol Number 21-17), according to the Declaration of Helsinki[19].

### Histopathology

Double reads in a blinded manner by pathologists specializing in hepatobiliary cancers were applied to ensure the diagnosis of AAC and classification into INT intestinal (INT)- and pancreatobiliary (PB)-type according to Kimura *et al*[9,20].

Morphologically, INT-type tumours are reminiscent of colorectal adenocarcinoma, with solid nests, tall columnar cells, and elongated pseudostratified nuclei[21]. A significant proportion of INT-type is related to intestinal adenomas, which correlates with the adenoma-carcinoma sequence[22]. Conversely, PB-type adenocarcinomas are similar to extrahepatic bile duct and pancreatic duct adenocarcinomas. The glandular units have more pleomorphism than the intestinal type, with no evident nuclear pseudostratification, and they are separated by stroma[21]. Additionally, a mixed subtype has been described as having more than 25% of each INT and PB differentiation or with hybrid features, such as intestinal architecture with pancreatobiliary cytology[23,24]. Immunohistochemistry has led to a better classification of this mixed subtype; nevertheless, a standard definition has not been established[24,25]. In the present study, the following antibodies were used to determine the dominant type: MUC1 (#6151, BioSB, California, United States), MUC2 (#6158, BioSB, California, United States), CDX2 (MAD-000645QD-12, Vitro S.A., Spain), CK20 (MAD-0005105QD-12, Vitro S.A., Spain), and MUC5AC (MAD-000434QD-12, Vitro S.A., Spain). In cases of no definite conclusion, the tumour was classified as tubular into "other subtypes".

Resection was classified as R0 when the 1-mm width of the surgical margin was free of neoplastic cells[26]. Tumour and nodal staging were categorized according to the AJCC 8$^{th}$ Edition.

### PD

PD was considered the treatment of choice because it was demonstrated to be a more radical approach to achieve satisfactory lymph node clearance and tumour-free surgical margins[27]. Patients were eligible for surgery after a comprehensive evaluation. The clinical parameters included performance and nutritional status, anatomy, and tumour extension (evaluated with contrast-enhanced computed tomography scan or magnetic resonance imaging). CA19-9 Levels were monitored within one month before surgery. We also assessed the vascular structures of the mesenteric and celiac axes along the diameter of the pancreatic duct.

Our surgical approach has been described previously[28]. In brief, the procedure was carried out using level 2 mesopancreas resection[29], and the pancreatic stump was managed using Blumgart, duct-to-mucosa, or modified dunking (at the discretion of the surgeon). In all cases, two Blake drains were placed around the pancreaticojejunostomy. Prophylactic octreotide was not used. External stents were applied in patients with a high risk of postoperative pancreatic fistula[30].

### Adjuvant therapy

Patients with adjuvant therapy (AT) were interpreted as those who received chemotherapy (two or more courses), radiotherapy (with or without a sensitizing

**Table 1 Clinical, laboratory and operative patient characteristics (*n* = 83)**

| Clinical, laboratory and operative patient characteristics (*n* = 83) | |
|---|---|
| Age (yr), median (IQR) | 59 (49–67) |
| Sex, male/female, *n* (%) | 36 (43)/47 (57) |
| Perioperative transfusion, *n* (%) | 21 (25) |
| Haemoglobin in g/L, median (IQR) | 115 (108–127) |
| Platelet count in $10^9$/L, median (IQR) | 285 (243–372) |
| International Normalized Ratio, median (IQR) | 1.06 (1.01–1.15) |
| Serum glucose in mmol/L, median (IQR) | 5.1 (4.8–5.7) |
| Serum creatinine in mmol/L, median (IQR) | 53 (47–65) |
| Serum albumin in g/L, median (IQR) | 38.1 (32–41.1) |
| Serum total bilirubin in μmol/L, median (IQR) | 23.9 (12.9–60) |
| Serum CA 19-9 in IU/mL, median (IQR) | 26.3 (10–91.4) |
| Pancreaticoduodenectomy | |
| Pylorus-preserving PD, *n* (%) | 69 (83) |
| Whipple procedure, *n* (%) | 14 (17) |

IQR: Interquartile range; PD: Pancreaticoduodenectomy.

chemotherapy drug), or a combination of both. The AT regimen was left at the discretion of treating physicians, according to the best evidence available and/or institutional protocol.

### *Patient follow-up*

Follow-ups and patient check-ups were performed on postoperative days 15, 30, and 90. computed tomography (CT) scans and CA 19-9 tests were scheduled every 4 mo after the index procedure during the first year, every 6 mo during the second year, and annually from the third year onward. The National Database for Civil Status (RENIEC) was solicited to determine the fate of patients. OS (months) was monitored from the date of surgery to the date of death or last follow-up, and patients with no events were censored. Any event (recurrence or death) was recorded during the follow-up. The cut-off for the last follow-up was 60 mo.

### *Statistical analysis*

Continuous variables were reported as medians (interquartile ranges), and categorical variables were reported as counts (percentages). For the univariate analysis, the log-rank test was used, and the histopathologically relevant variables were integrated into a Cox regression model. Statistical analyses were performed with an alpha significance level of 0.05 using IBM SPSS v.25 (IBM Corp., Armonk, NY, United States) and R software (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

### *Study population*

From 2010 to 2020, 297 PDs were performed at the National Cancer Institute of Peru. Patients with R1/R2 resection, unavailable slides for revision, incomplete medical records, or synchronic neoplasms were excluded from the study. All patients included in the study underwent R0 resection. After a thorough revision of the medical files, 83 patients were included in the present study. Clinical, laboratory, and operative patient characteristics are presented in Table 1. The median age of the patient cohort was 59 years [interquartile range (IQR), 49-67], with a predominance of women (ratio = 1.3). The mean follow-up time was 39 mo. Twenty-five patients (30%) died during the follow-up period.

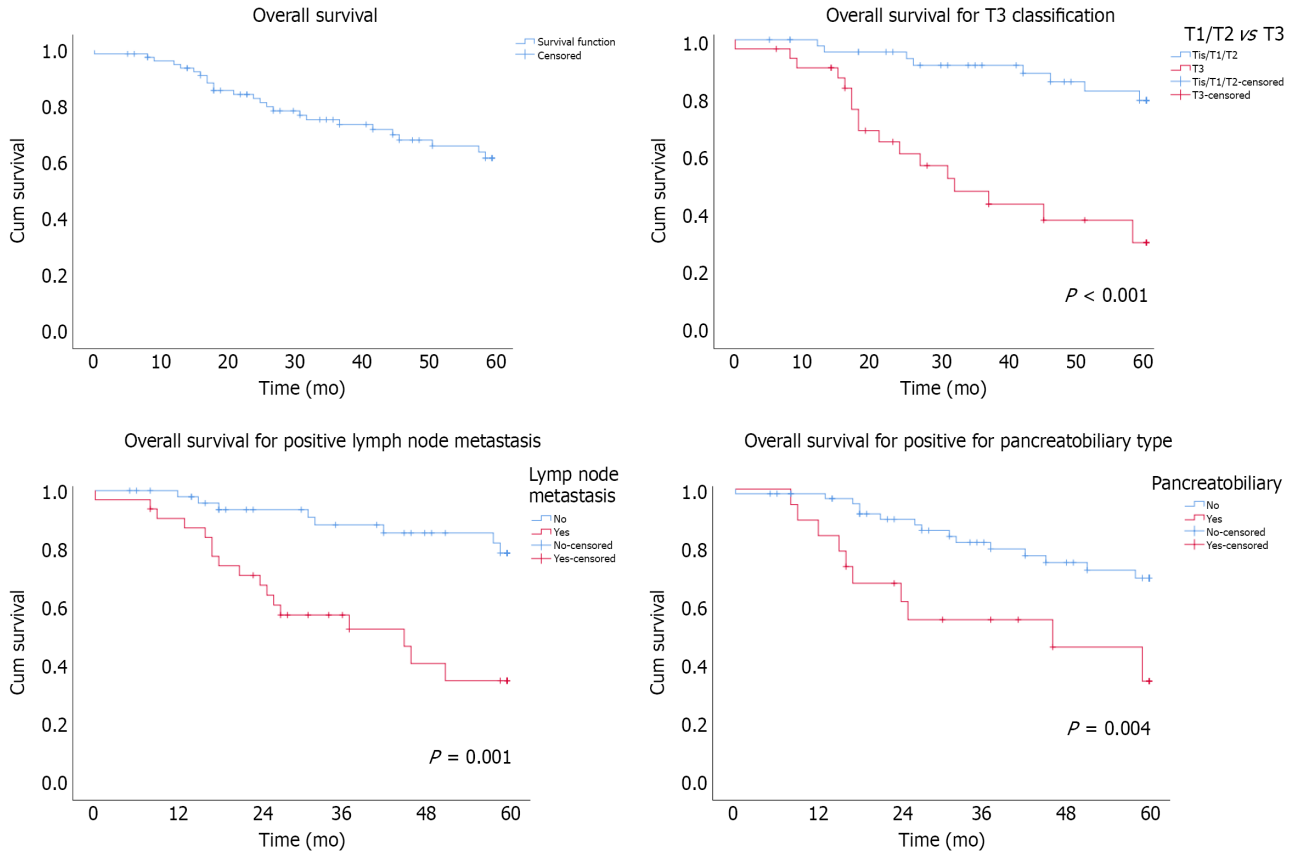



**Figure 1 Survival probability of patients with adenocarcinoma of the ampulla of Vater undergoing pancreaticoduodenectomy.**

### *Histopathologic characteristics*

Sixty-nine percent of patients had developed INT-type AAC (69%), 23% PB-type AAC, and 8% other subtypes (including five patients with the tubular subtype and two patients with the tubular subtype with signet ring cells). Approximately 40% of cases demonstrated pancreatic invasion (T3 tumour stage), and 40% of patients had lymph node metastasis. Thirty-four (41%), 20 (24%), and 29 (35%) patients had stage I, II, and III disease, respectively. The histopathological characteristics of the cohort are shown in Table 2.

### *Use of AT*

Twenty-four patients received AT (15 patients underwent chemotherapy, two patients underwent radiotherapy, and seven patients were subjected to both treatments). The most frequently employed chemotherapy regimen included gemcitabine, which was administered to 20 patients (24%). When chemoradiotherapy was applied, a dose of 4500 cGy in 25 sessions was administered using capecitabine as a sensitizing agent.

The evaluation of AT on OS was impaired by the heterogeneity of the AT regimen and the number of patients. Therefore, we decided not to include the AT variable in the survival analysis.

### *Patterns of recurrence*

Recurrent distant metastases were diagnosed during the postoperative period in the liver ($n$ = 12), peritoneum ($n$ = 8), and lung ($n$ = 7). Additionally, lymph node recurrences around the superior mesenteric artery and the retroperitoneal space were primarily observed in one and two patients, respectively (Table 3).

### *Overall survival and prognostic factors*

The 5-year OS rate in the cohort was 62% (Figure 1). Applying the Cox regression model, three predictive factors were identified, *i.e.*, T staging, lymph node metastasis, and PB type. Time and outliers had no impact on these independent factors, according to the modelling Supplementary Figures (Table 4).

**Table 2 Histopathologic characteristics (*n* = 83)**

| Histopathologic characteristics (*n* = 83) | |
|---|---|
| Tumour size in mm, median (IQR) | 27 (17–40) |
| Subtype, *n* (%) | |
| Intestinal | 57 (69) |
| Pancreatobiliary | 19 (23) |
| Others | 7 (8) |
| Tumour status, *n* (%) | |
| T1 | 7 (8) |
| T2 | 44 (53) |
| T3 | 32 (39) |
| Number of lymph nodes assessed, median (IQR) | 17 (12–24) |
| Lymph node status, *n* (%) | |
| N0 | 50 (60) |
| N1 | 22 (26) |
| N2 | 11 (14) |
| Differentiation, *n* (%) | |
| Well differentiated | 25 (30) |
| Moderately differentiated | 53 (64) |
| Poorly differentiated | 5 (6) |
| Lymphovascular invasion | 30 (36) |
| Perineural invasion | 26 (31) |

IQR: Interquartile range.

### *Impact of the T tumour classification*

Univariate analysis showed lower OS in patients with T3 classification ($P < 0.001$). The 5-year OS rates were 80% in T1/T2 patients and 30% in T3 patients, with a median OS of 30% in the latter group. According to the multivariate analysis, T3 patients had an HR of 6.4 (95%CI: 2.5-16.3, $P < 0.001$) (Figure 1).

### *Effect of lymph node invasion*

Patients with lymph node metastases (N+) had a lower survival rate than those with no lymph node invasion (N0) ($P = 0.001$). The 5-year OS rates in the N+ and N0 groups were 38% and 80%, respectively. The median OS was 46 mo in the N+ group. The HR was 4.5 (95%CI: 1.8-11.3, $P = 0.001$) (Figure 1).

### *Influence of the histopathologic subtype*

PB-type patients had a lower OS than patients with INT or other subtypes ($P = 0.004$). The 5-year OS rate for PB-type patients was 38%, whereas patients with INT or other subtypes had a 5-year OS rate of 70%. The median OS was 46 mo in PB-type patients, whereas the OS in the intestinal/other group was not reached during the follow-up period. The HR was 2.7 (95%CI: 1.2-6.2, $P = 0.025$) in PB-type patients (Figure 1).

## DISCUSSION

To the best of our knowledge, the present study represents the first retrospective histopathologic work on AAC performed in a tertiary centre in South America, in which PD and the multimodal approach are standard. Our findings indicate that T3 tumour classification (pancreatic invasion), positive lymph node metastasis, and PB type are independent prognostic factors of OS in AAC patients treated with PD (R0).

**Table 3 Recurrence patterns after pancreaticoduodenectomy (*n* = 19)**

| Organs involved | | | | | |
|---|---|---|---|---|---|
| **Distant metastasis, *n* (%)** | **(A) First organ** | **(B) Second organ** | **(C) Third organ** | **A + B + C** | **%** |
| Liver | 8 | 3 | 1 | 12 | 32 |
| Peritoneum | 4 | 3 | 1 | 8 | 22 |
| Lung | 4 | 2 | 1 | 7 | 19 |
| Supraclavicular lymph node | 1 | | | 1 | 3 |
| Bone | | 1 | | 1 | 3 |
| Suprarenal gland | | | 1 | 1 | 3 |
| Sub-table total | | | | 30 | 81 |
| Lymph nodal recurrence, *n* (%) | | | | | |
| Celiac trunk | | 1 | | 1 | 3 |
| Hepatic hilum | | 1 | | 1 | 3 |
| Mesenteric lymph nodes | 1 | 1 | | 2 | 5 |
| Retroperitoneal lymph nodes | 2 | 1 | | 3 | 8 |
| Sub-table total | | | | 7 | 19 |
| Total | | | | 37 | 100 |

Various factors have previously been described to be associated with AAC patient outcomes. In a meta-analysis, Zhou and colleagues identified age (> 65 years old), tumour size (> 20 mm), poor differentiation, PB-type, pT3-T4 stage diseases, lymph node metastasis, perineural invasion, lymphovascular invasion, pancreatic invasion, and positive surgical margins as independent factors associated with lower survival [32]. However, Koprowski and colleagues claimed that histotypes were not correlated with OS and concluded that disease stage was the primary determinant of patient outcomes[33]. In this study, the authors report 32% locoregional recurrence, despite the median number of retrieved lymph nodes and the low number of patients with R1 resection. Moreover, Quero and collaborators recently corroborated this finding about no difference between INT- and PB-types, but higher overall and recurrence-free survivals with excision of the mesopancreas[34].

Since AT allocation is based on tumour and nodal stages, we decided to consider these variables in the Cox model. We further stratified the patient cohort according to histopathologic subtypes (*i.e.*, INT, PB, and "others"). Of note, we did not observe the mixed subtype in our cohort from South America, contrasting with the studies published in other regions of the world[16,31].

Our model supports the predictive impact of the histology of AAC on survival in a patient cohort from South America. In our hands, PB type, pT3 stage, and lymph node metastases were associated with lower OS; other variables scrutinized were not significantly associated with OS. The low rate of locoregional recurrence reported in our cohort could be partly explained by the application of level 2 mesopancreas resection, in accordance with the data by Quero and collaborators[34].

AAC has been documented to have a better prognosis than PDAC. However, the present study suggests that there are detrimental factors associated with subgroups of AAC patients, with OS rates comparable to PDAC (Figure 2). In this regard, our data suggest that a better outcome would be primarily explained by the biology of the tumour and secondarily by its location. Hence, assessing the impact of AT in high-risk patients is of utmost relevance. In the ESPAC-3 study, which included 428 patients with periampullary adenocarcinoma, the use of chemotherapy (5-fluorouracil /leucovorin or gemcitabine) demonstrated a benefit in OS (HR 0.75) but no greater effectiveness based on the histological type[35]. Additionally, a multicentre retrospective analysis did not report any benefit of adjuvant chemotherapy in AAC patients, including those with high-risk criteria (N+ or advanced stages T3 and T4) [36]. Other studies have provided more contrasting results on the impact of adjuvant chemotherapy on OS[31,37-39]. Regarding adjuvant radiotherapy, benefits have essentially been analysed among PDAC patients, preventing definite conclusions in AAC patients[40-42]. A recent meta-analysis showed that AT, especially chemoradio-

**Table 4 Cox regression model analysis for predictors of overall survival**

| Variables | Hazard ratio | 95%CI | | *P* value |
|---|---|---|---|---|
| | | Lower | Upper | |
| Age in yr | | | | 0.355 |
| Tumour size in mm | 1.03 | 1 | 1.06 | 0.059 |
| Histopathologic subtype | | | | |
| Intestinal/other types | | | | |
| Pancreatobiliary type | 2.7 | 1.2 | 6.2 | 0.025 |
| T classification | | | | |
| T1-T2 | | | | |
| T3 | 6.4 | 2.5 | 16.3 | < 0.001 |
| Lymph node metastasis | | | | |
| No | | | | |
| Yes | 4.5 | 1.8 | 11.3 | 0.001 |
| Differentiation grade | | | | 0.54 |
| Well differentiated | | | | |
| Moderately differentiated | | | | 0.268 |
| Poorly differentiated | | | | 0.755 |
| Perineural invasion | | | | 0.517 |
| Lymphovascular invasion | | | | 0.26 |

CI: Confidence interval.

therapy, was associated with increased OS among patients with PB-type or high-risk factors[43].

There is a lack of specific guidelines for AAC, except one that comprises the management of biliary tract and ampullary carcinomas[44]. The authors recommend AT in patients with high-risk features (pancreatic invasion, lymph node metastasis, and perineural invasion) but did not specify any regimen. The predictive ability of mutation driver mutations (*e.g.*, TP53, KRAS, and ELF3) in AAC histotypes has not been studied in great detail[45]. The characterization of AAC patient subgroups, based on their molecular alterations, would provide information on the choice of AT after radical surgery.

There are some limitations to recognize in the present study. Our primary AAC patient population displayed a high perioperative mortality rate (10 patients were excluded from this study), which we addressed and analysed previously[28]. We consider this a very important drawback, in addition to the retrospective design of the study. Another weakness was the heterogeneity in the multimodal management of the patients, which is reflected in international practices[31,39,46]. Therefore, we decided not to evaluate the impact of AT, as few patients would have been included in each group. Accordingly, further prospective studies are required because of the limited evidence available to date.

## CONCLUSION

PB type, T3 tumour stage, and positive lymph node metastasis are independent predictors of lower survival in South American patients with ampullary adenocarcinoma treated by curative pancreaticoduodenectomy. Further evaluation of adjuvant and multimodal treatments is warranted, especially in patients with these high-risk factors.

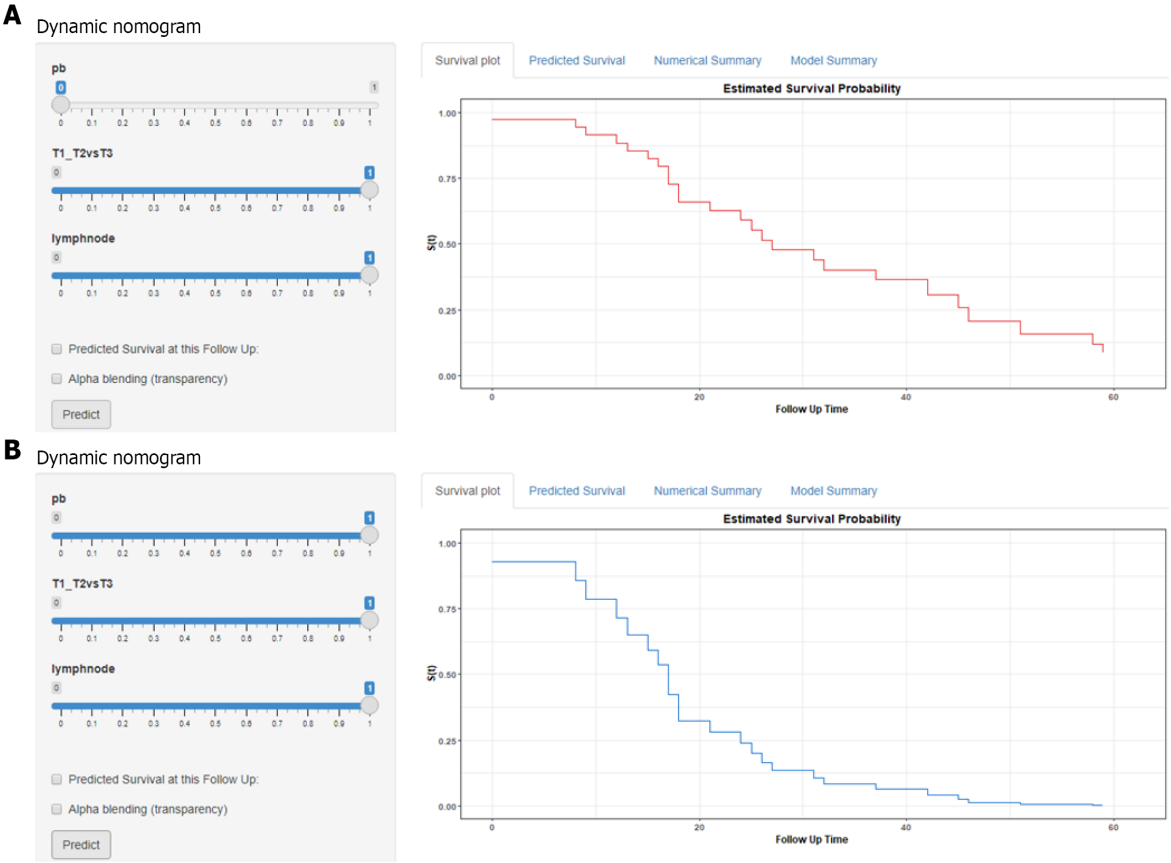



**Figure 2 Comparison of survival probability between the intestinal/other (A) and pancreaticobiliary (B) types in patients with pT3 and pN+ adenocarcinoma of the ampulla of Vater.**

## ARTICLE HIGHLIGHTS

### *Research background*

Ampullary adenocarcinoma (AAC) is a rare neoplasm that has not been studied previously in South American countries.

### *Research motivation*

AAC might have different patterns of recurrence and overall survival than what has been reported in centres from Europe, Asia or North America.

### *Research objectives*

To identify risk factors and their impact on overall survival in patients who underwent pancreaticoduodenectomy (PD) for AAC.

### *Research methods*

We conducted a retrospective cohort study and analysed histopathologic predictors of survival in a Cox regression model.

### *Research results*

Nearly two-thirds of patients had the intestinal-type AAC and around 25% had the Pancreatobiliary (PB)-type AAC. However, overall survival (OS) was lower for the latter subtype. Independently of the T3 and N+ tumour stage.

### *Research conclusions*

Patients with PB-type AAC, T3 and N+ tumour stage are at higher risk of lower survival after curative PD.

### *Research perspectives*

Identification of high-risk patients would guide the clinicians for the use of AT.

Further studies are warranted.

## ACKNOWLEDGEMENTS

We would like to thank Pr. Lorenzo-Bermejo J for his valuable support in the review of the statistical methods.

## REFERENCES

1 **Askew J**, Connor S. Review of the investigation and surgical management of resectable ampullary adenocarcinoma. *HPB (Oxford)* 2013; **15**: 829-838 [PMID: 23458317 DOI: 10.1111/hpb.12038]
2 **O'Connell JB**, Maggard MA, Manunga J Jr, Tomlinson JS, Reber HA, Ko CY, Hines OJ. Survival after resection of ampullary carcinoma: a national population-based study. *Ann Surg Oncol* 2008; **15**: 1820-1827 [PMID: 18369675 DOI: 10.1245/s10434-008-9886-1]
3 **Cameron JL**, He J. Two thousand consecutive pancreaticoduodenectomies. *J Am Coll Surg* 2015; **220**: 530-536 [PMID: 25724606 DOI: 10.1016/j.jamcollsurg.2014.12.031]
4 **Chandrasegaram MD**, Chiam SC, Chen JW, Khalid A, Mittinty ML, Neo EL, Tan CP, Dolan PM, Brooke-Smith ME, Kanhere H, Worthley CS. Distribution and pathological features of pancreatic, ampullary, biliary and duodenal cancers resected with pancreaticoduodenectomy. *World J Surg Oncol* 2015; **13**: 85 [PMID: 25890023 DOI: 10.1186/s12957-015-0498-5]
5 **Sommerville CAM**, Limongelli P, Pai M. Survival analysis after pancreatic resection for ampullary and pancreatic head carcinoma: An analysis of clinicopathological factors. *J Surg Oncol* 2009; **100**: 651-656 [PMID: 19722229 DOI: 10.1002/jso.21390]
6 **Morris-Stiff G**, Alabraba E, Tan YM, Shapey I, Bhati C, Tanniere P, Mayer D, Buckels J, Bramhall S, Mirza DF. Assessment of survival advantage in ampullary carcinoma in relation to tumour biology and morphology. *Eur J Surg Oncol* 2009; **35**: 746-750 [PMID: 19167859 DOI: 10.1016/j.ejso.2008.10.010]
7 **Okano K**, Oshima M, Yachida S, Kushida Y, Kato K, Kamada H, Wato M, Nishihira T, Fukuda Y, Maeba T, Inoue H, Masaki T, Suzuki Y. Factors predicting survival and pathological subtype in patients with ampullary adenocarcinoma. *J Surg Oncol* 2014; **110**: 156-162 [PMID: 24619853 DOI: 10.1002/jso.23600]
8 **Zheng-Pywell R**, Reddy S. Ampullary Cancer. *Surg Clin North Am* 2019; **99**: 357-367 [PMID: 30846039 DOI: 10.1016/j.suc.2018.12.001]
9 **Kimura W**, Futakawa N, Yamagata S. Different Clinicopathologic Findings in Two Histologic Types of Carcinoma of Papilla of Vater. *Japanese J Cancer Res* 1994; **85**: 161-166 [DOI: 10.1111/j.1349-7006.1994.tb02077.x]
10 **Yoen H**, Kim JH, Hur BY, Ahn SJ, Jeon SK, Choi SY, Lee KB, Han JK. Prediction of tumor recurrence and poor survival of ampullary adenocarcinoma using preoperative clinical and CT findings. *Eur Radiol* 2021; **31**: 2433-2443 [DOI: 10.1007/s00330-020-07316-4]
11 **Overman MJ**, Soifer HS, Schueneman AJ, Ensor J Jr, Adsay V, Saka B, Neishaboori N, Wolff RA, Wang H, Schnabel CA, Varadhachary G. Performance and prognostic utility of the 92-gene assay in the molecular subclassification of ampullary adenocarcinoma. *BMC Cancer* 2016; **16**: 668 [PMID: 27549176 DOI: 10.1186/s12885-016-2677-3]
12 **Schueneman A**, Goggins M, Ensor J, Saka B, Neishaboori N, Lee S, Maitra A, Varadhachary G, Rezaee N, Wolfgang C, Adsay V, Wang H, Overman MJ. Validation of histomolecular classification utilizing histological subtype, MUC1, and CDX2 for prognostication of resected ampullary adenocarcinoma. *Br J Cancer* 2015; **113**: 64-68 [PMID: 25989273 DOI: 10.1038/bjc.2015.172]
13 **Shroff S**, Overman MJ, Rashid A, Shroff RT, Wang H, Chatterjee D, Katz MH, Lee JE, Wolff RA, Abbruzzese JL, Fleming JB. The expression of PTEN is associated with improved prognosis in patients with ampullary adenocarcinoma after pancreaticoduodenectomy. *Arch Pathol Lab Med* 2013; **137**: 1619-1626 [PMID: 24168499 DOI: 10.5858/arpa.2012-0418-OA]
14 **Kim BJ**, Jang HJ, Kim JH, Kim HS, Lee J. KRAS mutation as a prognostic factor in ampullary adenocarcinoma: a meta-analysis and review. *Oncotarget* 2016; **7**: 58001-58006 [PMID: 27517148 DOI: 10.18632/oncotarget.11156]
15 **Valsangkar NP**, Ingkakul T, Correa-Gallego C, Mino-Kenudson M, Masia R, Lillemoe K. D, Ferná ndez-del Castillo C, Warshaw AL, Liss AS, Thayer SP. Survival in ampullary cancer: potential role of different KRAS mutations. *Surg (United States)* 2015; **157**: 260-268 [DOI: 10.1016/j.surg.2014.08.092]
16 **Asano E**, Okano K, Oshima M, Kagawa S, Kushida Y, Munekage M, Hanazaki K, Watanabe J, Takada Y, Ikemoto T, Shimada M, Suzuki Y; Shikoku Consortium of Surgical Research (SCSR). Phenotypic characterization and clinical outcome in ampullary adenocarcinoma. *J Surg Oncol* 2016; **114**: 119-127 [PMID: 27132476 DOI: 10.1002/jso.24274]
17 **Park HM**, Park SJ, Han SS, Hong SK, Hong EK, Kim SW. Very early recurrence following pancreaticoduodenectomy in patients with ampullary cancer. *Medicine (Baltimore)* 2019; **98**: e17711 [PMID: 31689805 DOI: 10.1097/MD.0000000000017711]

18 **Lino-Silva LS**, Gómez-Álvarez MA, Salcedo-Hernández RA, Padilla-Rosciano AE, López-Basave HN. Prognostic importance of lymph node ratio after resection of ampullary carcinomas. *J Gastrointest Oncol* 2018; **9**: 1144-1149 [PMID: 30603134 DOI: 10.21037/jgo.2018.07.04]

19 **World Medical Association**. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; **310**: 2191-2194 [PMID: 24141714 DOI: 10.1001/jama.2013.281053]

20 **Kimura W**, Futakawa N, Zhao B. Neoplastic diseases of the papilla of Vater. *J Hepatobiliary Pancreat Surg* 2004; **11**: 223-231 [PMID: 15368105 DOI: 10.1007/s00534-004-0894-7]

21 **Bowitz Lothe IM**, Kleive D, Pomianowska E, Cvancarova M, Kure E, Dueland S, Gladhaug IP, Labori KJ. Clinical relevance of pancreatobiliary and intestinal subtypes of ampullary and duodenal adenocarcinoma: Pattern of recurrence, chemotherapy, and survival after pancreatoduodenectomy. *Pancreatology* 2019; **19**: 316-324 [PMID: 30713128 DOI: 10.1016/j.pan.2019.01.019]

22 **Lisita Rosa VD**, Maris Peria F, Ottoboni Brunaldi M. Carcinoma of Ampulla of Vater: Carcinogenesis and Immunophenotypic Evaluation. J Clin Epigenetics. 2017;03(03):1-5. DOI:10.21767/2472-1158.100059 [DOI: 10.21767/2472-1158.100059]

23 **Zimmermann C**, Wolk S, Aust DE, Meier F, Saeger HD, Ehehalt F, Weitz J, Welsch T, Distler M. The pathohistological subtype strongly predicts survival in patients with ampullary carcinoma. *Sci Rep* 2019; **9**: 12676 [PMID: 31481741 DOI: 10.1038/s41598-019-49179-w]

24 **Ang DC**, Shia J, Tang LH, Katabi N, Klimstra DS. The utility of immunohistochemistry in subtyping adenocarcinoma of the ampulla of vater. *Am J Surg Pathol* 2014; **38**: 1371-1379 [PMID: 24832159 DOI: 10.1097/PAS.0000000000000230]

25 **Liu F**, Shen D, Ma Y, Song Q, Wang H. Identification of ampullary carcinoma mixed subtype using a panel of six antibodies and its clinical significance. *J Surg Oncol* 2019; **119**: 295-302 [PMID: 30548547 DOI: 10.1002/jso.25311]

26 **Verbeke CS**, Menon KV. Redefining resection margin status in pancreatic cancer. *HPB (Oxford)* 2009; **11**: 282-289 [PMID: 19718354 DOI: 10.1111/j.1477-2574.2009.00055.x]

27 **Amini A**, Miura JT, Jayakrishnan TT, Johnston FM, Tsai S, Christians KK, Gamblin TC, Turaga KK. Is local resection adequate for T1 stage ampullary cancer? *HPB (Oxford)* 2015; **17**: 66-71 [PMID: 25395092 DOI: 10.1111/hpb.12297]

28 **Fernandez-Placencia R**, Berrospi-Espinoza F, Uribe-Rivera K, Medina-Cana J, Chavez-Passiuri I, Sanchez-Bartra N, Paredes-Galvez K, Luque-Vasquez Vasquez C, Celis-Zapata J, Ruiz-Figueroa E. Preoperative Predictors for 90-Day Mortality after Pancreaticoduodenectomy in Patients with Adenocarcinoma of the Ampulla of Vater: A Single-Centre Retrospective Cohort Study. *Surg Res Pract* 2021; **2021**: 1-9 [DOI: 10.1155/2021/6682935]

29 **Inoue Y**, Saiura A, Yoshioka R, Ono Y, Takahashi M, Arita J, Takahashi Y, Koga R. Pancreatoduodenectomy With Systematic Mesopancreas Dissection Using a Supracolic Anterior Artery-first Approach. *Ann Surg* 2015; **262**: 1092-1101 [PMID: 25587814 DOI: 10.1097/SLA.0000000000001065]

30 **Ecker BL**, McMillan MT, Asbun HJ, Ball CG, Bassi C, Beane JD, Behrman SW, Berger AC, Dickson EJ, Bloomston M, Callery MP, Christein JD, Dixon E, Drebin JA, Castillo CF, Fisher WE, Fong ZV, Haverick E, Hollis RH, House MG, Hughes SJ, Jamieson NB, Javed AA, Kent TS, Kowalsky SJ, Kunstman JW, Malleo G, Poruk KE, Salem RR, Schmidt CR, Soares K, Stauffer JA, Valero V, Velu LKP, Watkins AA, Wolfgang CL, Zureikat AH, Vollmer CM Jr. Characterization and Optimal Management of High-risk Pancreatic Anastomoses During Pancreatoduodenectomy. *Ann Surg* 2018; **267**: 608-616 [PMID: 28594741 DOI: 10.1097/SLA.0000000000002327]

31 **Moekotte AL**, Malleo G, van Roessel S, Bonds M, Halimi A, Zarantonello L, Napoli N, Dreyer SB, Wellner UF, Bolm L, Mavroeidis VK, Robinson S, Khalil K, Ferraro D, Mortimer MC, Harris S, Al-Sarireh B, Fusai GK, Roberts KJ, Fontana M, White SA, Soonawalla Z, Jamieson NB, Boggi U, Alseidi A, Shablak A, Wilmink JW, Primrose JN, Salvia R, Bassi C, Besselink MG, Abu Hilal M. Gemcitabine-based adjuvant chemotherapy in subtypes of ampullary adenocarcinoma: international propensity score-matched cohort study. *Br J Surg* 2020; **107**: 1171-1182 [PMID: 32259295 DOI: 10.1002/bjs.11555]

32 **Zhou YM**, Liao S, Wei YZ, Wang SJ. Prognostic factors and benefits of adjuvant therapy for ampullary cancer following pancreatoduodenectomy: A systematic review and meta-analysis. *Asian J Surg* 2020; **43**: 1133-1141 [PMID: 32249101 DOI: 10.1016/j.asjsur.2020.03.007]

33 **Affi Koprowski M**, Sutton TL, Brinkerhoff BT, Grossberg A, Sheppard BC, Mayo SC. Oncologic outcomes in resected ampullary cancer: Relevance of histologic subtype and adjuvant chemotherapy. *Am J Surg* 2021; **221**: 1128-1134 [PMID: 33883071 DOI: 10.1016/j.amjsurg.2021.04.001]

34 **Quero G**, Fiorillo C, De Sio D, Laterza V, Menghi R, Cina C, Schena CA, Rosa F, Galiandro F, Alfieri S. The role of mesopancreas excision for ampullary carcinomas: a single center propensity-score matched analysis. *HPB (Oxford)* 2021; **23**: 1557-1564 [DOI: 10.1016/j.hpb.2021.03.011]

35 **Neoptolemos JP**, Moore MJ, Cox TF, Valle JW, Palmer DH, McDonald AC, Carter R, Tebbutt NC, Dervenis C, Smith D, Glimelius B, Charnley RM, Lacaine F, Scarfe AG, Middleton MR, Anthoney A, Ghaneh P, Halloran CM, Lerch MM, Oláh A, Rawcliffe CL, Verbeke CS, Campbell F, Büchler MW; European Study Group for Pancreatic Cancer. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. *JAMA* 2012; **308**: 147-156 [PMID: 22782416 DOI: 10.1001/jama.2012.7352]

36 **Kim HS**, Jang JY, Yoon YS, Park SJ, Kwon W, Kim SW, Han HS, Han SS, Park JS, Yoon DS. Does

adjuvant treatment improve prognosis after curative resection of ampulla of Vater carcinoma? *J Hepatobiliary Pancreat Sci* 2020; **27**: 721-730 [PMID: 32652820 DOI: 10.1002/jhbp.801]

37 **Kamarajah SK**. Adjuvant radiotherapy following pancreaticoduodenectomy for ampullary adenocarcinoma improves survival in node-positive patients: a propensity score analysis. *Clin Transl Oncol* 2018; **20**: 1212-1218 [PMID: 29497964 DOI: 10.1007/s12094-018-1849-9]

38 **Ecker BL**, Vollmer CM Jr, Behrman SW, Allegrini V, Aversa J, Ball CG, Barrows CE, Berger AC, Cagigas MN, Christein JD, Dixon E, Fisher WE, Freedman-Weiss M, Guzman-Pruneda F, Hollis RH, House MG, Kent TS, Kowalsky SJ, Malleo G, Salem RR, Salvia R, Schmidt CR, Seykora TF, Zheng R, Zureikat AH, Dickson PV. Role of Adjuvant Multimodality Therapy After Curative-Intent Resection of Ampullary Carcinoma. *JAMA Surg* 2019; **154**: 706-714 [PMID: 31141112 DOI: 10.1001/jamasurg.2019.1170]

39 **Narang AK**, Miller RC, Hsu CC. Evaluation of adjuvant chemoradiation therapy for ampullary adenocarcinoma: The Johns Hopkins Hospital - Mayo Clinic collaborative study. *Radiat Oncol* 2011; **6**: 126 [DOI: 10.1186/1748-717x-6-126]

40 **Regalla DKR**, Jacob R, Manne A, Paluri RK. Therapeutic options for ampullary carcinomas. A review. *Oncol Rev* 2019; **13**: 440 [PMID: 31565197 DOI: 10.4081/oncol.2019.440]

41 **Bonet M**, Rodrigo A, Vázquez S, Carrizo V, Vilardell F, Mira M. Adjuvant therapy for true ampullary cancer: a systematic review. *Clin Transl Oncol* 2020; **22**: 1407-1413 [PMID: 31927720 DOI: 10.1007/s12094-019-02278-6]

42 **Miura JT**, Jayakrishnan TT, Amini A, Johnston FM, Tsai S, Erickson B, Quebbeman EJ, Christians KK, Evans DB, Gamblin TC, Turaga KK. Defining the role of adjuvant external beam radiotherapy on resected adenocarcinoma of the ampulla of vater. *J Gastrointest Surg* 2014; **18**: 2003-2008 [PMID: 25159502 DOI: 10.1007/s11605-014-2629-7]

43 **Vo NP**, Nguyen HS, Loh EW, Tam KW. Efficacy and safety of adjuvant therapy after curative surgery for ampullary carcinoma: A systematic review and meta-analysis. *Surg (United States)* 2021; 1-10 [DOI: 10.1016/j.surg.2021.03.046]

44 **Kondo S**, Takada T, Miyazaki M, Miyakawa S, Tsukada K, Nagino M, Furuse J, Saito H, Tsuyuguchi T, Yamamoto M, Kayahara M, Kimura F, Yoshitomi H, Nozawa S, Yoshida M, Wada K, Hirano S, Amano H, Miura F; Japanese Association of Biliary Surgery; Japanese Society of Hepato-Biliary-Pancreatic Surgery; Japan Society of Clinical Oncology. Guidelines for the management of biliary tract and ampullary carcinomas: surgical treatment. *J Hepatobiliary Pancreat Surg* 2008; **15**: 41-54 [PMID: 18274843 DOI: 10.1007/s00534-007-1279-5]

45 **Mafficini A**, Amato E, Cataldo I, Rusev BC, Bertoncello L, Corbo V, Simbolo M, Luchini C, Fassan M, Cantù C, Salvia R, Marchegiani G, Tortora G, Lawlor RT, Bassi C, Scarpa A. Ampulla of Vater Carcinoma: Sequencing Analysis Identifies TP53 Status as a Novel Independent Prognostic Factor and Potentially Actionable ERBB, PI3K, and WNT Pathways Gene Mutations. *Ann Surg* 2018; **267**: 149-156 [PMID: 27611608 DOI: 10.1097/SLA.0000000000001999]

46 **Chavez MT**, Sharpe JP, O'Brien T, Patton KT, Portnoy DC, VanderWalde NA, Deneve JL, Shibata D, Behrman SW, Dickson PV. Management and outcomes following pancreaticoduodenectomy for ampullary adenocarcinoma. *Am J Surg* 2017; **214**: 856-861 [PMID: 28285709 DOI: 10.1016/j.amjsurg.2017.01.029]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 January 27; 14(1): 36-45

DOI: 10.4240/wjgs.v14.i1.36

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

# Application value of mixed reality in hepatectomy for hepatocellular carcinoma

Liu-Yang Zhu, Jian-Cun Hou, Long Yang, Zi-Rong Liu, Wen Tong, Yi Bai, Ya-Min Zhang

**ORCID number:** Liu-Yang Zhu 0000-0002-9981-0796; Jian-Cun Hou 0000-0002-1476-5018; Long Yang 0000-0002-9067-0213; Zi-Rong Liu 0000-0002-1731-0035; Wen Tong 0000-0002-2067-8121; Yi Bai 0000-0002-1179-3734; Ya-Min Zhang 0000-0001-7886-2901.

**Author contributions:** Zhu LY, Hou JC and Zhang YM designed the research; Zhu LY, Liu ZR, Tong W and Bai Y collected and analyzed the data; Zhu LY and Yang L wrote the paper; Hou JC and Zhang YM revised the paper.

**Institutional review board statement:** This study was reviewed and approved by the Ethics Committee of the Tianjin first Central Hospital.

**Informed consent statement:** Patients were not required to give informed consent for the study because the clinical data were obtained retrospectively after each patient agreed to treatment by written consent.

**Conflict-of-interest statement:** All the Authors have no conflict of interest related to the manuscript.

**Data sharing statement:** No additional data are available.

**STROBE statement:** The authors

**Liu-Yang Zhu, Wen Tong,** First Central Clinical College, Tianjin Medical University, Tianjin 300070, China

**Jian-Cun Hou, Long Yang, Zi-Rong Liu, Yi Bai, Ya-Min Zhang,** Department of Hepatobiliary Surgery, Tianjin First Central Hospital, Tianjin 300192, China

**Corresponding author:** Ya-Min Zhang, MD, Chief Doctor, Department of Hepatobiliary Surgery, Tianjin First Central Hospital, No. 24 Fukang road, Nankai District, Tianjin 300192, China. 13802122219@163.com

## Abstract

### *BACKGROUND*

As a new digital holographic imaging technology, mixed reality (MR) technology has unique advantages in determining the liver anatomy and location of tumor lesions. With the popularization of 5G communication technology, MR shows great potential in preoperative planning and intraoperative navigation, making hepatectomy more accurate and safer.

### *AIM*

To evaluate the application value of MR technology in hepatectomy for hepatocellular carcinoma (HCC).

### *METHODS*

The clinical data of 95 patients who underwent open hepatectomy surgery for HCC between June 2018 and October 2020 at our hospital were analyzed retrospectively. We selected 95 patients with HCC according to the inclusion criteria and exclusion criteria. In 38 patients, hepatectomy was assisted by MR (Group A), and an additional 57 patients underwent traditional hepatectomy without MR (Group B). The perioperative outcomes of the two groups were collected and compared to evaluate the application value of MR in hepatectomy for patients with HCC.

### *RESULTS*

We summarized the technical process of MR-assisted hepatectomy in the treatment of HCC. Compared to traditional hepatectomy in Group B, MR-assisted hepatectomy in Group A yielded a shorter operation time (202.86 ± 46.02 min *vs* 229.52 ± 57.13 min, $P = 0.003$), less volume of bleeding (329.29 ± 97.31 mL *vs* 398.23 ± 159.61 mL, $P = 0.028$), and shorter obstructive time of the portal vein (17.71 ±

have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

**Supported by** Science and Technology Planning Projects of Tianjin, No. 19ZXDBSY00010; and Science and Technology Project of Tianjin Health Commission, No. ZC20174.

**Country/Territory of origin:** China

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0



**Received:** October 4, 2021
**Peer-review started:** October 4, 2021
**First decision:** November 18, 2021
**Revised:** November 29, 2021
**Accepted:** December 25, 2021
**Article in press:** December 25, 2021
**Published online:** January 27, 2022

**P-Reviewer:** Broering DC, Kim BS
**S-Editor:** Fan JR
**L-Editor:** A

4.16 min *vs* 21.58 ± 5.24 min, $P$ = 0.019). Group A had lower alanine aminotransferas and higher albumin values on the third day after the operation (119.74 ± 29.08 U/L *vs* 135.53 ± 36.68 U/L, $P$ = 0.029 and 33.60 ± 3.21 g/L *vs* 31.80 ± 3.51 g/L, $P$ = 0.014, respectively). The total postoperative complications and hospitalization days in Group A were significantly less than those in Group B [14 (37.84%) *vs* 35 (60.34%), $P$ = 0.032 and 12.05 ± 4.04 d *vs* 13.78 ± 4.13 d, $P$ = 0.049, respectively].

*CONCLUSION*
MR has some application value in three-dimensional visualization of the liver, surgical planning, and intraoperative navigation during hepatectomy, and it significantly improves the perioperative outcomes of hepatectomy for HCC.

**Key Words:** Mixed reality; Hepatectomy; Hepatocellular carcinoma; Three-dimensional reconstruction; Surgical planning; Intraoperative navigation



**Core Tip:** Mixed reality (MR) is a new digital holographic imaging technology that enables real-world and virtual three-dimensional images to be displayed and interacted in the same visual space. MR has some application value in three-dimensional visualization of the liver, surgical planning, and intraoperative navigation during hepatectomy. We performed a retrospective study to evaluate the application value of MR technology in hepatectomy for hepatocellular carcinoma (HCC). MR significantly improved the perioperative outcomes of hepatectomy for HCC compared to hepatectomy with traditional methods, demonstrating the potential value of clinical application.

**Citation:** Zhu LY, Hou JC, Yang L, Liu ZR, Tong W, Bai Y, Zhang YM. Application value of mixed reality in hepatectomy for hepatocellular carcinoma. *World J Gastrointest Surg* 2022; 14(1): 36-45
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i1/36.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i1.36

## INTRODUCTION

Primary liver cancer (PLC) is a common malignant tumor of the digestive system worldwide. According to the new data released by GLOBOCAN2020, the annual number of new cases of liver cancer has reached 841000 worldwide, ranking seventh among malignant tumors[1]. Hepatocellular carcinoma (HCC) accounts for a large proportion (85%-90%) of PLCs[2]. Surgery remains the most important treatment for HCC, and radical resection significantly improves the patients prognosis[3]. With the in-depth understanding of the anatomical structure of the liver and the rapid development of surgical techniques, precise hepatectomy and anatomical hepatectomy have been widely performed. Three-dimensional (3D) visualization, indocyanine green fluorescence imaging, intraoperative ultrasound, augmented reality (AR), and virtual reality (VR) have been used to determine the location of the tumor and the boundary of the liver segment, which play important roles in hepatectomy[4-7]. In recent years, with the rapid development of mixed reality (MR) technology, it has been preliminarily applied in hepatectomy for HCC[8].

MR is a new digital holographic imaging technology that enables real-world and virtual 3D images to be displayed in an interactive fashion in the same visual space[9]. Given its unique advantages, MR technology not only changes the situation of separation of traditional two-dimensional (2D) images from surgery but also compensates for the shortcomings of AR and VR technology. Microsoft released its first MR head-mounted display (MR-HMD) in 2016; HoloLens allows surgeons to interact with 3D holograms and manipulate images from their point of view using MR-HMDs[10]. MR technology makes image-guided surgery possible, especially by plastically presenting 3D holograms on or above the surgical site.

**P-Editor:** Fan JR

MR has been proven to be a practical tool for intraoperative surgical guidance in the operating room[11]. Previous studies have shown that MR has been gradually applied to neurosurgery, orthopedics, and urology, yielding improvements in perioperative outcomes for patients[12-14]. In hepatectomy for patients with HCC, MR also exhibit great potential in preoperative planning and intraoperative navigation, which makes hepatectomy more accurate and personalized[15]. However, to our knowledge, few studies have evaluated the application value of MR in hepatectomy. In this study, 95 patients with HCC who underwent hepatectomy were retrospectively analyzed to evaluate the application value of MR.

## MATERIALS AND METHODS

### Patients

We retrospectively collected the clinical data of 132 patients who underwent hepatectomy between June 2018 and October 2020 in the Department of Hepatobiliary Surgery of Tianjin First Central Hospital. Patients who underwent resection of additional organs (except for the gallbladder), received immunotherapy or targeted therapy, had Child-Pugh C liver function or indocyanine green 15 min retention > 20%, or distant metastasis were excluded. All patients were confirmed to have HCC by postoperative pathology. Finally, 95 patients were enrolled in the study, including 38 patients who underwent MR-assisted hepatectomy in Group A and 57 patients who underwent hepatectomy with traditional methods in Group B. The general clinical data of the 95 patients are shown in Table 1. This study was approved by the hospital ethics committee, and informed consent was obtained from all the patients.

### 2D imaging and 3D reconstruction

Computed tomography (CT) images of the two groups were obtained using a 128-slice spiral CT system, including three-phase enhanced images and nonenhanced images. The CT images of 38 patients in Group A were stored in the format of Digital Imaging and Communications in Medicine and imported into MR diagnostic imaging processing software (TM-MIS 1.0, Tuomeng Science and Technology Ltd, Heilongjiang, China) for 3D reconstruction. MR software could depict liver, tumor, blood vessels, and other normal tissues automatically, which were distinguished by different colors. The 3D holograms were generated and optimized by the radiologist and surgeon with reference to the original CT images. Finally, they were uploaded to the web server.

### Preoperative planning and surgical process

In Group A, the hologram of each patient was downloaded to the MR-HMD from the web server. After wearing the MR-HMD, the surgeon could observe the liver anatomy and tumor location through the 3D hologram. Virtual surgery was performed on the 3D hologram, and the resection and residual liver volume were calculated in real time to evaluate the feasibility of the proposed surgical strategy. Surgical planning was performed to ensure the complete removal of the tumor while retaining a larger volume of the liver. During hepatectomy, the surgeon and assistant wore MR-HMDs, and the hologram was adjusted to fuse with the patient's liver or located above the surgical visual field to relocate the tumor location and guide the operation. In Group B, 2D CT images of the patient were used for surgical planning, and hepatectomy was performed based on the operator's clinical experience and spatial imagination. All operations were performed by laparotomy. The Pringle maneuver was used for hepatic vascular exclusion during hepatectomy, and abdominal drainage was routinely placed.

### Perioperative results

All patients received the same symptomatic treatment strategy before and after the operation. Various perioperative results, including operation time, volume of bleeding, implementation of the Pringle maneuver, obstructive time of the portal vein, laboratory examination at postoperative day 3, postoperative complications within 30 days, and hospitalization days, were collected and compared between the two groups. Postoperative complications included perioperative mortality, hepatic failure, abdominal bleeding, bile leakage, abdominal infection, pleural effusion, pulmonary infection, and wound infection, and these complications were assessed based on the Clavien-Dindo classification system[16].

**Table 1 The clinical characteristic of 95 patients**

| Characteristic | Patient (*n* = 95) | | *P* value |
|---|---|---|---|
| | Group A (*n* = 37) | Group B (*n* = 58) | |
| Age (yr), *n* (%) | 57.62 ± 9.16 | 60.22 ± 9.19 | 0.819 |
| Sex (female/male), *n* (%) | 13/24 | 15/43 | 0.334 |
| BMI | 23.91 ± 3.66 | 23.82 ± 3.42 | 0.471 |
| History of abdominal surgery (yes/no), *n* (%) | 9/28 | 11/47 | 0.532 |
| Tumor size (cm) | 5.52 ± 1.95 | 5.20 ± 1.88 | 0.428 |
| Tumor number, *n* (%) | | | 0.948 |
| 1 | 24 (64.86) | 38 (65.52) | |
| ≥ 2 | 13 (35.14) | 20 (34.48) | |
| Tumor location, *n* (%) | | | 0.637 |
| Right lobe | 17 (45.95) | 23 (39.66) | |
| Left lobe | 14 (37.84) | 21 (36.21) | |
| Bilateral lobes | 6 (16.22) | 14 (24.14) | |
| Liver cirrhosis (yes/no), *n* (%) | 31/6 | 51/7 | 0.566 |
| HBV infection (yes/no), *n* (%) | 29/8 | 44/14 | 0.777 |
| AFP, *n* (%) | | | 0.532 |
| < 400 (ng/mL) | 28 (75.68) | 47 (81.03) | |
| ≥ 400 (ng/mL) | 9 (24.32) | 11 (18.97) | |
| Liver function, *n* (%) | | | 1.000 |
| Child-Pugh A | 34 (91.89) | 54 (93.10) | |
| Child-Pugh B | 3 (8.11) | 4 (6.90) | |
| Preoperative lab examination | | | |
| ALB (g/L) | 41.38 ± 5.75 | 40.89 ± 5.30 | 0.675 |
| TBIL (μmol/L) | 12.75 ± 3.57 | 13.88 ± 4.87 | 0.198 |
| PT (s) | 12.39 ± 1.27 | 12.18 ± 1.19 | 0.424 |
| ALT (U/L) | 27.87 ± 9.69 | 29.58 ± 12.12 | 0.469 |
| AST (U/L) | 30.56 ± 10.25 | 33.42 ± 11.72 | 0.229 |

BMI: Body mass index; HBV: Hepatitis B virus; AFP: Alpha fetoprotein; ALB: Albumin; TBIL: Total bilirubin; PT: Prothrombin time; ALT: Alanine aminotransferas; AST: Aspartate aminotransferase.

### *Statistical analysis*

Data were analyzed using SPSS version 25.0 (IBM, United States). All measurement data are expressed as the mean ± SD or percentage. The data of patients before, during, and after surgery were compared by Student's t test, chi-square test, and Fisher's exact test to compare data from patients in Groups A and B. $P < 0.05$ was considered statistically significant.

## RESULTS

### *Clinical characteristics of patients*

A total of 95 patients with HCC were included in this study. Patients were divided into Group A (with MR, *n* = 37) and Group B (without MR, *n* = 58) based on whether MR technology was used. We collected basic patient information (age, sex, body mass index, and history of abdominal surgery), tumor data (tumor size, tumor number, and tumor location), Child-Pugh classification, liver cirrhosis, hepatitis B virus infection,

and preoperative laboratory data (alpha fetoprotein, albumin, total bilirubin, prothrombin time, alanine aminotransferas, aspartate aminotransferase). All the data are summarized in Table 1. No statistically significant differences in the baseline characteristics were noted between the two groups.

### The process of MR-assisted hepatectomy

To describe the process of MR-assisted hepatectomy in more detail, we presented a typical case in Group A. The 3D hologram was reconstructed from the preoperative CT image of the patient and downloaded to the MR-HMD (Figure 1), which could be brought into the operating room. Surgical planning was performed and evaluated before the operation, and it was reconfirmed in the operating room. The 3D hologram was placed above the surgical field or fused with the patient's liver to determine the location of the tumor and important blood vessels, which is of great help to guide the operation (Figure 2).

### Intraoperative results

The intraoperative results of the two groups of patients are shown in Table 2. The operation time of Group A patients, who underwent MR-assisted hepatectomy, was significantly shorter than that of Group B (202.86 ± 46.02 min *vs* 229.52 ± 57.13 min, $P$ = 0.003). Furthermore, patients in Group A had a lower intraoperative volume of bleeding than those in Group B (329.29 ± 97.31 mL *vs* 398.23 ± 159.61 mL, $P$ = 0.028). Although there was no significant difference in the intraoperative Pringle maneuver between the two groups ($P$ = 0.148), the obstructive time of the portal vein of Group A was shorter than that of Group B (17.71 ± 4.16 min *vs* 21.58 ± 5.24 min, $P$ = 0.019).

### Postoperative results

The postoperative laboratory results, postoperative complications, and hospitalization days of the two groups were collected and are shown in Table 3. Group A exhibited both lower alanine aminotransferas (ALT) and albumin (ALB) levels on the third day after the operation (119.74 ± 29.08 U/L *vs* 135.53 ± 36.68 U/L, $P$ = 0.029 and 33.60 ± 3.21 g/L *vs* 31.80 ± 3.51 g/L, $P$ = 0.014, respectively), but no significant differences in aspartate aminotransferase and TB were noted between the two groups ($P$ = 0.343 and $P$ = 0.557, respectively). The total postoperative complications within 30 d and hospitalization days in Group A were significantly lower than those in Group B [14 (37.84%) *vs* 35 (60.34%), $P$ = 0.032 and 12.05 ± 4.04 d *vs* 13.78 ± 4.13 d, $P$ = 0.049, respectively].

## DISCUSSION

Hepatectomy for liver cancer is still a high-risk operation with numerous postoperative complications, high mortality, and high risk for postoperative recurrence[17]. With the development of MR, it has been gradually applied to hepatectomy. We have established a complete technical process of MR-assisted hepatectomy in our center. To the best of our knowledge, this is the first study to explore the application value of MR in hepatectomy for HCC. The results suggested that MR-assisted hepatectomy yielded better perioperative outcomes than traditional hepatectomy.

Traditional hepatectomy mainly depends on the subjective "3D reconstruction" of CT, MRI, and other 2D images by surgeons, which requires extensive experience and long-term surgical practice. The development of 3D reconstruction technology makes the anatomy of the liver clearer, which in turn makes hepatectomy more efficient and safer[4,18]. MR allows 3D holograms to be downloaded to the MR-HMD, whereas traditional 3D reconstruction images are limited to flat screens. Furthermore, the spatial understanding of patient-specific liver anatomy is improved by MR[19]. Before the operation, surgeons could manipulate the 3D holograms to observe the anatomy of the liver and tumor location. The resection plane of the surgical plan was determined more accurately to retain sufficient residual liver volume and improve the safety of the operation[20]. On the other hand, 3D holograms could be used for virtual hepatectomy. Mise *et al*[21] reviewed and analyzed 1194 cases of hepatectomy for liver cancer and living donor liver transplantation and found that virtual hepatectomy with 3D reconstruction improved the vein reconstruction rate of transplantation and reduced the operation time, and the 5-year disease-free survival rate of patients with virtual hepatectomy was higher[21].

**Table 2 Surgical characteristics and surgical outcomes**

| Variable | Group A (*n* = 37) | Group B (*n* = 58) | *P* value |
|---|---|---|---|
| Surgical procedure, *n* (%) | | | |
| Extended left hepatectomy[1] | 4 (10.81) | 7 (12.07) | 1.000 |
| Extended right hepatectomy[2] | 2 (5.41) | 5 (8.62) | 0.855 |
| Left hepatectomy | 8 (21.62) | 12 (20.69) | 0.913 |
| Right hepatectomy | 5 (13.51) | 8 (13.79) | 0.969 |
| Sectionectomy | 8 (21.62) | 9 (15.52) | 0.449 |
| Segmentectomy | 7 (18.92) | 8 (13.79) | 0.505 |
| Partial resection | 3 (8.11) | 9 (15.52) | 0.457 |
| Operative time (min) | 202.86 ± 46.02 | 229.52 ± 57.13 | 0.003 |
| Volume of bleeding (mL) | 329.29 ± 97.31 | 398.23 ± 159.61 | 0.010 |
| Pringle maneuver (yes/no), *n* (%) | 14/23 | 31/27 | 0.148 |
| Obstructive time of portal vein (min) | 17.71 ± 4.16 | 21.58 ± 5.24 | 0.019 |

[1]Includes left trisectionectomy.
[2]Includes right trisectionectomy.

**Table 3 Postoperative results**

| Variable | Group A (*n* = 37) | Group B (*n* = 58) | *P* value |
|---|---|---|---|
| ALT at postoperative day 3 (U/L) | 119.74 ± 29.08 | 135.53 ± 36.68 | 0.029 |
| AST at postoperative day 3 (U/L) | 106.20 ± 20.99 | 110.91 ± 24.99 | 0.343 |
| ALB at postoperative day 3 (g/L) | 33.60 ± 3.21 | 31.80 ± 3.51 | 0.014 |
| TB at postoperative day 3 (μmol/L) | 43.07 ± 8.60 | 44.33 ± 11.04 | 0.557 |
| Perioperative complications, *n* (%) | | | |
| Perioperative mortality | 0 (0) | 1 (1.72) | 1.000 |
| Hepatic failure | 0 (0) | 2 (3.45) | 0.519 |
| Abdominal bleeding | 1 (2.70) | 2 (3.45) | 1.000 |
| Bile leakage | 0 (0) | 2 (3.45) | 0.519 |
| Abdominal infection | 1 (2.70) | 3 (5.17) | 0.952 |
| Pleural effusion | 2 (5.41) | 6 (10.34) | 0.641 |
| Pulmonary infection | 1 (2.70) | 3 (5.17) | 0.952 |
| Wound infection | 2 (5.41) | 4 (6.90) | 1.000 |
| Total complications | 7 (18.92) | 23 (39.66) | 0.034 |
| CDC, *n* (%) | | | 0.339 |
| 0-2 | 35 (94.59) | 50 (86.21) | |
| ≥ 3 | 2 (5.41) | 8 (13.79) | |
| Hospitalization days (d) | 12.05 ± 4.04 | 13.78 ± 4.13 | 0.049 |

ALT: Alanine aminotransferas; AST: Aspartate aminotransferase; ALB: Albumin; TB: Total bilirubin; CDC: Clavien-Dindo classification.

In the present study, MR-assisted hepatectomy significantly reduced the operation time and obstructive time of the portal vein, although it may take 10 min or more to adjust the hologram for intraoperative navigation. This advantage was probably the result of a better understanding of the tumor location and hepatic vascular anatomy

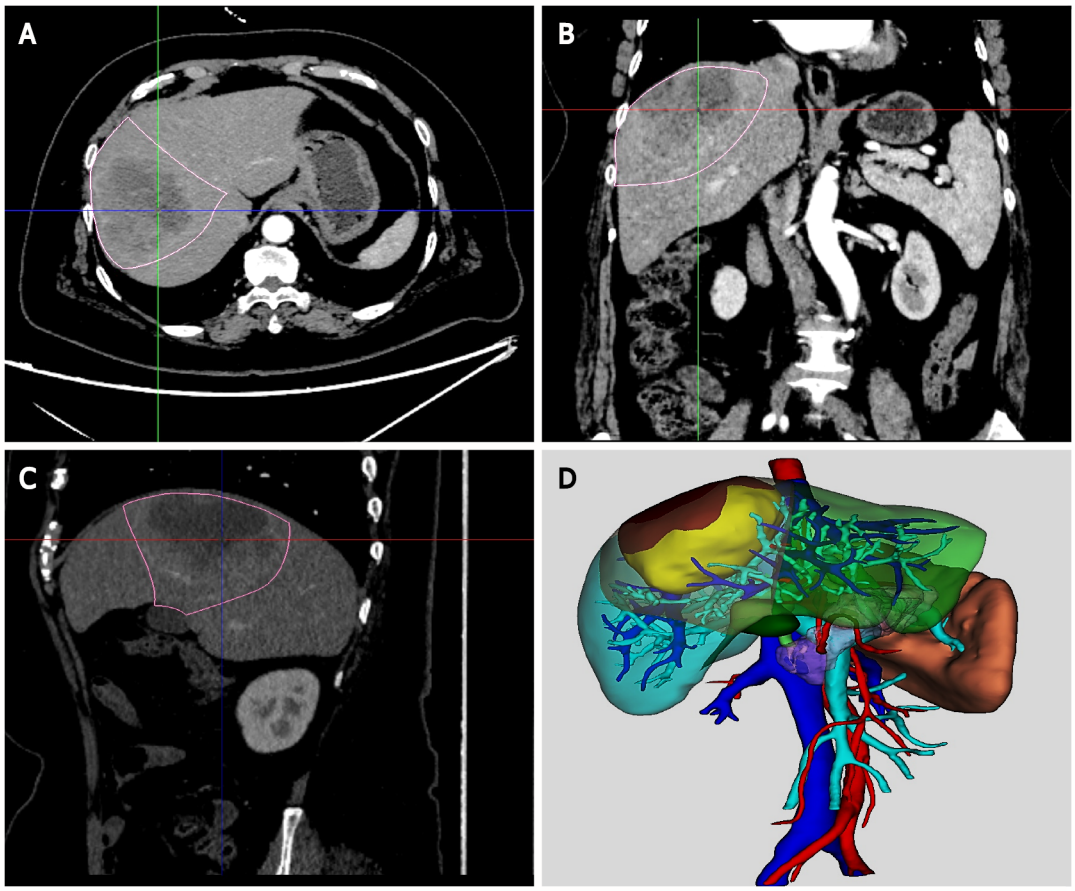



**Figure 1 Two-dimensional imaging and three-dimensional reconstruction.** A-C: Two-dimensional imaging (2D) abdominal enhanced computed tomography images of a patient with hepatocellular carcinoma; D: Three-dimensional (3D) hologram reconstructed by mixed reality software.

through 3D holograms. In addition, the operative approach and resection plane were clearer with the help of intraoperative navigation by fusing the 3D hologram with the liver. In addition, this was also one of the main reasons for reducing the volume of bleeding. Moreover, the recovery of ALT and ALB in patients with MR-assisted hepatectomy was faster, indicating better recovery of liver function. It has been suggested that a shorter operation time and shorter obstructive time of the portal vein could promote the recovery of liver function after the operation[22]. The operation time and volume of bleeding during the operation have an important influence on the incidence of postoperative complications. In our study, we found that there were fewer postoperative complications within 30 d in the MR-assisted hepatectomy group compared with the traditional hepatectomy group. This procedure also shortened the hospital stays of the patients undergoing MR-assisted hepatectomy.

In summary, MR-assisted hepatectomy significantly improved the perioperative outcomes of patients with HCC. MR technology gives surgeons a pair of "perspective eyes" to penetrate the liver, especially during the preoperative "last minute" and intraoperative navigation during hepatectomy[23]. Some studies have found that the "last minute" simulation before liver surgery can relieve the pressure on surgeons and help them operate more safely and accurately[15]. MR may also have certain application potential for laparoscopic and robotic hepatectomy, and it will be explored in the future. On the other hand, according to our center's experience in MR-assisted hepatectomy, MR technology has a great advantage in the localization of small liver cancers, and we will explore this advantage in the next step of studies.

In the teaching of surgery, MR technology significantly improves the surgeon's perception of the liver and provides a more realistic 3D virtual learning environment for junior surgeons[24]. After wearing the MR-HMD, surgeons can share computer-generated 3D holograms of the liver and observe the anatomical structure from all angles. Given that the real environment is not necessary, some studies have noted that VR may be better than MR for teaching[25]. However, the emergence of MR-HMD may change this concept. The virtual hepatectomy software developed by Uchida *et al* [26] simulates various types of anatomical hepatectomy, and its virtual hepatectomy

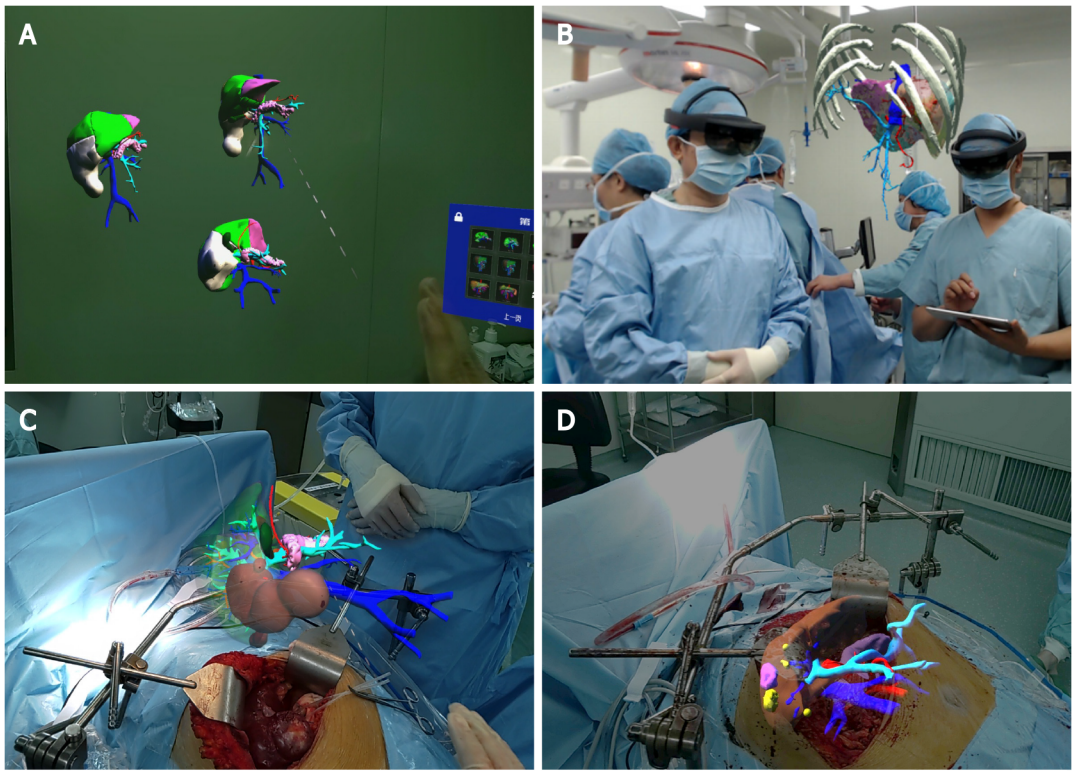



**Figure 2 Mixed reality-assisted hepatectomy guided by three-dimensional holograms.** A: Three-dimensional (3D) holograms were observed with the mixed reality head-mounted display in the operating room; B: The surgeon observed the tumor location and vascular anatomy with a 3D hologram and determined the surgical planning again; C: 3D hologram was placed above the surgical field; D: 3D holograms were fused with the patient's liver.

process increases the interactive experience of surgery[26]. Similarly, MR technology can also achieve virtual hepatectomy by using 3D holograms. In summary, virtual MR teaching is of great significance in promoting the progress of liver surgeons. On the other hand, patients could understand the operation plan more intuitively through MR, which is beneficial to the communication between doctors and patients.

However, this study has some limitations. First, this was a single-center retrospective study, and more cases from multiple centers are needed to further evaluate the value of MR. Second, the choice of MR-assisted hepatectomy was mixed with factors, such as the surgeon's preference and patient's financial status, rather than by defined indication. Third, it was still challenging to fuse 3D holograms directly into the liver due to the morphological changes of the liver caused by dissociating the liver, surgical operation, and respiratory movements of patients.

## CONCLUSION

MR has some application value in 3D visualization of the liver, surgical planning, and intraoperative navigation during hepatectomy, and it significantly improves the perioperative outcomes of hepatectomy for HCC.

## ARTICLE HIGHLIGHTS

### *Research background*

As a new digital holographic imaging technology, mixed reality (MR) it has been preliminarily applied in hepatectomy for hepatocellular carcinoma (HCC). In this study, 95 patients with HCC who underwent hepatectomy were retrospectively analyzed to evaluate the application value of MR.

### *Research motivation*

MR has been gradually applied to neurosurgery, orthopedics, and urology with an

improvement in perioperative outcomes. MR may also have great potential in hepatectomy by preoperative planning and intraoperative navigation.

### Research objectives

The aim of this study was to explore the application value of MR technology in hepatectomy for HCC.

### Research methods

Total 95 patients with HCC were enrolled in the study, including 38 patients who underwent MR-assisted hepatectomy in Group A and 57 patients who underwent hepatectomy with traditional methods in Group B. Perioperative variables of the two groups of patients were collected and compared.

### Research results

MR-assisted hepatectomy could significantly reduce the operation time, obstructive time of the portal vein, and the volume of bleeding. And the recovery of alanine aminotransferas and albumin in patients with MR-assisted hepatectomy was faster.

### Research conclusions

MR significantly improved the perioperative outcomes of hepatectomy for HCC.

### Research perspectives

MR may also have a certain application potential for laparoscopic and robotic hepatectomy, and it will be explored in future.

## ACKNOWLEDGEMENTS

The authors thank all the doctors in the Department of Hepatobiliary surgery of Tianjin first Central Hospital for their efforts and contributions to this study.

## REFERENCES

1 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]

2 **Forner A**, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018; **391**: 1301-1314 [PMID: 29307467 DOI: 10.1016/S0140-6736(18)30010-2]

3 **Chen Q**, Shu C, Laurence AD, Chen Y, Peng BG, Zhen ZJ, Cai JQ, Ding YT, Li LQ, Zhang YB, Zheng QC, Xu GL, Li B, Zhou WP, Cai SW, Wang XY, Wen H, Peng XY, Zhang XW, Dai CL, Bie P, Xing BC, Fu ZR, Liu LX, Mu Y, Zhang L, Zhang QS, Jiang B, Qian HX, Wang YJ, Liu JF, Qin XH, Li Q, Yin P, Zhang ZW, Chen XP. Effect of Huaier granule on recurrence after curative resection of HCC: a multicentre, randomised clinical trial. *Gut* 2018; **67**: 2006-2016 [PMID: 29802174 DOI: 10.1136/gutjnl-2018-315983]

4 **He YB**, Bai L, Aji T, Jiang Y, Zhao JM, Zhang JH, Shao YM, Liu WY, Wen H. Application of 3D reconstruction for surgical treatment of hepatic alveolar echinococcosis. *World J Gastroenterol* 2015; **21**: 10200-10207 [PMID: 26401085 DOI: 10.3748/wjg.v21.i35.10200]

5 **Vávra P**, Roman J, Zonča P, Ihnát P, Němec M, Kumar J, Habib N, El-Gendi A. Recent Development of Augmented Reality in Surgery: A Review. *J Healthc Eng* 2017; **2017**: 4574172 [PMID: 29065604 DOI: 10.1155/2017/4574172]

6 **Quero G**, Lapergola A, Soler L, Shahbaz M, Hostettler A, Collins T, Marescaux J, Mutter D, Diana M, Pessaux P. Virtual and Augmented Reality in Oncologic Liver Surgery. *Surg Oncol Clin N Am* 2019; **28**: 31-44 [PMID: 30414680 DOI: 10.1016/j.soc.2018.08.002]

7 **Majlesara A**, Golriz M, Hafezi M, Saffari A, Stenau E, Maier-Hein L, Müller-Stich BP, Mehrabi A. Indocyanine green fluorescence imaging in hepatobiliary surgery. *Photodiagnosis Photodyn Ther* 2017; **17**: 208-215 [PMID: 28017834 DOI: 10.1016/j.pdpdt.2016.12.005]

8 **Lungu AJ**, Swinkels W, Claesen L, Tu P, Egger J, Chen X. A review on the applications of virtual reality, augmented reality and mixed reality in surgical simulation: an extension to different kinds of surgery. *Expert Rev Med Devices* 2021; **18**: 47-62 [PMID: 33283563 DOI: 10.1080/17434440.2021.1860750]

9 **Gao Y**, Tan K, Sun J, Jiang T, Zou XW. Application of Mixed Reality Technology in Visualization of Medical Operations. *Chin Med Sci J* 2019; **34**: 103-109 [PMID: 31315751 DOI: 10.24920/003564]

10 **Tepper OM**, Rudy HL, Lefkowitz A, Weimer KA, Marks SM, Stern CS, Garfein ES. Mixed Reality with HoloLens: Where Virtual Reality Meets Augmented Reality in the Operating Room. *Plast*

*Reconstr Surg* 2017; **140**: 1066-1070 [PMID: 29068946 DOI: 10.1097/PRS.0000000000003802]
11 **Cartucho J**, Shapira D, Ashrafian H, Giannarou S. Multimodal mixed reality visualisation for intraoperative surgical guidance. *Int J Comput Assist Radiol Surg* 2020; **15**: 819-826 [PMID: 32333360 DOI: 10.1007/s11548-020-02165-4]
12 **Koike T**, Kin T, Tanaka S, Takeda Y, Uchikawa H, Shiode T, Saito T, Takami H, Takayanagi S, Mukasa A, Oyama H, Saito N. Development of Innovative Neurosurgical Operation Support Method Using Mixed-Reality Computer Graphics. *World Neurosurg X* 2021; **11**: 100102 [PMID: 33898969 DOI: 10.1016/j.wnsx.2021.100102]
13 **Verhey JT**, Haglin JM, Verhey EM, Hartigan DE. Virtual, augmented, and mixed reality applications in orthopedic surgery. *Int J Med Robot* 2020; **16**: e2067 [PMID: 31867864 DOI: 10.1002/rcs.2067]
14 **Li G**, Dong J, Wang J, Cao D, Zhang X, Cao Z, Lu G. The clinical application value of mixed-reality-assisted surgical navigation for laparoscopic nephrectomy. *Cancer Med* 2020; **9**: 5480-5489 [PMID: 32543025 DOI: 10.1002/cam4.3189]
15 **Saito Y**, Sugimoto M, Imura S, Morine Y, Ikemoto T, Iwahashi S, Yamada S, Shimada M. Intraoperative 3D Hologram Support With Mixed Reality Techniques in Liver Surgery. *Ann Surg* 2020; **271**: e4-e7 [PMID: 31425293 DOI: 10.1097/SLA.0000000000003552]
16 **Dindo D**, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205-213 [PMID: 15273542 DOI: 10.1097/01.sla.0000133083.54934.ae]
17 **Chen L**, Wang YB, Zhang YH, Gong JF, Li Y. Effective prediction of postoperative complications for patients after open hepatectomy: a simplified scoring system based on perioperative parameters. *BMC Surg* 2019; **19**: 128 [PMID: 31488117 DOI: 10.1186/s12893-019-0597-2]
18 **Li P**, Wang M, Yang Y, Liu H, Pan Z, Jiang B, Lau WY, Huang G, Zhou W. Preoperative three-dimensional *vs* two-dimensional evaluation in assessment of patients undergoing major liver resection for hepatocellular carcinoma: a propensity score matching study. *Ann Transl Med* 2020; **8**: 182 [PMID: 32309329 DOI: 10.21037/atm.2020.01.106]
19 **Pelanis E**, Kumar RP, Aghayan DL, Palomar R, Fretland ÅA, Brun H, Elle OJ, Edwin B. Use of mixed reality for improved spatial understanding of liver anatomy. *Minim Invasive Ther Allied Technol* 2020; **29**: 154-160 [PMID: 31116053 DOI: 10.1080/13645706.2019.1616558]
20 **Nakayama K**, Oshiro Y, Miyamoto R, Kohno K, Fukunaga K, Ohkohchi N. The Effect of Three-Dimensional Preoperative Simulation on Liver Surgery. *World J Surg* 2017; **41**: 1840-1847 [PMID: 28271263 DOI: 10.1007/s00268-017-3933-7]
21 **Mise Y**, Hasegawa K, Satou S, Shindoh J, Miki K, Akamatsu N, Arita J, Kaneko J, Sakamoto Y, Kokudo N. How Has Virtual Hepatectomy Changed the Practice of Liver Surgery? *Ann Surg* 2018; **268**: 127-133 [PMID: 28288065 DOI: 10.1097/SLA.0000000000002213]
22 **Famularo S**, Giani A, Di Sandro S, Sandini M, Giacomoni A, Pinotti E, Lauterio A, Gianotti L, De Carlis L, Romano F. Does the Pringle maneuver affect survival and recurrence following surgical resection for hepatocellular carcinoma? *J Surg Oncol* 2018; **117**: 198-206 [PMID: 29082526 DOI: 10.1002/jso.24819]
23 **Kumar RP**, Pelanis E, Bugge R, Brun H, Palomar R, Aghayan DL, Fretland ÅA, Edwin B, Elle OJ. Use of mixed reality for surgery planning: Assessment and development workflow. *J Biomed Inform* 2020; **112S**: 100077 [PMID: 34417006 DOI: 10.1016/j.yjbinx.2020.100077]
24 **Barteit S**, Lanfermann L, Bärnighausen T, Neuhann F, Beiersmann C. Augmented, Mixed, and Virtual Reality-Based Head-Mounted Devices for Medical Education: Systematic Review. *JMIR Serious Games* 2021; **9**: e29080 [PMID: 34255668 DOI: 10.2196/29080]
25 **Andolfi C**, Plana A, Kania P, Banerjee PP, Small S. Usefulness of Three-Dimensional Modeling in Surgical Planning, Resident Training, and Patient Education. *J Laparoendosc Adv Surg Tech A* 2017; **27**: 512-515 [PMID: 27813710 DOI: 10.1089/Lap.2016.0421]
26 **Uchida Y**, Taura K, Nakao M, Uemoto S. A clinical pilot study of Resection Process Map: A novel virtual hepatectomy software to visualize the resection process, case series. *Int J Surg* 2019; **71**: 36-40 [PMID: 31525504 DOI: 10.1016/j.ijsu.2019.09.002]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 January 27; 14(1): 46-55

DOI: 10.4240/wjgs.v14.i1.46

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

# Association of anastomotic leakage with long-term oncologic outcomes of patients with esophagogastric junction cancer

Masashi Takeuchi, Hirofumi Kawakubo, Satoru Matsuda, Shuhei Mayanagi, Tomoyuki Irino, Jun Okui, Kazumasa Fukuda, Rieko Nakamura, Norihito Wada, Hiroya Takeuchi, Yuko Kitagawa

**ORCID number:** Masashi Takeuchi 0000-0003-3797-432X; Hirofumi Kawakubo 0000-0002-4929-5482; Satoru Matsuda 0000-0001-8441-2755; Shuhei Mayanagi 0000-0002-0120-3497; Tomoyuki Irino 0000-0002-2056-0721; Jun Okui 0000-0002-5226-1347; Kazumasa Fukuda 0000-0001-6126-6118; Rieko Nakamura 0000-0003-0947-6358; Norihito Wada 0000-0003-4857-8453; Hiroya Takeuchi 0000-0002-3947-0128; Yuko Kitagawa 0000-0001-6469-2155.

**Author contributions:** All authors give final approval of the manuscript and agree to be accountable for all aspects of the work; Takeuchi M contributed to the literature search, study design, analysis plan, data analysis and interpretation, drafting of manuscript; Kawakubo H contributed to the study design, data analysis and interpretation, manuscript revision; Matsuda S and Mayanagi S contributed to the data interpretation and analysis, manuscript revision; Irino T, Fukuda K, Nakamura R and Wada N contributed to the study design, data interpretation and analysis; Okui J contributed to the data interpretation and analysis; Takeuchi H contributed to the study design, analysis plan, data interpretation and analysis;

**Masashi Takeuchi, Hirofumi Kawakubo, Satoru Matsuda, Shuhei Mayanagi, Tomoyuki Irino, Kazumasa Fukuda, Rieko Nakamura, Norihito Wada, Yuko Kitagawa,** Department of Surgery, Keio University School of Medicine, Tokyo 160-8582, Japan

**Jun Okui,** Department of Preventive Medicine and Public Health, Keio University School of Medicine, Tokyo 160-8582, Japan

**Hiroya Takeuchi,** Department of Surgery, Hamamatsu University School of Medicine, Shizuoka 431-3192, Japan

**Corresponding author:** Hirofumi Kawakubo, MD, PhD, Associate Professor, Department of Surgery, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. hkawakubo@z3.keio.jp

## Abstract

***BACKGROUND***

Despite improvements in surgical procedures and peri-operative patients management, the postoperative complications in esophagogastric junction (EGJ) cancer remain high because of technical aspects. Several studies have indicated the negative influence of postoperative infectious complications on long-term survival after gastrointestinal surgery. However, no study has shown the association between postoperative complications and long-term survival of patients with EGJ cancer.

***AIM***

To elucidate influence of postoperative complications on the long-term outcomes of patients with EGJ cancer.

***METHODS***

A total of 122 patients who underwent surgery for EGJ cancer at the Keio University were included in this study. We examined the association between complications and long-term oncologic outcomes.

***RESULTS***

In all patients, the 3-year overall survival (OS) rate was 71.9%, and the recurrence-free survival (RFS) rate was 67.5%. Compared with patients without anastomotic leakage, those with anastomotic leakage had poor median OS (8 mo *vs* not

Kitagawa Y contributed to the study design, manuscript revision.

**Institutional review board statement:** This study was conducted with the approval of the ethics committee of the Keio University School of Medicine.

**Informed consent statement:** The study participant was provided with an informed written consent prior to study enrollment.

**Conflict-of-interest statement:** Kitagawa Y received lecture fees from Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd, Asahi Kasei Pharma Corporation, Otsuka Pharmaceutical Factory Inc., Shionogi & Co., Ltd., Nippon Covidien Inc., Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb K.K.. Kitagawa Y was supported by grants from Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd, Yakult Honsha Co. Ltd., Asahikasei Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Tsumura & Co., Kyouwa Hakkou Kirin Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Ea Pharma Co., Ltd., Astellas Pharma Inc., Toyama Chemical Co., Ltd., Medicon Inc., Kaken Pharmaceutical Co. Ltd., Eisai Co., Ltd., Otsuka Pharmaceutical Factory Inc., Teijin Pharma Limited., Nihon Pharmaceutical Co., Ltd., and Nippon Covidien Inc. Kitagawa Y held an endowed chair provided by Chugai Pharmaceutical Co., Ltd. and Taiho Pharmaceutical Co., Ltd, outside the submitted work. Other authors declare no conflict-of-interest.

**Data sharing statement:** Technical appendix, statistical code, and dataset available from the corresponding author at hkawakubo@z3.keio.jp.

**Country/Territory of origin:** Japan

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:**

reached, $P$ = 0.028) and median RFS (5 mo *vs* not reached, $P$ = 0.055). Among patients with cervical anastomosis, there were not significant differences between patients with and without anastomotic leakage. However, among patients who underwent intrathoracic anastomosis, patients with anastomotic leakage had significantly worse OS ($P$ = 0.002) and RFS ($P$ = 0.005).

*CONCLUSION*

Anastomotic leakage was significantly associated with long-term oncologic outcomes of patients with EGJ cancer, especially those who underwent intrathoracic anastomosis. Cervical anastomosis with subtotal esophagectomy may be an option for the patients who are at high risk for anastomotic leakage.

**Key Words:** Esophagogastric junction cancer; Complication; Long-term outcome



**Core Tip:** The postoperative complications of gastrointestinal surgery had been reported to have a remarkable effect on the long-term outcomes, but no study had examined this association in esophagogastric junction (EGJ) cancer. This retrospective study found that anastomotic leakage was remarkably associated with the survival of patients with EGJ cancer who underwent intrathoracic anastomosis but not cervical anastomosis. Cervical anastomosis with subtotal esophagectomy may be an option for patients who have a high risk for anastomotic leakage.

**Citation:** Takeuchi M, Kawakubo H, Matsuda S, Mayanagi S, Irino T, Okui J, Fukuda K, Nakamura R, Wada N, Takeuchi H, Kitagawa Y. Association of anastomotic leakage with long-term oncologic outcomes of patients with esophagogastric junction cancer. *World J Gastrointest Surg* 2022; 14(1): 46-55

**URL:** https://www.wjgnet.com/1948-9366/full/v14/i1/46.htm

**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i1.46

## INTRODUCTION

Esophagogastric junction (EGJ) cancer has been increasing not only in the United States and Western countries but also in Japan[1-5]. However, the optimal surgical approach for EGJ cancer remains controversial[6]. Despite improvements in surgical procedures and peri-operative patients management, the complications after surgery for EGJ cancer remain high because of technical aspects[7]. EGJ has complex anatomical features with several adjacent organs, such as the spleen, diaphragm, and some thoracic organs[8]. Therefore, obtaining a negative surgical margin is often difficult because of the restricted space. In some cases, intrathoracic anastomosis is needed to achieve a clear margin, both macroscopically and microscopically[5]. A multicenter prospective study showed the occurrence of postoperative complications of any grade in around 40% of patients; in particular, postoperative anastomotic leakage developed in 11.9% after a transhiatal approach and in 13.2% after a transthoracic approach[9].

Postoperative infectious complications have been reported to have an adverse influence on the long-term outcomes after esophagectomy [10-12]. The negative influence of these complications may be attributed to cytokines changes which are associated with residual cancer cell progression[13,14]. However, to date, no study has shown the influence of postoperative complications on the long-term outcomes of patients with EGJ cancer.

We hypothesized the association of postoperative complications, including anastomotic leakage, which is the most common, with the long-term oncologic outcomes after surgery for EGJ cancer. The aim of this study is to elucidate the influence of postoperative complications on the long-term outcomes of patients with EGJ cancer.

Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0



**Received:** March 25, 2021
**Peer-review started:** March 25, 2021
**First decision:** June 16, 2021
**Revised:** June 29, 2021
**Accepted:** December 22, 2021
**Article in press:** December 22, 2021
**Published online:** January 27, 2022

**P-Reviewer:** Herbella FAM
**S-Editor:** Zhang H
**L-Editor:** A
**P-Editor:** Zhang H

## MATERIALS AND METHODS

### Patients

This study included 122 patients who had undergone surgery for EGJ cancer at the Keio University between 2003 and 2017. We defined EGJ cancer according to Nishi's classification[15]. The location of the EGJ was defined at the level of macroscopic change in the caliber of the resected esophagus and stomach. A tumor that had an epicenter in the area of the EGJ and extended from 2 cm above to 2 cm below the EGJ was diagnosed as EGJ cancer. We included patients who were diagnosed as cM1 if there was involvement of the supraclavicular lymph node[16].

Using hospital records, the patients' clinical characteristics, surgical procedure, and outcomes were evaluated retrospectively. The OS and recurrence-free survival (RFS) were calculated from the start date of surgery. The clinical and pathologic stages of the cancer were based on the seventh edition of the Union Against Cancer for esophageal cancer[17]. The tumor status was determined by the residual tumor classification: R0, no residual tumor or R1, microscopic residual tumor[18]. This study had approval from the ethics committee of Keio University School of Medicine.

### Surgical procedures

At our institution, the decision making for the surgical procedures for EGJ cancer included the performance of subtotal esophagectomy for: (1) advanced cancer deeper than T2, with the tumor epicenter on the esophageal side; (2) advanced cancer deeper than T2, with the tumor epicenter on the gastric side and with > 30 mm of esophageal invasion; or (3) cancer with clinically positive upper and/or middle mediastinal lymph node. The remaining patients mainly underwent transhiatal approach for lower esophageal resection; however, transthoracic approach was selected if performing transhiatal anastomosis or obtaining a negative proximal margin was expected to be difficult.

The thoracic approach was performed through a right thoracic incision or by video-assisted thoracic surgery in a hybrid position that combined the left decubitus and prone positions. Posterior mediastinal routes were mainly used for esophageal reconstructions with gastric conduits or colons. Moreover, we usually performed intrathoracic anastomosis in the cervical site by hand sewing but have elected to use a circular stapler in some cases. Transhiatal procedures are approached from the abdominal side. In this approach, we performed a total or proximal gastrectomy with resection of the distal esophagus. We used the jejunum for the double-tract or Roux-en-Y reconstruction or performed an esophagogastrostomy. Esophagogastrostomy was done mainly using the double-flap method with hand-sewn anastomosis. Double-tract or Roux-en-Y were performed using a circular stapler, hand -sewn or linear stapler.

We routinely performed esophagogastric roentgenography and computed tomography for 7 d after surgery to assess the presence of any complications, including anastomotic leakage. The Clavien–Dindo classification was used to assess postoperative complications[19]: Grade 3 was defined as complications requiring surgical, endoscopic, or radiologic intervention. Grade 4 was defined as a life-threatening complication requiring intensive care unit management. Anastomotic leakage was diagnosed based on computed tomography scan or esophagography findings and/or the characteristics of the anastomotic drains. Pneumonia was diagnosed on the basis of the postoperative body temperature, leukocyte count, and pulmonary radiograph findings[3].

### Statistical analysis

We used Stata/SE 12.1 for Mac (StataCorp, College Station, TX, United States) for statistical analyses. For the univariate analysis, categorical variables were analyzed using the chi-square test and continuous variables were analyzed using the Mann–Whitney U-test. We entered significant variables with $P$ values < 0.10 into a logistic regression model for multivariate analysis. Moreover, we examined prognosis using the Kaplan-Meier method and log-rank test; we entered significant variables with $P$ values < 0.10 into a Cox hazard regression model for multivariate analysis.

## RESULTS

### Patient characteristics

The clinicopathologic characteristics of the study patients are shown in Table 1. Of the 122 patients (96 men and 26 women), 95 patients (77.9%) had adenocarcinoma and 27 patients (22.1%) had squamous cell carcinoma. Transhiatal approach was performed on 75 patients (61.5%); transthoracic approach was performed on 47 patients (38.5%). Subtotal esophagectomy was performed on 41 patients (33.6%), and total gastrectomy was performed on 37 patients (30.3%).

The most commonly observed complication after surgery was pneumonia in 12 patients (9.8%), followed by anastomotic leakage in eight patients (6.6%) and recurrent laryngeal nerve paralysis in six patients (5%). However, the most common grade 2 or higher complication was anastomotic leakage. Hospital death occurred in one patient (0.8%) (Table 2).

### Long-term outcomes

The 3 year OS rate and RFS rate was 71.9% and 67.5%, respectively. During the term of the surveillance, 35 patients (28.7%) developed recurrence and 34 patients (27.9%) died. There weren't significant differences between patients with and without pneumonia, both in the OS ($P$ = 0.325) and RFS ($P$ = 0.149) (Figure 1). However, compared with patients without anastomotic leakage, those with anastomotic leakage had poor median OS (8 mo *vs* not reached, $P$ = 0.028) and median RFS (5 mo *vs* not reached, $P$ = 0.055) (Figure 2).

According to the univariate analyses, age, histology, neoadjuvant therapy, pStage, R1, and anastomotic leakage were the risk factors for death. On multivariate analyses, age, pStage III/IV, and anastomotic leakage were identified as the significant risk factors for death (Table 3). Moreover, anastomotic leakage was a significant risk factor for RFS (Supplementary Table 1).

Among patients with cervical anastomosis, there weren't significant differences between patients with and without anastomotic leakage. However, among patients who underwent intrathoracic anastomosis, patients with anastomotic leakage, compared with those without anastomotic leakage, had significantly worse OS ($P$ = 0.002) and RFS ($P$ = 0.005) (Figure 3).

### Recurrence pattern

Lymph node metastases were the most common pattern of recurrence (23 patients), followed by hematogenous (19 patients), peritoneal (seven patients), and local (four patients). These three patterns of recurrence were significantly observed in patients with anastomotic leakage (Table 4).

### Risk factors for anastomotic leakage

We examined the risk factors for anastomotic leakage using the clinicopathologic characteristics and the surgical procedural factors. On univariate analyses, amount of bleeding, operating time, and tumor diameter were the risk factors for anastomotic leakage. Notably, surgical procedural factors were not identified as predictors of anastomotic leakage. On multivariate analysis that included these factors, only tumor diameter was identified as a predictor of anastomotic leakage (HR: 1.04, 95%CI: 1.01–1.08, $P$ = 0.020) (Supplementary Table 2). On subanalysis, tumor diameter was a significant risk factor for anastomotic leakage in patients who underwent intrathoracic anastomosis ($P$ = 0.009) but not in those who underwent cervical anastomosis ($P$ = 0.886).

## DISCUSSION

The present retrospective study demonstrated that anastomotic leakage was significantly associated with the long-term oncologic outcomes, including OS and RFS, in patients with EGJ cancer. Notably, these tendencies were observed not in patients who underwent cervical anastomosis but in those who underwent intrathoracic anastomosis. Although several studies have indicated the relationship between survival and postoperative complications, this was the first report that demonstrated the negative influence of postoperative complications on the oncological outcomes of patients with EGJ cancer.

**Table 1 Clinicopathologic characteristics of the study population**

| | All (*n* = 122) |
|---|---|
| Sex | |
| Male/female | 96 (78.7%)/26 (21.3%) |
| Age, median (min, max) | 68 (35-87) |
| Histology | |
| Adenocarcinoma/squamous cell carcinoma | 95 (77.9%)/27 (22.1%) |
| Neoadjuvant | 32 (26.2%) |
| Adjuvant | 27 (22.1%) |
| Approach | |
| Transthoracic/transhiatal | 47 (38.5%)/75 (61.5%) |
| Reconstruction site | |
| Cervical/Intrathoracic | 22 (18.0%)/100 (82.0%) |
| Subtotal esophagectomy | 41 (33.6%) |
| Total gastrectomy | 37 (30.3%) |
| Splenectomy | 16 (13.1%) |
| Operating time (min); median (range) | 299 (114-775) |
| Amount of bleeding (mL); median (range) | 180 (10-4858) |
| Tumor epicenter | |
| Esophageal side/gastric side | 52 (42.6%)/70 (57.4%) |
| Distance from the EGJ to the tumor center (mm) | 1.5 (-20[1]-20) |
| Esophageal invasion (mm) | 11.5 (0-55) |
| Tumor diameter (mm) | 32 (6-100) |
| Pathologic stage of esophageal cancer | |
| Stage I/stage II/stage III/stage IV | 44 (36.1%)/24 (19.7%)/38 (31.2%)/16 (13.1%) |
| Residual cancer | |
| R0/R1 | 111 (91.0%)/11 (9.0%) |

[1]This indicates that tumor epicenter is located on gastric side. EGJ: Esophagogastric junction.

Some studies have reported that postoperative anastomotic leakage had a negative influence on the long-term outcomes of upper gastrointestinal surgery. Markar *et al*[20] reported that anastomotic leakage after esophagectomy was associated with poor OS and disease-specific survival rates and with an increase in cancer recurrence rates. Likewise, Andreou *et al*[21] showed that anastomotic leakage had a negative influence on the long-term survival after gastric and esophageal resection. In our study, the recurrence rate was also significant higher in patients with anastomotic leakage than in those without anastomotic leakage. As previously indicated, cytokine changes due to postoperative complications may be relevant to tumor proliferation, survival, and progression to metastasis[13]. Therefore, inflammatory response secondary to anastomotic leakage was suggested to promote tumor regrowth and lead to poor long-term outcomes. In particular, patients with leakage of the intrathoracic anastomosis after surgery may have suffered more severe systemic inflammation, compared with the patients who had leakage of the cervical anastomosis, because inflammation can spread inside the thoracic cavity and easily develop to mediastinitis. Therefore, these trends were more prevalent in patients with intrathoracic anastomosis than in those with cervical anastomosis. On the other hand, in cases of cervical anastomosis leakage, inflammation can often be localized.

Our previous study indicated that postoperative pneumonia, not anastomotic leakage, was associated with the long-term outcomes after esophagectomy[10]; however, patients with EGJ cancer had the opposite tendency. This is due to the

**Table 2 Postoperative complications**

| | All grades | Grade 3/4 |
|---|---|---|
| Overall complications | 40 (32.8%) | 17 (13.9%) |
| Pneumonia | 12 (9.8%) | 1 (0.8%) |
| Anastomotic leakage | 8 (6.6%) | 7 (5.7%) |
| Recurrent laryngeal nerve paralysis | 6 (5%) | 0 |
| Wound infection | 4 (3.3%) | 0 |
| Chyle leakage | 3 (2.5%) | 2 (1.7%) |
| Hemorrhage | 2 (1.7%) | 2 (1.7%) |
| Pancreatic fistula | 3 (2.5%) | 0 |
| Atrial fibrillation | 2 (1.7%) | 0 |
| Abdominal abscess | 3 (2.5%) | 1 (0.8%) |
| Gastric tube-bronchial fistula | 1 (0.8%) | 1 (0.8%) |
| Others | 9 (7.4%) | 3 (2.5%) |

**Table 3 Predictors for overall survival on univariate and multivariate analyses**

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95%CI) | *P* value | HR (95%CI) | *P* value |
| Male (*vs* female) | 0.71 (0.34–1.49) | 0.365 | | |
| Age (per 1 year increase) | 1.06 (1.02-1.09) | 0.004 | 1.05 (1.01-1.08) | 0.014 |
| SCC (*vs* AC) | 2.06 (1.02-4.16) | 0.045 | 1.20 (0.50-2.87) | 0.674 |
| Neoadjuvant + (*vs* neoadjuvant-) | 2.22 (1.11-4.44) | 0.025 | 1.61 (0.72-3.58) | 0.244 |
| Adjuvant + (*vs* adjuvant-) | 1.76 (0.86-3.62) | 0.122 | | |
| Transthoracic approach (*vs* transhiatal approach) | 1.64 (0.83-3.22) | 0.148 | | |
| pStage III/IV (*vs* pStage I/II) | 9.55 (3.68-24.76) | < 0.001 | 7.14 (2.67-19.13) | < 0.001 |
| R1 (*vs* R0) | 2.62 (1.08-6.35) | 0.033 | 1.79 (0.69-4.68) | 0.232 |
| Anastomotic leakage | 3.07 (1.07-8.80) | 0.037 | 3.59 (1.11-11.58) | 0.032 |
| Postoperative pneumonia | 1.68 (0.59-4.78) | 0.332 | | |

P: Pathologic; SCC: Squamous cell carcinoma; AC: Adenocarcinoma; R0: No residual tumor; R1: Microscopic residual tumor; HR: Hazard ratio.

**Table 4 Patterns of recurrence**

| | All (*n* = 122) | Anastomotic leakage | | *P* value |
|---|---|---|---|---|
| | | Yes (*n* = 8) | No (*n* = 114) | |
| Hematogenous | 19 (15.6%) | 4 (50%) | 15 (13.2%) | 0.005 |
| Lymphatic | 23 (18.9%) | 3 (37.5%) | 20 (17.5%) | 0.163 |
| Peritoneal | 7 (5.7%) | 2 (25%) | 5 (4.4%) | 0.015 |
| Local | 4 (3.3%) | 2 (25%) | 2 (1.8%) | < 0.001 |

difference in the surgical approach between esophageal cancer and EGJ cancer. As we described above, patients with leakage of intrathoracic anastomosis may have suffered relatively worse systemic inflammation; this may explain the association of anastomotic leakage with the long-term outcomes after surgery for EGJ cancer in those with intrathoracic anastomosis but not in those with cervical anastomosis. Conversely,

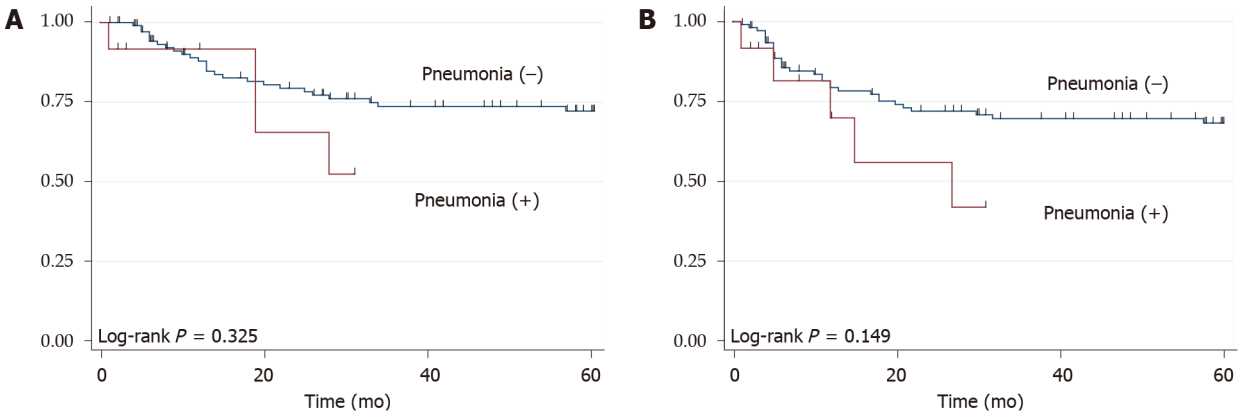



**Figure 1 Kaplan-Meier survival curves, according to the presence of pneumonia.** A: Overall survival; B: Recurrence-free survival. Red and blue lines indicate the groups with and without pneumonia, respectively.

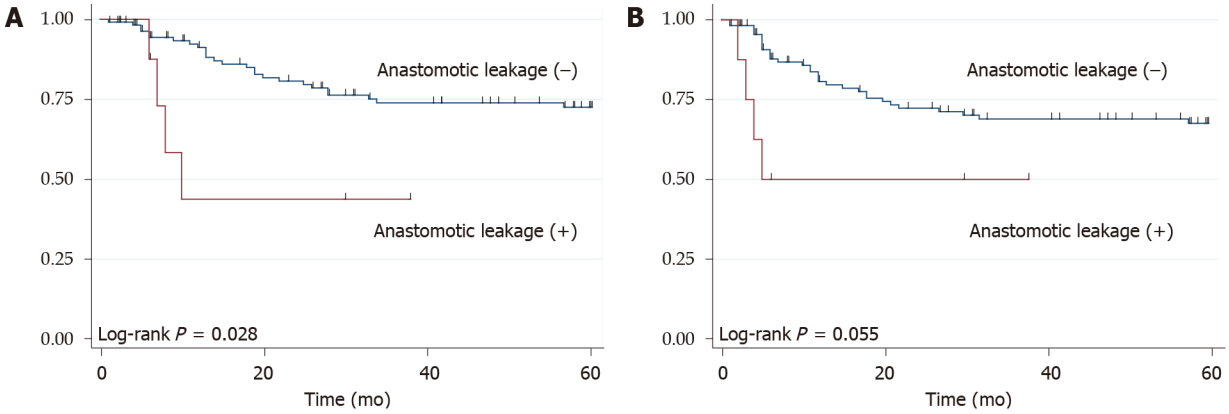



**Figure 2 Kaplan–Meier survival curves, according to the presence of anastomotic leakage.** A: Overall survival; B: Recurrence-free survival. Red and blue lines indicate the groups with and without anastomotic leakage, respectively.

pneumonia was not associated with the long-term outcomes after surgery for EGJ cancer, probably because of the manipulation and effects on the lungs during surgery. On the other hand, the procedure of esophagectomy for esophageal cancer is mainly performed in the thoracic cavity, therefore, pneumonia after esophagectomy should be considered as a possible poor prognostic factor with a large impact on pulmonary function.

In this study, tumor diameter was a significant risk factor for anastomotic leakage, especially in patients who underwent intrathoracic anastomosis. This result suggested that performing anastomosis for a large tumor invading the esophageal side may cause anastomotic leakage because of technical difficulties. Therefore, cervical anastomosis with subtotal esophagectomy should be chosen for patients who have a high risk for anastomotic leakage, including those with large tumor diameter. Conversely, pStage is not a significant risk factor. Moreover, anastomotic leakage was a significant predictor for oncological outcomes, independent of tumor, node and metastasis stage, according to the multivariate analyses. Therefore, we concluded that anastomotic leakage also is associated with survival, in addition to pStage.

We have used Nishi's classification in this study; however, the Siewert classification has been adopted mainly in Western countries as the histological type is predominantly adenocarcinoma. Although an EGJ tumor defined by Nishi's classification and Siewert type 2 is almost similar, the tumor epicenter with Nishi's classification is 1 cm higher than is that of Siewert type 2. Therefore, performing intrathoracic anastomosis may be difficult in EGJ cancer defined with Nishi's classification *vs* Siewert type 2 cancer, and the relationship between survival and anastomotic leakage may be weak if only patients with Siewert type 2 cancers were enrolled in the study.

This study had several limitations. First, the retrospective single-center study design that was limited to a Japanese population was an element of selection bias. Second, we did not consider the association between the complication's grades and long-term

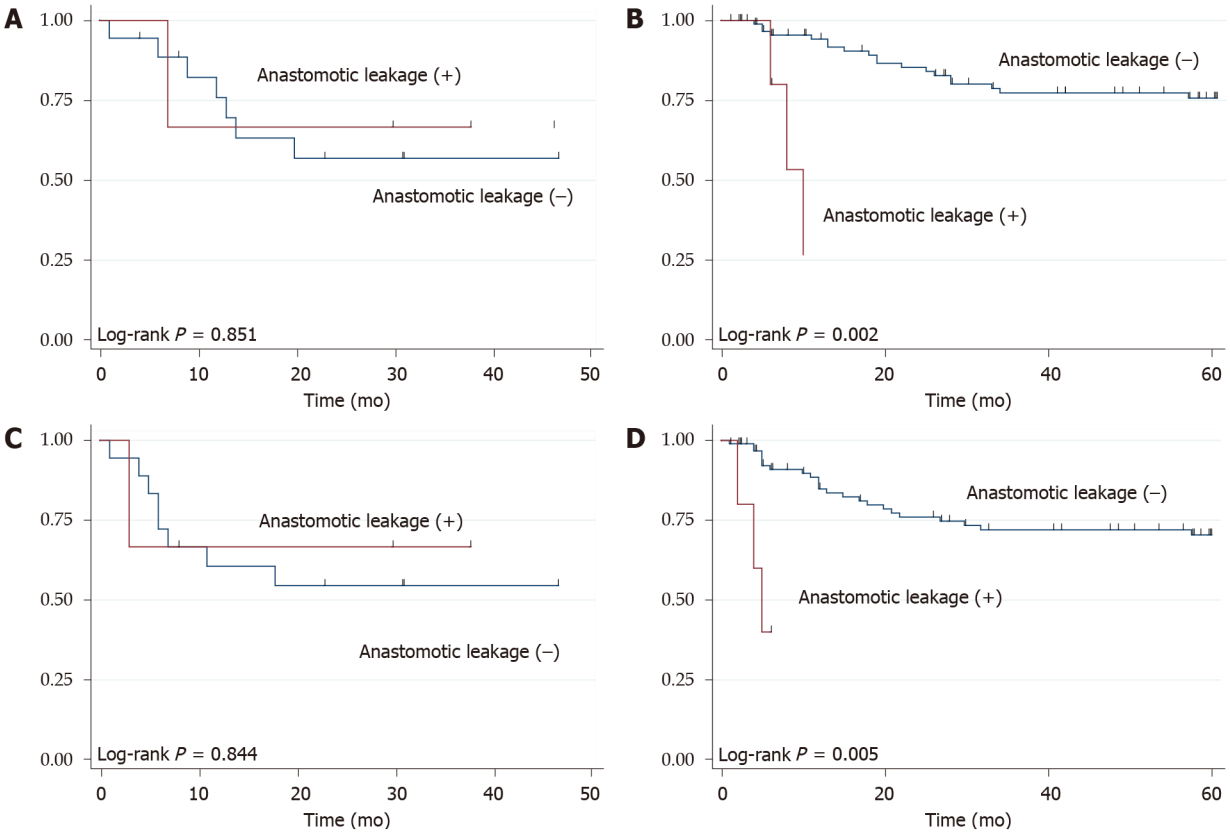



**Figure 3 Kaplan–Meier survival curves, according to the presence of anastomotic leakage and type of anastomosis.** A and B: The overall survival (A) in patients with cervical anastomosis and (B) in patients with intrathoracic anastomosis; C and D: The recurrence-free survival (C) in patients with cervical anastomosis and (D) in patients with intrathoracic anastomosis. Red and blue lines indicate the groups with and without anastomotic leakage, respectively.

outcome in this study. In particular, we did not examine the difference in anastomotic leakage severity between cervical anastomosis and intrathoracic anastomosis.

## CONCLUSION

Anastomotic leakage was significantly associated with the long-term oncologic outcomes of patients with EGJ cancer in patients who underwent intrathoracic anastomosis but not in those who underwent cervical anastomosis. Cervical anastomosis with subtotal esophagectomy may be an option for patients who have a high risk of anastomotic leakage.

## ARTICLE HIGHLIGHTS

### *Research background*

Despite improvements in surgical procedures and peri-operative patients management, complications after surgery for esophagogastric junction (EGJ) cancer remain high because of technical difficulty.

### *Research motivation*

No study has shown the influence of postoperative complications on the long-term outcomes of patients with EGJ cancer.

### *Research objectives*

To elucidate the influence of postoperative complications, such as anastomotic leakage and pneumonia, on the long-term outcomes of patients with EGJ cancer.

### Research methods

We retrospectively analyzed 122 patients who underwent surgery for EGJ cancer, investigating the association between postoperative complications and oncological outcomes.

### Research results

We identified anastomotic leakage as a significant risk factor for death and cancer recurrence. We did not observe this tendency in patients who underwent cervical anastomosis but did see this tendency in patients who underwent intrathoracic anastomosis.

### Research conclusions

Postoperative anastomotic leakage was significantly associated with survival in patients with EGJ cancer. Cervical anastomosis with esophagectomy may be an option for patients with a high risk of anastomotic leakage.

### Research perspectives

A prospective study is required to confirm the association between complications and long-term outcomes of patients with EGJ cancer.

## ACKNOWLEDGEMENTS

The authors thank Kumiko Motooka, a staff member at the Department of Surgery in the Keio University School of Medicine, for her help in the preparation of this manuscript.

## REFERENCES

1 **Kusano C**, Gotoda T, Khor CJ, Katai H, Kato H, Taniguchi H, Shimoda T. Changing trends in the proportion of adenocarcinoma of the esophagogastric junction in a large tertiary referral center in Japan. *J Gastroenterol Hepatol* 2008; **23**: 1662-1665 [PMID: 19120859 DOI: 10.1111/j.1440-1746.2008.05572.x]

2 **Dikken JL**, Lemmens VE, Wouters MW, Wijnhoven BP, Siersema PD, Nieuwenhuijzen GA, van Sandick JW, Cats A, Verheij M, Coebergh JW, van de Velde CJ. Increased incidence and survival for oesophageal cancer but not for gastric cardia cancer in the Netherlands. *Eur J Cancer* 2012; **48**: 1624-1632 [PMID: 22317953 DOI: 10.1016/j.ejca.2012.01.009]

3 **Dubecz A**, Solymosi N, Stadlhuber RJ, Schweigert M, Stein HJ, Peters JH. Does the Incidence of Adenocarcinoma of the Esophagus and Gastric Cardia Continue to Rise in the Twenty-First Century? *J Gastrointest Surg* 2013 [PMID: 24234242 DOI: 10.1007/s11605-013-2345-8]

4 **Vizcaino AP**, Moreno V, Lambert R, Parkin DM. Time trends incidence of both major histologic types of esophageal carcinomas in selected countries, 1973-1995. *Int J Cancer* 2002; **99**: 860-868 [PMID: 12115489 DOI: 10.1002/ijc.10427]

5 **Chevallay M**, Bollschweiler E, Chandramohan SM, Schmidt T, Koch O, Demanzoni G, Mönig S, Allum W. Cancer of the gastroesophageal junction: a diagnosis, classification, and management review. *Ann N Y Acad Sci* 2018; **1434**: 132-138 [PMID: 30138540 DOI: 10.1111/nyas.13954]

6 **Shiraishi O**, Yasuda T, Kato H, Iwama M, Hiraki Y, Yasuda A, Shinkai M, Kimura Y, Imano M. Risk Factors and Prognostic Impact of Mediastinal Lymph Node Metastases in Patients with Esophagogastric Junction Cancer. *Ann Surg Oncol* 2020; **27**: 4433-4440 [PMID: 32409967 DOI: 10.1245/s10434-020-08579-3]

7 **Ji L**, Wang T, Tian L, Gao M. The early diagnostic value of C-reactive protein for anastomotic leakage post radical gastrectomy for esophagogastric junction carcinoma: A retrospective study of 97 patients. *Int J Surg* 2016; **27**: 182-186 [PMID: 26854957 DOI: 10.1016/j.ijsu.2016.02.021]

8 **Delattre JF**, Avisse C, Marcus C, Flament JB. Functional anatomy of the gastroesophageal junction. *Surg Clin North Am* 2000; **80**: 241-260 [PMID: 10685151 DOI: 10.1016/s0039-6109(05)70404-7]

9 **Kurokawa Y**, Takeuchi H, Doki Y, Mine S, Terashima M, Yasuda T, Yoshida K, Daiko H, Sakuramoto S, Yoshikawa T, Kunisaki C, Seto Y, Tamura S, Shimokawa T, Sano T, Kitagawa Y. Mapping of Lymph Node Metastasis From Esophagogastric Junction Tumors: A Prospective Nationwide Multicenter Study. *Ann Surg* 2021; **274**: 120-127 [PMID: 31404008 DOI: 10.1097/SLA.0000000000003499]

10 **Booka E**, Takeuchi H, Nishi T, Matsuda S, Kaburagi T, Fukuda K, Nakamura R, Takahashi T, Wada N, Kawakubo H, Omori T, Kitagawa Y. The Impact of Postoperative Complications on Survivals After Esophagectomy for Esophageal Cancer. *Medicine (Baltimore)* 2015; **94**: e1369 [PMID: 26287423 DOI: 10.1097/MD.0000000000001369]

11 **Baba Y**, Yoshida N, Shigaki H, Iwatsuki M, Miyamoto Y, Sakamoto Y, Watanabe M, Baba H. Prognostic Impact of Postoperative Complications in 502 Patients With Surgically Resected Esophageal Squamous Cell Carcinoma: A Retrospective Single-institution Study. *Ann Surg* 2016; **264**: 305-311 [PMID: 26670288 DOI: 10.1097/SLA.0000000000001510]

12 **Yamashita K**, Makino T, Miyata H, Miyazaki Y, Takahashi T, Kurokawa Y, Yamasaki M, Nakajima K, Takiguchi S, Mori M, Doki Y. Postoperative Infectious Complications are Associated with Adverse Oncologic Outcomes in Esophageal Cancer Patients Undergoing Preoperative Chemotherapy. *Ann Surg Oncol* 2016; **23**: 2106-2114 [PMID: 26753750 DOI: 10.1245/s10434-015-5045-7]

13 **Yamamoto M**, Shimokawa M, Yoshida D, Yamaguchi S, Ohta M, Egashira A, Ikebe M, Morita M, Toh Y. The survival impact of postoperative complications after curative resection in patients with esophageal squamous cell carcinoma: propensity score-matching analysis. *J Cancer Res Clin Oncol* 2020; **146**: 1351-1360 [PMID: 32185488 DOI: 10.1007/s00432-020-03173-2]

14 **Tsujimoto H**, Kobayashi M, Sugasawa H, Ono S, Kishi Y, Ueno H. Potential mechanisms of tumor progression associated with postoperative infectious complications. *Cancer Metastasis Rev* 2021; **40**: 285-296 [PMID: 33389285 DOI: 10.1007/s10555-020-09945-z]

15 **Japanese Gastric Cancer Association**. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101-112 [PMID: 21573743 DOI: 10.1007/s10120-011-0041-5]

16 **Japan Esophageal Society**. Japanese Classification of Esophageal Cancer, 11th Edition: part II and III. *Esophagus* 2017; **14**: 37-65 [PMID: 28111536 DOI: 10.1007/s10388-016-0556-2]

17 **Sobin LH**, Gospodarowicz MK, Wittekind C. TNM Classification of Malignant Tumours. 7th ed. New York: Wiley-Liss, 2009

18 **Japan Esophageal Society**. Japanese Classification of Esophageal Cancer, 11th Edition: part I. *Esophagus* 2017; **14**: 1-36 [PMID: 28111535 DOI: 10.1007/s10388-016-0551-7]

19 **Dindo D**, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205-213 [PMID: 15273542 DOI: 10.1097/01.sla.0000133083.54934.ae]

20 **Markar S**, Gronnier C, Duhamel A, Mabrut JY, Bail JP, Carrere N, Lefevre JH, Brigand C, Vaillant JC, Adham M, Msika S, Demartines N, Nakadi IE, Meunier B, Collet D, Mariette C; FREGAT (French Eso-Gastric Tumors) working group, FRENCH (Fédération de Recherche EN CHirurgie), and AFC (Association Française de Chirurgie). The Impact of Severe Anastomotic Leak on Long-term Survival and Cancer Recurrence After Surgical Resection for Esophageal Malignancy. *Ann Surg* 2015; **262**: 972-980 [PMID: 26469952 DOI: 10.1097/SLA.0000000000001011]

21 **Andreou A**, Biebl M, Dadras M, Struecker B, Sauer IM, Thuss-Patience PC, Chopra S, Fikatas P, Bahra M, Seehofer D, Pratschke J, Schmidt SC. Anastomotic leak predicts diminished long-term survival after resection for gastric and esophageal cancer. *Surgery* 2016; **160**: 191-203 [PMID: 27067160 DOI: 10.1016/j.surg.2016.02.020]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 January 27; 14(1): 56-63

DOI: 10.4240/wjgs.v14.i1.56

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

# Laparoscopic Kasai portoenterostomy can be a standard surgical procedure for treatment of biliary atresia

Chiyoe Shirota, Akinari Hinoki, Takahisa Tainaka, Wataru Sumida, Fumie Kinoshita, Kazuki Yokota, Satoshi Makita, Hizuru Amano, Yoichi Nakagawa, Hiroo Uchida

**ORCID number:** Chiyoe Shirota 0000-0001-5829-2059; Akinari Hinoki 0000-0001-6878-2043; Takahisa Tainaka 0000-0002-3965-2087; Wataru Sumida 0000-0002-1302-7048; Fumie Kinoshita 0000-0002-3008-0748; Kazuki Yokota 0000-0003-3473-2472; Satoshi Makita 0000-0003-4658-8471; Hizuru Amano 0000-0001-5373-9069; Yoichi Nakagawa 0000-0003-1570-8661; Hiroo Uchida 0000-0002-1818-6697.

**Author contributions:** Shirota C, Tainaka T, Sumida W, Yokota K, and Makita S collected the patient data; Shirota C and Hinoki A analyzed patient images; Hinoki A and Nakagawa Y interpreted the patient data regarding operation; Kinoshita F analyzed the statistics; Shirota C and Uchida H were main contributors in writing the manuscript; and all authors have read and approved the final manuscript.

**Institutional review board statement:** The study was reviewed and approved by the (Nagoya University Hospital) Institutional Review Board (Approval No. 2020-0593).

**Conflict-of-interest statement:** All authors have no conflicts of interest to disclose.

**Chiyoe Shirota, Takahisa Tainaka, Wataru Sumida, Kazuki Yokota, Satoshi Makita, Hizuru Amano, Yoichi Nakagawa, Hiroo Uchida,** Department of Pediatric Surgery, Nagoya University Graduate School of Medicine, Nagoya 4668550, Aichi, Japan

**Akinari Hinoki,** Rare/Intractable Cancer Analysis Research, Nagoya University Graduate School of Medicine, Nagoya 4668550, Aichi, Japan

**Fumie Kinoshita,** Department of Advanced Medicine, Nagoya University Hospital, Nagoya 466-8560, Aichi, Japan

**Corresponding author:** Hiroo Uchida, MD, PhD, Doctor, Professor, Department of Pediatric Surgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Syowa-ku, Nagoya 4668550, Aichi, Japan. hiro2013@med.nagoya-u.ac.jp

## Abstract

*BACKGROUND*

Biliary atresia (BA) is a rare pediatric disease.

*AIM*

To compare the outcomes of laparoscopic portoenterostomy (Lap-PE) with those of laparotomy (Open-PE) at a single institution.

*METHODS*

The surgical outcomes of PE were retrospectively analyzed for patients with a non-correctable type of BA from 2003 to 2020.

*RESULTS*

Throughout the assessment period, 119 patients received PE for BA treatment, including 66 Open-PE and 53 Lap-PE cases. Although the operation duration was longer (medians: for Open-PE, 242 min; for Lap-PE, 341 min; $P < 0.001$), blood loss was considerably less (medians: for Open-PE, 52 mL; for Lap-PE, 24 mL; $P < 0.001$) in the Lap-PE group than in the Open-PE group. The postoperative recovery of the Lap-PE group was more favorable; specifically, both times to resume oral intake and drain removal were significantly shorter in the Lap-PE group. Complete resolution of jaundice was observed in 45 Open-PE cases and 42 Lap-PE cases, with no statistically significant difference ($P = 0.176$). Native liver survival rates were >80% for both groups for the first half year post surgery,

**Data sharing statement:** No additional data are available.

**Country/Territory of origin:** Japan

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0



**Received:** April 5, 2021
**Peer-review started:** April 5, 2021
**First decision:** July 3, 2021
**Revised:** July 31, 2021
**Accepted:** January 13, 2022
**Article in press:** January 13, 2022
**Published online:** January 27, 2022

**P-Reviewer:** Gunadi, Joshi D, Peruhova M
**S-Editor:** Ma YJ
**L-Editor:** Wang TQ
**P-Editor:** Ma YJ

followed by a gradual decrease with time; there were no statistically significant differences in the native liver survival rates for any durations assessed.

*CONCLUSION*
Lap-PE could be a standard therapy for BA.

**Key Words:** Laparoscopic Kasai portoenterostomy; Biliary atresia; Native liver survival; Pediatric; Liver Transplantation



**Core Tip:** The aim of this study was to compare the outcomes of laparoscopic portoenterostomy (Lap-PE) with those of laparotomy (Open-PE) at our single institution. Although the surgical operating time was longer, the lower blood loss and more favorable postsurgical recovery (shorter time to resume oral intake and time to drain removal as well as less postsurgical adhesion) were significant advantages of Lap-PE over Open-PE. There was no significant difference in native liver survival rates or short-term surgical outcomes between LapPE and OpenPE. Therefore, our study results support the efficacy of Lap-PE as a standard therapy.

**Citation:** Shirota C, Hinoki A, Tainaka T, Sumida W, Kinoshita F, Yokota K, Makita S, Amano H, Nakagawa Y, Uchida H. Laparoscopic Kasai portoenterostomy can be a standard surgical procedure for treatment of biliary atresia. *World J Gastrointest Surg* 2022; 14(1): 56-63
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i1/56.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i1.56

## INTRODUCTION

Although liver transplantation (LTx) is an established treatment for biliary atresia (BA), Kasai portoenterostomy (PE) is still the firstline standard treatment to maintain the native liver. However, the outcome of PE for treating BA has not improved over the past 20 years, and 35%–60% of the patients who have undergone PE eventually underwent LTx[1,2].

We followed a standard surgical protocol that involved minimally invasive therapies with a laparoscope or thoracoscope; this protocol had been initially established in adult surgeries and has been applied as a standard procedure in various pediatric surgeries. Even if PE for BA is successful, some patients subsequently need LTx. In comparison with OpenPE, LapPE is much less invasive, postsurgical recovery is favorable, and adhesions are minimal, which are significant advantages for patients who require LTx.

Laparoscopy in patients with BA has been studied previously. Evidence in favor of laparotomy (OpenPE) appeared to be stronger than that of LapPE[3-6]; however, the number of recent reports demonstrating favorable outcomes of LapPE comparable with those of OpenPE have been increasing[7]. Those studies supporting LapPE, however, were all small, and none of them had reasonable sample sizes at a single institution (*i.e.*, ≥50 cases each of LapPE and OpenPE) for comparing the outcomes with reasonable statistical power. Postoperative management after BA surgeries is complicated and requires a centralized procedure for consistency. Thus, it is considered important to perform a large-scale assessment at a single facility with a centralized management procedure for adequate comparison in the outcomes between LapPE and OpenPE [8,9].

In the case of BA, however, evidence for the usefulness of laparoscopic PE (LapPE) as a treatment option for BA, which is a rare pediatric disease, is still being obtained and evaluated. Therefore, the application of LapPE as a treatment option for BA remains controversial.

At our institution, we have made efforts to apply LapPE and improve our surgical technique and patient outcomes to increase the success rate of PE. The study aim was to compare the outcomes of LapPE at our single institution with those of OpenPE.

## MATERIALS AND METHODS

We obtained approval from our institutional ethics board for a retrospective review of the medical records of patients diagnosed with BA at our institution (approval number: 2020-0593).

The surgical outcomes of PE were retrospectively analyzed for patients with a noncorrectable type of BA who underwent PE at our institution from January 2003 to December 2020. The cases of correctable types of BA were excluded from the assessment. BA was diagnosed on the basis of a combination of radiographic findings, surgical findings of uncorrectable types, and liver histology. Complete resolution of jaundice was determined when the total bilirubin value was decreased by ≤ 1.2 mg/dL. Survival with the native liver was defined as the time when the liver functioned without LTx.

### *Surgical procedure*

Although there was a difference between laparotomy and laparoscopy, the operative procedure did not drastically change during the study period. In laparoscopic surgery, the ports were placed as shown in Figure 1. Intraoperative cholangiography was performed in all cases, during both laparotomy and laparoscopy, to confirm the presence of bile ducts. We used 5-0 monofilament absorbable sutures for portoenterostomy in both open and laparoscopic surgeries. One of the most important points is that the fibrous tissue in the hilar plate is dissected just before baring the liver parenchyma; it is not completely resected. Then, the area between the right porta hepatic, in which the right anterior branch of the hepatic artery and portal vein enter the hepatic parenchyma, and the left porta hepatic, in which the left branch of the portal vein enters the parenchyma, should be dissected for anastomosis. In our study, all patients were treated by the same team at a single institution, thereby minimizing any differences in surgical procedure or postoperative management.

### *Statistical analysis*

Data were statistically analyzed by performing the chi-squared test and Wilcoxon rank-sum test, with a $P$ value of < 0.05 taken to be indicative of statistical significance except for native liver survival rates, which were analyzed by performing Kaplan-Meier method and the log-rank test. We used JMP Pro 15 (SAS Institute Inc., NC, United States) statistical software for statistical analyses.

## RESULTS

Throughout the assessment period, 119 patients received PE for the treatment of a noncorrectable type of BA, including 66 OpenPE and 53 LapPE cases. No case was converted from laparoscopy to laparotomy. The median (range) values of key surgical parameters are shown by operation type (OpenPE group and LapPE group) in Table 1. The median age at surgery was significantly younger ($P$ = 0.0018) in the LapPE (53 d) group than in the OpenPE group (66 d). Although the operation duration was longer in the Lap-PE group (median: 341 min) than in the Open-PE group (median: 271.5 min; $P$ < 0.001), blood loss was significantly less in the Lap-PE group (median: 23.5 mL) than in the Open-PE group (52 mL; $P$ < 0.001).

The postoperative courses of recovery—specifically, both time to resume oral intake (medians: 3 and 6 postoperative days, respectively; $P$ < 0.001) and time to drain removal (medians: 6 and 7 postoperative days, respectively; $P$ < 0.001)—were significantly shorter in the Lap-PE group than in the Open-PE group. Complete resolution of jaundice was observed in 45 (68.2%) patients who underwent Open-PE and in 42 (79.3%) patients who underwent Lap-PE cases; the difference was not statistically significant (Table 1).

Forty-four patients underwent liver transplantation during the study period. The median duration from the Kasai operation to liver transplantation was 204 d (range: 54–1889 d) overall, with 156 d (range: 54–1889 d) for laparotomy and 249 d (range: 58–1479 d) for laparoscopy. Thirty-two patients did not achieve complete resolution from jaundice with the Kasai operation. Thirty of the 32 patients underwent liver transplantation, except for one patient who refused liver transplantation and one patient who died before the transplantation. The median duration between PE and liver transplantation was 156 d (range: 54–1889 d) after laparotomy and 127 d (range: 58–261 d) after laparoscopy. The remaining 14 patients underwent liver transplantation for the following reasons: Recurrent jaundice in 11 patients; hepatopul-

**Table 1 Comparison of patients' characteristics and outcomes of surgery between Open-PE and laparoscopic portoenterostomy groups**

| | Open-PE | Lap-PE | *P* value |
|---|---|---|---|
| Number of patients | 66 | 53 | |
| Age at surgery | 66.0 (32.0-144.0) | 55.0 (23.0-116.0) | 0.0013 |
| Operation duration | 271.5 (167.0-390.0) | 341.0 (242.0-512.0) | < 0.0001 |
| Blood loss | 52.0 (5.0-363.0) | 23.5 (1.0-160.0) | < 0.0001 |
| Time to resume oral intake | 6.0 (3.0-14.0) | 3.0 (2.0-6.0) | < 0.0001 |
| Time to drain removal | 7.0 (3.0-15.0) | 6.0 (3.0-16.0) | 0.0004 |
| Complete resolution from jaundice case (%) | 45 (68.2%) | 42 (79.2%) | 0.176 |

Values are presented as median (range) or *n* (%). *P* value: Chi-squared or Wilcoxon rank sum test. Open-PE: Open portoenterostomy; Lap-PE: Laparoscopic portoenterostomy.

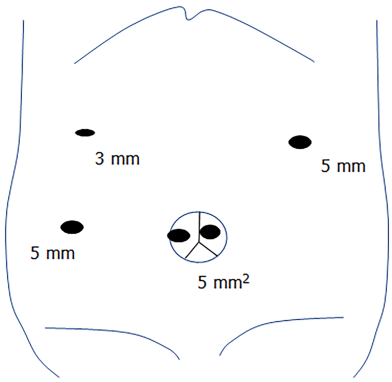



**Figure 1 Ports placed in laparoscopic surgery.**

monary syndrome, 1; repeated cholangitis, 1; and repeated melena, 1.

Native liver survival rates were > 80% for both groups for the first half year postsurgery, followed by a gradual decrease with time; there were no statistically significant differences in the native liver survival rates between the two groups for any durations assessed (log-rank test; $P = 0.1584$) (Figure 2).

During the study period, no intraoperative complications occurred in either open or laparoscopic procedures. Nine (13.6%) patients who underwent laparotomy and six (11.3%) who underwent laparoscopy were readmitted for cholangitis within 3 mo after surgery. Three patients underwent reoperation for bile stasis caused by adhesions of the Roux-en-Y anastomosis to the jejunum after laparotomy. Intestinal obstruction occurred after laparotomy in three patients and after laparoscopy in three patients. One patient underwent reoperation for anastomotic bleeding after laparoscopic surgery.

Operations by pediatric surgeons qualified by the Japanese Endoscopic Surgical Skill Qualification Committee were significantly shorter ($P = 0.0314$) than those performed by nonqualified surgeons, but neither intraoperative bleeding ($P = 0.9704$) nor the complete resolution rate ($P = 0.9681$) differed significantly (Table 2).

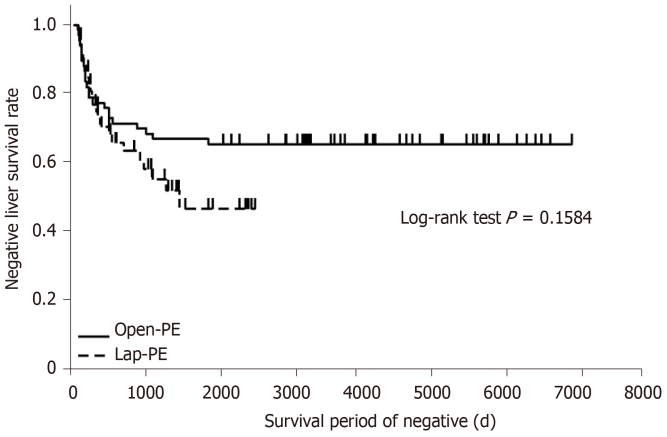
## DISCUSSION

Our study, a comparison of 66 OpenPE cases with 53 LapPE cases, indicated no significant difference in native liver survival rates. In addition, although the LapPE procedure was longer than the Open-PE procedure, less blood loss and more favorable postoperative recovery, including shorter time to resume oral intake and shorter time to drain removal, were observed after LapPE than after Open-PE. The majority of earlier comparisons of the surgical outcomes after Open-PE and Lap-PE have indicated the superiority of OpenPE over LapPE[3,4,6,7,10]. On the basis of these

**Table 2 Comparison of outcome of laparoscopic portoenterostomy between qualified and non-qualified surgeons**

| | Qualified | Non-qualified | *P* value |
|---|---|---|---|
| Number of patients | 34 | 19 | |
| Operation duration (minutes) | 324.5 (242-483) | 390.0 (253-512) | 0.0314 |
| Blood loss (mL) | 25.5 (1-160) | 23.0 (3-122) | 0.9704 |
| Complete release from jaundice (case) | 27 (79.4%) | 15 (78.9%) | 0.9681 |

Values are presented as median (range) or *n* (%). *P* value: Chi-squared or Wilcoxon rank sum test.




| | | Survival rate |
|---|---|---|
| Open-PE | 6 mo | 0.818 |
| | 1 yr | 0.773 |
| | 2 yr | 0.712 |
| Lap-PE | 6 mo | 0.866 |
| | 1 yr | 0.724 |
| | 2 yr | 0.632 |

**Figure 2 Kaplan-Meier curves of time to native liver survival from portoenterostomy, comparing open portoenterostomy and laparoscopic portoenterostomy groups.** Open-PE: Open portoenterostomy; Lap-PE: Laparoscopic portoenterostomy.

results, LapPE is no longer performed in some institutions[10]. Conversely, Ji *et al*[11] reported a higher native liver survival rate after Lap-PE than after Open-PE in their shortterm assessment up to 3 years after the operation. A recent metaanalysis showed no significant difference in native liver survival rates between OpenPE and LapPE, and assessments in 2016 and after indicated a significantly higher rate of complete resolution of jaundice in the Lap-PE group than in the Open-PE group in the early phase[12]. However, Lap-PE outcomes were reported in only a single study, that of Ji *et al*[13], which had a sample size of > 50 and was performed at a single institution; the rarity of BA has limited study sample sizes. Ji *et al*[13] reported no significant difference in short and mediumterm outcomes after LapPE and OpenPE performed by skilled surgeons. In no study thus far have the surgical outcomes of LapPE and OpenPE been compared for a reasonably adequate sample size of > 50 cases.

The jaundicefree native liver survival rates after OpenPE for the treatment of BA have not changed for over 20 years, and 35%–60% of patients have eventually required LTx[1,2]. In a previous study, because Lap-PE produced fewer adhesions, the time until completion of hepatectomy and the duration of hospital stay were significantly shorter for patients who underwent liver transplantation after Lap-PE than for those who underwent Open-PE. Patients who underwent Lap-PE also tended to have less bleeding. These results suggested that Lap-PE before liver transplantation is advantageous[14]. Thus, if native liver survival rates are similar between LapPE and OpenPE, Lap-PE may be the more optimal option with greater advantage if LTx is eventually needed.

In this study, we compared the outcomes of surgeries performed from 2003 to 2020 between the OpenPE and LapPE groups. There was a significant difference in the patient age at the time of surgery between the two groups. This statistically significant

difference can be explained by the difference in the year when the patients received either type of PE. Since 2011, stool color information has been added to the maternal handbooks in Japan for early detection of BA. This addition has enabled the mothers to visit hospitals earlier. We have applied LapPE as a standard procedure for the treatment of BA at our institution since December 2013; thus, LapPE has been performed for all BA cases since then, resulting in significantly younger age at the time of operation in the LapPE group than in the OpenPE group, which could be a potential confounding bias. However, according to a study of 3160 BA patients in Japan, the patient age at surgery is not a relevant confounding factor for surgical outcomes up to the age of 80 d[15]. Based on this published information, we performed an additional due diligence to compare the native liver survival rates between 47 patients in the Lap-PE group and 52 patients in the Open-PE group after excluding 20 patients who received PE at age ≥ 80 d, with similar results ($P$ = 0.1516). The relationship between the timing of surgery and outcome has been studied, and the optimal age is still under debate[16-19]. Some authors have reported that the results are not good at 30–45 d of age. BA is a rare disease; thus, the number of cases is small, and because age is not correlated with surgical outcome, it is difficult to compare outcomes statistically when age is a confounding factor.

According to a report by Yang *et al*[13], surgeons need to maintain much higher technical skills for LapPE surgery than for OpenPE and require extensive experience with ≥ 50 surgeries. At our institution, we have not limited surgeons on the basis of their experience. In the present study, the surgery was significantly shorter when it was performed by qualified surgeons, which suggest that the time varies greatly depending on the skill of the surgeon. However, there was no statistically significant association between surgical operating time and surgical outcomes. Surgical outcomes were also not associated with the number of PE surgeries that a surgeon had previously performed. We have been making an effort to share the information on LapPE technical skills and surgical findings with all surgeons involved in PE surgeries at our institution. Thus, we believe that surgical outcomes were not affected by the experience of surgeons at our institution. This belief can be explained by the fact that younger surgeons can develop their skills through shared insights obtained during operations even though they are not assigned as the primary surgeons; thus, they may develop the knowledge and skills that can lead to surgical outcomes similar to those of more experienced surgeons. Pediatric surgeons need to perform surgeries for various rare pediatric diseases. Establishing surgical procedures enabling consistently favorable outcomes irrespective of the experience of surgeons should be a critical goal; therefore, LapPE is considered to be an adequate surgical procedure superior to conventional surgery.

This study has some limitations. This was a retrospective study, which could possibly introduce selection bias. Since LapPE has been introduced relatively recently, the followup period was limited, precluding the capability to evaluate potential longterm complications. The rate of complications did not differ significantly, but long-term survival rates may differ. Therefore, further studies with a larger study size, longterm follow-up, and thorough evaluations are warranted.

## CONCLUSION

Complete resolution of jaundice was observed in 68.2% of patients who underwent Open-PE and 79.3% of those who underwent Lap-PE, but the difference was not statistically significant. Although the surgical operating time was longer, the lower blood loss and more favorable postsurgical recovery (shorter time to resume oral intake and time to drain removal as well as less postsurgical adhesion) were significant advantages of Lap-PE *vs* OpenPE. There was no significant difference in native liver survival rates or shortterm surgical outcomes between LapPE and OpenPE. Therefore, our study results support the efficacy of Lap-PE as a standard therapy.

## ARTICLE HIGHLIGHTS

### *Research background*

The application of laparoscopic portoenterostomy (LapPE) as a treatment option for BA remains controversial.

### Research motivation

Management after BA surgeries is complicated and requires a centralized procedure for consistency. Thus, it is considered important to perform a largescale assessment at a single facility with a centralized management procedure for adequate comparison in the outcomes between LapPE and OpenPE.

### Research objectives

The aim of this study was to compare the outcomes of Lap-PE with those of laparotomy (Open-PE) at our single institution.

### Research methods

The surgical outcomes of PE were retrospectively analyzed for patients with a non-correctable type of BA from 2003 to 2020.

### Research results

Throughout the assessment period, 119 patients received PE for BA treatment, including 66 Open-PE and 53 Lap-PE cases. Although the operation duration was longer (medians: for Open-PE, 242 min; for Lap-PE, 341 min; $P < 0.001$), blood loss was considerably less (medians: for Open-PE, 52 mL; for Lap-PE, 24 mL; $P < 0.001$) in the Lap-PE group than in the Open-PE group. Native liver survival rates were > 80% for both groups for the first half year post surgery, followed by a gradual decrease with time; there were no statistically significant differences in the native liver survival rates for any durations assessed.

### Research conclusions

Lap-PE could be a standard therapy for BA.

### Research perspectives

The rate of complications did not differ significantly, but long-term survival rates may differ. Therefore, further studies with a larger study size, longterm follow-up, and thorough evaluations are warranted.

## REFERENCES


1 **Ibrahim M**, Miyano T, Ohi R, Saeki M, Shiraki K, Tanaka K, Kamiyama T, Nio M. Japanese Biliary Atresia Registry, 1989 to 1994. *Tohoku J Exp Med* 1997; **181**: 85-95 [PMID: 9149343 DOI: 10.1620/tjem.181.85]

2 **Nio M**, Sasaki H, Wada M, Kazama T, Nishi K, Tanaka H. Impact of age at Kasai operation on short- and long-term outcomes of type III biliary atresia at a single institution. *J Pediatr Surg* 2010; **45**: 2361-2363 [PMID: 21129545 DOI: 10.1016/j.jpedsurg.2010.08.032]

3 **Hussain MH**, Alizai N, Patel B. Outcomes of laparoscopic Kasai portoenterostomy for biliary atresia: A systematic review. *J Pediatr Surg* 2017; **52**: 264-267 [PMID: 28007417 DOI: 10.1016/j.jpedsurg.2016.11.022]

4 **Lishuang M**, Zhen C, Guoliang Q, Zhen Z, Chen W, Long L, Shuli L. Laparoscopic portoenterostomy versus open portoenterostomy for the treatment of biliary atresia: a systematic review and meta-analysis of comparative studies. *Pediatr Surg Int* 2015; **31**: 261-269 [PMID: 25627699 DOI: 10.1007/s00383-015-3662-7]

5 **Chan KW**, Lee KH, Tsui SY, Wong YS, Pang KY, Mou JW, Tam YH. Laparoscopic versus open Kasai portoenterostomy in infant with biliary atresia: a retrospective review on the 5-year native liver survival. *Pediatr Surg Int* 2012; **28**: 1109-1113 [PMID: 22987040 DOI: 10.1007/s00383-012-3172-9]

6 **Ure BM**, Kuebler JF, Schukfeh N, Engelmann C, Dingemann J, Petersen C. Survival with the native liver after laparoscopic versus conventional kasai portoenterostomy in infants with biliary atresia: a prospective trial. *Ann Surg* 2011; **253**: 826-830 [PMID: 21475026 DOI: 10.1097/SLA.0b013e318211d7d8]

7 **Sun X**, Diao M, Wu X, Cheng W, Ye M, Li L. A prospective study comparing laparoscopic and conventional Kasai portoenterostomy in children with biliary atresia. *J Pediatr Surg* 2016; **51**: 374-378 [PMID: 26589186 DOI: 10.1016/j.jpedsurg.2015.10.045]

8 **Lampela H**, Ritvanen A, Kosola S, Koivusalo A, Rintala R, Jalanko H, Pakarinen M. National centralization of biliary atresia care to an assigned multidisciplinary team provides high-quality outcomes. *Scand J Gastroenterol* 2012; **47**: 99-107 [PMID: 22171974 DOI: 10.3109/00365521.2011.627446]

9 **Madadi-Sanjani O**, Fortmann D, Rolle U, Rodeck B, Sturm E, Pfister ED, Kuebler JF, Baumann U, Schmittenbecher P, Petersen C. Centralization of Biliary Atresia: Has Germany Learned Its Lessons? *Eur J Pediatr Surg* 2021 [PMID: 33663007 DOI: 10.1055/s-0041-1723994]

10 **Chan KW**, Lee KH, Wong HY, Tsui SY, Wong YS, Pang KY, Mou JW, Tam YH. From

laparoscopic to open Kasai portoenterostomy: the outcome after reintroduction of open Kasai portoenterostomy in infant with biliary atresia. *Pediatr Surg Int* 2014; **30**: 605-608 [PMID: 24722760 DOI: 10.1007/s00383-014-3499-5]

11 **Ji Y**, Yang K, Zhang X, Jin S, Jiang X, Chen S, Xu Z. The short-term outcome of modified laparoscopic Kasai portoenterostomy for biliary atresia. *Surg Endosc* 2021; **35**: 1429-1434 [PMID: 32253557 DOI: 10.1007/s00464-020-07530-7]

12 **Li Y**, Gan J, Wang C, Xu Z, Zhao Y, Ji Y. Comparison of laparoscopic portoenterostomy and open portoenterostomy for the treatment of biliary atresia. *Surg Endosc* 2019; **33**: 3143-3152 [PMID: 31190228 DOI: 10.1007/s00464-019-06905-9]

13 **Ji Y**, Yang K, Zhang X, Chen S, Xu Z. Learning curve of laparoscopic Kasai portoenterostomy for biliary atresia: report of 100 cases. *BMC Surg* 2018; **18**: 107 [PMID: 30477451 DOI: 10.1186/s12893-018-0443-y]

14 **Shirota C**, Murase N, Tanaka Y, Ogura Y, Nakatochi M, Kamei H, Kurata N, Hinoki A, Tainaka T, Sumida W, Yokota K, Makita S, Oshima K, Uchida H. Laparoscopic Kasai portoenterostomy is advantageous over open Kasai portoenterostomy in subsequent liver transplantation. *Surg Endosc* 2020; **34**: 3375-3381 [PMID: 31485932 DOI: 10.1007/s00464-019-07108-y]

15 **Nio M**. Japanese Biliary Atresia Registry. *Pediatr Surg Int* 2017; **33**: 1319-1325 [PMID: 29039049 DOI: 10.1007/s00383-017-4160-x]

16 **Okubo R**, Nio M, Sasaki H; Japanese Biliary Atresia Society. Impacts of Early Kasai Portoenterostomy on Short-Term and Long-Term Outcomes of Biliary Atresia. *Hepatol Commun* 2021; **5**: 234-243 [PMID: 33553971 DOI: 10.1002/hep4.1615]

17 **Fawaz R**, Baumann U, Ekong U, Fischler B, Hadzic N, Mack CL, McLin VA, Molleston JP, Neimark E, Ng VL, Karpen SJ. Guideline for the Evaluation of Cholestatic Jaundice in Infants: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2017; **64**: 154-168 [PMID: 27429428 DOI: 10.1097/MPG.0000000000001334]

18 **Tessier MEM**, Shneider BL. 60 Days in Biliary Atresia: A Historical Dogma Challenged. *Clin Liver Dis (Hoboken)* 2020; **15**: S3-S7 [PMID: 32140208 DOI: 10.1002/cld.843]

19 **Sasaki H**, Tanaka H, Wada M, Kazama T, Nakamura M, Kudo H, Okubo R, Sakurai T, Nio M. Analysis of the prognostic factors of long-term native liver survival in survivors of biliary atresia. *Pediatr Surg Int* 2016; **32**: 839-843 [PMID: 27464487 DOI: 10.1007/s00383-016-3934-x]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 January 27; 14(1): 64-77

DOI: 10.4240/wjgs.v14.i1.64

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

# Routine laboratory parameters in patients with necrotizing pancreatitis by the time of operative pancreatic debridement: Food for thought

Yaroslav M Susak, Kristina Opalchuk, Olexandr Tkachenko, Mariia Rudyk, Larysa Skivka

**ORCID number:** Yaroslav M Susak 0000-0002-5102-485X; Kristina Opalchuk 0000-0002-9632-4709; Olexandr Tkachenko 0000-0001-6211-7675; Mariia Rudyk 0000-0003-1252-885X; Larysa Skivka 0000-0002-2171-1085.

**Author contributions:** Susak YM was chief surgeon and performed the surgeries on patients included in this study; Opalchuk K was a surgeon and assisted with surgeries on patients who are included in this study and was involved with data collection; Tkachenko O was a supervisor and participated in design of the study; Rudyk M assisted with statistical analysis of the data; Skivka L drafted the manuscript, performed statistical analysis, and participated in design of the study; All authors have read and approved the final manuscript.

**Institutional review board statement:** The project has been reviewed and approved by the Committee on Human Rights Related to Research Involving Human Subjects of Kyiv City Clinical Emergency Hospital (Kyiv, Ukraine), based on the Declaration of Helsinki.

**Informed consent statement:** All

**Yaroslav M Susak,** Department of Surgery with the Course of Emergency and Vascular Surgery, O.O. Bogomolet's National Medical University, Kyiv 01601, Ukraine

**Kristina Opalchuk,** Department of Surgery, Anesthesiology and Intensive Care Postgraduate Education, O.O. Bogomolet's National Medical University, Kyiv 01601, Ukraine

**Olexandr Tkachenko,** Department of Surgery N2, Kyiv City Clinical Emergency Hospital, Kyiv City Clinical Emergency Hospital, Kyiv 02000, Ukraine

**Mariia Rudyk, Larysa Skivka,** Department of Microbiology and Immunology, Educational and Scientific Center "Institute of Biology and Medicine", Taras Shevchenko National University of Kyiv, Kyiv 01033, Ukraine

**Corresponding author:** Mariia Rudyk, PhD, Associate Professor, Department of Microbiology and Immunology, Educational and Scientific Center "Institute of Biology and Medicine", Taras Shevchenko National University of Kyiv, 2 Hlushkova Avenue, Kyiv 03127, Ukraine. rosiente@gmail.com

## Abstract

***BACKGROUND***

Timing of invasive intervention such as operative pancreatic debridement (OPD) in patients with acute necrotizing pancreatitis (ANP) is linked to the degree of encapsulation in necrotic collections and controlled inflammation. Additional markers of these processes might assist decision-making on the timing of surgical intervention. In our opinion, it is logical to search for such markers among routine laboratory parameters traditionally used in ANP patients, considering simplicity and cost-efficacy of routine laboratory methodologies.

***AIM***

To evaluate laboratory variables in ANP patients in the preoperative period for the purpose of their use in the timing of surgery.

***METHODS***

A retrospective analysis of routine laboratory parameters in 53 ANP patients undergoing OPD between 2017 and 2020 was performed. Dynamic changes of routine hematological and biochemical indices were examined in the preoperative

subjects gave their written informed consent prior to study inclusion.

**Conflict-of-interest statement:** The authors declare that they have no conflicts of interest.

**Data sharing statement:** There is no additional data available.

**STROBE statement:** The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

**Country/Territory of origin:** Ukraine

**Specialty type:** Surgery

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0



**Received:** May 18, 2021
**Peer-review started:** May 18, 2021
**First decision:** June 15, 2021
**Revised:** June 29, 2021
**Accepted:** December 22, 2021
**Article in press:** December 22, 2021
**Published online:** January 27, 2022

**P-Reviewer:** Inal V, Mannan F

period. Patients were divided into survivors and non-survivors. Survivors were divided into subgroups with short and long post-surgery length of stay (LOS) in hospital. Correlation analysis was used to evaluate association of laboratory variables with LOS. Logistic regression was used to assess risk factors for patient mortality.

*RESULTS*

Seven patients (15%) with severe acute pancreatitis (SAP) and 46 patients (85%) with moderately SAP (MSAP) were included in the study. Median age of participants was 43.2 years; 33 (62.3%) were male. Pancreatitis etiology included biliary (15%), alcohol (80%), and idiopathic/other (5%). Median time from diagnosis to OPD was ≥ 4 wk. Median postoperative LOS was at the average of 53 d. Mortality was 19%. Progressive increase of platelet count in preoperative period was associated with shortened LOS. Increased aspartate aminotransferase and direct bilirubin (DB) levels the day before the OPD along with weak progressive decrease of DB in preoperative period were reliable predictors for ANP patient mortality.

*CONCLUSION*

Multifactorial analysis of dynamic changes of routine laboratory variables can be useful for a person-tailored timing of surgical intervention in ANP patients.

**Key Words:** Acute necrotizing pancreatitis; Operative pancreatic debridement timing; Dynamic changes of laboratory variables; Preoperative period; Necrotic tissue encapsulation; Hospital length of stay



**Core Tip:** This is a retrospective study to evaluate laboratory variables in patients with acute necrotizing pancreatitis in the preoperative period for their use in the timing of operative pancreatic debridement (OPD). We demonstrated that progressive increase in platelet counts correlate with shortened length of hospital stay. It can indicate granulation tissue formation, and can be considered as an additional marker for OPD timing. Persistent hepatic malfunction, which is indicated by a weak progressive decrease of the direct bilirubin and increased aspartate aminotransferase level can signify a high risk of post-operative mortality. Multifactorial analysis of dynamic changes of laboratory variables can be useful for person-tailored timing of OPD.

**Citation:** Susak YM, Opalchuk K, Tkachenko O, Rudyk M, Skivka L. Routine laboratory parameters in patients with necrotizing pancreatitis by the time of operative pancreatic debridement: Food for thought. *World J Gastrointest Surg* 2022; 14(1): 64-77
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i1/64.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i1.64

## INTRODUCTION

Acute pancreatitis (AP) is the most prevalent and fairly unpredictable and potentially lethal gastrointestinal disease with an annual incidence ranging from 4.0 to 45 per 100000 persons[1,2]. About 20% of AP patients develop severe disease, and around 20% of them develop necrosis of the pancreas and peripancreatic tissues resulting in acute necrotizing pancreatitis (ANP). ANP development is associated with prolonged illness, organ failure and a high mortality rate, which can reach 30% in patients with infected pancreatic necrosis[3,4]. ANP patients usually need intensive care and frequent numerous procedures in the course of the treatment. Operative pancreatic debridement (OPD) is considered a gold standard treatment for ANP patients requiring surgical intervention. For a long time, this procedure was accompanied by significant morbidity and high mortality rates. Nowadays, refined operative techniques in combination with surgeon experience have allowed us to decrease perioperative mortality rates. In the past 10 years, minimally invasive techniques have

**S-Editor:** Chang KL
**L-Editor:** Filipodia
**P-Editor:** Chang KL

been applied to the treatment of NP patients. Nevertheless, many ANP patients require a combination of minimally invasive techniques and OPD in order to achieve complete debridement. Moreover, OPD remains an important treatment approach for ANP patients who are refractory to minimally invasive treatment[5-7]. Considering the complicated ANP pathophysiology and highly variable clinical course, a person-tailored approach to intervention methods including OPD makes sense according to the specific conditions of patients. One of the key points in these patient-tailored approaches is the timing of surgical intervention, in order to gain the most beneficial result[8,9].

Timing on invasive intervention in ANP patients is often linked to the degree of encapsulation in necrotic collections. The degree of necrotic collections encapsulation is important because walling-off allows the immune system demarcation between viable and necrotic tissues, thereby facilitating effective debridement[10-12]. It is commonly admitted that the timing of encapsulation takes about 4 wk (after symptom onset) and this timescale is included in the Revised Atlanta Classification[13]. However, the pathophysiology and time course of necrotic collection walling-off are not fully understood and remain a topic of debate. According to clinical observations of van Grinsven *et al*[14], and opposed to common opinion, largely or fully encapsulated necrotic collections can be observed in ANP patients at every phase of the disease. Assessment of the degree of encapsulation of necrotic collections is influenced by imaging and clinical features. Additional markers of this process might assist decision-making on the timing of surgical intervention. The search for these markers should be based on current knowledge of the biology of necrotic tissue encapsulation. In our opinion, it is logical to search for such markers among routine laboratory parameters traditionally used in ANP patients, considering simplicity and cost-efficacy of routine laboratory methodologies. This study was aimed to evaluate distinctive features of routine biochemical and hematological parameters in patients with ANP by the time of OPD for the purpose of their use as additional markers for the timing of surgical intervention.

## MATERIALS AND METHODS

### *Patients and treatments*

We conducted a retrospective analysis of a prospectively collected O.O. Bogomolets National Medical University (Kyiv, Ukraine) (Department of Surgery with a course of emergency and vascular surgery) database of 53 ANP patients who underwent OPD between 2017 and 2020 in Kyiv City Clinical Emergency Hospital, Ukraine. Approval was obtained from the Ethics Committee of Kyiv City Clinical Emergency Hospital (Protocol #25-15-60, from 20 November 2017), and consent was obtained from all subjects before the commencement of the study.

AP was diagnosed in all patients with clinical signs of acute abdominal pain and a three or more times increased level of serum amylase. AP severity was established according to the revised Atlanta classification and Marshall scoring system[13]. Pancreatic and peripancreatic necrosis was detected in the patients using ultrasound imaging and contrast-enhanced computed tomography.

All patients were treated according to the local treatment protocol that was clinically approved for AP patients from year 2014. After admission, patients were managed on the intensive care unit (ICU) using the "four catheters" rule[15]: Catheter for epidural anesthesia, installment of the feeding intestinal probe further than the Treitz ligament level, the central venous catheterization and the programmed laparocentesis. Median length of ICU stay was 3.2 d.

All patients were initially treated with a minimally invasive technique: laparocentesis, percutaneous drainage of the retroperitoneal space, pleural and abdominal cavities. Primarily, percutaneous drainage was used in all patients under ultrasound control of infected necrotic areas. Abdominal drainage was conducted on each patient two or more times.

Indications for necrosectomy were persisting organ failure and documented infected necrosis. Organ failure was defined as follows; Pulmonary insufficiency: $PaO_2$ ≤ 60 mmHg in spite of receiving 4 L of oxygen per minute *via* a nasal tube or need for mechanical ventilation. Cardiocirculatory insufficiency: Systolic blood pressure ≤ 90 mmHg or necessity for catecholamine support. Renal failure: a serum creatinine level ≥150 μmol/L and/or necessity for hemofiltration/hemodialysis. Metabolic disorders: A serum calcium level ≤ 1.87 mmol/L or a platelet (PLT) count ≤ 100 × $10^9$/L. Multiple organ failure (MOF) was established as failure of 2 or more organ systems. Infected

pancreatic/peripancreatic necrosis was revealed according to the imaging (the presence of extraluminal gas in the pancreatic and/or peripancreatic tissues) and/or bacteriological (positive bacterial culture of aspiration and drainage content of pancreatic and/or peripancreatic tissues) findings. During laparotomy, blunt debridement of necrotic tissue and tissues of the retroperitoneal space was performed. Drainage PVC tubes were inserted through separate incisions (3-4 cm) on the lateral areas of the abdomen with their tips placed to the necrotic cavities under the colon. The abdomen was closed afterwards, and local continuous lavage was started.

### Endpoints and laboratory variables

Outcome variables were: (1) Total hospital length of stay (LOS); (2) Post-OPD LOS in survivors; (3) LOS between OPD and death ($LOS_{OPD-D}$) in non-survivors; and (4) Hospital mortality.

For each enrolled patient, routine laboratory variables were measured for time period from the time of admission until surgical intervention (OPD). EDTA-anticoagulated venous blood samples for all laboratory tests were drawn between 7 am and 8 am in the morning, and laboratory indices were calculated within 1.5-2.5 h.

Routine biochemical parameters [serum level of total bilirubin (TB) direct bilirubin (DB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), α-amylase (AML), as well as gamma-glutamyl transpeptidase (GGT), glucose, creatinine, blood urea nitrogen] were measured using automatic biochemical analyzer Olympus AU-800 (Olympus, Tokyo, Japan). Routine hematological parameters [hemoglobin (Hgb), hematocrit (HCT), total red blood cell count (RBC), total white blood cell count (WBC), PLT] were determined using automatic hematological analyzer Mindray BC-2800 (Mindray, Shenzhen, China).

The dynamic changes of all laboratory variables were calculated as follows: A - Day 1 (on admission); B - Day 3-7; Δ (B-A); C - Day 12-16; Δ (C-B); D - Day 21-24; Δ (D-C); E - Day before the OPD; Δ (E-D); Δ (E-C); Δ (E-D); Δ (E-A); Δ (A-E); A to E ratio (A/E).

Hematological and biochemical reference values in our hospital are as follows: Hgb, 130-160 g/L (male) and 120-140 g/L (female); HCT, 40%-48% (male) and 36%-46% (female); RBC, 4.5-5.9 × $10^{12}$/L (male) and 4.1-5.1 × $10^{12}$/L (female); WBC, 3.9-10 × $10^{9}$/L; PLT, 180-320 × $10^{9}$/L; TB, 2-21 μmol/L; DB, 0-5 μmol/L; ALT, 0.1-0.68 μkat/L; AST, 0.1-0.45 μkat/L; AML, 12-32 U/L; GGT, 9–48 U/L; glucose, 3.3-6.5 mmol/L; creatinine 71-106 μmol/L; blood urea nitrogen, 2.5-8.3 mmol/L. Permissible error of the assay was ≤ 5% of the total coefficient of variation according to the manufacturer statement.

### Statistical analysis

Normally distributed variables were compared using Student's *t*-test, non-normally distributed variables using Mann-Whitney *U*-test. Data are presented as means ± SD.

Spearman correlation test was used to determine the statistical relationships between the preoperative values of measured laboratory variables and different LOS indices. A 2-tailed $P \leq 0.05$ was considered statistically significant in all analyses. The prognostic validities of measured laboratory variables values was analyzed using receiver operating characteristic (ROC) analysis.

To identify the variables associated with mortality, univariate and multivariate logistic regression analysis was conducted. Odds ratios (OR) are represented with their respective 95% confidence intervals (CI). The Hosmer-Lemeshow test was applied to verification the goodness-of-fit of the logistic regression. All tests were assessed by odds ratio OR and their 95%CI. Statistical analyses were performed by SPSS software (version 19.0; SPSS Inc., Chicago, IL, USA).

The statistical methods of this study were reviewed and approved by Vitaliy Gurianov, associate professor of Healthcare Management Department, Bogomolets National Medical University, Kyiv, Ukraine.

## RESULTS

### General characteristics of patients

General characteristics of study participants are summarized in Table 1. Fifty-three ANP patients were enrolled during this study: 7 patients (15%) with severe AP (SAP) and 46 patients (85%) with moderately severe AP (MSAP). Thirty-three (62.3 %) were male and 20 (37.7%) were female. Median age of the patients was 43.2 years. Pancreatitis etiology included: Alcohol, biliary, posttraumatic, and idiopathic. Single and MOF included cardiocirculatory insufficiency, renal failure, and pulmonary insuffi-

**Table 1 General characteristics of study participants and preoperative manipulations**

| Characteristic | Value |
|---|---|
| **Sex, age, severity scores** | |
| Male, *n* (%) | 33 (62.3) |
| Female, *n* (%) | 20 (37.7) |
| Age, yr [range] | 43 [23-68] |
| APACHE II score | 8 |
| Marshall score | 4 |
| Mortality, % | 19 |
| **Etiology**, *n* (%) | |
| Alcohol | 42 (79) |
| Biliary | 4 (7) |
| Posttraumatic | 4 (7) |
| Idiopathic | 3 (5) |
| **Comorbidity**, *n* (%) | |
| Multiple organ failure | 5 (9) |
| Cardiovascular | 11 (20) |
| Renal | 4 (7) |
| Respiratory | 10 (18) |
| Pneumonia | 12 (22) |
| Necrosis infection | 53 (100) |
| Extrapancreatic infection | 53 (100) |
| Sepsis | 8 (15) |
| **Preoperative interventions** | |
| Laparocentesis | 53 |
| Thoracocentesis | 31 |
| Percutaneous drain | 147 |
| Endoscopic | 33 |

ciency. Other complications included an omental abscess (*n* = 42), erosive bleeding (*n* = 7), a pancreatic fistula (*n* = 4), an intestinal fistula (*n* = 4), and a post-necrotic cyst (*n* = 7). The mean total LOS was 85 d. Median timing of the OPD was 30 d [range, 20-86 d] from the onset of the disease. Median post-surgical LOS was at the average of 53 d. Mortality rate was 19%.

According to hospital mortality, 53 patients were divided into the survivor's group ( *n* = 43), and non-survivor's group (*n* = 10). There were no significant differences with respect to age and gender between the two groups. It is necessary to note, that non-survivors were characterized by the increased sepsis rate [6 (60%) *vs* 4 (9%) in survivors] and MOF rate [3 (33.3%) *vs* 2 (4.7%) in survivor's].

According to post-OPD LOS 43 survivors were divided into two subgroups: Post-OPD LOS ≤ 50 d (*n* = 12), and post-OPD LOS ≥ 50 d (*n* = 31). There were no significant differences with respect to age and severity scores between the two subgroups. It is necessary to point, that females prevailed in subgroup with post-OPD LOS ≤ 50 d.

### *Comparison of laboratory variables between survivors with different post-surgical LOS*

The dynamic changes of laboratory variables in the survivors with different post-OPD LOS are summarized in Table 2. Baseline values (Day 1) of many of laboratory variables were not significantly different between survivors with different post-OPD LOS. Compared with patients with post-OPD LOS ≤ 50, patients with post-OPD LOS ≥

**Table 2 The dynamic changes of laboratory variables in the survivors with different Length of stay in hospital**

| Laboratory variable | Post-OPD LOS ≤ 50 d, *n* = 12 | post-OPD LOS ≥ 50 d, *n* = 31 |
|---|---|---|
| Hgb (g/L) | | |
| Day 1 (A) | 111.4 ± 12.1 | 176.3 ± 31.2[a] |
| Day 3-9 (B) | 93.6 ± 8.9 | 116.4 ± 26.6 |
| Δ (B-A) | -35.5 ± 12.9 | -46.4 ± 7.5 |
| Day before OPD (E) | 89.4 ± 7.8 | 83.6 ± 7.2 |
| Δ (E-A) | -22.0 ± 11.4 | -79.2 ± 12.0[a] |
| WBC (× $10^9$/L) | | |
| Day 1 (A) | 9.6 ± 3.9 | 11.5 ± 1.7 |
| Day 3-9 (B) | 16.5 ± 9.8 | 13.1 ± 4.6 |
| Δ (B-A) | 3.6 ± 6.3 | -0.6 ± 6.6 |
| Day before OPD (E) | 10.1 ± 2.5 | 13.8 ± 4.7 |
| Δ (E-A) | 0.6 ± 2.4 | 2.4 ± 4.3 |
| PLT (× $10^9$/L) | | |
| Day 1 (A) | 236.5 ± 57.8 | 223.5 ± 64.2 |
| Day 3-9 (B) | 453.5 ± 58.3 | 224.0 ± 44.5[a] |
| Δ (B-A) | 232.8 ± 50.9 | -7.5 ± 57.8[a] |
| Day before OPD (E) | 648.0 ± 74.7 | 360.2 ± 104.8[a] |
| Δ (E-A) | 430.5 ± 76.4 | 181.0 ± 48.7[a] |
| AST (μkat/L) | | |
| Day 1 (A) | 0.56 ± 0.31 | 0.99 ± 0.35 |
| Day 3-9 (B) | 0.44 ± 0.06 | 0.72 ± 0.13[a] |
| Δ (B-A) | -0.18 ± 0.27 | -0.84 ± 0.41 |
| Day before OPD (E) | 0.36 ± 0.11 | 0.42 ± 0.19 |
| Δ (E-A) | -0.19 ± 0.28 | -1.0 ± 1.0 |
| ALT (μkat/L) | | |
| Day 1 (A) | 0.71 ± 0.52 | 1.79 ± 1.31 |
| Day 3-9 (B) | 0.46 ± 0.18 | 1.02 ±0.52[a] |
| Δ (B-A) | -0.34 ± 0.43 | -1.32 ± 0.84 |
| Day before OPD (E) | 0.51 ± 0.22 | 0.51 ± 0.16 |
| Δ (E-A) | -0.21 ± 0.39 | -1.28 ± 1.24 |
| DB (μmol/L) | | |
| Day 1 (A) | 15.73 ± 19.79 | 14.95 ± 11.53 |
| Day 3-9 (B) | 3.21 ± 0.87 | 6.78 ± 4.37 |
| Δ (B-A) | -18.5 ± 22.19 | -10.02 ± 10.81 |
| Day before OPD (E) | 1.72 ± 1.01 | 2.55 ± 0.74 |
| Δ (E-A) | -14.02 ± 19.79 | -12.4 ± 11.53 |
| AML (U/L) | | |
| Day 1 (A) | 65.8 ± 48.07 | 56.3 ± 24.47 |
| Day 3-9 (B) | 26.62 ± 8.11 | 38.94 ± 27.03 |
| Δ (B-A) | -32.34 ± 43.11 | -17.36 ± 16.55 |
| Day before OPD (E) | 21.18 ± 4.85 | 27.46 ± 16.61 |

| | | |
|---|---|---|
| Δ (E-A) | -44.62 ± 47.55 | -28.84 ± 41.51 |

[a]*P* ≤ 0.05 as compared to patients with post-OPD LOS ≤ 50 d. A: Day 1 (on admission); B: Day 3-7; C: Day 12-16; D: Day 21-24; E: Day before the operative pancreatic debridement. ALT: Alanine aminotransferase; AML: α-amylase; AST: Aspartate aminotransferase; DB: Direct bilirubin; Hgb: Hemoglobin; LOS: Length of stay in hospital; OPD: Operative pancreatic debridement; PLT: Total platelets count; WBC: Total white blood cell count.

50 had moderately higher Hgb (176.3 ± 31.2 *vs* 111.4 ± 12.1, *P* ≤ 0.05). Patients with post-OPD LOS ≥ 50 also tended to exhibit higher baseline ALT and AST (1.79 ± 1.31 *vs* 0.71 ± 0.52 and 0.99 ± 0.35 *vs* 0.56 ± 0.31 respectively). However, these values were characterized by significant individual variability. Significant differences were observed in PLT count in patients with different post-OPD LOS. PLT count increased progressively in the preoperative period in patients from both subgroups. However, in participants with post-OPD LOS ≥ 50, it did not go beyond the reference range, while in patients with post-OPD LOS ≤ 50 it exceeded the reference values by at least two times the day before OPD. Slightly increased WBC count was observed in all survivors until the OPD with significant individual variability, which indicates persistent inflammation. Initially increased DB levels decreased progressively in preoperative period without statistically significant differences between subgroups. AML levels remained higher than reference values the day before OPD in all survivors. There were no significant differences with respect to other measured laboratory variables (data not shown).

### *Correlations between dynamic changes of laboratory variables and total and post-OPD LOS*

There was a significant correlation between total LOS and Hgb level Δ(A-E) (Figure 1A), indicating that a significant decrease of Hgb concentration is associated with prolonged total and post-surgical LOS. A significant inverse correlation was observed between total LOS and WBC count Δ(A-E) (Figure 1B), suggesting that a progressive decrease of WBC count during the pre-operative period till reference values is associated with shortened post-OPD LOS. A significant inverse correlation was also registered between total LOS and PLT count Δ(E-A) (Figure 1C), indicating that a substantial increase of PLT count before the surgery accompanies shortened post-surgery recovery. Moderate correlation was revealed between total LOS and AML Δ(A-E) (Figure 1D). Considering that AML values were near reference range in all survivors the day before surgery, this correlation suggests that a highly increased AML value on admission is associated with the disease severity, and as a result with prolonged pre- and post-surgery LOS. High values of ALT Δ(A-E) significantly correlated with both total LOS and post-OPD LOS (Figure 1E and F). Considering that ALT values did not exceed the reference range in all survivors the day before the OPD, these correlations indicate that increased baseline ALT value (as a marker of ongoing liver disease process[16]) is associated with disease severity and prolonged recovery.

### *Univariate logistic regression analysis*

We further performed univariate logistic regression analysis to find out potential risk factors associated with hospital mortality, as shown in Table 3. Four laboratory variables were associated with mortality, including AST, AML and DB serum levels the day before the surgery (E values), as well as E to A ratio for DB. Other measured laboratory parameters were unrelated to outcomes.

### *Predictive value of laboratory variables for hospital mortality in ANP patients*

To investigate the predictive values of laboratory variables, ROC analysis was conducted (Table 4, Figure 2). The AUC of AML (E) (AUC: 0.729, 95%CI: 0.550-0.866, *P* < 0.032) was greater than the other biomarkers. The optimal cutoff value of AML (E) was ≤ 17.2 U/L, with 66.7% sensitivity, 84.0% specificity, 60.0% PPV and 87.5% NPV. In addition, a DB (E) value of > 4.2 μmol/L allowed discrimination between ANP survivors and non-survivors, with a sensitivity of 44.4% and a specificity of 100.0% (AUC: 0.782, 95%CI: 0.608-0.905, PPV: 100.0%, NPV: 83.3%, *P* < 0.001). The AUC of ΔPCT7 was 0.834 (95%CI: 0.759-0.906, *P* < 0.001), with 80.5% sensitivity, 81.6% specificity, 76.6% PPV and 88.2% NPV at the best threshold value of < 5.3 ng/mL. The predictive value of AST and DB (A/E) were less accurate with the sensitivity less than 50%. None of the other variables was useful to predict mortality in ANP patients (data not shown).

**Table 3 Logistic regression analysis of laboratory variables to differentiate survivors and non-survivors**

| Variable | OR | 95%CI | *P* value |
|---|---|---|---|
| AST (E), μkat/L | 1.0377 | 1.6514-1.3392 | 0.3612 |
| α-amylase (E), U/L | 0.8771 | 0.7657-1.0046 | 0.7543 |
| DB (E), μmol/L | 2.2201 | 1.0475-4.7051 | 0.6374 |
| DB (A/E) | 0.6941 | 0.4613-1.0445 | 0.5221 |

A: Day 1 (on admission); E: Day before the operative pancreatic debridement. AST: Aspartate aminotransferase; CI: Confidential intervals; DB: Direct bilirubin; OR: Odds ratio.

**Table 4 Predictive value of laboratory variables for hospital mortality in acute necrotizing pancreatitis patients**

| Variables | Cutoff | Sensitivity | Specificity | AUC | 95%CI | PPV | NPV | *P* value |
|---|---|---|---|---|---|---|---|---|
| AST (E), μkat/L | > 0.53 | 33.3% | 92.0% | 0.727 | 0.547-0.865 | 60.0% | 79.3% | 0.016 |
| α-amylase (E), U/L | ≤ 17.2 | 66.7% | 84.0% | 0.729 | 0.550-0.866 | 60.0% | 87.5% | < 0.032 |
| DB (E), μmol/L | > 4.2 | 44.4% | 100.0% | 0.782 | 0.608-0.905 | 100.0% | 83.3% | < 0.001 |
| DB(A/E) | ≤ 1 | 22.2% | 95.8% | 0.764 | 0.584-0.894 | 66.7% | 76.7% | 0.0015 |

A: Day 1 (on admission); E: Day before the operative pancreatic debridement. ANP: Acute necrotizing pancreatitis; AST: Aspartate aminotransferase; AUC: area under the curve; CI: Confidential intervals; DB: Direct bilirubin; NPV: negative predictive values; PPV: positive predictive values.

Next, we attempted to evaluate whether a combination of different laboratory variables could promote the predictive accuracy further (Table 5). Notably, the combination form of (AST(E) > 0.53 μkat/L + AML (E) ≤ 17.2 U/L + DB(E) > 4.2 μmol/L + DB (A/E) < 1) resulted in the greatest AUC (AUC: 0.935, $P < 0.0005$) than other variables, either alone or in combination.

## DISCUSSION

In this study, we monitored routine laboratory variables for the purpose of their use as additional markers to assist decision-making on the timing of surgical intervention in ANP patients. Hospital mortality, as well as total and post-OPD LOS were chosen as criteria, associated with optimal OPD timing. Routine laboratory variables and their dynamic changes were examined in the preoperative period in order to compare key hematological and biochemical indices and their changes in survivors and non-survivors, as well as in ANP patients with short and long post-surgical LOS at the recommended time point of surgical intervention (about 4 wk after symptom onset). Surprisingly, the AML value within the reference range the day before the OPD was quite a reliable predictor of hospital mortality in ANP patients. One can suggest, that discrepancy between clinical picture and normal value of this laboratory index can be considered as an alarming marker for disease outcome and surgery timing. Increased values of AST and DB the day before the OPD as well as the absence of a substantial decrease of DB level in the preoperative period (A/D ratio < 1) were also reliable predictors of hospital mortality. Taken in combination, these biomarkers provided greater predictive accuracy than individual markers. Hyperbilirubinemia including increased level of DB is considered as an independent risk factor for mortality in critically ill patients[17]. Liver malfunction represents a sometimes serious and fatal complication during the ANP progression, since the liver can mediate extra pancreatic organ impairment by releasing toxic substances[18]. Hepatic injury caused by inflammatory mediators generated in ANP patients cannot only aggravate the disease course, but also develop into severe hepatic failure and can cause patient death[19]. Increased AST the day before the OPD can indicate persistent severe hepatic dysfunction. Hyperbilirubinemia can be considered as a consequence of severe hepatic dysfunction, and additionally can be a risk factor of the impairment of the oxygen-dependent bactericidal activity of innate immunity cells and as a result the sepsis development[20]. The alteration trend of variables is an important component of

**Table 5 Predictive value of combined variables for hospital mortality in acute necrotizing pancreatitis patients**

| Multivariable model | AUC | 95%CI | *P* value |
|---|---|---|---|
| AST (E) + AML (E) | 0.791 | 0.618-0.911 | 0.016 |
| AST (E) + DB (E) | 0.784 | 0.610-0.906 | 0.0011 |
| AML (E) + DB (E) | 0.884 | 0.777-0.908 | 0.0002 |
| AST (E) + AML (E) + DB (E) | 0.884 | 0.728-0.968 | 0.003 |
| DB (E) + DB (A/E) | 0.87 | 0.708-0.961 | 0.0006 |
| AST (E) + DB (A/E) | 0.87 | 0.708-0.961 | 0.0016 |
| AML (E) + DB (A/E) | 0.84 | 0.674-0.945 | 0.0026 |
| AST (E) + AML (E) + DB (A/E) | 0.88 | 0.719-0.966 | 0.0023 |
| AST (E) + AML (E) + DB (E) + DB (A/E) | 0.935 | 0.792-0.991 | 0.0005 |

A: Day 1 (on admission); E: Day before the operative pancreatic debridement. ANP: Acute necrotizing pancreatitis; AST: Aspartate aminotransferase; CI: Confidential intervals; DB: Direct bilirubin.

multivariable predictive model. In the current study, we revealed that DB (A/E) had good prognostic capacity among other laboratory variables. The course of ANP is a rapidly-changing process which is too complicated to be estimated by a single measurement. The trend of laboratory indices alteration can reflect disease development more accurately, in particular when absolute baseline values are high. In this study, we emphasize the importance of combined analysis of absolute values and dynamic alterations of laboratory variables. Thus, according to our multivariable prognostic model, persistent hepatic failure along with a normal AML level should be taken into account in OPD timing as a predictive marker of a high mortality risk.

The estimated time of readiness of the ANP patient for surgery is the time period of the summation of the two most important events. First is the systemic inflammatory response syndrome (SIRS) down-regulation, since it is SIRS that is the most important cause of high mortality that accompanies surgical intervention in the early period after symptoms onset. The second is the necrotic collection encapsulation, since this phenomenon technically facilitates effective debridement. Therefore, the whole set of routine laboratory parameters should be viewed from the angle of these two events.

ANP course progresses in two phases. First phase is characterized by SIRS development with single or MOF. This phase continues at the average 10-14 d, and then consistently gives way to compensatory systemic anti-inflammatory syndrome. *Inter alia*, SIRS is usually characterized by persistent leukocytosis[21]. SIRS in ANP is commonly associated with the liver injury and, as a result with the rise of such routine laboratory indices as serum Alkaline Phosphatase, AST, ALT, TB, DB, AML and lipase levels. Therefore, routine laboratory variables such as WBC count and biochemical markers of liver injury can be indicative for the evaluation of SIRS and of Multiple Organ Dysfunction Syndrome in ANP patients.

Necrotic collection walling-off is, in effect, the development of a granulation tissue (GT) capsule around the necrotic area[22,23]. Primary function of the GT capsule is to prevent the systemic spread of inflammatory mediators (*e.g.*, cytokines and eicosanoids) and signals danger for the immune system which originated from necrotic cells. Thus, this temporary barrier is aimed at compartmentalization of the inflammatory response[24]. Another important function of the GT capsule is to protect the encapsulated area from the infection. The basis of GT is usually composed of a fibrous capsule, and its core cell component is commonly represented by fibroblasts. Fibroblasts deposit fibronectin in a soft extracellular matrix. This matrix separates necrotic collection from the surrounding tissues and can then be used for the recruitment of other cells into GT[25]. Therefore, one can suppose, that fibroblast migration into the necrotic area is a crucial step of the encapsulation. Fibroblast recruitment into the necrotic area is orchestrated by the coordinated effect of numerous cytokines and growth factors. Among others, fibroblast growth factor and platelet-derived growth factor (PDGF) are the major cytokines that initiate and afterward support fibroblast proliferation and chemotactic activity resulting in the necrotic area encapsulation[26-28]. Clinical observations of Stojek *et al*[29] indirectly confirmed this assumption. According to findings of this scientific group, serum levels of PDGF-BB is significantly increased in patients with chronic pancreatitis, which is

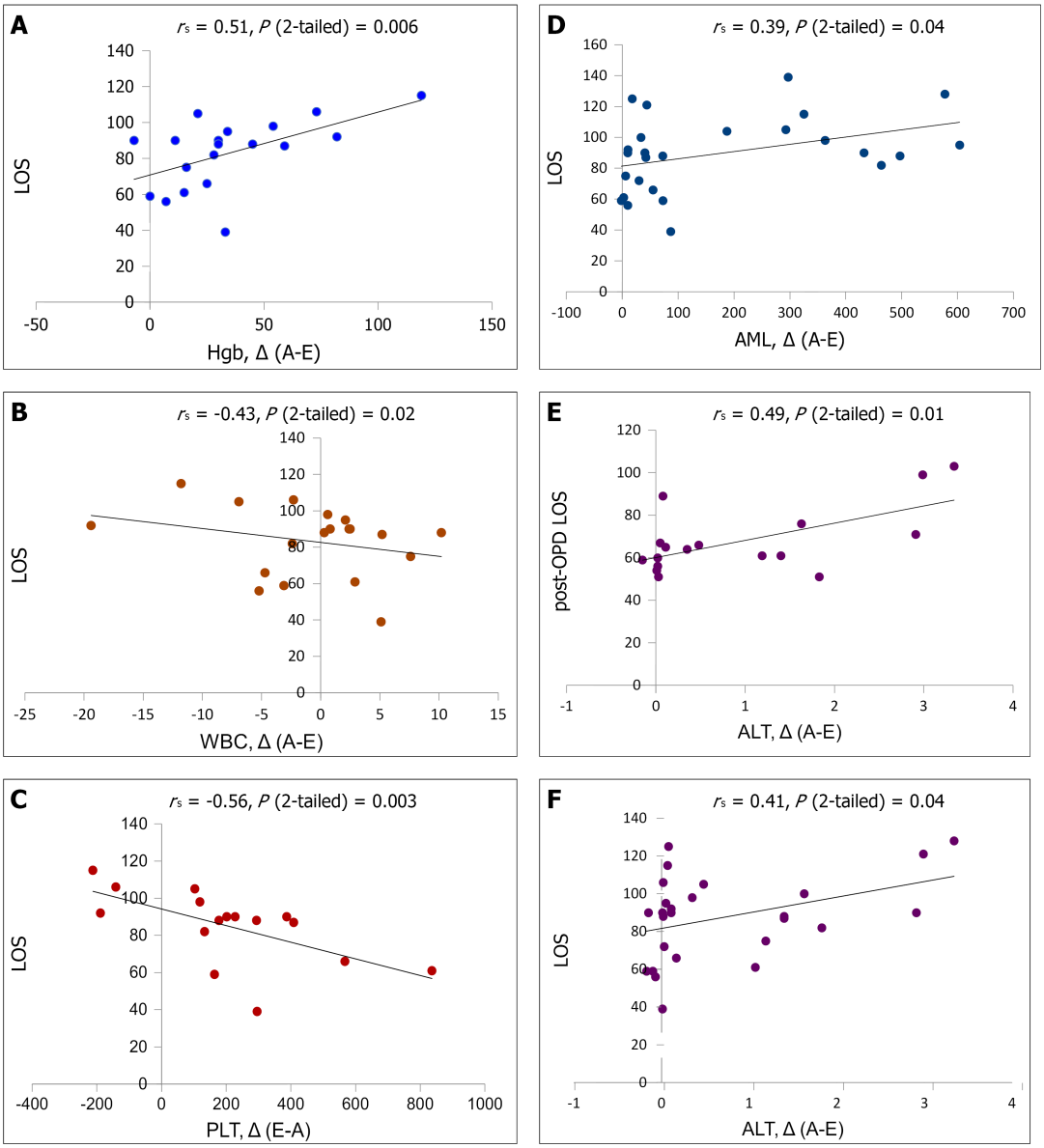



**Figure 1 Correlations between dynamic changes of laboratory variables.** A: Hemoglobin; B: Total white blood cell count; C: Total platelets count; D: α-amylase; E: Alanine aminotransferase; F: total and post-surgical length of stay. Δ(A-E) = value on admission – value the day before the surgery; Δ(E-A) = value the day before the surgery - value the day before the surgery. ALT: Alanine aminotransferase; AML: α-amylase; Hgb: Hemoglobin; LOS: Length of stay in hospital; OPD: Operative pancreatic debridement; PLT: Total platelets count; WBC: Total white blood cell count.

associated with chronic inflammation and fibrosis. Activated platelets represent one of the main sources of these growth factors[30,31]. Given the above, we assumed, that leukocytosis diminishing (as a marker of SIRS down-regulation) along with the increase of PLT count (as a marker of necrotic tissue encapsulation) could indicate a beneficial condition for OPD timing. In this study, a substantial progressive increase of PLT count along with moderate decrease of WBC count strongly correlated with shortened LOS. We suppose that progressive increase of PLT count in the preoperative period can be considered as one of the additional markers indicating the development of the GT capsule around the necrotic area.

There are several limitations in the present study. First, the number of patients was small, and further analysis needs to be done with a larger number of ANP patients to confirm its reproducibility. Second, comprehensive sex-centered evaluation would be more desirable considering the prevalence of female patients in the subgroup with shortened LOS. Third, it is desirable to complement the examination of the dynamic changes in PLT count with the determining of serum levels of cytokines involved in GT formation.

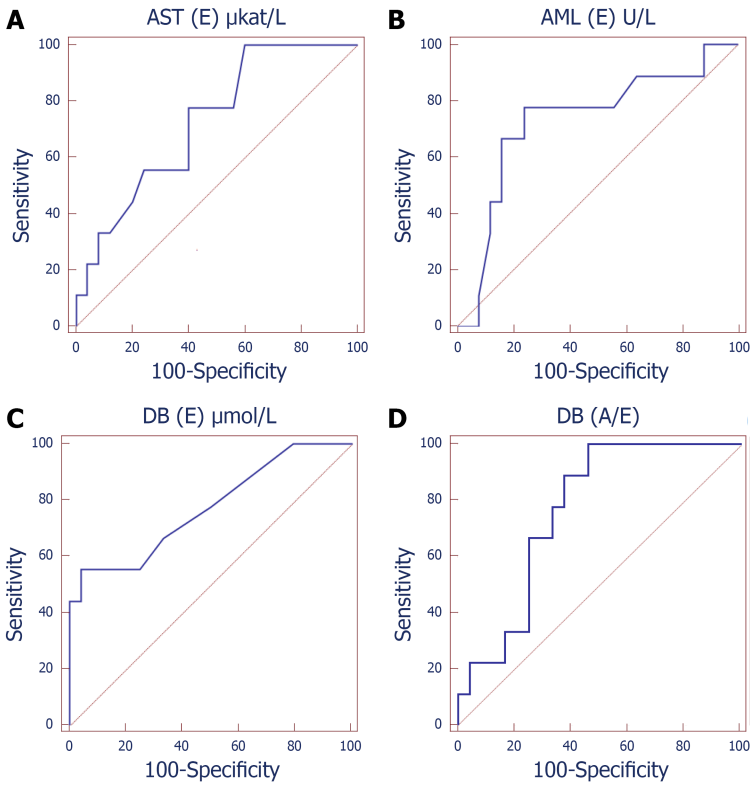



**Figure 2 Receiver operating characteristic curves of aspartate aminotransferase, α-amylase, and direct bilirubin for hospital mortality prediction in acute necrotizing pancreatitis patients.** A: Receiver operating characteristic (ROC) curves of aspartate aminotransferase the day before the surgery; B: ROC curves of α-amylase the day before the surgery; C: ROC curves of direct bilirubin (DB) (E) the day before the surgery; D: ROC curves of DB (A/E=value on admission/value the day before the surgery). AML: α-amylase; AST: Aspartate aminotransferase; DB: Direct bilirubin; (E): Day before the operative pancreatic debridement; (A/E): Day of admission/the day before the surgery.

## CONCLUSION

By focusing on dynamic changes of routine laboratory variables in the preoperative period in ANP patients, we demonstrated that a progressive increase in PLT count along with a decrease of leukocytosis correlates with a shortened LOS and can indicate GT formation, and can be considered as an additional marker for OPD timing. Whereas persistent hepatic malfunction, which is indicated by a weak progressive decrease of DB in the preoperative period and increased AST level can signify a high risk of post-operative mortality. Thus, multifactorial analysis of dynamic changes of routine laboratory variables can be useful for a person-tailored timing of surgical intervention in ANP patients.

## ARTICLE HIGHLIGHTS

### *Research background*

Timing on invasive intervention in patients with acute necrotizing pancreatitis is linked to the degree of encapsulation in necrotic collections. Assessment of the degree of encapsulation of necrotic collections is influenced by imaging and clinical features. However, the pathophysiology and time course of necrotic collection walling-off are not fully understood and vary significantly between patients.

### *Research motivation*

Additional markers of necrosis encapsulation might assist decision-making on the timing of surgical intervention. The search for these markers should be based on current knowledge of the biology of necrotic tissue encapsulation. In our opinion, it is logical to search for such markers among routine laboratory parameters traditionally used in acute necrotizing pancreatitis (ANP) patients, considering simplicity and cost-efficacy of routine laboratory methodologies.

### Research objectives

To evaluate laboratory variables in ANP patients in the preoperative period for the purpose of their use for the timing of surgery.

### Research methods

This was a retrospective study of 53 ANP patients undergoing operative pancreatic debridement (OPD). Dynamic changes of routine hematological and biochemical indices were examined in the preoperative period. Patients were divided into survivors and non-survivors. Survivors were further divided into a subgroup with short and long post-surgery length of stay (LOS) in hospital. Correlation analysis was used to evaluate the association of laboratory variables with LOS. Logistic regression was used to assess risk factors for patient mortality.

### Research results

Progressive increase of platelet count in the preoperative period was associated with shortened total and post-surgery LOS. Increased aspartate aminotransferase and direct bilirubin (DB) levels the day before the OPD as well as the absence of substantial decrease of DB level in preoperative period were reliable predictors for ANP patient mortality.

### Research conclusions

Multifactorial analysis of dynamic changes of routine laboratory variables can be useful for a person-tailored timing of surgical intervention in ANP patients.

### Research perspectives

Comprehensive sex-centered evaluation of routine laboratory variables should be performed considering sex differences in the course of inflammation. Dynamic changes of serum levels of cytokines associated with fibro granulation tissue formation should also be studied for the person-tailored invasive intervention timing.

## ACKNOWLEDGEMENTS

The authors are very grateful to all participants recruited in this study. The authors express their sincere thanks to Dr. Olexander Gorbach for the technical support.

## REFERENCES

1 **Boxhoorn L**, Voermans RP, Bouwense SA, Bruno MJ, Verdonk RC, Boermeester MA, van Santvoort HC, Besselink MG. Acute pancreatitis. *Lancet* 2020; **396**: 726-734 [PMID: 32891214 DOI: 10.1016/S0140-6736(20)31310-6]

2 **Cofaru FA**, Nica S, FierbinŢeanu-Braticevici C. Assessment of severity of acute pancreatitis over time. *Rom J Intern Med* 2020; **58**: 47-54 [PMID: 32097123 DOI: 10.2478/rjim-2020-0003]

3 **Aparna D**, Kumar S, Kamalkumar S. Mortality and morbidity in necrotizing pancreatitis managed on principles of step-up approach: 7 years experience from a single surgical unit. *World J Gastrointest Surg* 2017; **9**: 200-208 [PMID: 29109852 DOI: 10.4240/wjgs.v9.i10.200]

4 **Leonard-Murali S**, Lezotte J, Kalu R, Blyden DJ, Patton JH, Johnson JL, Gupta AH. Necrotizing pancreatitis: A review for the acute care surgeon. *Am J Surg* 2021; **221**: 927-934 [PMID: 32878690 DOI: 10.1016/j.amjsurg.2020.08.027]

5 **Maatman TK**, Flick KF, Roch AM, Zyromski NJ. Operative pancreatic debridement: Contemporary outcomes in changing times. *Pancreatology* 2020; **20**: 968-975 [PMID: 32622760 DOI: 10.1016/j.pan.2020.05.024]

6 **van Santvoort HC**, Bakker OJ, Bollen TL, Besselink MG, Ahmed Ali U, Schrijver AM, Boermeester MA, van Goor H, Dejong CH, van Eijck CH, van Ramshorst B, Schaapherder AF, van der Harst E, Hofker S, Nieuwenhuijs VB, Brink MA, Kruyt PM, Manusama ER, van der Schelling GP, Karsten T, Hesselink EJ, van Laarhoven CJ, Rosman C, Bosscha K, de Wit RJ, Houdijk AP, Cuesta MA, Wahab PJ, Gooszen HG; Dutch Pancreatitis Study Group. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology* 2011; **141**: 1254-1263 [PMID: 21741922 DOI: 10.1053/j.gastro.2011.06.073]

7 **Wroński M**, Cebulski W, Witkowski B, Jankowski M, Kluciński A, Krasnodębski IW, Słodkowski M. Comparison between minimally invasive and open surgical treatment in necrotizing pancreatitis. *J Surg Res* 2017; **210**: 22-31 [PMID: 28457332 DOI: 10.1016/j.jss.2016.10.022]

8 **Yin T**, Wang CY. [Rediscussion of the individualized surgical intervention and timing for necrotizing pancreatitis]. *Zhonghua Wai Ke Za Zhi* 2019; **57**: 1-5 [PMID: 31510724 DOI:

10.3760/cma.j.issn.0529-5815.2019.10.001]
9 **Garg PK**, Zyromski NJ, Freeman ML. Infected Necrotizing Pancreatitis: Evolving Interventional Strategies From Minimally Invasive Surgery to Endoscopic Therapy-Evidence Mounts, But One Size Does Not Fit All. *Gastroenterology* 2019; **156**: 867-871 [PMID: 30776344 DOI: 10.1053/j.gastro.2019.02.015]
10 **Baron TH**, DiMaio CJ, Wang AY, Morgan KA. American Gastroenterological Association Clinical Practice Update: Management of Pancreatic Necrosis. *Gastroenterology* 2020; **158**: 67-75.e1 [PMID: 31479658 DOI: 10.1053/j.gastro.2019.07.064]
11 **Leppäniemi A**, Tolonen M, Tarasconi A, Segovia-Lohse H, Gamberini E, Kirkpatrick AW, Ball CG, Parry N, Sartelli M, Wolbrink D, van Goor H, Baiocchi G, Ansaloni L, Biffl W, Coccolini F, Di Saverio S, Kluger Y, Moore E, Catena F. 2019 WSES guidelines for the management of severe acute pancreatitis. *World J Emerg Surg* 2019; **14**: 27 [PMID: 31210778 DOI: 10.1186/s13017-019-0247-0]
12 **Besselink MG**, Verwer TJ, Schoenmaeckers EJ, Buskens E, Ridwan BU, Visser MR, Nieuwenhuijs VB, Gooszen HG. Timing of surgical intervention in necrotizing pancreatitis. *Arch Surg* 2007; **142**: 1194-1201 [PMID: 18086987 DOI: 10.1001/archsurg.142.12.1194]
13 **Banks PA**, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; **62**: 102-111 [PMID: 23100216 DOI: 10.1136/gutjnl-2012-302779]
14 **van Grinsven J**, van Brunschot S, van Baal MC, Besselink MG, Fockens P, van Goor H, van Santvoort HC, Bollen TL; Dutch Pancreatitis Study Group. Natural History of Gas Configurations and Encapsulation in Necrotic Collections During Necrotizing Pancreatitis. *J Gastrointest Surg* 2018; **22**: 1557-1564 [PMID: 29752684 DOI: 10.1007/s11605-018-3792-z]
15 **Susak IaM**, Tkachenko OA, Malysh IR, Dirda OO, Fedorchuk OH. [Prognostication of course and treatment of peripancreatic infiltrate in patients, suffering an acute necrotic pancreatitis]. *Klin Khir* 2014; 20-22 [PMID: 25097970]
16 **Kim WR**, Flamm SL, Di Bisceglie AM, Bodenheimer HC; Public Policy Committee of the American Association for the Study of Liver Disease. Serum activity of alanine aminotransferase (ALT) as an indicator of health and disease. *Hepatology* 2008; **47**: 1363-1370 [PMID: 18366115 DOI: 10.1002/hep.22109]
17 **Nagae M**, Egi M, Kubota K, Makino S, Mizobuchi S. Association of direct bilirubin level with postoperative outcome in critically ill postoperative patients. *Korean J Anesthesiol* 2018; **71**: 30-36 [PMID: 29441172 DOI: 10.4097/kjae.2018.71.1.30]
18 **Miyahara S**, Isaji S. Liver injury in acute pancreatitis and mitigation by continuous arterial infusion of an antibiotic *via* the superior mesenteric artery. *Pancreas* 2001; **23**: 204-211 [PMID: 11484923 DOI: 10.1097/00006676-200108000-00011]
19 **Zhang XP**, Wang L, Zhang J. Study progress on mechanism of severe acute pancreatitis complicated with hepatic injury. *J Zhejiang Univ Sci B* 2007; **8**: 228-236 [PMID: 17444596 DOI: 10.1631/jzus.2007.B0228]
20 **Field E**, Horst HM, Rubinfeld IS, Copeland CF, Waheed U, Jordan J, Barry A, Brandt MM. Hyperbilirubinemia: a risk factor for infection in the surgical intensive care unit. *Am J Surg* 2008; **195**: 304-6; discussion 306 [PMID: 18206848 DOI: 10.1016/j.amjsurg.2007.12.010]
21 **Caserta S**, Mengozzi M, Kern F, Newbury SF, Ghezzi P, Llewelyn MJ. Severity of Systemic Inflammatory Response Syndrome Affects the Blood Levels of Circulating Inflammatory-Relevant MicroRNAs. *Front Immunol* 2017; **8**: 1977 [PMID: 29459855 DOI: 10.3389/fimmu.2017.01977]
22 **Kokosis G**, Perez A, Pappas TN. Surgical management of necrotizing pancreatitis: an overview. *World J Gastroenterol* 2014; **20**: 16106-16112 [PMID: 25473162 DOI: 10.3748/wjg.v20.i43.16106]
23 **Boškoski I**, Costamagna G. Walled-off pancreatic necrosis: where are we? *Ann Gastroenterol* 2014; **27**: 93-94 [PMID: 24733647]
24 **Cavaillon JM**, Annane D. Compartmentalization of the inflammatory response in sepsis and SIRS. *J Endotoxin Res* 2006; **12**: 151-170 [PMID: 16719987 DOI: 10.1179/096805106X102246]
25 **Alhajj M**, Bansal P, Goyal A. Physiology, Granulation Tissue. 2020 Nov 2. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan- [PMID: 32119289]
26 **Tu HJ**, Zhao CF, Chen ZW, Lin W, Jiang YC. Fibroblast Growth Factor (FGF) Signaling Protects Against Acute Pancreatitis-Induced Damage by Modulating Inflammatory Responses. *Med Sci Monit* 2020; **26**: e920684 [PMID: 32283546 DOI: 10.12659/MSM.920684]
27 **di Mola FF**, Friess H, Riesle E, Koliopanos A, Büchler P, Zhu Z, Brigstock DR, Korc M, Büchler MW. Connective tissue growth factor is involved in pancreatic repair and tissue remodeling in human and rat acute necrotizing pancreatitis. *Ann Surg* 2002; **235**: 60-67 [PMID: 11753043 DOI: 10.1097/00000658-200201000-00008]
28 **Johnson CL**, Weston JY, Chadi SA, Fazio EN, Huff MW, Kharitonenkov A, Köester A, Pin CL. Fibroblast growth factor 21 reduces the severity of cerulein-induced pancreatitis in mice. *Gastroenterology* 2009; **137**: 1795-1804 [PMID: 19664632 DOI: 10.1053/j.gastro.2009.07.064]
29 **Stojek M**, Adrych K, Rojek L, Smoczynski M, Sledzinski T, Szrok S, Swierczynski J. Decreased serum platelet derived growth factor BB levels in acute and increased in chronic pancreatitis. *World J Gastroenterol* 2014; **20**: 13127-13132 [PMID: 25278706 DOI: 10.3748/wjg.v20.i36.13127]
30 **Eisinger F**, Patzelt J, Langer HF. The Platelet Response to Tissue Injury. *Front Med (Lausanne)* 2018; **5**: 317 [PMID: 30483508 DOI: 10.3389/fmed.2018.00317]
31 **Deptuła M**, Karpowicz P, Wardowska A, Sass P, Sosnowski P, Mieczkowska A, Filipowicz N,

Dzierżyńska M, Sawicka J, Nowicka E, Langa P, Schumacher A, Cichorek M, Zieliński J, Kondej K, Kasprzykowski F, Czupryn A, Janus Ł, Mucha P, Skowron P, Piotrowski A, Sachadyn P, Rodziewicz-Motowidło S, Pikuła M. Development of a Peptide Derived from Platelet-Derived Growth Factor (PDGF-BB) into a Potential Drug Candidate for the Treatment of Wounds. *Adv Wound Care (New Rochelle)* 2020; **9**: 657-675 [PMID: 33124966 DOI: 10.1089/wound.2019.1051]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
**Telephone:** +1-925-3991568
**E-mail:** bpgoffice@wjgnet.com
**Help Desk:** https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 1948-9366 (online)

# World Journal of

# *Gastrointestinal Surgery*

*World J Gastrointest Surg* 2022 February 27; 14(2): 78-210

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 14 Number 2 February 27, 2022

## FRONTIER



## ORIGINAL ARTICLE

### Retrospective Cohort Study



### Retrospective Study



## SYSTEMATIC REVIEWS



## CASE REPORT

*World Journal of Gastrointestinal Surgery*

**Monthly Volume 14 Number 2 February 27, 2022**

# Contents

## ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Tomas Poskus, MD, PhD, Professor, Institute of Clinical Medicine, Clinic of Gastroenterology, Nephrourology and Surgery, Faculty of Medicine, Vilnius University, Vilnius 08661, Lithuania. toshcus@yahoo.com

## AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJGS* mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

## INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJGS* as 2.582; IF without journal self cites: 2.564; 5-year IF: 3.378; Journal Citation Indicator: 0.53; Ranking: 97 among 212 journals in surgery; Quartile category: Q2; Ranking: 73 among 92 journals in gastroenterology and hepatology; and Quartile category: Q4.

## RESPONSIBLE EDITORS FOR THIS ISSUE



**NAME OF JOURNAL**
*World Journal of Gastrointestinal Surgery*

**ISSN**
ISSN 1948-9366 (online)

**LAUNCH DATE**
November 30, 2009

**FREQUENCY**
Monthly

**EDITORS-IN-CHIEF**
Peter Schemmer

**EDITORIAL BOARD MEMBERS**
https://www.wjgnet.com/1948-9366/editorialboard.htm

**PUBLICATION DATE**
February 27, 2022



**INSTRUCTIONS TO AUTHORS**
https://www.wjgnet.com/bpg/gerinfo/204

**GUIDELINES FOR ETHICS DOCUMENTS**
https://www.wjgnet.com/bpg/GerInfo/287

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**
https://www.wjgnet.com/bpg/gerinfo/240

**PUBLICATION ETHICS**
https://www.wjgnet.com/bpg/GerInfo/288

**PUBLICATION MISCONDUCT**
https://www.wjgnet.com/bpg/gerinfo/208

**ARTICLE PROCESSING CHARGE**
https://www.wjgnet.com/bpg/gerinfo/242

**STEPS FOR SUBMITTING MANUSCRIPTS**
https://www.wjgnet.com/bpg/GerInfo/239

**ONLINE SUBMISSION**
https://www.f6publishing.com

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 February 27; 14(2): 78-106

DOI: 10.4240/wjgs.v14.i2.78

ISSN 1948-9366 (online)

FRONTIER

# Therapeutic strategies for gastroenteropancreatic neuroendocrine neoplasms: State-of-the-art and future perspectives

Elettra Merola, Andrea Michielan, Umberto Rozzanigo, Marco Erini, Sandro Sferrazza, Stefano Marcucci, Chiara Sartori, Chiara Trentin, Giovanni de Pretis, Franca Chierichetti

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Ramirez RA, Wang WQ

**Received:** March 20, 2021
**Peer-review started:** March 20, 2021
**First decision:** October 3, 2021
**Revised:** October 18, 2021
**Accepted:** January 25, 2022
**Article in press:** January 25, 2022
**Published online:** February 27, 2022

**Elettra Merola, Andrea Michielan, Sandro Sferrazza, Giovanni de Pretis,** Department of Gastroenterology, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari (APSS), Trento 38122, Italy

**Umberto Rozzanigo,** Department of Radiology, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari (APSS), Trento 38122, Italy

**Marco Erini, Franca Chierichetti,** Department of Nuclear Medicine, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari (APSS), Trento 38122, Italy

**Stefano Marcucci,** Department of Surgery, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari (APSS), Trento 38122, Italy

**Chiara Sartori,** Department of Pathology, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari (APSS), Trento 38122, Italy

**Chiara Trentin,** Department of Medical Oncology, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari (APSS), Trento 38122, Italy

**Corresponding author:** Elettra Merola, MD, PhD, Department of Gastroenterology, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari (APSS), Largo Medaglie D'Oro 9, Trento 38122, Italy. elettra.merola@apss.tn.it

## Abstract

Although gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) have always been considered rare tumors, their incidence has risen over the past few decades. They represent a highly heterogeneous group of neoplasms with several prognostic factors, including disease stage, proliferative index (Ki67), and tumor differentiation. Most of these neoplasms express somatostatin receptors on the cell surface, a feature that has important implications in terms of prognosis, diagnosis, and therapy. Although International Guidelines propose algorithms aimed at guiding therapeutic strategies, GEP-NEN patients are still very different from one another, and the need for personalized treatment continues to increase. Radical surgery is always the best option when feasible; however, up to 80% of cases are metastatic upon diagnosis. Regarding medical treatments, as GEP-NENs are characterized by relatively long overall survival, multiple therapy lines are adopted during the lifetime of these patients, but the optimum sequence to be followed has never been clearly defined. Furthermore, although new molecular

markers aimed at predicting the response to therapy, as well as prognostic scores, are currently being studied, their application is still far from being part of daily clinical practice. As they represent a complex disease, with therapeutic protocols that are not completely standardized, GEP-NENs require a multidisciplinary approach. This review will provide an overview of the available therapeutic options for GEP-NENs and attempts to clarify the possible approaches for the management of these patients and to discuss future perspectives in this field.

**Key Words:** Gastroenteropancreatic neuroendocrine neoplasms; Therapeutic strategies; Radical surgery; Medical treatments; Overview; Future perspectives



**Core Tip:** Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) have shown an increasing incidence over the past few decades. Although International Guidelines propose algorithms aimed guiding therapeutic strategies, the need for personalized treatment continues to increase. Radical resection is always the best option when feasible; however, up to 80% of cases are metastatic upon diagnosis. Several medical therapies are available for unresectable cases: Somatostatin analogs, peptide receptor radionuclide therapy, targeted drugs (primarily everolimus and sunitinib), chemotherapy and immunotherapy. This review provides an updated overview of the available therapeutic options for GEP-NENs and attempts to discuss future perspectives in this field.

**Citation:** Merola E, Michielan A, Rozzanigo U, Erini M, Sferrazza S, Marcucci S, Sartori C, Trentin C, de Pretis G, Chierichetti F. Therapeutic strategies for gastroenteropancreatic neuroendocrine neoplasms: State-of-the-art and future perspectives. *World J Gastrointest Surg* 2022; 14(2): 78-106
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i2/78.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i2.78

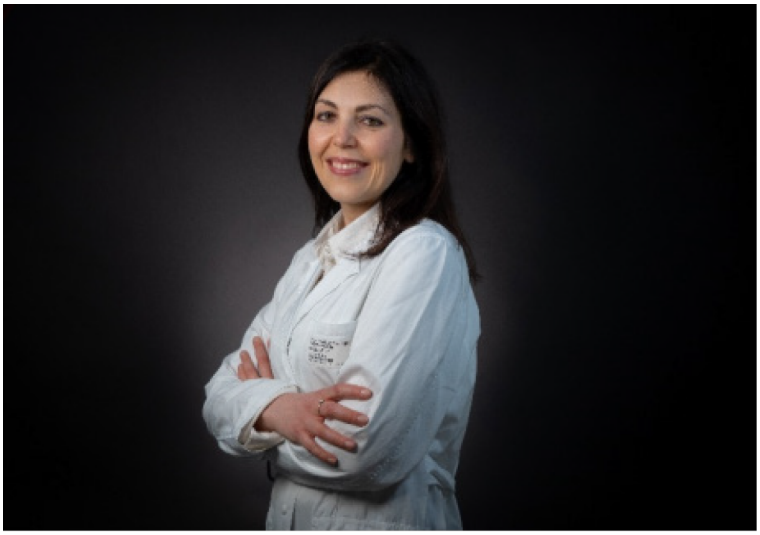
## BIOGRAPHY

**Elettra Merola, MD, PhD:** She is a gastroenterologist and researcher currently working at the Department of Gastroenterology of Santa Chiara Hospital (APSS), Trento (Italy). She received her MD degree with honors in 2005 from Campus Bio Medico University, Rome (Italy), and during medical school she was visiting student and researcher at the University of Illinois in Chicago (United States) and at Temple University in Philadelphia (United States). In 2009, she completed her residency in Gastroenterology and in 2013 her PhD in Digestive Oncology at Sant'Andrea Hospital, Sapienza University, Rome (Italy), where she developed a particular interest in neuroendocrine neoplasms (NENs). Her experience in this field grew, joining as a visiting researcher the European Neuroendocrine Tumor Society (ENETS) center of excellence of Charité University, Berlin (Germany) (2015-2017), and then working as an NEN specialist at the NEN center of FAU Erlangen University, Erlangen (Germany) (2017-2018). Dr. Merola is internationally recognized for her expertise in NENs and she has led several cooperative studies aimed at improving the clinical management of these patients. In March 2017 she was awarded the ENETS Center of Excellence Academy Fellowship Grant for an international, cooperative research project regarding curative surgery in neuroendocrine tumors. She moved to Santa Chiara Hospital (APSS) in Trento (Italy) in 2018, where she promoted the management of NEN patients in a multidisciplinary setting, coordinating a dedicated NEN tumor board. She is also responsible for the outpatient clinic of neuroendocrine neoplasms in the Gastroenterology Department (Figure 1).

## INTRODUCTION

Although gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) have always been considered rare tumors, their incidence has risen in recent decades, up to 3-5 cases *per* 100000 persons *per* year[1,2]. They represent a highly heterogeneous group of neoplasms with varying biological behavior. Several prognostic factors have an impact on GEP-NEN survival, including the proliferative index (Ki67)[3], disease stage according to the European Neuroendocrine Tumor Society (ENETS) tumor-node-metastasis (TNM) staging system[4,5], and the World Health Organization (WHO) classification[6].

In particular, if the definition of NENs is adopted for all neoplasms with a neuroendocrine differentiation in general, based on immunolabeling for chromogranin A and synaptophysin, the novel WHO 2019 classification[6] distinguishes two different subgroups in terms of morphology, genetics, response



DOI: 10.4240/wjgs.v14.i2.78 

**Figure 1 Elettra Merola, MD, PhD,** Department of Gastroenterology, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari (APSS), Largo Medaglie D'Oro 9, Trento 38122, Italy

to therapy, and prognosis: NETs and neuroendocrine carcinomas (NECs). NETs are well-differentiated neuroendocrine neoplasms, characterized by a population of cells with uniform nuclear features, "salt and pepper" chromatin, organoid architecture and sometimes minimal necrosis. NETs are classified according to proliferation fraction in G1 (mitotic count < 2 *per* 2 $mm^2$ and/or < 3% Ki-67 index), G2 (mitotic count 2-20 *per* 2 $mm^2$ and/or 3%-20% Ki-67 index), and G3 (mitotic count > 20 *per* 2 $mm^2$ and/or > 20% Ki-67 index). Instead, NECs are highly aggressive poorly differentiated neoplasms that grow in sheets, usually with abundant necrosis. They are further classified into small cell NECs or large cell NECs, based on the cell morphology. NECs are high grade by definition; grading for these neoplasms is not assigned to avoid confusion regarding the NET G3 category.

The expression of somatostatin receptors (SSTRs) also has an important role in therapy selection and characterizes nearly 90% of NENs. This feature is mainly identified by functional imaging tests, which are pivotal in diagnosis, disease staging, and the therapeutic management of NENs. They include octreotide scintigraphy with radiolabeled somatostatin analogs (SSAs) (Octreoscan®), limited by the low accuracy in detecting small lesions (< 1 cm in diameter) and by a difficult semiquantitative analysis[7]. The subsequent development of different radiolabeled DOTA-conjugated peptides (DOTANOC, DOTATOC, DOTATATE) for positron emission tomography/computed tomography (PET/CT) has changed the landscape of nuclear medicine. Following the first published paper introducing $^{68}$Ga-DOTATOC-PET/CT, a series of further papers showed that this test could detect no less than 30% more neuroendocrine lesions than Octreoscan® and conventional CT[8].

Although International Guidelines propose algorithms aimed at guiding therapeutic strategies[9-13], NEN patients are still very different from one another and the need for personalized treatments continues to increase. Although radical surgery is always the best option when feasible, up to 80% of cases are metastatic upon diagnosis and data on adjuvant treatments are still insufficient for this disease. Regarding medical treatments, as NENs are characterized by a relatively long overall survival (OS), multiple therapy lines are adopted for these patients during their lifetime, but the best sequence to be followed has never been clearly defined. Furthermore, new molecular markers aimed at predicting therapy response and prognostic scores[14,15] are currently being studied, but their application is still far from being part of daily clinical practice. A recent network meta-analysis including only phase-III randomized controlled trials (RCTs) has attempted to identify the best therapeutic strategy for controlling tumor growth, proposing the combination of peptide receptor radionuclide therapy (PRRT) and SSAs as the option with the best progression-free survival (PFS). However, this analysis seems very speculative and hard to apply to real-life settings.

This review will explore the available antiproliferative therapeutic options for GEP-NENs, based on evidence reported in the literature and on many years of experience in the field. It also includes the contribution of the specialists working in the multidisciplinary setting dedicated to NEN patients at Santa Chiara Hospital (APSS) in Trento (Italy). A separate session will be dedicated to new frontiers in the therapy landscape. Genetic syndromes and management of clinical syndrome (*i.e.* carcinoid syndrome) will not be discussed in this manuscript.

## RESECTABLE DISEASE

### *Endoscopic treatment*

The incidence of GEP-NENs has increased in the last two decades also due to the extensive use of endoscopy, particularly following the worldwide implementation of bowel cancer screening programs. Endoscopic resection is reserved to small, localized NETs, mainly located in the rectum, stomach and duodenum. The endoscopist must have extensive knowledge of the macroscopic appearance of these lesions and perform endoscopic ultrasound (EUS) for staging when an invasive NET is suspected, and perform a biopsy when lesions arise from the deep mucosal layer and then extend into the submucosa [16]. A thorough evaluation of tumor location, size, and depth of invasion are mandatory and a multidisciplinary consultation is recommended prior to resection even in case of small and low-grade lesions[17,18].

In this session, the endoscopic approach for gastrointestinal NETs will be discussed according to site, and our proposal for endoscopic management is reported in Table 1.

**Colorectal NETs:** Colonic NETs are located in the right colon in 70% of cases, can reach a very large size without obstructive symptoms, and are usually aggressive[19]. Given their advanced stage at the time of diagnosis, endoscopic treatment has only been reported in case series, with a significant burden of complications and incomplete resections[17].

Rectal NETs (r-NETs) appear as small, sessile lesions, located within 5-10 cm of the anal verge, with overlying normal or yellowish mucosa. Larger lesions may also be semi-pedunculated or have central depression or ulceration[19].

Staging with EUS is not required for lesions < 10 mm in size due to the negligible risk of invasion[16,20]. The endoscopist may be tempted to perform a standard snare resection but must bear in mind that the complete removal rate for polypectomy is approximately 30%, and for conventional endoscopic mucosal resection (EMR) it is highly variable (17%-90%) due to the submucosal nature of these nodules [19,21,22].

Modified EMR techniques have been employed to obtain a deeper resection. Cap-assisted EMR (EMR-C) uses a dedicated cap with a circumferential rim that can lodge a crescent snare. After saline injection of the submucosa, the lesion is suctioned within the cap and cut. Band-ligation EMR (EMR-L) also requires saline injection. Once the lesion has been adequately captured by the deployment of an elastic band (usually employed for variceal ligation), a snare resection is performed below the band.

The rate of histologically complete resection by modified EMR is high, particularly for EMR-L (93%-100% *vs* 71%-100% for EMR-C) and comparative studies and a meta-analysis confirmed a higher complete resection rate than conventional EMR[20,23,24]. Resection by EMR-C and EMR-L are both used for r-NETs, and the only comparative retrospective study available to date demonstrated similar effectiveness[23]. The higher *en bloc* resection rate for EMR-L was explained by the authors by the larger quantity of submucosa captured by the thickness of the elastic band.

Another technique for advanced endoscopic resection is endoscopic submucosal dissection (ESD). This technique is superior in terms of radical histologic resection in r-NETs ≥ 10 mm[17], but has similar outcomes to EMR-C and EMR-L for small r-NETs (< 10 mm) despite a longer procedure time[20,25].

**Gastric NETs:** Gastric NENs (g-NENs) usually arise from enterochromaffin-like (ECL) cells and are divided into three types. More specifically, Type I arises in the setting of a chronic atrophic gastritis, Type II is associated with gastrinomas, and Type III is sporadic and independent from gastrin levels. Two additional categories of g-NENs have been recently described and are currently being investigated: Type IV lesions arise from non-ECL endocrine cells, whereas another subtype of g-NETs might be determined by the chronic use of proton pump inhibitors[19,26,27].

Type I and II g-NETs have a highly variable endoscopic aspect (red or yellow, depending on the vascular supply) and are sometimes characterized by a central depression. They usually appear as smooth and rounded multiple polypoid lesions, with size < 20 mm and located in the gastric body and fundus[19,28,29]. As Type I g-NETs are mainly characterized by indolent behavior, conservative management with endoscopic surveillance +/- resection is safe and effective also in the case of recurrent lesions[17,30,31].

Disease staging by EUS prior to resection is not required for small Type I g-NETs (< 10 mm) but it is mandatory when lesions are ≥ 10 mm, when Ki67 is > 3% or in the case of Type II g-NETs[17]. The data regarding ESD show complete resection achieved in 75%-100% of cases, with a lower rate of positive vertical margins at histology compared to standard EMR[32-34]. Modified EMR techniques (EMR-L or EMR-C) are currently being used for Type I g-NETs, and should be considered for small lesions (≤ 10 mm) that can be completely suctioned within the cap in order to obtain the *en bloc* resection (Figure 2).

Type II lesions are extremely rare, and in the absence of high-quality level data, their management is generally similar to Type I[27]. However, considering their size upon presentation (≥ 10 mm) they usually require ESD for complete *en bloc* resection that is better than EMR.

Type III g-NENs are larger, solitary lesions located anywhere in the stomach, sometimes with a broad fixed base and ulceration indicating deeper invasion[17,28,29]. They require a complete disease staging, including EUS. As lymph node involvement is present in more than 50% of cases upon diagnosis and

**Table 1 Proposed endoscopic management for gastrointestinal neuroendocrine tumors**

| | r-NETs | g-NETs | d-NETs | e-NETs |
|---|---|---|---|---|
| Prevalence (% of GI-NETs) | 8-30 | 4.6-7 | 1-3 | 0.2 |
| Indications to EUS | ≥ 10 mm | (1) Type I ≥ 10 mm; and (2) Type II-III | Always | Always |
| Indications to endoscopic resection | < 20 mm, no signs of deep invasion or lymphadenopathy | G1/G2, 10-20 mm, no signs of deep invasion or lymphadenopathy | (1) < 10 mm, no signs of deep invasion or lymphadenopathy; (2) 10-20 mm, G1/G2, no signs of deep invasion or lymphadenopathy (debated); and (3) Periampullary region: G1, no signs of deep invasion or lymphadenopathy(debated) | ≤ 10 mm, confined to submucosa, no ulceration |
| Resection techniques | (1) EMR-C, EMR-L (< 10 mm); and (2) ESD (10-20 mm) | (1) EMR-C, EMR-L (Type I < 10 mm); and (2) ESD (Type I 10-20 mm, Type II-III) | (1) EMR, EMR-C, EMR-L, ESD; and (2) Endoscopic papillectomy in referral centers | EMR-C, EMR-L, ESD |

d-NETS: Duodenal neuroendocrine tumors; EMR-C: Cap-assisted endoscopic mucosal resection; EMR-L: Band-ligation endoscopic mucosal resection; e-NETs: Esophageal neuroendocrine tumors; ESD: Endoscopic submucosal dissection; EUS: Endoscopic ultrasound; GI: Gastrointestinal; g-NETs: Gastric neuroendocrine tumors; r-NETs: Rectal neuroendocrine tumors.

liver metastases is in 22%-75%, an endoscopic approach is not frequent in these cases[18,27]. A recent systematic review included 121 patients from eight studies with small localized Type III g-NETs who underwent endoscopic resection. The complete resection rate varied from 72% to 87%, but details about the endoscopic technique were often not reported, preventing comparisons of the EMR and ESD outcomes[18].

Type IV g-NENs are described as aggressive lesions, with a size of > 40 mm upon diagnosis, and in the case of localized disease, surgical resection is preferable[19].

**Small bowel NETs:** Jejunal and ileal NETs are usually > 20 mm, multifocal in 40% of cases, and with lymphatic involvement upon diagnosis in 70% of cases[19]. Due to these features, and as they are often beyond the reach of a device-assisted enteroscopy, a surgical approach is recommended for localized disease. Endoscopy may instead be helpful for diagnosis, in the case of bleeding, or for tattooing of the lesion[19].

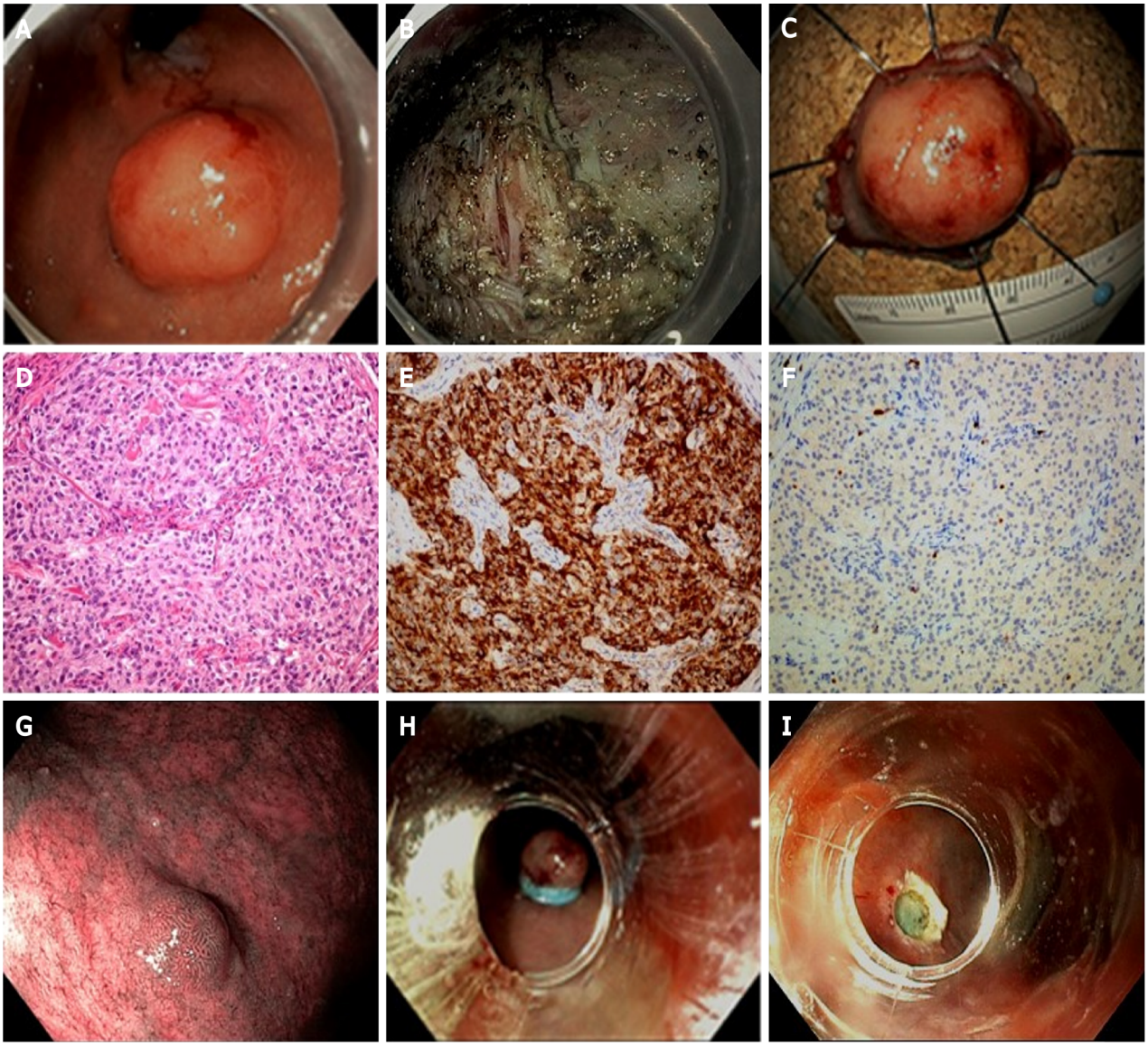
Duodenal NETs (d-NETs) are usually small, sessile and solitary lesions, mainly located in the duodenal bulb or second part[28]. As even sub centimetric tumors present lymphatic spread in 40%-60% upon diagnosis, EUS is mandatory, and resection by EMR or ESD is reserved to submucosal lesions < 10 mm with no lymphatic involvement[17,19]. The management of intermediate (10-20 mm) lesions is controversial and based on local expertise[28]. Considering the thin duodenal wall, some authors prefer to use standard EMR rather than modified EMR[29]. Standard EMR has indeed shown outcomes that are comparable to EMR-C and EMR-L, although higher rates of complete histological removal (70%-92%) has been reported for EMR-L in a small case series[35-38]. Some authors even suggest the autoamputation of small d-NETs using band ligation without snare resection[39].

The rate of radical resection by ESD in the duodenum is variable (67%-100%), due to the technical challenge of scope maneuvering in this anatomical district and the scarce submucosal lifting[36,40]. Moreover, the complication rate may be higher than in other gastrointestinal districts, especially perforation (13%-67% in small case series)[36,41,42]. Based on these considerations, ESD may be offered depending on local expertise and preferentially reserved to poor surgically-suited candidates.

Endoscopic full-thickness resection (EFTR) is usually reserved for subepithelial tumors originating from the muscularis propria. It has only been described for NETs in small case series and ideally should not provide a clear advantage compared to ESD as most NETs remain submucosal[17,43]. The ability of EFTR to secure the intestinal wall with an over-the-scope clip under the cutting plane may overcome the risks of endoscopic resection in the duodenum[40]. However, this advantage may be hampered by the technical drawbacks of operating this unwieldy device in the already difficult duodenal anatomy.

Duodenal NETs originate from the periampullary region in 20% of patients. In these cases, current guidelines recommend surgical resection because they have a more aggressive biology and their metastatic potential is independent of tumor size[18,28,30,35]. Nevertheless, a growing body of evidence favors a prior attempt with endoscopic papillectomy[21,44]. Prospective data are needed to evaluate the efficacy of this approach.

**Esophageal NETs:** Esophageal NETs (e-NETs) account for only 0.2% of total gastrointestinal NETs. Their appearance is similar to other gastrointestinal NETs, but they tend to have a central ulceration and may sometimes be multiple[29]. Endoscopic resection can be considered in low-risk cases: Lesions ≤ 10 mm, without ulceration and confined to the submucosa according to EUS evaluation. Both *en bloc* EMR and ESD have been effectively used for complete removal. However, the exceptionally rare incidence of e-NETs does not allow high level comparative studies for these techniques[17]. Regarding EMR, EMR-C




DOI: 10.4240/wjgs.v14.i2.78 

**Figure 2 Endoscopic management of gastric neuroendocrine tumors presentation of a clinical case referred to our hospital.** A 78-year-old female patient was referred to our Endoscopy Unit for resection of a lesion of the gastric fundus. Staging by endoscopic ultrasound showed hypoechoic lesion of 19 mm × 12 mm, with well-defined margins, originating from the third hyperechoic layer. Fine-needle cytology diagnosed a NET G1 (Ki67 < 2%). The lesion was then resected by endoscopic submucosa dissection (ESD). Histological evaluation described a gastric NET (g-NET) G1, associated with autoimmune gastritis (Type I). During follow-up, another minor lesion (< 10 mm) suspected for NET was reported along the greater curvature, and resected by Band-ligation endoscopic mucosal resection (EMR-L). Histological report confirmed a Type I g-NET. A: Cardial area reflexed view; B: Resection base after ESD; C: Oriented and pinned specimen; D: Hematoxylin-eosin stain showing monomorphic cells in a nested architecture without necrosis; E: Corresponding Chromogranin A immunostain (20 × magnification); F: Corresponding Ki67 immunostain (20 × magnification); G: Endoscopic appearance of the lesion detected during follow-up; H: EMR-L: Rubber band release; I: Resection base after EMR-L.

and EMR-L are advocated to obtain a deeper submucosal resection than standard EMR.

**Future perspectives and open questions:** The available data regarding the use of SSAs in the management of Type I g-NETs derive from small, retrospective cohorts, resulting in controversial conclusions[45]. Prospective trials exploring this approach would be useful in understanding the indications and the potential benefit of this alternative option which is currently considered only experimental. A prospective study describing the endoscopic appearance of gastrointestinal NETs and proposing an endoscopic classification would help recognize these lesions and select the suitable technique for endoscopic resection.

### *Surgery with radical intent*

Surgery with radical intent is the preferred option in the management of all GEP-NENs, when feasible. Preoperative work should include complete disease staging with both morphological and functional

imaging tests. We will discuss the surgical approach of these patients according to the tumor primary site and focusing on the main critical issues regarding this therapeutic option.

**NETs of the appendix:** Appendiceal NETs are usually incidental found during surgery for acute appendicitis. For this reason, radicality of the intervention and the indications to right hemicolectomy with lymphadenectomy still represent critical issues in the management of these patients. The European Guidelines for NETs have established, based on the literature, certain criteria aimed at guiding this decision according to the features of the tumor[46]. More specifically, appendicectomy is considered sufficient when the tumor is < 1 cm and resection is R0. Right hemicolectomy is instead recommended when the tumor is > 2 cm. Regarding the "grey zone" of intermediate tumor size (1-2 cm), additional risk factors indicating a surgical re-intervention are represented by a G2 histology, signs of histological vascular or lymphatic invasion (V1 and/or L1) or a mesoappendiceal infiltration > 3 mm.

**Small bowel NETs:** Pre-operative tests to be performed in the case of small bowel NETs (Sb-NETs) should also include echocardiography (to evaluate carcinoid heart disease) and colonoscopy. The surgical procedures for resection should include the intraoperative exploration of all abdominal cavities and extensive lymphadenectomy, as one-third of the cases (regardless of primary tumor size) have lymph node metastases upon diagnosis. As these lesions are in almost 80% of cases small, multiple nodules, undetectable by conventional imaging tests, palpation of the entire jejunum and ileum is mandatory to achieve radical resection. These tumors are often characterized by mesenteric fibrosis, and in 5% of cases by small peritoneal implants. For this reason, Sb-NETs are sometimes diagnosed for acute intestinal obstruction. Resection of mesenteric metastases is usually feasible, unless in cases of complete vascular encasement or retroperitoneal involvement[12,47].

**Pan-NETs:** Regarding pre-operative evaluation for Pan-NETs, vascular involvement (superior mesenteric vein, superior mesenteric artery, coeliac axis and common hepatic artery) must be accurately assessed in order to discuss the feasibility of a curative resection. When patients are candidate to enucleation, EUS or magnetic resonance cholangiopancreatography help evaluate the relationship of the tumor with the pancreatic duct[12]. There is an open debate about the management of non-functioning Pan-NETs < 2 cm and with no involvement of the main pancreatic duct. The two possible proposals are surgical resection *vs* follow-up. As long-term data concerning safety of the conservative management are insufficient, surgery can be considered in young, healthy patients. Parenchyma-sparing pancreatic resections (enucleation or central pancreatectomy) can be performed in these cases; however, complete surgery with these techniques is uncertain because lymphadenectomy is crucial to reach the radicality. In fact, recent data report that 12% of resected small Pan-NETs have lymph nodal metastases at surgery, with poorer recurrence-free survival (RFS) rates in the case of tumors of 15-20 mm[12,48]. The decision to operate or just observe these patients also needs to be based on the general conditions of patients, as the benefit of surgery can be counterbalanced by significant morbidity and mortality rates compared to conservative management[49].

**Locally advanced or metastatic disease:** Regarding advanced Sb-NETs, surgery can be considered when patients suffer from symptoms due to mesenteric involvement but must be performed in specialized centers. In fact, radical resection or debulking surgery can significantly improve the quality of life of these patients[12]. Encouraging results of curative resection are also available for GEP-NEN patients with TNM stage IV disease, but after ruling out the presence of extra-abdominal disease. When radical resection is feasible, survival rates are indeed better than debulking or medical treatments. For Pan-NETs, median OS for these three options accounts for 97, 89, and 36 mo, respectively[50]. However, careful patient selection is mandatory in order to reduce the risk of complications. The data regarding the use of neoadjuvant treatment associated with radical surgery are scarce. The RMPanNET trial will compare the survival outcomes of metastatic Pan-NETs treated with resection on the primary tumor and metastases after neoadjuvant systemic treatment (SSAs, targeted therapy or chemotherapy) *vs* continuing only systemic treatment (Supplementary Table 1). The NEONEC trial will instead investigate the role of neoadjuvant treatment in terms of RFS in patients with localized NECs, adopting a cisplatin (or carboplatin)/etoposide regimen (Supplementary Table 1).

**Role of adjuvant treatments:** Unlike other cancers, the data regarding adjuvant treatments in GEP-NENs after curative surgery are scarce, and this approach is not routinely applied in clinical practice. This limitation is probably due to the relatively long survival rates after radical resection without any other treatments (especially for GEP-NETs G1-G2) and to the lack of validated risk scores aimed at identifying patients at high risk of disease recurrence.

A recent retrospective, multicenter study from the United States has reported survival outcomes of 91 GEP-NETs treated with adjuvant treatments (chemotherapy or SSAs) after curative-intended surgery, compared to patients receiving surgery only[51]. The results showed that adjuvant therapy had negative impact on RFS rates, with no benefit in terms of OS. Another piece of analysis from the Surveillance, Epidemiology, and End Results-Medicare (SEER) database included 318 colorectal NENs treated with radical surgery. Focusing on stage I-III TNM disease, no benefit in terms of OS or RFS was observed when adopting adjuvant chemotherapy compared to surgery only[52]. These data discourage the use of

adjuvant treatments, but might be read with caution due to the inevitable selection bias of retrospective studies. In fact, patients receiving post-surgical treatment, in a retrospective analysis, are characterized by more aggressive tumor features, and should not be compared to patients with theoretically less aggressive tumors.

Focusing on NENs G3, the available data concerning the use of adjuvant treatments after curative surgery are derived from retrospective cohorts and provide controversial results. In a series of 73 digestive NECs, with the majority having a colorectal primary tumor site, 43 received chemotherapy, either neoadjuvant and/or adjuvant. The median OS and RFS for patients receiving chemotherapy were 62 and 13 mo, respectively, showing the potential prognostic impact of chemotherapy on survival outcomes[53]. Another study compared the survival rates of 394 radically resected non-metastatic colorectal NECs receiving adjuvant chemotherapy *vs* 412 undergoing radical surgery only. The median OS was significantly longer for patients treated with adjuvant therapy [57.4 *vs* 38.2 mo for patients treated with surgery only; hazard ratio (HR): 0.73, $P < 0.01$], especially in the subgroup of patients with left-sided NECs[54]. Discouraging results were reported by Lin *et al*[55], who analyzed the data of 804 gastric NECs or MiNENs treated with radical surgery +/- adjuvant therapy. The study showed no statistically significant different OS between the two groups. In another retrospective series of 60 GEP-NENs G3 with TNM stage I-III disease receiving radical surgery, the 2-year OS of the total population was 64.5% and the median RFS was 14 mo. Adjuvant therapy, adopted in 20 patients, did not improve either the OS or RFS rates[56].

**Future perspectives and open questions:** The ASPEN study is prospectively assessing clinical outcomes of patients with Pan-NENs < 2 cm managed by radical surgery *vs* follow-up[57] (Supplementary Table 1). The validation of risk scores in prospective cohorts might help stratify resected GEP-NENs according to the risk of disease recurrence. Patients at high risk might be enrolled in RCT evaluating the potential benefit of adjuvant therapies compared to curative surgery only. Studies evaluating response to adjuvant treatments should also include NETs, as data showing a potential benefit of this therapeutic option so far available were mainly obtained in the setting of NEC patients.

## ADVANCED OR METASTATIC DISEASE

### *Surgical resection of the primary tumor*

Beyond the need for debulking in uncontrolled functioning syndrome, resection of the primary tumor is another possible surgical indication in metastatic disease. Some series have recently proved that, in addition to symptomatic relief (for example, for obstruction due to the mesenteric involvement in Sb-NETs), this approach has also a prognostic impact. In fact, in a retrospective series of 14510 GEP-NETs, a benefit in terms of survival has been observed for G1 and G2 patients[58]. A very recent publication from the SEER Registry, including 2219 GEP-NETs, confirms these results for all sites excluding the rectum, with an overall HR of 0.65. In addition, the study highlights the importance of a careful patient selection in a multidisciplinary setting[59]. These conclusions may however be limited by a selection bias, as in retrospective analysis the surgical approach might be reserved to patients with a better performance status or more localized disease[60].

**Future perspectives and open questions:** Prospective studies comparing the survival outcomes of patients with metastatic GEP-NENs treated with primary tumor resection *vs* patients not undergoing this option would assess the potential prognostic impact of this surgical approach.

### *Locoregional treatments*

**Indications, efficacy, and safety:** Up to 80% of GEP-NETs present liver metastases at the time of initial diagnosis. Current guidelines recommend vascular and ablative locoregional treatments only for NETs G1-G2 in the case of metastases involving only or predominantly the liver with stable extrahepatic disease. The goals are the relief of symptoms caused by hormone secretion or mass effect in order to improve quality of life, and survival prolongation by slowing the growth of liver lesions. In very select cases, locoregional treatments can be bridging therapies to liver transplantation[61,62]. These treatments should be offered after discussion in a multidisciplinary team consultation, in the case of hepatic disease progression (DP), and might be also considered in conjunction with other systemic therapies or combined with surgery. The choice is based on liver tumor burden, patient symptoms, general clinical condition, but also on the local expertise and availability of the various procedures.

Liver-directed therapies for metastatic GEP-NETs include thermal ablation, transarterial embolization (TAE) or transarterial chemoembolization (TACE) and transarterial radioembolization (TARE), also known as selective internal radiation therapy (SIRT). The data regarding their anti-tumor efficacy primarily comes from retrospective studies using heterogeneous protocols, and consequently it is currently unclear which technique is preferable.

Ablation techniques (radiofrequency ablation, microwave ablation, and cryotherapy) require imaging guidance, and are only applied in the case of limited liver disease: Less than three lesions ≤ 3 cm, or a

single lesion < 5 cm, or even in association with liver surgery[61]. When feasible, thermal ablation shows lower complication rates than surgery (3.9% *vs* 20%, respectively) and a good clinical response (with relief of symptoms in up to 92%)[63]. Unfortunately, the benefits of ablation alone in terms of survival rates are difficult to demonstrate, due to the influence of subsequent lines of therapy in the calculation.

Vascular treatments are based on the rationale that neuroendocrine liver metastases are hypervascular, deriving all their blood supply from the hepatic artery, whereas the normal hepatic parenchyma is mainly supplied by the portal vein (75%). Arterial embolization makes it possible to deliver a tumoricidal dose of chemotherapy (TACE) or β-radiation (SIRT) in association with the ischemic effect on the lesions, thereby reducing systemic adverse effects (AEs) and limiting toxicity for the normal liver parenchyma through the use of a selective technique. The feared carcinoid crisis due to massive release of serotonin or vasoactive peptides in the case of secreting GEP-NETs is prevented by octreotide premedication and by scheduling the presence of the anesthesiologist during the procedure [11]. A multicenter retrospective study showed better results for catheter-based therapies in terms of OS and hepatic PFS for lower grade NETs and for liver tumor burden ≤ 50%, regardless of the primary tumor site (Pan-NETs or Sb-NETs)[64]. Previous studies have instead reported a higher morphological response rate (RR) and/or better OS for non-pancreatic cases[65].

The TACE uses a mixture of chemotherapy drugs and a temporary embolic agent (degradable starch microspheres of 50 μm, with a half-life of approximately 35–50 min), with the aim of preserving arterial patency for further cycles of treatment (Figure 3). Negative predictive factors for response to TACE treatment in GEP-NETs are represented by impaired liver function (ascites, bilirubin ≥ 2 mg/dL, albumin ≤ 3.5 mg/dL), tumor burden ≥ 70% and previous treatment with three or more systemic lines of therapy[61]. In the case of bilobar liver involvement, a sequential approach with multiple selective or lobar TACE treatment sessions is recommended, usually at a 6-8 wk interval, with assessments for patient tolerance and response after each course. Possible complications include portal vein narrowing or thrombosis, bile duct dilatation leading to biloma formation, and liver necrosis with the possible development of abscesses. Caution is therefore recommended especially in the case of bilio-enteric anastomoses, when initial bile duct dilatation or segmental portal vein thrombosis is detected by pretreatment imaging, representing relative contraindications to the performing of TACE.

Another technique, TARE with $^{90}$Y-loaded microspheres, has a more favorable safety profile than TACE or TAE, with fewer AEs (pain, post-embolization syndrome, liver/biliary toxicity) in the early post-treatment period; however, hepatic cirrhosis with portal hypertension may appear as a long-term complication, especially in the case of bilobar treatment[66]. Patients should undergo preprocedural evaluation for hepatopulmonary shunts to ensure that no more than 20% of the blood flow is diverted to the lungs to avoid radiation pneumonitis.

A recent meta-analysis revealed that patients treated with TACE had significantly better OS than those treated with TARE[67]. TARE proved to be more effective than TAE/TACE when Ki67 ≥ 3%, whereas Ki67 < 3% predicts a greater benefit with TACE[68]. TARE is indicated in the case of TACE failure or in patients at risk for TACE including major portal vein thrombosis, bilio-enteric anastomoses, and heart problems contraindicating doxorubicin administration. The cost *per* procedure for TARE is nearly double that of TACE; however, there is usually no need for multiple treatment sessions[61]. The ArTisaN study will provide data on the efficacy of TARE in metastatic NETs in a phase II-designed study (Supplementary Table 1).

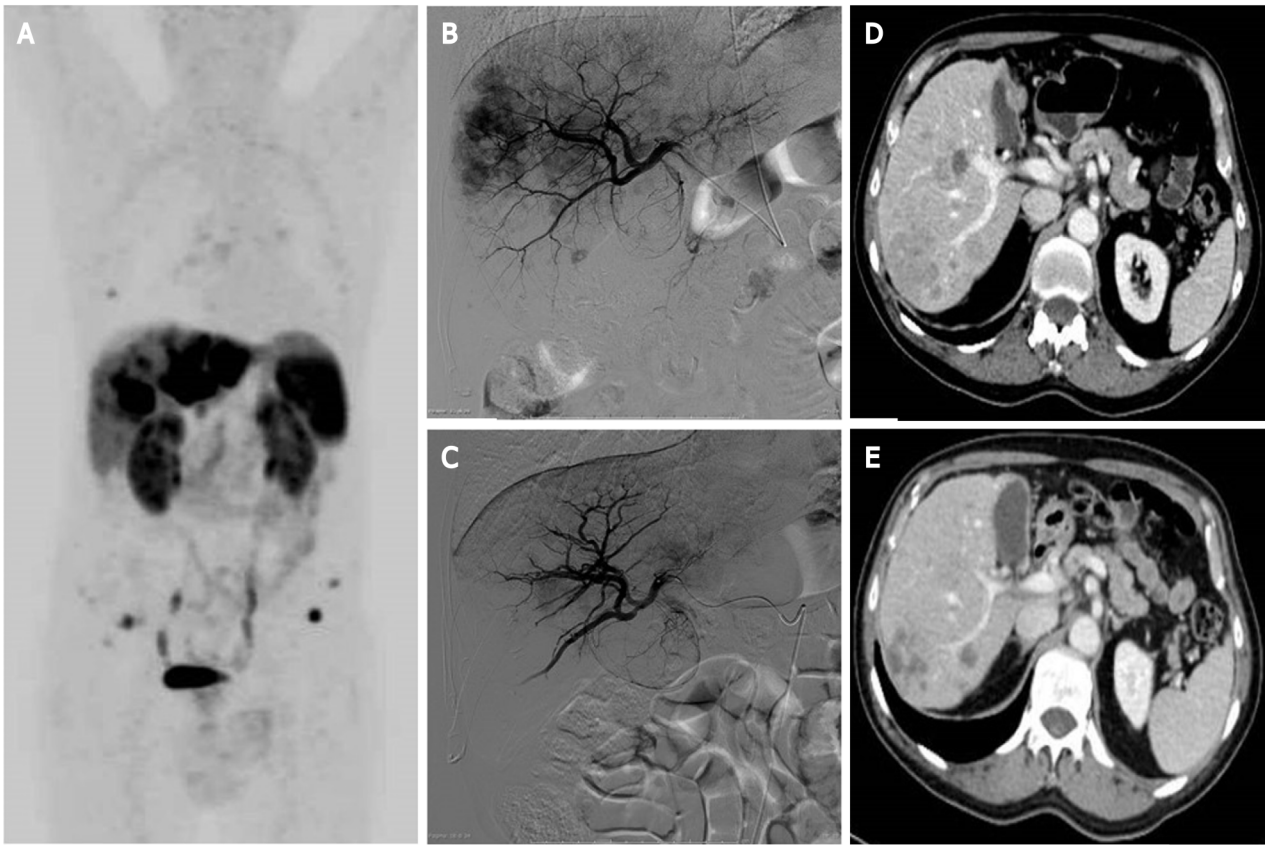
**Future perspectives and open questions:** Studies also including GEP-NETs G3 might explore the efficacy of locoregional treatments for liver metastases in these patients, especially cases with a lower proliferative index (*e.g.*, Ki67 < 55%). The LUTIA trial will investigate the efficacy of the intraarterial administration of $^{177}$Lu-DOTATATE in patients with neuroendocrine liver metastases, and the impact on intra-hepatic biodistribution (Supplementary Table 1). The synergistic effect of liver directed-therapies with immunotherapy represents a further interesting approach to be investigated[69].

### *SSAs*

**Indications, efficacy, and safety:** The expression of SSTRs is the prerequisite for benefiting from SSAs. These drugs bind with high affinity to the G protein-coupled transmembrane SSTR2 and with moderate affinity to SSTR5. They are usually adopted at the first-line stage in advanced GEP-NETs, with good tolerability. They have a double effect: Clinical syndrome control in functionally active NENs (*i.e.* carcinoid syndrome or duodenopancreatic functioning tumors), and antiproliferative effect[13].

Different formulations are available. The short-acting Octreotide is administered subcutaneously, usually to test the tolerability of the therapy. Long-acting formulations for antiproliferative treatment include Octreotide LAR (10, 20, or 30 mg) with intramuscular injection, and Lanreotide autogel (60, 90, or 120 mg) with deep subcutaneous injection. Pasireotide will not be discussed in this review, due to the limited and controversial results regarding its role as an antineoplastic treatment.

The antiproliferative effect of SSAs compared to placebo has been proved by two double-blind RCTs: The PROMID study[70] for Octreotide LAR and the CLARINET trial[71] for Lanreotide. Thanks to these publications, Octreotide LAR was registered for intestinal NETs and NETs of unknown primary tumor site, whereas Lanreotide autogel for intestinal NETs, Pan-NETs, or for cases with unknown primary tumor site. The recommended dosage for the antiproliferative use is the maximum available (Octreotide




DOI: 10.4240/wjgs.v14.i2.78 

**Figure 3 Locoregional treatments for neuroendocrine liver metastases-presentation of a clinical case referred to our hospital, with progressive liver disease after multiple systemic treatments.** A: $^{68}$Ga-DOTATOC-positron emission tomography/computed tomography (CT) whole-body maximum intensity projection image reveals multiple liver metastases involving both hepatic lobes, the left lobe being almost completely replaced by tumor. Bone and lymph nodal small metastases are also evident; B: Selective angiography of the right hepatic artery performed before lobar chemoembolization shows multiple hypervascular liver lesions; C: Selective angiography of the right hepatic artery performed 1 mo after two sessions of degradable starch microsphere transarterial chemoembolization (DSM-TACE). A marked reduction of the liver metastases enhancement is visible, preserved patency of the arterial intra-hepatic branches; D: Portal-phase CT scan before arterial chemoembolization: Multiple confluent hypodense lesions compared to liver parenchyma are detected in the right liver lobe; E: Portal-phase CT scan control after two DSM-TACE: Partial response of the liber metastases, which appear reduced in size and without contrast enhancement. Right portal vein branch narrowing represents an initial sign of liver/biliary toxicity.

LAR 30 mg or Lanreotide autogel 120 mg, administered every 4 wk)[13].

The cumulative antineoplastic effect of Octreotide and Lanreotide compared to placebo has been assessed by a meta-analysis with an overall population of 289 patients, showing a reduction of DP risk of 41% by adopting SSAs compared to placebo [HR: 0.41; 95% confidence interval (CI): 0.29-0.58, $P < 0.01$][72]. The meta-analysis also showed no statistically significant difference in terms of serious AEs (SAEs) between the two arms. However, a higher frequency of biliary stones occurred in the treatment arm (10.5% *vs* 2.7%, respectively)[72]. The elective prophylactic cholecystectomy in advanced GEP-NETs undergoing primary tumor resection represents a possible, but still debated, option in case SSAs are required.

Other possible side effects observed during treatment with SSAs are hypo/hyperglycemia, gastrointestinal symptoms (abdominal pain and diarrhea), and pancreatic insufficiency, which can be confirmed by fecal elastase test, and treated by pancreatic enzyme supplementation[73].

**SSAs for highly proliferating Pan-NETs:** Focusing on Pan-NETs, the available data regarding the efficacy of SSAs as antineoplastic treatment are limited to the CLARINET study, which however included only G2 cases with Ki67 < 10%[71]. Thus the question regarding their use in the case of higher proliferative index remains open. A recent cooperative real-world study analyzed the antiproliferative effect of SSAs when adopted at the first-line stage for non-functioning, metastatic Pan-NETS with Ki67 ≥ 10%[74]. The total population of 73 patients also included five Pan-NETs G3. The median PFS was 11.9 mo (95%CI: 8.6, 14.1), but a higher efficacy was shown in G2 patients and with limited hepatic tumor involvement. In detail, the median PFS was 12.4 mo in G2 patients *vs* 4 mo in G3 cases ($P < 0.01$). Patients with liver load ≤ 25% had a median PFS of 15 mo *vs* 9.7 mo in the case of higher hepatic tumor load ($P = 0.04$).

**Dose escalation:** After the occurrence of DP during the treatment with SSAs, GEP-NET patients receive more aggressive and less tolerable drugs. A possible alternative option to this approach is a dose escalation of SSAs. A recent systematic review regarding this therapeutic strategy has reported a disease control rate (DCR) of 30%-100%, and a median PFS of 6.8-32 mo. These wide ranges are probably due to the heterogeneity of the included studies, as they are both retrospective and prospective and they adopt different SSA formulations and at different disease statuses[75].

The NETTER-1 study evaluated the administration of Octreotide 60 mg every 4 wk, but in clinical practice, the dose increase is usually performed by shortening the time interval between injections[76]. The CLARINET FORTE study recently investigated, for the first time in a prospective setting, the potential benefit of this strategy in a series of Sb-NETs G1-G2 or Pan-NETs (NCT02651987)[77]. After experiencing DP during monthly injections of Lanreotide 120 mg, patients were treated with the same dosage but every 2 wk, respectively for 48 and 24 cycles. The results were presented at the last ESMO Conference 2020, showing a duration of stable disease of 13.8 mo for Sb-NETs and 8.3 mo for Pan-NETs. The DCR after 48 wk was 33.3% and 22.9%, respectively. Toxicity was similar to the data observed in the CLARINET trial[71], additionally highlighting the good safety profile of SSAs also after dose escalation, with rare Grade 3 side effects. Considering the efficacy, the good safety profile and the absence of deterioration of quality of life with SSA dose escalation, this approach might represent a valid option for progressive NENs, as it can delay the switch to other potentially more toxic drugs.

**Novel biomarkers:** Measuring the transcript profile of blood in NET patients is more sensitive and specific than chromogranin A or other blood tests available, and might overcome the limits of imaging tests in assessing the tumor response. The "NETest" represents a transcriptomic signature of NETs, being a multianalyte algorithm analysis PCR-based test. It evaluates, using peripheral blood real-time PCR, the tumor biological activity by measuring the expression of 51 genes, which are associated with neoplastic behavior. In a prospective study, its role in predicting tumor progression during SSAs for GEP-NETs was assessed, showing an earlier prediction of DP than chromogranin A, with an accuracy of 80%-100%[15]. Besides the potential applications of the NETest both for NET diagnosis and follow-up, this test is currently only experimental and it is unavailable in daily clinical practice[78].

**Future perspectives and open questions:** Besides the use of SSAs at the first-line stage in advanced GEP-NETs G1-G2, the role of these drugs in maintaining therapy is being explored. The REMINET trial is assessing whether Lanreotide 120 mg can maintain a stable disease in duodenopancreatic NETs G1-G2, after response to first-line chemotherapy. The preliminary results were presented at the last ENETS Conference 2021, but a phase III trial is needed for their validation (Supplementary Table 1). The TNE-IDC-COLE trial is evaluating, in a prospective randomized setting, the potential benefit of prophylactic cholecystectomy in advanced GEP-NETs receiving SSAs (Supplementary Table 1). The indication of SSAs in G3 cases needs to be further investigated, as well as the potential benefit of SSAs in cases with low or heterogeneous expression of SSTRs. Prospective studies assessing the role of NETest in predicting response to SSAs, as well as other therapeutic options, are needed for validation of this test in clinical practice.

### *Interferon*

Interferon alpha (IFN-α) is licensed in Europe for functioning GEP-NETs, but it can also control tumor growth. This latter function is based both on a direct antiproliferative effect (influencing the cell cycle, the production of growth factors, and angiogenesis), and an indirect immunomodulatory effect. Several prospective studies have investigated its efficacy as antineoplastic therapy, with conflicting results.

Bajetta *et al*[79] prospectively enrolled 53 patients affected by progressive, metastatic NETs. Patients received IFN-α-2a with the following scheme: 3 × $10^6$ IU for the first 3 d, progressively increased to 6 × $10^6$ IU for 8 wk, and then three times *per* week. After a median treatment duration of 6 mo, 64% of patients showed partial or complete tumor regression, lasting 1-11 mo. Less enthusiastic results were reported by Faiss *et al*[80], showing no benefit in terms of PFS adopting in naïve GEP-NETs the association of IFN-α/Lanreotide alone. Regarding comparison with chemotherapy, a study showed, in naïve patients with functioning tumor, a better DCR with IFN-α than with streptozotocin (STZ)/5-fluorouracil (5-FU) ($P < 0.01$)[81].

The most common clinical AEs that occur during IFN-therapy (nearly 50% of the patients) are: Flu-like syndrome (fatigue, fever), which can be prevented by paracetamol, neurological disorders (depression), weight loss, abdominal pain, alopecia, pain at the injection site, and headache. Biochemical toxicity includes: Impaired liver functional test (one third of patients), leukopenia, autoimmune diseases (thyroiditis) in 20% of cases, anemia (31%), thrombocytopenia, hyper/hypoglycemia, and the production of neutralizing interferon antibodies. Considering the balance of pros and cons, and the fact that we currently have several alternative options for unresectable GEP-NENs, IFN therapy is currently reserved for only very select cases, mostly syndromic[13]. Regarding the increase in dosage of IFN at DP, as well as its use in G3 patients, no consistent data are available in the literature.

### *PRRT*

**Indications, efficacy, and safety:** PRRT is based on radiolabeled somatostatin receptor agonists binding SSTRs on tumor cells. After binding, they are internalized and stored in lysosomes, thereby delivering the radioactivity to the tumor cells. The target of PRRT is DNA damage induced by radiation and suboptimal repair, and this effect is more active during mitosis. Before PRRT begins, a basal Octreoscan®, $^{68}$Ga-DOTA-PET/CT or $^{64}$Cu-DOTA-PET/CT is mandatory in order to obtain *in vivo* mapping of all lesions expressing SSTRs. Suitable patients for PRRT have strong SSTR expression, whereas extensive hepatic and/or bone disease, as well as decreased renal function, may limit its indication. According to ENETS Consensus Guidelines "PRRT is a therapeutic option in progressive SSTR-positive NET with homogenous SSTR expression (all lesions are positive)"[82].

Radiolabeled DOTA pharmaceuticals include $^{90}$Y- or $^{177}$Lu-DOTATOC, and currently, $^{177}$Lu-DOTATATE (LutaThera®), which was approved for GEP-NETs by the United States Food and Drug Administration in 2018. Due to the high renal toxicity, $^{90}$Y is now used for the locoregional treatments of liver metastases. The usual schedule for PRRT comprises four cycles of $^{177}$Lu-DOTATATE over 6-8 mo, achieving total radioactivity of 25-30 GBq. Toxicity includes myelotoxicity, which can be mitigated with extracorporeal affinity adsorption treatment. This side effect is usually mild and reversible; however, up to 10% of patients may develop WHO Grade 3/4 hematotoxicity, and rarely myelodysplastic syndrome or leukemia[10,83]. Nephrotoxicity may also be caused by PRRT, as the radiopeptides accumulate in the renal interstitium; however, this AE can be reduced by administering a positively charged amino acid infusion. Nausea, vomiting, or (rarely) carcinoid crisis may also occur with PRRT[10].

After a long series of retrospective studies investigating PRRT and proving its ability to inhibit tumor growth in 50%-70% of GEP-NETs[84], the first phase III RCT (the NETTER-1 study)[76] was published. It included 229 patients affected by progressive, unresectable, Sb-NETs G1-G2, and showed an improved outcome with Lutathera® + best supportive care (including Octreotide 30 mg) than with Octreotide 60 mg administered every 4 wk. More specifically, PFS rates at month 20 were 65.2% in the $^{177}$Lu-DOTATATE group and 10.8% in the control group, and a benefit was also observed in terms of quality of life[85]. Based on this trial, Lutathera® has been registered for advanced, progressive GEP-NETs (although Pan-NETs had not been included in this RCT). Further analysis of the NETTER-1 results showed that in the PRRT arm, PFS was not significantly affected by tumor shrinkage, suggesting that this treatment prolonged PFS even when tumor objective response was not detected at imaging[86]. A delayed response to PRRT was indeed observed 3 years after PRRT in a patient participating in this trial [87]. These encouraging results have been strengthened by a meta-analysis of 22 RCTs investigating the efficacy of Lu-DOTATATE/DOTATOC in a cumulative population of 1758 advanced/inoperable NETs [88]. The pooled disease RR was 25.0%-35.0%, while the pooled DCR was around 80.0%, proving the efficacy of PRRT as an antineoplastic treatment in these patients.

In a recent consensus, the indication for PRRT was confirmed as a second-line treatment for GEP-NETs with $^{68}$Ga-DOTA-SSA-uptake in all lesions, in NET G1-G2 at DP, and in a subset of NETs G3 when all lesions are positive at $^{68}$Ga-DOTA-PET/TC[89]. Regarding the efficacy of PRRT in improving OS, the data are still scarce. A new analysis from the NETTER-1 trial, presented at the American Society of Clinical Oncology conference 2021, has however observed no significant benefit from PRRT compared to high-dose SSAs in terms of OS[90].

**PRRT for G3 patients:** The data regarding the use of PRRT in GEP-NENs G3 are derived from retrospective series, suggesting the potential active role of this treatment for highly proliferating cases. A recent review of the literature with the same topic has shown a median PFS of 19 mo when adopting PRRT in NETs G3 patients *vs* 11 mo for NECs with Ki67 < 55%, and only 4 mo for NECs with higher Ki67[91]. Based on these results, PRRT can be considered for patients with increased uptake on somatostatin-based imaging tests, both in GEP-NETs G3 and NECs, but with a Ki67 < 55%, inoperable disease, life expectancy of at least 3–6 mo, and reasonable performance status (Karnofski Score > 50%) [82]. A potential role for highly proliferating NEC patients might be reserved to very selected cases, and probably a dual tracer using somatostatin-based imaging tests and $^{18}$Fluorine-fluorodeoxyglucose ($^{18}$F-FDG) PET/CT might be necessary for these patients.

**Novel biomarkers and potential role of $^{18}$F-FDG-PET/CT:** DP during PRRT is reported in 15%–30% of patients, and the lack of predictive biomarkers helping identify responders *vs* non-responders represents an open issue for NEN management. Proposed tests are the PRRT prediction quotient (PPQ), which is a blood-based assay for eight genes useful to predict PRRT efficacy with an accuracy of 97%, and the NETest, showing an accuracy of 98% in assessing response to PRRT. Trends of NETest correlate with PPQ prediction, but no tests can predict toxicity[92,93]. The $^{18}$F-FDG-PET/CT might also help select patients who are candidate for PRRT. It is commonly used in many tumors, but its value for NENs had been initially reserved only for poorly differentiated cases. The recent International Consensus regarding the role of theragnostic in NENs considered it suitable to employ $^{18}$F-FDG PET/CT in NECs, in NETs G3 and also in NETs G1-G2, in order to identify the mismatched ($^{18}$F-FDG-PET/CT-positive/$^{68}$Ga-DOTA-SSA-negative) lesions[89]. Indeed, as up to 45% of patients referred to PRRT may present heterogeneous SSTR expression, $^{18}$F-FDG PET/CT might differentiate GEP-NETs G1-G2 disease into low- and high-risk patients of poor response to PRRT[94].

**Re-treatment with PRRT:** The opportunity to perform a second PRRT regimen, in patients already undergoing this therapy, is currently being discussed. Rudisile *et al*[95] re-treated 35 patients, who had previously received four cycles with $^{177}$Lu-DOTATATE, obtaining a stable disease in 26 patients (81.3%). They concluded that salvage therapy with $^{177}$Lu-DOTATATE is safe and effective, even in patients with extensive previous multimodal therapies during DP. The experience from Denmark reports a better response for G1-G2 cases than G3, but shorter survival outcomes upon retreatment (median PFS 19 mo, median OS 54 mo)[96]. In 2021, a meta-analysis of seven studies regarding PRRT re-treatment in 414 patients with advanced NETs showed a median PFS of 12.52 mo, with a safety profile similar to the initial PRRT treatment[97]. These encouraging data have been recently supported by a consensus on theragnostic in NENs, proposing PRRT rechallenge in patients with a stable disease for at least 1 year following therapy completion[89].

**Neoadjuvant PRRT:** The use of pre-surgical PRRT, aimed at obtaining disease downstaging, primarily derives from small retrospective series. The largest series includes 57 GEP-NETs with unresectable primary tumor due to vascular involvement, with or without liver metastases. After receiving pre-operative $^{177}$Lu-DOTATATE, resectable primary tumor was observed in 15 (26.3%) cases. The estimated PFS rate at 2 years was 90%-95%, and OS accounted for 92.1%. A better response was observed in the case of: Duodenal NETs, GEP-NETs with no regional lymph node involvement, primary tumor < 5 cm, liver lesions ≤ 1.5 cm, number of liver lesions ≤ 3, and $^{18}$FDG-uptake as a maximum standard uptake value < 5 in the primary tumor[98]. Regarding Pan-NETs, neoadjuvant PRRT seems to reduce the size of the primary tumor, the size of metastatic lymph nodes, and the risk of pancreatic fistula, maintaining the same post-operative survival outcomes[99].

**Future perspectives and open questions:** Besides the available data supporting PRRT as a second-line treatment after SSA-failure, the efficacy of PRRT at first line will be evaluated by the NETTER-2 study, which adopts Lutathera® in combination with long-acting Octreotide in advanced GEP-NETs G2-G3 compared to high-dose (60 mg) long-acting Octreotide (Supplementary Table 1). The RCT is including both naïve patients and cases previously treated with SSAs in the absence of DP. The study will also provide more data regarding the use of PRRT in the treatment of GEP-NETs G3, probably also at first line. The identification of novel biomarkers helping select the right candidates for PRRT from the NENs would pave the way for the application of precision medicine in this field. The NeoLuPaNET trial will assess the role of neoadjuvant PRRT in resectable Pan-NETs at high risk of disease recurrence. The study endpoints will include post-operative 90-d morbidity and mortality rates, and objective RRs (Supplementary Table 1). Somatostatin receptor antagonists rather than agonists, labeled with radionuclides, are being investigated and seem to provide a longer tumor residence time of the administered dose. New alpha, beta, gamma, and Auger electron-emitting radionuclides are being investigated. In particular, $^{212}$Pb-DOTAMTATE seems to be a possible alternative to $^{177}$Lutethium (NCT03466216). The first results from a dose-escalation study on 6 patients were presented at the NANETS 2020 Conference[100], and the results are promising.

### *Targeted therapies: Everolimus*

**Indications, efficacy, and safety:** Everolimus is an inhibitor of the mammalian target of rapamycin, which is an intracellular protein kinase downstream of the phosphoinositide 3-kinase (PI3K)/Akt pathway involved in tumorigenesis. It has been approved as an antineoplastic drug for progressive GEP-NETs as a result of several trials and also "real-life" experiences. It is usually prescribed at a standard dosage of 10 mg/d as continuous oral intake, but in the case of toxicity it can be reduced to 5 mg/d or interrupted (in the case of Grade 3 or 4 side effects).

Focusing on metastatic Pan-NETs, the phase II trial RADIANT-1 proved the efficacy in tumor control after chemotherapy failure of both everolimus alone (10 mg/d) and combined with Octreotide LAR, led to a median PFS of 9.7 mo and 16.7, respectively[101]. The subsequent phase III RADIANT-3 study assessed tumor control by everolimus in 140 progressive Pan-NETs, and showed a significantly different median PFS compared to placebo: 11.0 mo *vs* 4.6 mo, respectively ($P < 0.01$)[102].

Regarding non-pancreatic NETs, the RADIANT-4 RCT evaluated the efficacy of everolimus 10 mg/d compared to placebo in progressive, well-differentiated, non-functioning lung and non-pancreatic digestive NETs[103]. A significantly higher PFS was observed in the treatment arm compared to placebo (11 mo *vs* 3.9 mo; $P < 0.001$), with a rate of disease stabilization respectively of 81% *vs* 64%. The efficacy of everolimus was also proved in terms of OS, with a 36% reduction in the risk of death (HR: 0.64; $P = 0.037$). However, a recent meta-analysis of all available trials adopting everolimus for NENs confirmed the benefit in terms of PFS, but not in terms of OS[104].

The efficacy of everolimus and the good safety profile in advanced progressive GEP-NETs were also confirmed in the real-world setting. In 169 patients receiving this drug for compassionate use, the median PFS was 12 mo and the median OS was 32 mo. The results of the study also suggested the use of everolimus before chemotherapy and PRRT, as the subgroup of patients previously treated with these therapies had suffered due to higher toxicity[105].

Reported toxicity during treatment with everolimus includes: Stomatitis (up to 67% of cases), skin rash (29%–49%), fatigue (33%), infections (20%), diarrhea (30%), cytopenias (< 20%), pulmonary toxicity (10.4%), metabolic impairment (hyperglycemia 5%-13%, increased triglyceride and cholesterol levels 39%-66%, hypophosphatemia 40%), peripheral oedema (13%-20%), and renal impairment (rare and transient)[13,106,107]. Regarding stomatitis, a systematic review observed a longer PFS when it occurs within 8 wk from the start of therapy[106].

**Everolimus for G3 patients:** A potential antiproliferative effect of everolimus in NENs G3 far been reported in well-differentiated cases. A median PFS of 6 mo and a median OS of 28 mo were observed in a small, retrospective cohort of 15 cases with Ki67 20%-55%[108]. In this series, disease stabilization was maintained in 40% of cases for at least 1 year. Focusing on prospective studies, the NECTOR study (a phase II multicenter trial) has evaluated the safety and efficacy of everolimus after failure of platinum-containing chemotherapy in Pan-NECs, providing discouraging results[109]. In the enrolled 25 patients, the median PFS was only 1.2 mo and median OS was 7.5 mo. Disease control was obtained in 39.1% of cases, with no objective response.

**Resistance to everolimus:** The antiproliferative effect of everolimus may be limited by primary and secondary drug resistance. In detail, patients showing DP at their first evaluation after starting treatment are primary refractory, whereas cases facing DP after an initial tumor response are patients with acquired resistance[110]. Several strategies are being investigated to overcome the resistance to everolimus. Retreatment after a pause might be an option, but this strategy is only supported by clinical experience and not by published data. A possibility reported in the literature is represented by BEZ-235, which is a dual inhibitor for PI3K and mammalian target of rapamycin (mTOR) (PI3K/mTOR kinase inhibitors), and has a potential synergistic effect when adopted in combination with everolimus. Passing from preclinical to clinical studies, about 250 patients affected by several tumor types were treated with this drug. Since the patients experienced high toxicity of the gastrointestinal tract and bone marrow, as well as early progression, the trials including Pan-NETs were prematurely stopped[111,112].

**Future perspectives and open questions:** The EVINEC study is currently enrolling patients with G3 neuroendocrine disease, after platinum-based chemotherapy failure, to be treated with everolimus (Supplementary Table 1). This trial will provide further data regarding the use of this therapy in NEC patients. The possibility to retreat patients with everolimus, alone or in combination with other drugs, has never been investigated but may represent another option to be evaluated in future studies. This strategy might also help overcome the resistance to everolimus.

### *Targeted therapies: Sunitinib*

**Indications, efficacy, and safety:** Sunitinib is an oral multikinase inhibitor competing with ATP for binding within the intracellular domain of various wild-type and/or mutated receptor tyrosine kinases. This antiangiogenetic drug acts against vascular endothelial growth factor receptors, platelet-derived growth factor receptors, KIT, fms-like tyrosine kinase 3, and RET. It has been registered for advanced progressive Pan-NETs at a standard oral daily dose of 37.5 mg, based on a double-blind phase III RCT including 171 well-differentiated, advanced, progressive Pan-NETs receiving sunitinib or placebo[113]. The trial was interrupted early due to the significantly different outcomes and toxicity observed in the two arms: Median PFS 11.4 mo with sunitinib *vs* only 5.5 mo in the placebo arm ($P < 0.01$), OS at 6 mo 92.6% *vs* 85.2%, respectively ($P = 0.02$). A re-analysis of this study[114] showed no significant difference in terms of quality of life between the two arms, with the exception of a worsening of diarrhea observed in the treated patients ($P < 0.05$). Reported toxicity observed during treatment with sunitinib generally includes gastrointestinal symptoms (diarrhea, nausea, vomiting) in 33%-59% of cases, and fatigue (41% of patients). Other possible side effects can be hypertension, headache, the hand-foot syndrome, and neutropenia (Grade 3-4 in 12%). Treatment discontinuation due to side effects occurs in 15% of patients, and 31% require a dose reduction[13]. Experiences from the real-world setting reported, in 62 Pan-NETs receiving Sunitinib for a median time of 165 d, objective response in 13.7% of patients, but the need for dose reduction in 41.9%[115]. In an Italian retrospective study[116] of 80 pre-treated Pan-NETs receiving sunitinib, the median PFS was very close to the results of the trial by Raymond *et al*[113] (10 mo), with 7.5% of patients stopping the treatment due to toxicity. The data concerning the efficacy of sunitinib in non-pancreatic NENs are scare and disappointing. One study from Korea[117] adopted sunitinib in 10 non-pancreatic patients, observing a disease stabilization in 50% of the series, but a poorer median PFS than in cases treated with everolimus: 1.7 mo *vs* 14.7 mo, respectively ($P < 0.01$).

**Sunitinib for G3 patients:** Regarding G3 disease, data regarding the use of sunitinib are scarce. Mizuno *et al*[118] observed, in 15 unresectable Pan-NENs G3 receiving sunitinib, a significantly better outcome for Pan-NETs G3 than Pan-NECs ($P < 0.05$), and no significant difference between Pan-NETs G3 and G1-G2 cases. A tumor response in G3 cases treated with sunitinib was also observed by Pellat *et al*[119] in an open-label study, who described in 31 GEP-NENs G3 a median PFS of 42 d, and median OS of 181 d. However, this study was primarily focused on biomarkers, and did not report further details regarding survival.

**Future perspectives and open questions:** Prospective studies should assess the efficacy of sunitinib in non-pancreatic, digestive NENs, as well as in GEP-NENs G3.

### *Targeted therapies: Surufatinib*

Surufatinib is an oral tyrosine kinase inhibitor targeting immune cells and angiogenesis. To date, few data are available on its efficacy in GEP-NENs, but they are encouraging. Results of the SANET-ep RCT [120] enrolling 198 patients with progressive, unresectable or metastatic, well differentiated, extra-pancreatic NETs showed a better median PFS for the surufatinib arm compared to placebo (9.2 mo *vs* 3.8 mo, respectively, $P < 0.01$). The SANET-p trial included 172 progressive, advanced, Pan-NETs, receiving surufatinib or placebo. The median PFS rates were 10.9 mo *vs* 3.7 mo, respectively ($P < 0.01$)[121]. Based on these results, surufatinib might represent a possible further therapeutic option for advanced GEP-NENs, but it also needs to be evaluated in a real-life setting to draw definitive conclusions, especially if we consider the reported toxicity. The two available trials[120,121], in fact, showed more frequent AEs, the occurrence of Grade 3 or worse hypertension, proteinuria, and hypertriglyceridemia. SAEs were reported in 22%-25% of cases in the surufatinib group, and death was observed in 3 patients in both trials.

### *Chemotherapy*

According to the ENETS Guidelines[9], chemotherapy in general represents a valid option for progressive or advanced Pan-NETs and GEP-NENs G3. Besides these indications, it may also be considered in other particular situations, such as GEP-NENs G2 with high Ki67, in the case of rapidly progressive disease, after the failure of other treatments, or even in cases not expressing SSTRs.

### *Chemotherapy: STZ*

**Indications, efficacy, and safety:** STZ is generally adopted in advanced/metastatic Pan-NETs G1-G2 with high tumor burden, with the aim of obtaining an objective response. STZ is an alkylating agent, usually administered intravenously as a daily regimen for a 6-wk schedule, by rapid injection or short (15–30 min) infusion with a maximum single dose of 1500 mg/m$^2$. The data concerning its efficacy are controversial, and this drug is not available in some European countries (including Italy). A retrospective study from Germany adopted STZ/5-FU in 96 Pan-NETs, including 56.3% naïve patients, and 6.3% G3. Objective response was reached in 42.7% of patients and stable disease in 40.6%. The median time to progression and OS were 19.4 and 54.8 mo, respectively. A better outcome was observed for Pan-NETs with Ki67 < 15%[122]. Besides the association with 5-FU, an alternative combination of STZ with doxorubicin (or even the STZ/5-FU/doxorubicin regimen) has been investigated, and a better response was observed compared to STZ/5-FU; however, the application of these regimens was limited by a significant cardiotoxicity[123,124].

The most frequent AEs caused by STZ are renal toxicity (dose-related and cumulative), gastrointestinal symptoms (nausea, vomiting, diarrhea), glucose intolerance, liver dysfunction, and hematotoxicity. STZ is mutagenic and carcinogenic and its extravasation causes necrotic tissue lesions [9]. With regard to toxicity, a Japanese retrospective, multicenter study[125] reported in 110 patients the same efficacy adopting a daily *vs* weekly administration of STZ-based chemotherapy, and with monotherapy *vs* combination therapy, but with a significantly better tolerability when STZ was adopted as a monotherapy. The objective response observed in the overall population was 21.8%, with median PFS of 9.8 mo. Schrader *et al*[126] proposed maintaining therapy with STZ/5-FU, using an extended cycle protocol. After the 6-wk protocol, resulting in a median PFS of 21 mo and a median OS of 69 mo, 13 of the 28 included patients were switched to an extended 3-mo cycle protocol for maintaining therapy. This treatment provided an additional median PFS of 23 mo.

**Future perspectives and open questions:** The use of STZ for non-pancreatic GEP-NETs needs to be further investigated, and might represent a potential option as a neoadjuvant treatment. There are a few studies that evaluate a potential role of STZ in the management of G3 cases and these provided conflicting results[122,127,128]. This option should be further investigated in a prospective setting. Therapy combination with PRRT might be explored as a possible additional therapeutic option for GEP-NETs.

### *Chemotherapy: Temozolomide and capecitabine*

**Indications, efficacy, and safety:** Temozolomide is an oral alkylator, whereas capecitabine is an oral prodrug for 5-FU. Their association (CAPTEM) usually follows a scheme consisting of capecitabine 750 mg/m$^2$ twice daily (days 1–14) and temozolomide 200 mg/m$^2$ once daily at bedtime (days 10–14) every 28 d[129]. Chemotherapy with CAPTEM has been initially adopted in advanced Pan-NETs G1-G2, based on retrospective studies showing a synergistic effect of these two drugs against tumor proliferation. A randomized phase II study (NCT01824875) including Pan-NETs has definitely proved its superiority in disease control compared to only temozolomide, observing a median PFS of 22.7 mo *vs* 14.4 mo, respectively ($P = 0.023$), whereas median OS was not reached *vs* 38 mo[130].

The cumulative antineoplastic effect of CAPTEM regimen has been calculated by a recent meta-analysis including 15 studies and a total population of 384 NENs: Median OS was at least 12 mo and DCR was 72.89%[131]. The efficacy of CAPTEM has also been assessed at first line for Pan-NETs, resulting in an objective response in 70% of patients and median PFS of 18 mo[129]. Regarding toxicity, most frequent AEs due to temozolomide are gastrointestinal symptoms (vomiting, mild nausea, constipation, anorexia), rash, headache, and fatigue, but convulsions may also occur. Grade 3-4 events have been observed in more than 40% of cases after 4 mo of therapy, and may remain in more than 30% for 12 mo following the stopping of treatment. They include thrombocytopenia (3.36%), neutropenia (0.69%), lymphopenia (0.65%), anemia (0.59%), mucositis (0.57%), and transaminase elevation (0.13%)[9,131]. Capecitabine is associated with hand-foot syndrome and liver toxicity (usually hyperbilirubinemia). Less frequently, hematological toxicity may also occur. Side effects are usually reversible and do not require permanent drug discontinuation, but only a dose reduction[9].

**CAPTEM for non-pancreatic GEP-NETs and G3 patients:** Some series report the use of CAPTEM regimen also for non-pancreatic GEP-NETs. Ostwal *et al*[132] included in their series of 29 NENs G2-G3 also 12 Sb-NENs, obtaining a median PFS for the overall cohort of 33.7 mo. Spada *et al*[133] analyzed data regarding 170 NETs treated with temozolomide-based chemotherapy, including 21 gastrointestinal primary cases and G1 cases. Objective response of the overall population was 28%, median OS 35.6 mo, and median PFS 14.7 mo. The efficacy and safety of CAPTEM regimen have also been proven after prolonged administration in a retrospective study from Israel[134] including 79 NENs with median treatment duration of 12.1 mo (range 0.6-55.6). The median PFS was 10.1 mo and median OS 102.9 mo, with DCR achieved in 59.5% patients. SAEs were rare, with a low discontinuation rate. Regarding the use of temozolomide-based therapy for NENs G3, data from the literature describes CAPTEM as the most commonly used treatment for NETs G3, with a DCR of 65% (35% objective response) and a median PFS of 9.4-12 mo[135]. Instead, the few data available regarding the use of this temozolomide-based regimen in GEP-NECs report poorer disease control in this subset of patients compared to all NETs (HR: 2.70)[136], with a median PFS of 1.8 mo and a median OS of 7.8 mo observed in unresectable extra-pulmonary NECs after platinum-based chemotherapy failure[137].

**Neoadjuvant use of TEMCAP:** Only two series sought to exploit the downstaging effect of TEMCAP as a neoadjuvant treatment. In a series of 30 Pan-NETs with advanced disease or hepatic metastases, partial response after CAPTEM was achieved in 43% of cases[138]. Another report from the United States adopted in six Pan-NETs with borderline criteria for resectability the CAPTEM regimen +/- radiotherapy before surgery, and obtained in all the patients a radiologic response, and a R0 resection in four[139].

**Future perspectives and open questions:** Alkylating agents (temozolomide, dacarbazine, DTZ) transfer methyl adducts on DNA bases. Of these, O6-methylguanine accounts for many of their cytotoxic effects and can be repaired by the O6-methylguanine-methyltransferase (MGMT). Approximately half of Pan-NETs are MGMT-deficient, as determined by impaired tumor MGMT expression or by MGMT promoter methylation[133]. An open issue is whether the MGMT deficiency may be a relevant biomarker for increased response and improved survival in these patients. Prospective studies evaluating this possibility and attempting to standardize the assessment of MGMT status are needed. Prospective studies investigating the potential benefit from neoadjuvant CAPTEM for advanced GEP-NETs would provide data regarding a possible further cytotoxic role of this chemotherapy regimen.

### *Chemotherapy: Platinum-based regimens*

**Indications, efficacy, and safety:** Platinum-based chemotherapies are considered the standard of care for unresectable GEP-NECs[9]. Sorbye *et al*[140] showed a better outcome for advanced GEP-NENs G3 adopting palliative chemotherapy compared to best supportive care. Median OS was indeed 11 mo *vs* 1 mo, respectively. Patients with Ki67 < 55% had a lower RR to the treatment (15% *vs* 42%, $P < 0.001$) but a better OS than cases with higher Ki67 (14 mo *vs* 10 mo, $P < 0.001$). Furthermore, the analysis identified negative prognostic factors for survival a poor performance status, a primary tumor colorectal site, and elevated platelets or lactate dehydrogenase levels.

A recent study performed a reclassification of G3 patients previously treated with platinum-based chemotherapy based on the new WHO classification[6]. In this analysis, a higher RR was observed for NECs with Ki67 ≥ 55% (44%) than NECs with Ki67 < 55% (25%) or NETs G3 (24%). Median PFS was instead 5 mo for all the subgroups[141]. The cisplatin-etoposide regimen (or alternatively carboplatin-etoposide, or irinotecan-cisplatin) is usually adopted at first line in these neoplasms, with an expected RR of 30%-70% and high toxicity. An adequate organ function and performance status are thereby required to receive this systemic treatment[9,142,143].

Cisplatin is usually administered by intravenous infusion, after intensive pre- and post-treatment intravenous hydration +/- osmotic diuretic (to prevent renal toxicity)[9]. Etoposide is usually administered by intravenous infusion, but oral formulation is also available[144]. Regarding toxicity, cisplatin is contraindicated in the case of renal impairment or allergic reactions against platinum compounds, whereas dose reduction is not needed in the case of liver function impairment. Side effects (involving at least 10% of patients) include gastrointestinal symptoms (anorexia, nausea, vomiting, and

diarrhea), hematotoxicity (leukopenia, thrombocytopenia, and anemia), renal disorders, hearing impairment, fever, and peripheral sensory neurotoxicity (transient or permanent)[9]. The data concerning the possibility to adopt carboplatin in the case of renal failure as an alternative to cisplatin are still scarce; however, AEs, including liver failure, may occur also with carboplatin[9]. Etoposide is carcinogenic and mutagenic. The dose-limiting effect of etoposide is myelosuppression. Impaired hepatic or renal function may increase etoposide concentration in tissue. Gastrointestinal symptoms may also occur, as well as stomatitis and temporary hair loss[9]. The association of oxaliplatin-based chemotherapy with 5-FU, leucovorin, and oxaliplatin (FOLFOX) or with capecitabine (XELOX) are usually adopted for NECs as a second or further line of therapy, with an expected DCR of 62%-84%[145,146]. Some series have shown activity also in GEP-NENs G1-G2[145,147], and a retrospective series has reported promising results with FOLFOX also adopted at first line for GEP-NETs G2 and GEP-NENs G3 [148]. Toxicity from FOLFOX includes hematotoxicity (84.1%), chemotherapy-induced peripheral sensory neuropathy, renal toxicity, and infections[148].

**Platinum-based chemotherapy for GEP-NETs G3:** The efficacy of platinum-based chemotherapy in unresectable GEP-NETs G3 is uncertain. A recent retrospective series analyzed the efficacy of platinum-based treatment, regardless of tumor differentiation and grading[149]. The data regarding 50 Pan-NETs and 29 Pan-NECs were collected, observing partial response in 20% and 41%, respectively. Median OS was 10.9 mo *vs* 29.2 mo, respectively, and no statistically significant difference in terms of PFS was observed. A potential role of cisplatin-etoposide and FOLFOX-regimens in NETs G3 have been suggested, but with a short-lived response[135]. These data also suggest a potential role of platinum-based regimen in Pan-NETs, but patient selection still represents a critical issue. Some molecular markers have been proposed to help select patients (*e.g.*, retinoblastoma protein, KRAS, and TP53 mutations), but the data are still scarce and only based on retrospective series[150-152].

**Future perspectives and open questions:** Prospective studies investigating new biomarkers predicting tumor response to platinum-based chemotherapy would help select the right candidates for this treatment, including a subgroup of GEP-NETs G3.

Prospective studies adopting FOLFOX at first line in GEP-NENs G3 would definitely assess the potential efficacy of this regimen in these aggressive neoplasms.

### *Chemotherapy: Fluorouracil, leucovorin, and irinotecan*

Regarding GEP-NECs, chemotherapy with fluorouracil, leucovorin, and irinotecan (FOLFIRI) is a possible second-line option for GEP-NENs after cisplatin-etoposide failure. The series published to date are small and retrospective[153]. A randomized, non-comparative, multicenter phase II trial (the SENECA study) will assess the efficacy of CAPTEM *vs* FOLFIRI in GEP-NECs as a second-line treatment after failure of platinum-based therapy (Supplementary Table 1).

### *Immunotherapy*

**Indications, efficacy, and safety:** In the last decade, immunotherapy has revolutionized the prognosis of many solid tumors, such as melanoma and non-small cell lung cancer. However, the efficacy of immune checkpoint inhibitors (ICIs) in NENs is disappointing. The reasons for this failure might be related to their tumor biology, since NETs are usually characterized by a slow growth rate, a relatively low tumor mutational burden and a rare microsatellite instability[154,155]. Instead, although NECs are highly aggressive neoplasms with high tumor mutational burden, ICIs have not achieved the expected results with these patients[154,156,157].

One of the first ICIs tested in NENs is pembrolizumab, a highly selective, humanized monoclonal antibody blocking the interaction of programmed cell death protein 1 (PD-1) with its ligands [programmed death-ligand 1 (PD-L1) and PD-L2]. The multicohort, single-arm, phase 1 KEYNOTE-028 basket trial evaluated the safety and efficacy of pembrolizumab monotherapy across 20 tumor cohorts, including a cohort of 25 non-pancreatic NETs and a cohort of 16 Pan-NETs. Patients had a PD-L1-positive tumor and were mostly heavily pre-treated. The median follow-up was 20 mo and the overall RR 12.0% in non-pancreatic NETs and 6.3% in Pan-NETs, respectively. The range of response duration was 6.9-17.6 mo. No complete response was observed[158]. In the subsequent phase II KEYNOTE-158 basket trial, pembrolizumab was administered in a cohort of 107 progressive NETs. Patients were enrolled regardless of PD-L1 expression. Objective (only partial) response was achieved in 3.7% of patients, and they all had PD-L1-negative neoplasms. The treatment provided disease stabilization se in 57% of cases, a median PFS of 4.1 mo and a median OS of 24.2 mo. Although these results seem encouraging, they need to be read with caution, as NETs are characterized by a slow growth[159].

**ICI for G3 patients:** The role of ICIs was also analyzed in NENs G3. Vijayvergia *et al*[160] published a joint analysis of two prospective, non-randomized trials with pembrolizumab in 29 advanced NENs G3 after failure of platinum-based treatment. In 1 patient (3.4%), an objective response was observed, while 6 (20.7%) achieved stable disease. The median PFS was 8.9 wk, with no significant differences between the PD-L1-positive and PD-L1-negative groups. Similar and no clinically relevant results were obtained with avelumab[161]. Another humanized anti-PD-1 antibody, spartalizumab, was evaluated in a phase

II, multicenter, single-arm study of 95 patients including 55 GEP-NETs and 21 GEP-NECs[162]. All patients were progressive at study entry and had received prior treatment for advanced disease. The DCR was 64.2% in the NET group and 19% in the GEP-NEC group, with a better outcome observed for thoracic NETs. However, this study was formally negative because the primary endpoint (objective response > 10%) was not reached.

**Combination immunotherapy:** Studies of combination immunotherapy with dual blockade of PD-1 and cytotoxic T-lymphocyte antigen 4 (CTLA-4) have shown more promising results. In the DART SWOG 1609 basket trial, ipilimumab was adopted in combination with nivolumab[163]. The cohort of rare tumors also included 32 extra-pancreatic NENs (18 with high-grade disease). One patient obtained complete response (3%), whereas 7 (22%) achieved a partial response, with a better outcome achieved by NECs than NETs ($P$ = 0.004). The combination of durvalumab with tremelimumab in patients with progressive NETs was investigated in the phase II DUNE trial. This study recruited 123 patients, including GEP-NENs after the failure of standard therapies. The immune-related RECIST objective response was 0% for gastrointestinal NETs, 6.3% for Pan-NETs, and 9.1% for GEP-NENs G3[164].

**Future perspectives and open questions:** Considering the poor results obtained by adopting immunotherapy in NENs, compared to other solid cancers, new biomarkers able to identify the right candidates for immunotherapy are needed. New prospective trials investigating further immunotherapy combination are also needed to provide further therapeutic options to progressive, heavily pretreated patients. More data concerning immunotherapy for GEP-NECs are also needed, as therapeutic options for these aggressive cases are still scarce.

## NEW FRONTIERS

The concept of new frontiers in the field of therapy for GEP-NENs can have several interpretations. Besides the introduction of novel medications, new perspectives also include: Endoscopic ablation for Pan-NETs, medical therapy combination, and the optimization of therapy sequences.

### *Endoscopic ablation for Pan-NETs*

The development of specifically designed accessories and suitable technologies for locoregional treatments with EUS guidance has made it possible to perform tumor ablations in Pan-NETs not eligible for surgery, resulting in a lower morbidity rate.

These treatments include EUS-guided radiofrequency ablation (EUS-RFA), which is utilized for the treatment of small functional Pan-NETs to improve symptoms without serious complications[165]. The same technique has also been used to treat non-functional asymptomatic Pan-NETs, with complete response obtained in 71.4%-85.7%[166].

Another technique that has demonstrated good safety and reproducible results is ablation by ethanol injection. Multiple case reports and case series have been published with a procedure success rate ranging from 50% to 60% for non-functioning Pan-NETs and 93% for functioning Pan-NETs[167]. Similar results were achieved in a larger cohort by Choi *et al*[168], treating 33 Pan-NETs with a mixture of 1:1 ethanol and lipidiol. Complete ablation was observed in 60% of the lesions, with complete necrosis at the 3-year follow-up in 41%.

The RAPNEN trial is currently recruiting patients with Pan-NENs to be treated with EUS-RFA, and will investigate the efficacy of this treatment in both functioning and non-functioning cases, including G3 patients (Supplementary Table 1).

### *Therapy combination*

Several studies have investigated the antiproliferative effect of therapy combinations, thereby exploiting the potential synergistic effect of the different treatments. This approach must however be investigated with caution, also considering the possible superior toxicity compared to single treatments.

**Therapy combination with PRRT:** In one phase II clinical trial[169], $^{177}$Lu-DOTATATE PRRT was implemented with capecitabine and temozolomide in advanced low-grade NETs, achieving DCR in 71% of patients, a median PFS of 31 mo and median OS not reached. AEs were mild to moderate, and most frequently represented by nausea, thrombocytopenia and neutropenia. In another phase II study[170], the efficacy and toxicity of PRRT with $^{177}$Lu-DOTATATE were assessed in combination with metronomic capecitabine, as a radio-sensitizer agent, in advanced, progressive $^{18}$FDG-positive GEP NETs with Ki67 < 55%. The DCR was obtained in 85% of cases, with a median PFS of 31.4 mo, and a median OS not reached. No renal toxicity was observed in this series.

The combination with CAPTEM was also investigated as a sandwich chemo-PRRT treatment. More specifically, within 2 wk after PRRT, CAPTEM was administered followed by a 2-wk rest period; the next cycle of CAPTEM was repeated similarly and followed by 1 mo break, and the next cycle of PRRT was administered at about 3 mo. Two cycles of CAPTEM were therefore sandwiched between two

cycles of PRRT. With this treatment schedule, DCR was observed in 84% of cases, while the median PFS and OS were not reached at a median follow-up of 36 mo[171]. Regarding first-line PRRT, a series from India investigated its efficacy in association with Capecitabine in 45 consecutive unresectable NETs, with favorable outcomes. In detail, partial response was observed in 30% of cases, and the median PFS was 48 mo[172].

**Therapy combination with everolimus:** Bajetta *et al*[173] adopted the everolimus + LAR Octreotide combination regimen in naïve advanced NETs, and obtained positive conclusions. More specifically, 18% and 74% of the cases showed objective response and disease stabilization for at least 6 mo, respectively. The EVERLAR study[174] reported prospective data on everolimus in combination with SSAs in non-functioning gastrointestinal NETs, with encouraging results in terms of both safety and efficacy. Indeed, the 24-mo PFS rate was 43.6%, with objective response achieved in 2.3% and stable disease in 58.1%. The median OS was not reached after 24 mo. Focusing on chemotherapy, the combination of everolimus and temozolomide offered interesting results in advanced Pan-NETs. In 40 patients treated with these two therapies for 6 mo, no synergistic toxicities were observed and 40% of patients experienced a partial response. The median PFS rate was 15.4 mo, whereas the median OS was not reached[175]. A single-arm trial (NCT02248012) will show the potential synergy of everolimus and temozolomide in NET G3 patients with Ki67 ranging from 20% to 55% (Supplementary Table 1).

**Therapy combination with sunitinib:** The combination of sunitinib and SSAs adopted in 50 NET patients lead to a "not reached" median PFS, with DCR of 86%. These results come from real-world studies and may be limited by retrospective design and heterogeneous population[176]. Sunitinib was also investigated to potentiate tumor control after TAE in 23 NETs, administered for 1 year after the procedure, achieving a median PFS of 15.2 mo and RR of 72%[177].

**Chemotherapy combination:** A recent retrospective study has evaluated response to treatment with 5-FU, doxorubicin and STZ (FAS) in Pan-NETs. Median PFS was 20 mo and median OS 63 mo. A better outcome was observed when adopting the FAS regimen at first line, without significant safety concerns [178]. The BEVANEC trial is currently recruiting GEP-NEC patients, after failure of platinum-based chemotherapy, to receive a combination of bevacizumab with FOLFIRI *vs* FOLFIRI alone (Supplementary Table 1)[179].

### *Therapy sequence*

Although the therapeutic landscape for NENs offers several options, the correct therapy sequence to be adopted is so far unknown. Several trials are attempting to compare different sequences in order to understand, on the basis of benefit and toxicity, which alternative option should be preferred. The safety and efficacy of everolimus after prior treatment with PRRT was investigated in a multicenter study including 24 GEP-NETs[180]. Major clinical AEs during treatment with everolimus were hyperglycemia (20.8%), thrombocytopenia (8.3%), fatigue (8.3%) and elevated alanine transaminase levels (8.3%). The median PFS was 13.1 mo, longer than observed in previous trials, suggesting that pretreatment with PRRT might not affect response to everolimus. A retrospective series of Pan-NETs pretreated with chemotherapy followed by PRRT showed that previous treatment with more than one chemotherapy line was a negative prognostic factor for survival outcome, whereas resection of the primary tumor had a positive impact on survival[181]. The COMPETE trial is currently recruiting unresectable, progressive GEP-NETs G1-G2 to receive treatment by PRRT with $^{177}$Lu-Edotreotide *vs* everolimus (Supplementary Table 1). The SEQTOR study, which has been developed in Europe, aims instead to investigate the optimal sequence for everolimus and chemotherapy (Supplementary Table 1).

## CONCLUSION

In summary, as GEP-NENs represent a highly heterogeneous disease treated with therapeutic protocols that are not fully standardized, a multidisciplinary approach is mandatory for their management. Great advances have been made in the last decade in terms of treatments. Current trials will help answer the open questions regarding therapies for these patients, offering new perspectives in terms of novel drugs, therapy sequence and therapy combination. These data, together with molecular profiling and the application of radiomics in the understanding of tumor features and behavior, will also pave the way for precision medicine in this oncological field.

## FOOTNOTES

**Author contributions:** All authors performed the literature research, wrote the manuscript, and read and approved the final manuscript.

**Conflict-of-interest statement:** All Authors declare no conflict of interest related to this publication.

**Country/Territory of origin:** Italy

**ORCID number:** Elettra Merola 0000-0001-9553-7684; Andrea Michielan 0000-0003-1353-0935; Umberto Rozzanigo 0000-0002-9541-2555; Marco Erini 0000-0002-6314-0196; Sandro Sferrazza 0000-0002-7595-0129; Stefano Marcucci 0000-0001-9144-9038; Chiara Sartori 0000-0003-3137-0082; Chiara Trentin 0000-0002-5213-0208; Giovanni de Pretis 0000-0001-7636-0422; Franca Chierichetti 0000-0002-1898-4736.

**S-Editor:** Fan JR
**L-Editor:** Filipodia
**P-Editor:** Fan JR

## REFERENCES

1 **Dasari A**, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T, Yao JC. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol* 2017; **3**: 1335-1342 [PMID: 28448665 DOI: 10.1001/jamaoncol.2017.0589]
2 **Leoncini E**, Boffetta P, Shafir M, Aleksovska K, Boccia S, Rindi G. Increased incidence trend of low-grade and high-grade neuroendocrine neoplasms. *Endocrine* 2017; **58**: 368-379 [PMID: 28303513 DOI: 10.1007/s12020-017-1273-x]
3 **Klöppel G**, La Rosa S. Ki67 Labeling index: assessment and prognostic role in gastroenteropancreatic neuroendocrine neoplasms. *Virchows Arch* 2018; **472**: 341-349 [PMID: 29134440 DOI: 10.1007/s00428-017-2258-0]
4 **Rindi G**, Klöppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, Erikssson B, Falchetti A, Falconi M, Komminoth P, Körner M, Lopes JM, McNicol AM, Nilsson O, Perren A, Scarpa A, Scoazec JY, Wiedenmann B; all other Frascati Consensus Conference participants; European Neuroendocrine Tumor Society (ENETS). TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2006; **449**: 395-401 [PMID: 16967267 DOI: 10.1007/s00428-006-0250-1]
5 **Rindi G**, Klöppel G, Couvelard A, Komminoth P, Körner M, Lopes JM, McNicol AM, Nilsson O, Perren A, Scarpa A, Scoazec JY, Wiedenmann B. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2007; **451**: 757-762 [PMID: 17674042 DOI: 10.1007/s00428-007-0452-1]
6 **WHO**. Classification of Tumors Editorial Board: digestive system tumors, 5th ed. WHO 2019
7 **Bakker WH**, Albert R, Bruns C, Breeman WA, Hofland LJ, Marbach P, Pless J, Pralet D, Stolz B, Koper JW. [111In-DTPA-D-Phe1]-octreotide, a potential radiopharmaceutical for imaging of somatostatin receptor-positive tumors: synthesis, radiolabeling and *in vitro* validation. *Life Sci* 1991; **49**: 1583-1591 [PMID: 1658515 DOI: 10.1016/0024-3205(91)90052-d]
8 **Gabriel M**, Decristoforo C, Kendler D, Dobrozemsky G, Heute D, Uprimny C, Kovacs P, Von Guggenberg E, Bale R, Virgolini IJ. 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. *J Nucl Med* 2007; **48**: 508-518 [PMID: 17401086 DOI: 10.2967/jnumed.106.035667]
9 **Garcia-Carbonero R**, Rinke A, Valle JW, Fazio N, Caplin M, Gorbounova V, O Connor J, Eriksson B, Sorbye H, Kulke M, Chen J, Falkerby J, Costa F, de Herder W, Lombard-Bohas C, Pavel M; Antibes Consensus Conference participants. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasms. Systemic Therapy 2: Chemotherapy. *Neuroendocrinology* 2017; **105**: 281-294 [PMID: 28380493 DOI: 10.1159/000473892]
10 **Hicks RJ**, Kwekkeboom DJ, Krenning E, Bodei L, Grozinsky-Glasberg S, Arnold R, Borbath I, Cwikla J, Toumpanakis C, Kaltsas G, Davies P, Hörsch D, Tiensuu Janson E, Ramage J; Antibes Consensus Conference participants. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasia: Peptide Receptor Radionuclide Therapy with Radiolabeled Somatostatin Analogues. *Neuroendocrinology* 2017; **105**: 295-309 [PMID: 28402980 DOI: 10.1159/000475526]
11 **Kaltsas G**, Caplin M, Davies P, Ferone D, Garcia-Carbonero R, Grozinsky-Glasberg S, Hörsch D, Tiensuu Janson E, Kianmanesh R, Kos-Kudla B, Pavel M, Rinke A, Falconi M, de Herder WW; Antibes Consensus Conference participants. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Pre- and Perioperative Therapy in Patients with Neuroendocrine Tumors. *Neuroendocrinology* 2017; **105**: 245-254 [PMID: 28253514 DOI: 10.1159/000461583]
12 **Partelli S**, Bartsch DK, Capdevila J, Chen J, Knigge U, Niederle B, Nieveen van Dijkum EJM, Pape UF, Pascher A, Ramage J, Reed N, Ruszniewski P, Scoazec JY, Toumpanakis C, Kianmanesh R, Falconi M; Antibes Consensus Conference participants. ENETS Consensus Guidelines for Standard of Care in Neuroendocrine Tumours: Surgery for Small Intestinal and Pancreatic Neuroendocrine Tumours. *Neuroendocrinology* 2017; **105**: 255-265 [PMID: 28237989 DOI: 10.1159/000464292]
13 **Pavel M**, Valle JW, Eriksson B, Rinke A, Caplin M, Chen J, Costa F, Falkerby J, Fazio N, Gorbounova V, de Herder W, Kulke M, Lombard-Bohas C, O'Connor J, Sorbye H, Garcia-Carbonero R; Antibes Consensus Conference Participants; Antibes Consensus Conference participants. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasms: Systemic Therapy - Biotherapy and Novel Targeted Agents. *Neuroendocrinology* 2017; **105**: 266-280 [PMID: 28351033 DOI: 10.1159/000471880]

14 **Malczewska A**, Oberg K, Kos-Kudla B. NETest is superior to chromogranin A in neuroendocrine neoplasia: a prospective ENETS CoE analysis. *Endocr Connect* 2021; **10**: 110-123 [PMID: 33289691 DOI: 10.1530/EC-20-0417]

15 **Ćwikła JB**, Bodei L, Kolasinska-Ćwikła A, Sankowski A, Modlin IM, Kidd M. Circulating Transcript Analysis (NETest) in GEP-NETs Treated With Somatostatin Analogs Defines Therapy. *J Clin Endocrinol Metab* 2015; **100**: E1437-E1445 [PMID: 26348352 DOI: 10.1210/jc.2015-2792]

16 **Standards of Practice Committee**, Faulx AL, Kothari S, Acosta RD, Agrawal D, Bruining DH, Chandrasekhara V, Eloubeidi MA, Fanelli RD, Gurudu SR, Khashab MA, Lightdale JR, Muthusamy VR, Shaukat A, Qumseya BJ, Wang A, Wani SB, Yang J, DeWitt JM; Standards of Practice Committee. The role of endoscopy in subepithelial lesions of the GI tract. *Gastrointest Endosc* 2017; **85**: 1117-1132 [PMID: 28385194 DOI: 10.1016/j.gie.2017.02.022]

17 **Yazici C**, Boulay BR. Evolving role of the endoscopist in management of gastrointestinal neuroendocrine tumors. *World J Gastroenterol* 2017; **23**: 4847-4855 [PMID: 28785139 DOI: 10.3748/wjg.v23.i27.4847]

18 **Exarchou K**, Howes N, Pritchard DM. Systematic review: management of localised low-grade upper gastrointestinal neuroendocrine tumours. *Aliment Pharmacol Ther* 2020; **51**: 1247-1267 [PMID: 32390152 DOI: 10.1111/apt.15765]

19 **Ahmed M**. Gastrointestinal neuroendocrine tumors in 2020. *World J Gastrointest Oncol* 2020; **12**: 791-807 [PMID: 32879660 DOI: 10.4251/wjgo.v12.i8.791]

20 **Yang DH**, Park Y, Park SH, Kim KJ, Ye BD, Byeon JS, Myung SJ, Yang SK. Cap-assisted EMR for rectal neuroendocrine tumors: comparisons with conventional EMR and endoscopic submucosal dissection (with videos). *Gastrointest Endosc* 2016; **83**: 1015-22; quiz 1023 [PMID: 26460225 DOI: 10.1016/j.gie.2015.09.046]

21 **Lee SH**, Lee TH, Jang SH, Choi CY, Lee WM, Min JH, Cho HD, Park SH. Ampullary neuroendocrine tumor diagnosed by endoscopic papillectomy in previously confirmed ampullary adenoma. *World J Gastroenterol* 2016; **22**: 3687-3692 [PMID: 27053861 DOI: 10.3748/wjg.v22.i13.3687]

22 **Kim J**, Kim JH, Lee JY, Chun J, Im JP, Kim JS. Clinical outcomes of endoscopic mucosal resection for rectal neuroendocrine tumor. *BMC Gastroenterol* 2018; **18**: 77 [PMID: 29866049 DOI: 10.1186/s12876-018-0806-y]

23 **Lee J**, Park YE, Choi JH, Heo NY, Park J, Park SH, Moon YS, Nam KH, Kim TO. Comparison between cap-assisted and ligation-assisted endoscopic mucosal resection for rectal neuroendocrine tumors. *Ann Gastroenterol* 2020; **33**: 385-390 [PMID: 32624659 DOI: 10.20524/aog.2020.0485]

24 **Zhou X**, Xie H, Xie L, Li J, Cao W, Fu W. Endoscopic resection therapies for rectal neuroendocrine tumors: a systematic review and meta-analysis. *J Gastroenterol Hepatol* 2014; **29**: 259-268 [PMID: 24118068 DOI: 10.1111/jgh.12395]

25 **Harada H**, Suehiro S, Murakami D, Nakahara R, Shimizu T, Katsuyama Y, Miyama Y, Hayasaka K, Tounou S. Endoscopic submucosal dissection for small submucosal tumors of the rectum compared with endoscopic submucosal resection with a ligation device. *World J Gastrointest Endosc* 2017; **9**: 70-76 [PMID: 28250899 DOI: 10.4253/wjge.v9.i2.70]

26 **Trinh VQ**, Shi C, Ma C. Gastric neuroendocrine tumours from long-term proton pump inhibitor users are indolent tumours with good prognosis. *Histopathology* 2020; **77**: 865-876 [PMID: 32702178 DOI: 10.1111/his.14220]

27 **Roberto GA**, Rodrigues CMB, Peixoto RD, Younes RN. Gastric neuroendocrine tumor: A practical literature review. *World J Gastrointest Oncol* 2020; **12**: 850-856 [PMID: 32879663 DOI: 10.4251/wjgo.v12.i8.850]

28 **Sato Y**, Hashimoto S, Mizuno K, Takeuchi M, Terai S. Management of gastric and duodenal neuroendocrine tumors. *World J Gastroenterol* 2016; **22**: 6817-6828 [PMID: 27570419 DOI: 10.3748/wjg.v22.i30.6817]

29 **Chin JL**, O'Toole D. Diagnosis and Management of Upper Gastrointestinal Neuroendocrine Tumors. *Clin Endosc* 2017; **50**: 520-529 [PMID: 29207862 DOI: 10.5946/ce.2017.181]

30 **Delle Fave G**, O'Toole D, Sundin A, Taal B, Ferolla P, Ramage JK, Ferone D, Ito T, Weber W, Zheng-Pei Z, De Herder WW, Pascher A, Ruszniewski P; Vienna Consensus Conference participants. ENETS Consensus Guidelines Update for Gastroduodenal Neuroendocrine Neoplasms. *Neuroendocrinology* 2016; **103**: 119-124 [PMID: 26784901 DOI: 10.1159/000443168]

31 **Merola E**, Sbrozzi-Vanni A, Panzuto F, D'Ambra G, Di Giulio E, Pilozzi E, Capurso G, Lahner E, Bordi C, Annibale B, Delle Fave G. Type I gastric carcinoids: a prospective study on endoscopic management and recurrence rate. *Neuroendocrinology* 2012; **95**: 207-213 [PMID: 21811050 DOI: 10.1159/000329043]

32 **Ngamruengphong S**, Ferri L, Aihara H, Draganov PV, Yang DJ, Perbtani YB, Jue TL, Munroe CA, Boparai ES, Mehta NA, Bhatt A, Kumta NA, Othman MO, Mercado M, Javaid H, Aadam AA, Siegel A, James TW, Grimm IS, DeWitt JM, Novikov A, Schlachterman A, Kowalski T, Samarasena J, Hashimoto R, Chehade NEH, Lee J, Chang K, Su B, Ujiki MB, Mehta A, Sharaiha RZ, Carr-Locke DL, Chen A, Chen M, Chen YI, Pourmousavi Khoshknab M, Wang R, Kerdsirichairat T, Tomizawa Y, von Renteln D, Kumbhari V, Khashab MA, Bechara R, Karasik M, Patel NJ, Fukami N, Nishimura M, Hanada Y, Wong Kee Song LM, Laszkowska M, Wang AY, Hwang JH, Friedland S, Sethi A, Kalloo AN. Efficacy of Endoscopic Submucosal Dissection for Superficial Gastric Neoplasia in a Large Cohort in North America. *Clin Gastroenterol Hepatol* 2021; **19**: 1611-1619.e1 [PMID: 32565290 DOI: 10.1016/j.cgh.2020.06.023]

33 **Sato Y**, Takeuchi M, Hashimoto S, Mizuno K, Kobayashi M, Iwafuchi M, Narisawa R, Aoyagi Y. Usefulness of endoscopic submucosal dissection for type I gastric carcinoid tumors compared with endoscopic mucosal resection. *Hepatogastroenterology* 2013; **60**: 1524-1529 [PMID: 23933946 DOI: 10.5754/hge121185]

34 **Kim HH**, Kim GH, Kim JH, Choi MG, Song GA, Kim SE. The efficacy of endoscopic submucosal dissection of type I gastric carcinoid tumors compared with conventional endoscopic mucosal resection. *Gastroenterol Res Pract* 2014; **2014**: 253860 [PMID: 24693280 DOI: 10.1155/2014/253860]

35 **Gincul R**, Ponchon T, Napoleon B, Scoazec JY, Guillaud O, Saurin JC, Ciocirlan M, Lepilliez V, Pioche M, Lefort C, Adham M, Pialat J, Chayvialle JA, Walter T. Endoscopic treatment of sporadic small duodenal and ampullary neuroendocrine tumors. *Endoscopy* 2016; **48**: 979-986 [PMID: 27494453 DOI: 10.1055/s-0042-112570]

36 **Kim GH**, Kim JI, Jeon SW, Moon JS, Chung IK, Jee SR, Kim HU, Seo GS, Baik GH, Lee YC; Korean College of Helicobacter and Upper Gastrointestinal Research. Endoscopic resection for duodenal carcinoid tumors: a multicenter, retrospective study. *J Gastroenterol Hepatol* 2014; **29**: 318-324 [PMID: 24117946 DOI: 10.1111/jgh.12390]

37 **Fujimoto A**, Sasaki M, Goto O, Maehata T, Ochiai Y, Kato M, Nakayama A, Akimoto T, Kuramoto J, Hayashi Y,

Kameyama K, Yahagi N. Treatment Results of Endoscopic Mucosal Resection with a Ligation Device for Duodenal Neuroendocrine Tumors. *Intern Med* 2019; **58**: 773-777 [PMID: 30449790 DOI: 10.2169/internalmedicine.1517-18]

38 **Oono Y**, Shinmura K, Hori K, Yoda Y, Ishii G, Ikematsu H, Yano T. Endoscopic submucosal resection using a ligation device without injection for duodenal neuroendocrine tumors. *Surg Endosc* 2019; **33**: 2008-2014 [PMID: 30604268 DOI: 10.1007/s00464-018-06642-5]

39 **Scherer JR**, Holinga J, Sanders M, Chennat J, Khalid A, Fasanella K, Singhi AD, McGrath K. Small duodenal carcinoids: a case series comparing endoscopic resection and autoamputation with band ligation. *J Clin Gastroenterol* 2015; **49**: 289-292 [PMID: 24518797 DOI: 10.1097/MCG.0000000000000085]

40 **Kobara H**, Miyaoka Y, Ikeda Y, Yamada T, Takata M, Fujihara S, Nishiyama N, Fujita K, Tani J, Kobayashi N, Chiyo T, Yachida T, Okano K, Suzuki Y, Mori H, Masaki T. Outcomes of Endoscopic Submucosal Dissection for Subepithelial Lesions Localized Within the Submucosa, Including Neuroendocrine Tumors: A Multicenter Prospective Study. *J Gastrointestin Liver Dis* 2020; **29**: 41-49 [PMID: 32176758 DOI: 10.15403/jgld-510]

41 **Suzuki S**, Ishii N, Uemura M, Deshpande GA, Matsuda M, Iizuka Y, Fukuda K, Suzuki K, Fujita Y. Endoscopic submucosal dissection (ESD) for gastrointestinal carcinoid tumors. *Surg Endosc* 2012; **26**: 759-763 [PMID: 21993939 DOI: 10.1007/s00464-011-1948-y]

42 **Nishio M**, Hirasawa K, Ozeki Y, Sawada A, Ikeda R, Fukuchi T, Kobayashi R, Makazu M, Sato C, Maeda S. Short- and long-term outcomes of endoscopic submucosal dissection for non-ampullary duodenal neuroendocrine tumors. *Ann Gastroenterol* 2020; **33**: 265-271 [PMID: 32382229 DOI: 10.20524/aog.2020.0477]

43 **Cai MY**, Martin Carreras-Presas F, Zhou PH. Endoscopic full-thickness resection for gastrointestinal submucosal tumors. *Dig Endosc* 2018; **30** Suppl 1: 17-24 [PMID: 29658639 DOI: 10.1111/den.13003]

44 **Fukasawa H**, Tounou S, Nabetani M, Michida T. Endoscopic Resection of Ampullary Neuroendocrine Tumor. *Intern Med* 2017; **56**: 499-503 [PMID: 28250294 DOI: 10.2169/internalmedicine.56.7520]

45 **Rossi RE**, Invernizzi P, Mazzaferro V, Massironi S. Response and relapse rates after treatment with long-acting somatostatin analogs in multifocal or recurrent type-1 gastric carcinoids: A systematic review and meta-analysis. *United European Gastroenterol J* 2020; **8**: 140-147 [PMID: 32213066 DOI: 10.1177/2050640619890465]

46 **Pape UF**, Niederle B, Costa F, Gross D, Kelestimur F, Kianmanesh R, Knigge U, Öberg K, Pavel M, Perren A, Toumpanakis C, O'Connor J, Krenning E, Reed N, O'Toole D; Vienna Consensus Conference participants. ENETS Consensus Guidelines for Neuroendocrine Neoplasms of the Appendix (Excluding Goblet Cell Carcinomas). *Neuroendocrinology* 2016; **103**: 144-152 [PMID: 26730583 DOI: 10.1159/000443165]

47 **de Mestier L**, Lardière-Deguelte S, Brixi H, O'Toole D, Ruszniewski P, Cadiot G, Kianmanesh R. Updating the surgical management of peritoneal carcinomatosis in patients with neuroendocrine tumors. *Neuroendocrinology* 2015; **101**: 105-111 [PMID: 25592061 DOI: 10.1159/000371817]

48 **Dong DH**, Zhang XF, Poultsides G, Rocha F, Weber S, Fields R, Idrees K, Cho C, Maithel SK, Pawlik TM; other members of the US Neuroendocrine Tumor Study Group. Impact of tumor size and nodal status on recurrence of nonfunctional pancreatic neuroendocrine tumors ≤2 cm after curative resection: A multi-institutional study of 392 cases. *J Surg Oncol* 2019; **120**: 1071-1079 [PMID: 31571225 DOI: 10.1002/jso.25716]

49 **Barenboim A**, Lahat G, Nachmany I, Nakache R, Goykhman Y, Geva R, Osher E, Scapa E, Wolf I, Orbach L, Brazowski E, Isakov O, Klausner JM, Lubezky N. Resection Versus Observation of Small Asymptomatic Nonfunctioning Pancreatic Neuroendocrine Tumors. *J Gastrointest Surg* 2020; **24**: 1366-1374 [PMID: 31197692 DOI: 10.1007/s11605-019-04285-y]

50 **Partelli S**, Inama M, Rinke A, Begum N, Valente R, Fendrich V, Tamburrino D, Keck T, Caplin ME, Bartsch D, Thirlwell C, Fusai G, Falconi M. Long-Term Outcomes of Surgical Management of Pancreatic Neuroendocrine Tumors with Synchronous Liver Metastases. *Neuroendocrinology* 2015; **102**: 68-76 [PMID: 26043944 DOI: 10.1159/000431379]

51 **Barrett JR**, Rendell V, Pokrzywa C, Lopez-Aguiar AG, Cannon J, Poultsides GA, Rocha F, Crown A, Beal E, Michael Pawlik T, Fields R, Panni RZ, Smith P, Idrees K, Cho C, Beems M, Maithel S, Weber S, Erik Abbott D. Adjuvant therapy following resection of gastroenteropancreatic neuroendocrine tumors provides no recurrence or survival benefit. *J Surg Oncol* 2020; **121**: 1067-1073 [PMID: 32153032 DOI: 10.1002/jso.25896]

52 **Wu Z**, Yu D, Zhao S, Gao P, Song Y, Sun Y, Chen X, Wang Z. The efficacy of chemotherapy and operation in patients with colorectal neuroendocrine carcinoma. *J Surg Res* 2018; **225**: 54-67 [PMID: 29605035 DOI: 10.1016/j.jss.2017.12.035]

53 **Pellat A**, Walter T, Augustin J, Hautefeuille V, Hentic O, Do Cao C, Lievre A, Coriat R, Hammel P, Dubreuil O, Cohen R, Couvelard A, André T, Svrcek M, Baudin E, Afchain P. Chemotherapy in Resected Neuroendocrine Carcinomas of the Digestive Tract: A National Study from the French Group of Endocrine Tumours. *Neuroendocrinology* 2020; **110**: 404-412 [PMID: 31430756 DOI: 10.1159/000502825]

54 **Mao R**, Li K, Cai JQ, Luo S, Turner M, Blazer D 3rd, Zhao H. Adjuvant Chemotherapy Versus Observation Following Resection for Patients With Nonmetastatic Poorly Differentiated Colorectal Neuroendocrine Carcinomas. *Ann Surg* 2021; **274**: e126-e133 [PMID: 31478977 DOI: 10.1097/SLA.0000000000003562]

55 **Lin JP**, Zhao YJ, He QL, Hao HK, Tian YT, Zou BB, Jiang LX, Lin W, Zhou YB, Li Z, Xu YC, Zhao G, Xue FQ, Li SL, Fu WH, Li YX, Zhou XJ, Li Y, Zhu ZG, Chen JP, Xu ZK, Cai LH, Li E, Li HL, Xie JW, Huang CM, Li P, Lin JX, Zheng CH. Adjuvant chemotherapy for patients with gastric neuroendocrine carcinomas or mixed adenoneuroendocrine carcinomas. *Br J Surg* 2020; **107**: 1163-1170 [PMID: 32323879 DOI: 10.1002/bjs.11608]

56 **Merola E**, Rinke A, Partelli S, Gress TM, Andreasi V, Kollár A, Perren A, Christ E, Panzuto F, Pascher A, Jann H, Arsenic R, Cremer B, Kaemmerer D, Kump P, Lipp RW, Agaimy A, Wiedenmann B, Falconi M, Pavel ME. Surgery with Radical Intent: Is There an Indication for G3 Neuroendocrine Neoplasms? *Ann Surg Oncol* 2020; **27**: 1348-1355 [PMID: 31720931 DOI: 10.1245/s10434-019-08049-5]

57 **Partelli S**, Ramage JK, Massironi S, Zerbi A, Kim HB, Niccoli P, Panzuto F, Landoni L, Tomazic A, Ibrahim T, Kaltsas G, Bertani E, Sauvanet A, Segelov E, Caplin M, Coppa J, Armstrong T, Weickert MO, Butturini G, Staettner S, Boesch F, Cives M, Moulton CA, He J, Selberherr A, Twito O, Castaldi A, De Angelis CG, Gaujoux S, Almeamar H, Frilling A, Vigia E, Wilson C, Muffatti F, Srirajaskanthan R, Invernizzi P, Lania A, Kwon W, Ewald J, Rinzivillo M, Nessi C, Smid LM, Gardini A, Tsoli M, Picardi EE, Hentic O, Croagh D, Toumpanakis C, Citterio D, Ramsey E, Mosterman B, Regi P,

Gasteiger S, Rossi RE, Smiroldo V, Jang JY, Falconi M. Management of Asymptomatic Sporadic Nonfunctioning Pancreatic Neuroendocrine Neoplasms (ASPEN) ≤2 cm: Study Protocol for a Prospective Observational Study. *Front Med (Lausanne)* 2020; **7**: 598438 [PMID: 33425946 DOI: 10.3389/fmed.2020.598438]

58 **Tierney JF**, Chivukula SV, Wang X, Pappas SG, Schadde E, Hertl M, Poirier J, Keutgen XM. Resection of primary tumor may prolong survival in metastatic gastroenteropancreatic neuroendocrine tumors. *Surgery* 2019; **165**: 644-651 [PMID: 30366604 DOI: 10.1016/j.surg.2018.09.006]

59 **Tsilimigras DI**, Hyer JM, Paredes AZ, Ejaz A, Cloyd JM, Beane JD, Dillhoff M, Tsung A, Pawlik TM. Resection of Primary Gastrointestinal Neuroendocrine Tumor Among Patients with Non-Resected Metastases Is Associated with Improved Survival: A SEER-Medicare Analysis. *J Gastrointest Surg* 2021; **25**: 2368-2376 [PMID: 33403563 DOI: 10.1007/s11605-020-04898-8]

60 **Zhou B**, Zhan C, Ding Y, Yan S, Zheng S. Role of palliative resection of the primary pancreatic neuroendocrine tumor in patients with unresectable metastatic liver disease: a systematic review and meta-analysis. *Onco Targets Ther* 2018; **11**: 975-982 [PMID: 29503572 DOI: 10.2147/OTT.S158171]

61 **de Baere T**, Deschamps F, Tselikas L, Ducreux M, Planchard D, Pearson E, Berdelou A, Leboulleux S, Elias D, Baudin E. GEP-NETS update: Interventional radiology: role in the treatment of liver metastases from GEP-NETs. *Eur J Endocrinol* 2015; **172**: R151-R166 [PMID: 25385817 DOI: 10.1530/EJE-14-0630]

62 **Kennedy A**, Bester L, Salem R, Sharma RA, Parks RW, Ruszniewski P; NET-Liver-Metastases Consensus Conference. Role of hepatic intra-arterial therapies in metastatic neuroendocrine tumours (NET): guidelines from the NET-Liver-Metastases Consensus Conference. *HPB (Oxford)* 2015; **17**: 29-37 [PMID: 25186181 DOI: 10.1111/hpb.12326]

63 **Eriksson J**, Stålberg P, Nilsson A, Krause J, Lundberg C, Skogseid B, Granberg D, Eriksson B, Akerström G, Hellman P. Surgery and radiofrequency ablation for treatment of liver metastases from midgut and foregut carcinoids and endocrine pancreatic tumors. *World J Surg* 2008; **32**: 930-938 [PMID: 18324347 DOI: 10.1007/s00268-008-9510-3]

64 **Chen JX**, Rose S, White SB, El-Haddad G, Fidelman N, Yarmohammadi H, Hwang W, Sze DY, Kothary N, Stashek K, Wileyto EP, Salem R, Metz DC, Soulen MC. Embolotherapy for Neuroendocrine Tumor Liver Metastases: Prognostic Factors for Hepatic Progression-Free Survival and Overall Survival. *Cardiovasc Intervent Radiol* 2017; **40**: 69-80 [PMID: 27738818 DOI: 10.1007/s00270-016-1478-z]

65 **Hur S**, Chung JW, Kim HC, Oh DY, Lee SH, Bang YJ, Kim WH. Survival outcomes and prognostic factors of transcatheter arterial chemoembolization for hepatic neuroendocrine metastases. *J Vasc Interv Radiol* 2013; **24**: 947-56; quiz 957 [PMID: 23602421 DOI: 10.1016/j.jvir.2013.02.030]

66 **Tomozawa Y**, Jahangiri Y, Pathak P, Kolbeck KJ, Schenning RC, Kaufman JA, Farsad K. Long-Term Toxicity after Transarterial Radioembolization with Yttrium-90 Using Resin Microspheres for Neuroendocrine Tumor Liver Metastases. *J Vasc Interv Radiol* 2018; **29**: 858-865 [PMID: 29724520 DOI: 10.1016/j.jvir.2018.02.002]

67 **Ngo L**, Elnahla A, Attia AS, Hussein M, Toraih EA, Kandil E, Killackey M. Chemoembolization Versus Radioembolization for Neuroendocrine Liver Metastases: A Meta-analysis Comparing Clinical Outcomes. *Ann Surg Oncol* 2021; **28**: 1950-1958 [PMID: 33393019 DOI: 10.1245/s10434-020-09469-4]

68 **Singla S**, LeVea CM, Pokuri VK, Attwood KM, Wach MM, Tomaszewski GM, Kuvshinoff B, Iyer R. Ki67 score as a potential predictor in the selection of liver-directed therapies for metastatic neuroendocrine tumors: a single institutional experience. *J Gastrointest Oncol* 2016; **7**: 441-448 [PMID: 27284478 DOI: 10.21037/jgo.2016.02.02]

69 **Hickey RM**, Kulik LM, Nimeiri H, Kalyan A, Kircher S, Desai K, Riaz A, Lewandowski RJ, Salem R. Immuno-oncology and Its Opportunities for Interventional Radiologists: Immune Checkpoint Inhibition and Potential Synergies with Interventional Oncology Procedures. *J Vasc Interv Radiol* 2017; **28**: 1487-1494 [PMID: 28912090 DOI: 10.1016/j.jvir.2017.07.018]

70 **Rinke A**, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, Mayer C, Aminossadati B, Pape UF, Bläker M, Harder J, Arnold C, Gress T, Arnold R; PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol* 2009; **27**: 4656-4663 [PMID: 19704057 DOI: 10.1200/JCO.2009.22.8510]

71 **Caplin ME**, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, Cadiot G, Wolin EM, Capdevila J, Wall L, Rindi G, Langley A, Martinez S, Blumberg J, Ruszniewski P; CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med* 2014; **371**: 224-233 [PMID: 25014687 DOI: 10.1056/NEJMoa1316158]

72 **Merola E**, Panzuto F, Delle Fave G. Antiproliferative effect of somatostatin analogs in advanced gastro-entero-pancreatic neuroendocrine tumors: a systematic review and meta-analysis. *Oncotarget* 2017; **8**: 46624-46634 [PMID: 28402955 DOI: 10.18632/oncotarget.16686]

73 **Lamarca A**, McCallum L, Nuttall C, Barriuso J, Backen A, Frizziero M, Leon R, Mansoor W, McNamara MG, Hubner RA, Valle JW. Somatostatin analogue-induced pancreatic exocrine insufficiency in patients with neuroendocrine tumors: results of a prospective observational study. *Expert Rev Gastroenterol Hepatol* 2018; **12**: 723-731 [PMID: 29923433 DOI: 10.1080/17474124.2018.1489232]

74 **Merola E**, Alonso Gordoa T, Zhang P, Al-Toubah T, Pellè E, Kolasińska-Ćwikła A, Zandee W, Laskaratos F, de Mestier L, Lamarca A, Hernando J, Cwikla J, Strosberg J, de Herder W, Caplin M, Cives M, van Leeuwaarde R. Somatostatin Analogs for Pancreatic Neuroendocrine Tumors: Any Benefit When Ki-67 Is ≥10%? *Oncologist* 2021; **26**: 294-301 [PMID: 33301235 DOI: 10.1002/onco.13633]

75 **Chan DL**, Ferone D, Albertelli M, Pavlakis N, Segelov E, Singh S. Escalated-dose somatostatin analogues for antiproliferative effect in GEPNETS: a systematic review. *Endocrine* 2017; **57**: 366-375 [PMID: 28726183 DOI: 10.1007/s12020-017-1360-z]

76 **Strosberg J**, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, Mittra E, Kunz PL, Kulke MH, Jacene H, Bushnell D, O'Dorisio TM, Baum RP, Kulkarni HR, Caplin M, Lebtahi R, Hobday T, Delpassand E, Van Cutsem E, Benson A, Srirajaskanthan R, Pavel M, Mora J, Berlin J, Grande E, Reed N, Seregni E, Öberg K, Lopera Sierra M, Santoro P, Thevenet T, Erion JL, Ruszniewski P, Kwekkeboom D, Krenning E; NETTER-1 Trial Investigators. Phase 3 Trial of

$^{177}$Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med* 2017; **376**: 125-135 [PMID: 28076709 DOI: 10.1056/NEJMoa1607427]

77 **Pavel M**, Dromain C, Massien C, Houchard A. Safety and efficacy of lanreotide autogel/depot (LAN) every 14 days for patients with pancreatic or midgut neuroendocrine tumours (NETs) progressing on LAN every 28 days: The prospective, international CLARINET FORTE study. Proceedings of the ESMO; 2020. *Ann Oncol* 2020; **31** (suppl_4)

78 **Malczewska A**, Kos-Kudła B, Kidd M, Drozdov I, Bodei L, Matar S, Oberg K, Modlin IM. The clinical applications of a multigene liquid biopsy (NETest) in neuroendocrine tumors. *Adv Med Sci* 2020; **65**: 18-29 [PMID: 31841822 DOI: 10.1016/j.advms.2019.10.002]

79 **Bajetta E**, Zilembo N, Di Bartolomeo M, Di Leo A, Pilotti S, Bochicchio AM, Castellani R, Buzzoni R, Celio L, Dogliotti L. Treatment of metastatic carcinoids and other neuroendocrine tumors with recombinant interferon-alpha-2a. A study by the Italian Trials in Medical Oncology Group. *Cancer* 1993; **72**: 3099-3105 [PMID: 7693327 DOI: 10.1002/1097-0142(19931115)72:10<3099::aid-cncr2820721035>3.0.co;2-4]

80 **Faiss S**, Pape UF, Böhmig M, Dörffel Y, Mansmann U, Golder W, Riecken EO, Wiedenmann B; International Lanreotide and Interferon Alfa Study Group. Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors--the International Lanreotide and Interferon Alfa Study Group. *J Clin Oncol* 2003; **21**: 2689-2696 [PMID: 12860945 DOI: 10.1200/JCO.2003.12.142]

81 **Oberg K**, Norheim I, Alm G. Treatment of malignant carcinoid tumors: a randomized controlled study of streptozocin plus 5-FU and human leukocyte interferon. *Eur J Cancer Clin Oncol* 1989; **25**: 1475-1479 [PMID: 2480243 DOI: 10.1016/0277-5379(89)90107-7]

82 **Kwekkeboom DJ**, Krenning EP, Lebtahi R, Komminoth P, Kos-Kudła B, de Herder WW, Plöckinger U; Mallorca Consensus Conference participants; European Neuroendocrine Tumor Society. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: peptide receptor radionuclide therapy with radiolabeled somatostatin analogs. *Neuroendocrinology* 2009; **90**: 220-226 [PMID: 19713714 DOI: 10.1159/000225951]

83 **Merola E**, Capurso G, Campana D, Panzuto F, Monarca B, Tomassetti P, Delle Fave G. Acute leukaemia following low dose peptide receptor radionuclide therapy for an intestinal carcinoid. *Dig Liver Dis* 2010; **42**: 457-458 [PMID: 19783489 DOI: 10.1016/j.dld.2009.08.004]

84 **Valkema R**, Pauwels S, Kvols LK, Barone R, Jamar F, Bakker WH, Kwekkeboom DJ, Bouterfa H, Krenning EP. Survival and response after peptide receptor radionuclide therapy with [90Y-DOTA0,Tyr3]octreotide in patients with advanced gastroenteropancreatic neuroendocrine tumors. *Semin Nucl Med* 2006; **36**: 147-156 [PMID: 16517236 DOI: 10.1053/j.semnuclmed.2006.01.001]

85 **Strosberg J**, Wolin E, Chasen B, Kulke M, Bushnell D, Caplin M, Baum RP, Kunz P, Hobday T, Hendifar A, Oberg K, Sierra ML, Thevenet T, Margalet I, Ruszniewski P, Krenning E; NETTER-1 Study Group. Health-Related Quality of Life in Patients With Progressive Midgut Neuroendocrine Tumors Treated With $^{177}$Lu-Dotatate in the Phase III NETTER-1 Trial. *J Clin Oncol* 2018; **36**: 2578-2584 [PMID: 29878866 DOI: 10.1200/JCO.2018.78.5865]

86 **Pavel ME**, Broberg P, Caplin M, Ruszniewski P, Strosberg J, Santoro P, Ravasi L, Krenning E. Relation between objective tumor shrinkage and progression-free survival (PFS) in the NETTER-1 population. ESMO. *Ann Oncol* 2019; **30** (suppl_5): v564-v573 [DOI: 10.1093/annonc/mdz256.002]

87 **Zhang J**, Kulkarni HR, Singh A, Baum RP. Delayed Response (Partial Remission) 3 Years After Peptide Receptor Radionuclide Therapy in a Patient Participating in the NETTER-1 Trial. *Clin Nucl Med* 2019; **44**: 223-226 [PMID: 30672759 DOI: 10.1097/RLU.0000000000002456]

88 **Wang LF**, Lin L, Wang MJ, Li Y. The therapeutic efficacy of 177Lu-DOTATATE/DOTATOC in advanced neuroendocrine tumors: A meta-analysis. *Medicine (Baltimore)* 2020; **99**: e19304 [PMID: 32150065 DOI: 10.1097/MD.0000000000019304]

89 **Ambrosini V**, Kunikowska J, Baudin E, Bodei L, Bouvier C, Capdevila J, Cremonesi M, de Herder WW, Dromain C, Falconi M, Fani M, Fanti S, Hicks RJ, Kabasakal L, Kaltsas G, Lewington V, Minozzi S, Cinquini M, Öberg K, Oyen WJG, O'Toole D, Pavel M, Ruszniewski P, Scarpa A, Strosberg J, Sundin A, Taïeb D, Virgolini I, Wild D, Herrmann K, Yao J. Consensus on molecular imaging and theranostics in neuroendocrine neoplasms. *Eur J Cancer* 2021; **146**: 56-73 [PMID: 33588146 DOI: 10.1016/j.ejca.2021.01.008]

90 **Strosberg JR**, Kunz PL, Ruszniewski PB, Bodei L, Hendifar AE, Mittra E, Wolin EM, Yao JC, Pavel ME, Grande E, Van Cutsem E, Seregni E, Duarte H, Gericke G, Bartalotta A, Demange A, Mutevelic S, Krenning E, On behalf of the NETTER-1 study group. Final overall survival in the phase 3 NETTER-1 study of lutetium-177-DOTATATE in patients with midgut neuroendocrine tumors. *ASCO: J Clin Oncol* 2021; 4112-4112

91 **Sorbye H**, Kong G, Grozinsky-Glasberg S. PRRT in high-grade gastroenteropancreatic neuroendocrine neoplasms (WHO G3). *Endocr Relat Cancer* 2020; **27**: R67-R77 [PMID: 31846429 DOI: 10.1530/ERC-19-0400]

92 **Bodei L**, Schöder H, Baum RP, Herrmann K, Strosberg J, Caplin M, Öberg K, Modlin IM. Molecular profiling of neuroendocrine tumours to predict response and toxicity to peptide receptor radionuclide therapy. *Lancet Oncol* 2020; **21**: e431-e443 [PMID: 32888472 DOI: 10.1016/S1470-2045(20)30323-5]

93 **Bodei L**, Kidd MS, Singh A, van der Zwan WA, Severi S, Drozdov IA, Malczewska A, Baum RP, Kwekkeboom DJ, Paganelli G, Krenning EP, Modlin IM. PRRT neuroendocrine tumor response monitored using circulating transcript analysis: the NETest. *Eur J Nucl Med Mol Imaging* 2020; **47**: 895-906 [PMID: 31838581 DOI: 10.1007/s00259-019-04601-3]

94 **Binderup T**, Knigge U, Johnbeck CB, Loft A, Berthelsen AK, Oturai P, Mortensen J, Federspiel B, Langer SW, Kjaer A. $^{18}$F-FDG PET is Superior to WHO Grading as a Prognostic Tool in Neuroendocrine Neoplasms and Useful in Guiding PRRT: A Prospective 10-Year Follow-up Study. *J Nucl Med* 2021; **62**: 808-815 [PMID: 33067340 DOI: 10.2967/jnumed.120.244798]

95 **Rudisile S**, Gosewisch A, Wenter V, Unterrainer M, Böning G, Gildehaus FJ, Fendler WP, Auernhammer CJ, Spitzweg C, Bartenstein P, Todica A, Ilhan H. Salvage PRRT with $^{177}$Lu-DOTA-octreotate in extensively pretreated patients with metastatic neuroendocrine tumor (NET): dosimetry, toxicity, efficacy, and survival. *BMC Cancer* 2019; **19**: 788 [PMID:

31395036 DOI: 10.1186/s12885-019-6000-y]

96 **Zacho MD**, Iversen P, Villadsen GE, Baunwall SMD, Arveschoug AK, Grønbaek H, Dam G. Clinical efficacy of first and second series of peptide receptor radionuclide therapy in patients with neuroendocrine neoplasm: a cohort study. *Scand J Gastroenterol* 2021; **56**: 289-297 [PMID: 33470864 DOI: 10.1080/00365521.2021.1872095]

97 **Strosberg J**, Leeuwenkamp O, Siddiqui MK. Peptide receptor radiotherapy re-treatment in patients with progressive neuroendocrine tumors: A systematic review and meta-analysis. *Cancer Treat Rev* 2021; **93**: 102141 [PMID: 33418096 DOI: 10.1016/j.ctrv.2020.102141]

98 **Parghane RV**, Bhandare M, Chaudhari V, Ostwal V, Ramaswamy A, Talole S, Shrikhande SV, Basu S. Surgical Feasibility, Determinants, and Overall Efficacy of Neoadjuvant $^{177}$Lu-DOTATATE PRRT for Locally Advanced Unresectable Gastroenteropancreatic Neuroendocrine Tumors. *J Nucl Med* 2021; **62**: 1558-1563 [PMID: 33637590 DOI: 10.2967/jnumed.120.258772]

99 **Partelli S**, Bertani E, Bartolomei M, Perali C, Muffatti F, Grana CM, Schiavo Lena M, Doglioni C, Crippa S, Fazio N, Zamboni G, Falconi M. Peptide receptor radionuclide therapy as neoadjuvant therapy for resectable or potentially resectable pancreatic neuroendocrine neoplasms. *Surgery* 2018; **163**: 761-767 [PMID: 29284590 DOI: 10.1016/j.surg.2017.11.007]

100 **Delpassand E**. 212Pb-AlphaMedixTM Targeted Alpha Therapy (TAT): a potential breakthrough in treatment of metastatic SSTR expressing NET. NANET 2020: Virtual. Abstract 193, 2020

101 **Yao JC**, Lombard-Bohas C, Baudin E, Kvols LK, Rougier P, Ruszniewski P, Hoosen S, St Peter J, Haas T, Lebwohl D, Van Cutsem E, Kulke MH, Hobday TJ, O'Dorisio TM, Shah MH, Cadiot G, Luppi G, Posey JA, Wiedenmann B. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. *J Clin Oncol* 2010; **28**: 69-76 [PMID: 19933912 DOI: 10.1200/JCO.2009.24.2669]

102 **Yao JC**, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, Hobday TJ, Okusaka T, Capdevila J, de Vries EG, Tomassetti P, Pavel ME, Hoosen S, Haas T, Lincy J, Lebwohl D, Öberg K; RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011; **364**: 514-523 [PMID: 21306238 DOI: 10.1056/NEJMoa1009290]

103 **Yao JC**, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, Tomasek J, Raderer M, Lahner H, Voi M, Pacaud LB, Rouyrre N, Sachs C, Valle JW, Fave GD, Van Cutsem E, Tesselaar M, Shimada Y, Oh DY, Strosberg J, Kulke MH, Pavel ME; RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet* 2016; **387**: 968-977 [PMID: 26703889 DOI: 10.1016/S0140-6736(15)00817-X]

104 **Zhuo ZG**, Zhu YK, Deng HY, Li G, Luo J, Alai GH, Lin YD. Role of everolimus in the treatment of advanced neuroendocrine tumor: a meta-analysis of randomized trials. *J BUON* 2019; **24**: 368-373 [PMID: 30941993]

105 **Panzuto F**, Rinzivillo M, Fazio N, de Braud F, Luppi G, Zatelli MC, Lugli F, Tomassetti P, Riccardi F, Nuzzo C, Brizzi MP, Faggiano A, Zaniboni A, Nobili E, Pastorelli D, Cascinu S, Merlano M, Chiara S, Antonuzzo L, Funaioli C, Spada F, Pusceddu S, Fontana A, Ambrosio MR, Cassano A, Campana D, Cartenì G, Appetecchia M, Berruti A, Colao A, Falconi M, Delle Fave G. Real-world study of everolimus in advanced progressive neuroendocrine tumors. *Oncologist* 2014; **19**: 966-974 [PMID: 25117065 DOI: 10.1634/theoncologist.2014-0037]

106 **Rugo HS**, Hortobagyi GN, Yao J, Pavel M, Ravaud A, Franz D, Ringeisen F, Gallo J, Rouyrre N, Anak O, Motzer R. Meta-analysis of stomatitis in clinical studies of everolimus: incidence and relationship with efficacy. *Ann Oncol* 2016; **27**: 519-525 [PMID: 26759276 DOI: 10.1093/annonc/mdv595]

107 **Iacovelli R**, Palazzo A, Mezi S, Morano F, Naso G, Cortesi E. Incidence and risk of pulmonary toxicity in patients treated with mTOR inhibitors for malignancy. A meta-analysis of published trials. *Acta Oncol* 2012; **51**: 873-879 [PMID: 22909392 DOI: 10.3109/0284186X.2012.705019]

108 **Panzuto F**, Rinzivillo M, Spada F, Antonuzzo L, Ibrahim T, Campana D, Fazio N, Delle Fave G. Everolimus in Pancreatic Neuroendocrine Carcinomas G3. *Pancreas* 2017; **46**: 302-305 [PMID: 28099254 DOI: 10.1097/MPA.0000000000000762]

109 **Okuyama H**, Ikeda M, Okusaka T, Furukawa M, Ohkawa S, Hosokawa A, Kojima Y, Hara H, Murohisa G, Shioji K, Asagi A, Mizuno N, Kojima M, Yamanaka T, Furuse J. A Phase II Trial of Everolimus in Patients with Advanced Pancreatic Neuroendocrine Carcinoma Refractory or Intolerant to Platinum-Containing Chemotherapy (NECTOR Trial). *Neuroendocrinology* 2020; **110**: 988-993 [PMID: 31986515 DOI: 10.1159/000505550]

110 **Tijeras-Raballand A**, Neuzillet C, Couvelard A, Serova M, de Gramont A, Hammel P, Raymond E, Faivre S. Resistance to targeted therapies in pancreatic neuroendocrine tumors (PNETs): molecular basis, preclinical data, and counteracting strategies. *Target Oncol* 2012; **7**: 173-181 [PMID: 22923165 DOI: 10.1007/s11523-012-0229-6]

111 **Vandamme T**, Beyens M, de Beeck KO, Dogan F, van Koetsveld PM, Pauwels P, Mortier G, Vangestel C, de Herder W, Van Camp G, Peeters M, Hofland LJ. Long-term acquired everolimus resistance in pancreatic neuroendocrine tumours can be overcome with novel PI3K-AKT-mTOR inhibitors. *Br J Cancer* 2016; **114**: 650-658 [PMID: 26978006 DOI: 10.1038/bjc.2016.25]

112 **Marone R**, Erhart D, Mertz AC, Bohnacker T, Schnell C, Cmiljanovic V, Stauffer F, Garcia-Echeverria C, Giese B, Maira SM, Wymann MP. Targeting melanoma with dual phosphoinositide 3-kinase/mammalian target of rapamycin inhibitors. *Mol Cancer Res* 2009; **7**: 601-613 [PMID: 19372588 DOI: 10.1158/1541-7786.MCR-08-0366]

113 **Raymond E**, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, Valle J, Metrakos P, Smith D, Vinik A, Chen JS, Hörsch D, Hammel P, Wiedenmann B, Van Cutsem E, Patyna S, Lu DR, Blanckmeister C, Chao R, Ruszniewski P. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011; **364**: 501-513 [PMID: 21306237 DOI: 10.1056/NEJMoa1003825]

114 **Vinik A**, Bottomley A, Korytowsky B, Bang YJ, Raoul JL, Valle JW, Metrakos P, Hörsch D, Mundayat R, Reisman A, Wang Z, Chao RC, Raymond E. Patient-Reported Outcomes and Quality of Life with Sunitinib Versus Placebo for Pancreatic Neuroendocrine Tumors: Results From an International Phase III Trial. *Target Oncol* 2016; **11**: 815-824 [PMID: 27924459 DOI: 10.1007/s11523-016-0462-5]

115 **Sato K**, Toyoshima Y, Moriyama S, Endo Y, Ito T, Ohki E. Real-world use of sunitinib in Japanese patients with pancreatic neuroendocrine tumors: results from a post-marketing surveillance study. *Cancer Chemother Pharmacol* 2019; **83**: 201-207 [PMID: 30413868 DOI: 10.1007/s00280-018-3724-3]

116 **Rinzivillo M**, Fazio N, Pusceddu S, Spallanzani A, Ibrahim T, Campana D, Marconcini R, Partelli S, Badalamenti G, Brizzi MP, Catena L, Schinzari G, Carnaghi C, Berardi R, Faggiano A, Antonuzzo L, Spada F, Gritti S, Femia D, Gelsomino F, Bongiovanni A, Ricci S, Brighi N, Falconi M, Delle Fave G, Panzuto F. Sunitinib in patients with pre-treated pancreatic neuroendocrine tumors: A real-world study. *Pancreatology* 2018; **18**: 198-203 [PMID: 29361429 DOI: 10.1016/j.pan.2018.01.005]

117 **Yoo C**, Cho H, Song MJ, Hong SM, Kim KP, Chang HM, Chae H, Kim TW, Hong YS, Ryu MH, Kang YK, Kim SC, Ryoo BY. Efficacy and safety of everolimus and sunitinib in patients with gastroenteropancreatic neuroendocrine tumor. *Cancer Chemother Pharmacol* 2017; **79**: 139-146 [PMID: 27942928 DOI: 10.1007/s00280-016-3215-3]

118 **Mizuno Y**, Kudo A, Akashi T, Akahoshi K, Ogura T, Ogawa K, Ono H, Mitsunori Y, Ban D, Tanaka S, Tateishi U, Tanabe M. Sunitinib shrinks NET-G3 pancreatic neuroendocrine neoplasms. *J Cancer Res Clin Oncol* 2018; **144**: 1155-1163 [PMID: 29602973 DOI: 10.1007/s00432-018-2636-2]

119 **Pellat A**, Dreyer C, Couffignal C, Walter T, Lombard-Bohas C, Niccoli P, Seitz JF, Hentic O, André T, Coriat R, Faivre S, Zappa M, Ruszniewski P, Pote N, Couvelard A, Raymond E. Clinical and Biomarker Evaluations of Sunitinib in Patients with Grade 3 Digestive Neuroendocrine Neoplasms. *Neuroendocrinology* 2018; **107**: 24-31 [PMID: 29518779 DOI: 10.1159/000487237]

120 **Xu J**, Shen L, Zhou Z, Li J, Bai C, Chi Y, Li Z, Xu N, Li E, Liu T, Bai Y, Yuan Y, Li X, Wang X, Chen J, Ying J, Yu X, Qin S, Yuan X, Zhang T, Deng Y, Xiu D, Cheng Y, Tao M, Jia R, Wang W, Fan S, Peng M, Su W. Surufatinib in advanced extrapancreatic neuroendocrine tumours (SANET-ep): a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2020; **21**: 1500-1512 [PMID: 32966811 DOI: 10.1016/S1470-2045(20)30496-4]

121 **Xu J**, Shen L, Bai C, Wang W, Li J, Yu X, Li Z, Li E, Yuan X, Chi Y, Yin Y, Lou W, Xu N, Bai Y, Zhang T, Xiu D, Wang X, Yuan Y, Chen J, Qin S, Jia R, Lu M, Cheng Y, Zhou Z, He J, Su W. Surufatinib in advanced pancreatic neuroendocrine tumours (SANET-p): a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2020; **21**: 1489-1499 [PMID: 32966810 DOI: 10.1016/S1470-2045(20)30493-9]

122 **Dilz LM**, Denecke T, Steffen IG, Prasad V, von Weikersthal LF, Pape UF, Wiedenmann B, Pavel M. Streptozocin/5-fluorouracil chemotherapy is associated with durable response in patients with advanced pancreatic neuroendocrine tumours. *Eur J Cancer* 2015; **51**: 1253-1262 [PMID: 25935542 DOI: 10.1016/j.ejca.2015.04.005]

123 **Moertel CG**, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *N Engl J Med* 1992; **326**: 519-523 [PMID: 1310159 DOI: 10.1056/NEJM199202203260804]

124 **Krug S**, Boch M, Daniel H, Nimphius W, Müller D, Michl P, Rinke A, Gress TM. Streptozocin-Based Chemotherapy in Patients with Advanced Neuroendocrine Neoplasms--Predictive and Prognostic Markers for Treatment Stratification. *PLoS One* 2015; **10**: e0143822 [PMID: 26630134 DOI: 10.1371/journal.pone.0143822]

125 **Shibuya H**, Hijioka S, Sakamoto Y, Ito T, Ueda K, Komoto I, Kobayashi N, Kudo A, Yasuda H, Miyake H, Arita J, Kiritani S, Ikeda M, Imaoka H, Ueno M, Kobayashi S, Furuta M, Nagashio Y, Murohisa G, Aoki T, Matsumoto S, Motoya M, Azemoto N, Itakura J, Horiguchi S, Yogi T, Kawagoe T, Miyaoka Y, Imamura F, Senju M, Arioka H, Hara K, Imamura M, Okusaka T. Multi-center clinical evaluation of streptozocin-based chemotherapy for advanced pancreatic neuroendocrine tumors in Japan: focus on weekly regimens and monotherapy. *Cancer Chemother Pharmacol* 2018; **82**: 661-668 [PMID: 30054710 DOI: 10.1007/s00280-018-3656-y]

126 **Schrader J**, Henes FO, Blaeker M, Zimmermann-Fraedrich K, Pace A, Perez D, Izbicki JR, Lohse AW, Benten D. Extended cycle streptozotocin/5-FU chemotherapy for maintenance therapy in pancreatic neuroendocrine tumors. *Endocrine* 2019; **65**: 460-467 [PMID: 31037707 DOI: 10.1007/s12020-019-01941-w]

127 **Ono H**, Kudo A, Akahoshi K, Ogura T, Ogawa K, Ban D, Tanaka S, Tanabe M. Combination of weekly streptozocin and oral S-1 treatment for patients of unresectable or metastatic pancreatic neuroendocrine neoplasms. *J Cancer Res Clin Oncol* 2020; **146**: 793-799 [PMID: 31844980 DOI: 10.1007/s00432-019-03109-5]

128 **Clewemar Antonodimitrakis P**, Sundin A, Wassberg C, Granberg D, Skogseid B, Eriksson B. Streptozocin and 5-Fluorouracil for the Treatment of Pancreatic Neuroendocrine Tumors: Efficacy, Prognostic Factors and Toxicity. *Neuroendocrinology* 2016; **103**: 345-353 [PMID: 26279284 DOI: 10.1159/000439086]

129 **Strosberg JR**, Fine RL, Choi J, Nasir A, Coppola D, Chen DT, Helm J, Kvols L. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. *Cancer* 2011; **117**: 268-275 [PMID: 20824724 DOI: 10.1002/cncr.25425]

130 **Kunz PL**, Catalano PJ, Nimeiri H, Fisher GA, Longacre TA, Suarez CJ, Yao JC, Kulke MH, Hendifar AE, Shanks JC, Shah MH, Zalupski M, Schmulbach EL, Reidy DL, Strosberg JR, O'Dwyer PJ, Benson AB. A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: a trial of the ECOG-ACRIN Cancer Research Group (E2211). *J Clin Oncol* 2018

131 **Lu Y**, Zhao Z, Wang J, Lv W, Lu L, Fu W, Li W. Safety and efficacy of combining capecitabine and temozolomide (CAPTEM) to treat advanced neuroendocrine neoplasms: A meta-analysis. *Medicine (Baltimore)* 2018; **97**: e12784 [PMID: 30313101 DOI: 10.1097/MD.0000000000012784]

132 **Ostwal V**, Basu S, Bhargava P, Shah M, Parghane RV, Srinivas S, Chaudhari V, Bhandare MS, Shrikhande SV, Ramaswamy A. Capecitabine-Temozolomide in Advanced Grade 2 and Grade 3 Neuroendocrine Neoplasms: Benefits of Chemotherapy in Neuroendocrine Neoplasms with Significant 18FDG Uptake. *Neuroendocrinology* 2021; **111**: 998-1004 [PMID: 33017827 DOI: 10.1159/000511987]

133 **Spada F**, Maisonneuve P, Fumagalli C, Marconcini R, Gelsomino F, Antonuzzo L, Campana D, Puliafito I, Rossi G, Faviana P, Messerini L, Barberis M, Fazio N. Temozolomide alone or in combination with capecitabine in patients with advanced neuroendocrine neoplasms: an Italian multicenter real-world analysis. *Endocrine* 2021; **72**: 268-278 [PMID: 32700133 DOI: 10.1007/s12020-020-02421-2]

134 **Chatzellis E**, Angelousi A, Daskalakis K, Tsoli M, Alexandraki KI, Wachuła E, Meirovitz A, Maimon O, Grozinsky-

Glasberg S, Gross D, Kos-Kudła B, Koumarianou A, Kaltsas G. Activity and Safety of Standard and Prolonged Capecitabine/Temozolomide Administration in Patients with Advanced Neuroendocrine Neoplasms. *Neuroendocrinology* 2019; **109**: 333-345 [PMID: 31167197 DOI: 10.1159/000500135]

135 **Apostolidis L**, Dal Buono A, Merola E, Jann H, Jäger D, Wiedenmann B, Winkler EC, Pavel M. Multicenter Analysis of Treatment Outcomes for Systemic Therapy in Well Differentiated Grade 3 Neuroendocrine Tumors (NET G3). *Cancers (Basel)* 2021; **13** [PMID: 33923759 DOI: 10.3390/cancers13081936]

136 **Bongiovanni A**, Liverani C, Foca F, Fausti V, Di Menna G, Mercatali L, De Vita A, Riva N, Calpona S, Miserocchi G, Spadazzi C, Cocchi C, Ibrahim T. Temozolomide Alone or Combined with Capecitabine for the Treatment of Metastatic Neuroendocrine Neoplasia: A "Real-World" Data Analysis. *Neuroendocrinology* 2021; **111**: 895-906 [PMID: 33221806 DOI: 10.1159/000513218]

137 **Kobayashi N**, Takeda Y, Okubo N, Suzuki A, Tokuhisa M, Hiroshima Y, Ichikawa Y. Phase II study of temozolomide monotherapy in patients with extrapulmonary neuroendocrine carcinoma. *Cancer Sci* 2021; **112**: 1936-1942 [PMID: 33453146 DOI: 10.1111/cas.14811]

138 **Squires MH**, Worth PJ, Konda B, Shah MH, Dillhoff ME, Abdel-Misih S, Norton JA, Visser BC, Dua M, Pawlik TM, Schmidt CR, Poultsides G, Cloyd JM. Neoadjuvant Capecitabine/Temozolomide for Locally Advanced or Metastatic Pancreatic Neuroendocrine Tumors. *Pancreas* 2020; **49**: 355-360 [PMID: 32132509 DOI: 10.1097/MPA.0000000000001500]

139 **Ambe CM**, Nguyen P, Centeno BA, Choi J, Strosberg J, Kvols L, Hodul P, Hoffe S, Malafa MP. Multimodality Management of "Borderline Resectable" Pancreatic Neuroendocrine Tumors: Report of a Single-Institution Experience. *Cancer Control* 2017; **24**: 1073274817729076 [PMID: 28975822 DOI: 10.1177/1073274817729076]

140 **Sorbye H**, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, Dueland S, Hofsli E, Guren MG, Ohrling K, Birkemeyer E, Thiis-Evensen E, Biagini M, Gronbaek H, Soveri LM, Olsen IH, Federspiel B, Assmus J, Janson ET, Knigge U. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol* 2013; **24**: 152-160 [PMID: 22967994 DOI: 10.1093/annonc/mds276]

141 **Elvebakken H**, Perren A, Scoazec JY, Tang LH, Federspiel B, Klimstra DS, Vestermark LW, Ali AS, Zlobec I, Myklebust TÅ, Hjortland GO, Langer SW, Gronbaek H, Knigge U, Tiensuu Janson E, Sorbye H. A Consensus-Developed Morphological Re-Evaluation of 196 High-Grade Gastroenteropancreatic Neuroendocrine Neoplasms and Its Clinical Correlations. *Neuroendocrinology* 2021; **111**: 883-894 [PMID: 33002892 DOI: 10.1159/000511905]

142 **Kulke MH**, Wu B, Ryan DP, Enzinger PC, Zhu AX, Clark JW, Earle CC, Michelini A, Fuchs CS. A phase II trial of irinotecan and cisplatin in patients with metastatic neuroendocrine tumors. *Dig Dis Sci* 2006; **51**: 1033-1038 [PMID: 16865563 DOI: 10.1007/s10620-006-8001-3]

143 **Lu ZH**, Li J, Lu M, Zhang XT, Zhou J, Wang XC, Gong JF, Gao J, Li Y, Shen L. Feasibility and efficacy of combined cisplatin plus irinotecan chemotherapy for gastroenteropancreatic neuroendocrine carcinomas. *Med Oncol* 2013; **30**: 664 [PMID: 23864251 DOI: 10.1007/s12032-013-0664-y]

144 **Ali AS**, Grönberg M, Langer SW, Ladekarl M, Hjortland GO, Vestermark LW, Österlund P, Welin S, Grønbæk H, Knigge U, Sorbye H, Janson ET. Intravenous *vs* oral etoposide: efficacy and correlation to clinical outcome in patients with high-grade metastatic gastroenteropancreatic neuroendocrine neoplasms (WHO G3). *Med Oncol* 2018; **35**: 47 [PMID: 29511910 DOI: 10.1007/s12032-018-1103-x]

145 **Spada F**, Antonuzzo L, Marconcini R, Radice D, Antonuzzo A, Ricci S, Di Costanzo F, Fontana A, Gelsomino F, Luppi G, Nobili E, Galdy S, Cella CA, Sonzogni A, Pisa E, Barberis M, Fazio N. Oxaliplatin-Based Chemotherapy in Advanced Neuroendocrine Tumors: Clinical Outcomes and Preliminary Correlation with Biological Factors. *Neuroendocrinology* 2016; **103**: 806-814 [PMID: 26789262 DOI: 10.1159/000444087]

146 **Bajetta E**, Catena L, Procopio G, De Dosso S, Bichisao E, Ferrari L, Martinetti A, Platania M, Verzoni E, Formisano B, Bajetta R. Are capecitabine and oxaliplatin (XELOX) suitable treatments for progressing low-grade and high-grade neuroendocrine tumours? *Cancer Chemother Pharmacol* 2007; **59**: 637-642 [PMID: 16937105 DOI: 10.1007/s00280-006-0306-6]

147 **Faure M**, Niccoli P, Autret A, Cavaglione G, Mineur L, Raoul JL. Systemic chemotherapy with FOLFOX in metastatic grade 1/2 neuroendocrine cancer. *Mol Clin Oncol* 2017; **6**: 44-48 [PMID: 28123727 DOI: 10.3892/mco.2016.1097]

148 **Merola E**, Dal Buono A, Denecke T, Arsenic R, Pape UF, Jann H, Wiedenmann B, Pavel ME. Efficacy and Toxicity of 5-Fluorouracil-Oxaliplatin in Gastroenteropancreatic Neuroendocrine Neoplasms. *Pancreas* 2020; **49**: 912-917 [PMID: 32658073 DOI: 10.1097/MPA.0000000000001593]

149 **Pulvirenti A**, Raj N, Cingarlini S, Pea A, Tang LH, Luchini C, Chou JF, Grego E, Marinova I, Capanu M, Landoni L, Scarpa A, Allen PJ, Klimstra DS, Reidy-Lagunes DL. Platinum-Based Treatment for Well- and Poorly Differentiated Pancreatic Neuroendocrine Neoplasms. *Pancreas* 2021; **50**: 138-146 [PMID: 33565789 DOI: 10.1097/MPA.0000000000001740]

150 **Lacombe C**, De Rycke O, Couvelard A, Turpin A, Cazes A, Hentic O, Gounant V, Zalcman G, Ruszniewski P, Cros J, de Mestier L. Biomarkers of Response to Etoposide-Platinum Chemotherapy in Patients with Grade 3 Neuroendocrine Neoplasms. *Cancers (Basel)* 2021; **13** [PMID: 33562726 DOI: 10.3390/cancers13040643]

151 **Hijioka S**, Hosoda W, Matsuo K, Ueno M, Furukawa M, Yoshitomi H, Kobayashi N, Ikeda M, Ito T, Nakamori S, Ishii H, Kodama Y, Morizane C, Okusaka T, Yanagimoto H, Notohara K, Taguchi H, Kitano M, Yane K, Maguchi H, Tsuchiya Y, Komoto I, Tanaka H, Tsuji A, Hashigo S, Kawaguchi Y, Mine T, Kanno A, Murohisa G, Miyabe K, Takagi T, Matayoshi N, Yoshida T, Hara K, Imamura M, Furuse J, Yatabe Y, Mizuno N. Rb Loss and *KRAS* Mutation Are Predictors of the Response to Platinum-Based Chemotherapy in Pancreatic Neuroendocrine Neoplasm with Grade 3: A Japanese Multicenter Pancreatic NEN-G3 Study. *Clin Cancer Res* 2017; **23**: 4625-4632 [PMID: 28455360 DOI: 10.1158/1078-0432.CCR-16-3135]

152 **Tanaka H**, Hijioka S, Hosoda W, Ueno M, Kobayashi N, Ikeda M, Ito T, Kodama Y, Morizane C, Notohara K, Taguchi H, Kitano M, Komoto I, Tsuji A, Hashigo S, Kanno A, Miyabe K, Takagi T, Ishii H, Kojima Y, Yoshitomi H, Yanagimoto H, Furuse J, Mizuno N. Pancreatic neuroendocrine carcinoma G3 may be heterogeneous and could be

classified into two distinct groups. *Pancreatology* 2020; **20**: 1421-1427 [PMID: 32891532 DOI: 10.1016/j.pan.2020.07.400]

153 **Sugiyama K**, Shiraishi K, Sato M, Nishibori R, Nozawa K, Kitagawa C. Salvage Chemotherapy by FOLFIRI Regimen for Poorly Differentiated Gastrointestinal Neuroendocrine Carcinoma. *J Gastrointest Cancer* 2021; **52**: 947-951 [PMID: 32918273 DOI: 10.1007/s12029-020-00516-7]

154 **Cives M**, Pelle' E, Quaresmini D, Rizzo FM, Tucci M, Silvestris F. The Tumor Microenvironment in Neuroendocrine Tumors: Biology and Therapeutic Implications. *Neuroendocrinology* 2019; **109**: 83-99 [PMID: 30699437 DOI: 10.1159/000497355]

155 **Waddell N**, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, Johns AL, Miller D, Nones K, Quek K, Quinn MC, Robertson AJ, Fadlullah MZ, Bruxner TJ, Christ AN, Harliwong I, Idrisoglu S, Manning S, Nourse C, Nourbakhsh E, Wani S, Wilson PJ, Markham E, Cloonan N, Anderson MJ, Fink JL, Holmes O, Kazakoff SH, Leonard C, Newell F, Poudel B, Song S, Taylor D, Waddell N, Wood S, Xu Q, Wu J, Pinese M, Cowley MJ, Lee HC, Jones MD, Nagrial AM, Humphris J, Chantrill LA, Chin V, Steinmann AM, Mawson A, Humphrey ES, Colvin EK, Chou A, Scarlett CJ, Pinho AV, Giry-Laterriere M, Rooman I, Samra JS, Kench JG, Pettitt JA, Merrett ND, Toon C, Epari K, Nguyen NQ, Barbour A, Zeps N, Jamieson NB, Graham JS, Niclou SP, Bjerkvig R, Grützmann R, Aust D, Hruban RH, Maitra A, Iacobuzio-Donahue CA, Wolfgang CL, Morgan RA, Lawlor RT, Corbo V, Bassi C, Falconi M, Zamboni G, Tortora G, Tempero MA; Australian Pancreatic Cancer Genome Initiative, Gill AJ, Eshleman JR, Pilarsky C, Scarpa A, Musgrove EA, Pearson JV, Biankin AV, Grimmond SM. Whole genomes redefine the mutational landscape of pancreatic cancer. *Nature* 2015; **518**: 495-501 [PMID: 25719666 DOI: 10.1038/nature14169]

156 **Lawrence MS**, Stojanov P, Polak P, Kryukov GV, Cibulskis K, Sivachenko A, Carter SL, Stewart C, Mermel CH, Roberts SA, Kiezun A, Hammerman PS, McKenna A, Drier Y, Zou L, Ramos AH, Pugh TJ, Stransky N, Helman E, Kim J, Sougnez C, Ambrogio L, Nickerson E, Shefler E, Cortés ML, Auclair D, Saksena G, Voet D, Noble M, DiCara D, Lin P, Lichtenstein L, Heiman DI, Fennell T, Imielinski M, Hernandez B, Hodis E, Baca S, Dulak AM, Lohr J, Landau DA, Wu CJ, Melendez-Zajgla J, Hidalgo-Miranda A, Koren A, McCarroll SA, Mora J, Crompton B, Onofrio R, Parkin M, Winckler W, Ardlie K, Gabriel SB, Roberts CWM, Biegel JA, Stegmaier K, Bass AJ, Garraway LA, Meyerson M, Golub TR, Gordenin DA, Sunyaev S, Lander ES, Getz G. Mutational heterogeneity in cancer and the search for new cancer-associated genes. *Nature* 2013; **499**: 214-218 [PMID: 23770567 DOI: 10.1038/nature12213]

157 **Vijayvergia N**, Boland PM, Handorf E, Gustafson KS, Gong Y, Cooper HS, Sheriff F, Astsaturov I, Cohen SJ, Engstrom PF. Molecular profiling of neuroendocrine malignancies to identify prognostic and therapeutic markers: a Fox Chase Cancer Center Pilot Study. *Br J Cancer* 2016; **115**: 564-570 [PMID: 27482646 DOI: 10.1038/bjc.2016.229]

158 **Mehnert JM**, Bergsland E, O'Neil BH, Santoro A, Schellens JHM, Cohen RB, Doi T, Ott PA, Pishvaian MJ, Puzanov I, Aung KL, Hsu C, Le Tourneau C, Hollebecque A, Élez E, Tamura K, Gould M, Yang P, Stein K, Piha-Paul SA. Pembrolizumab for the treatment of programmed death-ligand 1-positive advanced carcinoid or pancreatic neuroendocrine tumors: Results from the KEYNOTE-028 study. *Cancer* 2020; **126**: 3021-3030 [PMID: 32320048 DOI: 10.1002/cncr.32883]

159 **Strosberg J**, Mizuno N, Doi T, Grande E, Delord JP, Shapira-Frommer R, Bergsland E, Shah M, Fakih M, Takahashi S, Piha-Paul SA, O'Neil B, Thomas S, Lolkema MP, Chen M, Ibrahim N, Norwood K, Hadoux J. Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Neuroendocrine Tumors: Results From the Phase II KEYNOTE-158 Study. *Clin Cancer Res* 2020; **26**: 2124-2130 [PMID: 31980466 DOI: 10.1158/1078-0432.CCR-19-3014]

160 **Vijayvergia N**, Dasari A, Deng M, Litwin S, Al-Toubah T, Alpaugh RK, Dotan E, Hall MJ, Ross NM, Runyen MM, Denlinger CS, Halperin DM, Cohen SJ, Engstrom PF, Strosberg JR. Pembrolizumab monotherapy in patients with previously treated metastatic high-grade neuroendocrine neoplasms: joint analysis of two prospective, non-randomised trials. *Br J Cancer* 2020; **122**: 1309-1314 [PMID: 32152503 DOI: 10.1038/s41416-020-0775-0]

161 **Fottner CA**, Ferrata M, Krug S, Michl P, Schad A, Roth W, Jaeger D, Galle PR, Weber MM. A phase II, open label, multicenter trial of avelumab in patients with advanced, metastatic high-grade neuroendocrine carcinomas NEC G3 (WHO 2010) progressive after first-line chemotherapy (AVENEC). *J Clin Oncol* 2019

162 **Yao JC**, Strosberg J, Fazio N, Pavel ME, Bergsland E, Ruszniewski P, Halperin DM, Li D, Tafuto S, Raj N, Campana D, Hijioka S, Raderer M, Guimbaud R, Gajate P, Pusceddu S, Reising A, Degtyarev E, Shilkrut M, Eddy S, Singh S. Spartalizumab in metastatic, well/poorly-differentiated neuroendocrine neoplasms. *Endocr Relat Cancer* 2021 [PMID: 33480358 DOI: 10.1530/ERC-20-0382]

163 **Patel SP**, Othus M, Chae YK, Giles FJ, Hansel DE, Singh PP, Fontaine A, Shah MH, Kasi A, Baghdadi TA, Matrana M, Gatalica Z, Korn WM, Hayward J, McLeod C, Chen HX, Sharon E, Mayerson E, Ryan CW, Plets M, Blanke CD, Kurzrock R. A Phase II Basket Trial of Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART SWOG 1609) in Patients with Nonpancreatic Neuroendocrine Tumors. *Clin Cancer Res* 2020; **26**: 2290-2296 [PMID: 31969335 DOI: 10.1158/1078-0432.CCR-19-3356]

164 **Capdevila JT**, López C, García-Carbonero R, Benavent M, Custodio A, Cubillo A, Alonso V, Alonso Gordoa T, Carmona-Bayonas A, Crespo G, Blanco-Codesido M, Jimenez-Fonseca P, Viúdez A, La Casta Muñoa A, Sevilla I, Llanos M, Segura A, Hernando-Cubero J, Manzano JL. A multi-cohort phase II study of durvalumab plus tremelimumab for the treatment of patients (pts) with advanced neuroendocrine neoplasms (NENs) of gastroenteropancreatic or lung origin: The DUNE trial (GETNE 1601). *J Clin Oncol* 2020

165 **Limmer S**, Huppert PE, Juette V, Lenhart A, Welte M, Wietholtz H. Radiofrequency ablation of solitary pancreatic insulinoma in a patient with episodes of severe hypoglycemia. *Eur J Gastroenterol Hepatol* 2009; **21**: 1097-1101 [PMID: 19685572 DOI: 10.1097/meg.0b013e328323d70e]

166 **Barthet M**, Giovannini M, Lesavre N, Boustiere C, Napoleon B, Koch S, Gasmi M, Vanbiervliet G, Gonzalez JM. Endoscopic ultrasound-guided radiofrequency ablation for pancreatic neuroendocrine tumors and pancreatic cystic neoplasms: a prospective multicenter study. *Endoscopy* 2019; **51**: 836-842 [PMID: 30669161 DOI: 10.1055/a-0824-7067]

167 **Larghi A**, Rimbaş M, Rizzatti G, Carbone C, Gasbarrini A, Costamagna G, Alfieri S, Tortora G. Endoscopic ultrasound-guided therapies for pancreatic solid tumors: An overview. *Semin Oncol* 2021; **48**: 95-105 [PMID: 33608132 DOI: 10.1053/j.seminoncol.2021.01.004]

168 **Choi JH**, Park DH, Kim MH, Hwang HS, Hong SM, Song TJ, Lee SS, Seo DW, Lee SK. Outcomes after endoscopic ultrasound-guided ethanol-lipiodol ablation of small pancreatic neuroendocrine tumors. *Dig Endosc* 2018; **30**: 652-658 [PMID: 29575213 DOI: 10.1111/den.13058]

169 **Claringbold PG**, Price RA, Turner JH. Phase I-II study of radiopeptide 177Lu-octreotate in combination with capecitabine and temozolomide in advanced low-grade neuroendocrine tumors. *Cancer Biother Radiopharm* 2012; **27**: 561-569 [PMID: 23078020 DOI: 10.1089/cbr.2012.1276]

170 **Nicolini S**, Bodei L, Bongiovanni A, Sansovini M, Grassi I, Ibrahim T, Monti M, Caroli P, Sarnelli A, Diano D, Di Iorio V, Grana CM, Cittanti C, Pieri F, Severi S, Paganelli G. Combined use of 177Lu-DOTATATE and metronomic capecitabine (Lu-X) in FDG-positive gastro-entero-pancreatic neuroendocrine tumors. *Eur J Nucl Med Mol Imaging* 2021; **48**: 3260-3267 [PMID: 33604690 DOI: 10.1007/s00259-021-05236-z]

171 **Parghane RV**, Ostwal V, Ramaswamy A, Bhandare M, Chaudhari V, Talole S, Shrikhande SV, Basu S. Long-term outcome of "Sandwich" chemo-PRRT: a novel treatment strategy for metastatic neuroendocrine tumors with both FDG- and SSTR-avid aggressive disease. *Eur J Nucl Med Mol Imaging* 2021; **48**: 913-923 [PMID: 32876706 DOI: 10.1007/s00259-020-05004-5]

172 **Satapathy S**, Mittal BR, Sood A, Kapoor R, Gupta R. Peptide Receptor Radionuclide Therapy as First-Line Systemic Treatment in Advanced Inoperable/Metastatic Neuroendocrine Tumors. *Clin Nucl Med* 2020; **45**: e393-e399 [PMID: 32604121 DOI: 10.1097/RLU.0000000000003170]

173 **Bajetta E**, Catena L, Fazio N, Pusceddu S, Biondani P, Blanco G, Ricci S, Aieta M, Pucci F, Valente M, Bianco N, Mauri CM, Spada F. Everolimus in combination with octreotide long-acting repeatable in a first-line setting for patients with neuroendocrine tumors: an ITMO group study. *Cancer* 2014; **120**: 2457-2463 [PMID: 24752410 DOI: 10.1002/cncr.28726]

174 **Capdevila J**, Teulé A, Barriuso J, Castellano D, Lopez C, Manzano JL, Alonso V, García-Carbonero R, Dotor E, Matos I, Custodio A, Casanovas O, Salazar R; EVERLAR study investigators. Phase II Study of Everolimus and Octreotide LAR in Patients with Nonfunctioning Gastrointestinal Neuroendocrine Tumors: The GETNE1003_EVERLAR Study. *Oncologist* 2019; **24**: 38-46 [PMID: 29794066 DOI: 10.1634/theoncologist.2017-0622]

175 **Chan JA**, Blaszkowsky L, Stuart K, Zhu AX, Allen J, Wadlow R, Ryan DP, Meyerhardt J, Gonzalez M, Regan E, Zheng H, Kulke MH. A prospective, phase 1/2 study of everolimus and temozolomide in patients with advanced pancreatic neuroendocrine tumor. *Cancer* 2013; **119**: 3212-3218 [PMID: 23733618 DOI: 10.1002/cncr.28142]

176 **Capdevila J**, Sevilla I, Alonso V, Antón Aparicio L, Jiménez Fonseca P, Grande E, Reina JJ, Manzano JL, Alonso Lájara JD, Barriuso J, Castellano D, Medina J, López C, Segura Á, Carrera S, Crespo G, Fuster J, Munarriz J, García Alfonso P. Evaluation of the efficacy and safety of lanreotide in combination with targeted therapies in patients with neuroendocrine tumours in clinical practice: a retrospective cross-sectional analysis. *BMC Cancer* 2015; **15**: 495 [PMID: 26138480 DOI: 10.1186/s12885-015-1512-6]

177 **Strosberg JR**, Weber JM, Choi J, Campos TL, Valone TL, Han G, Schell MJ, Kvols LK. A phase II clinical trial of sunitinib following hepatic transarterial embolization for metastatic neuroendocrine tumors. *Ann Oncol* 2012; **23**: 2335-2341 [PMID: 22317769 DOI: 10.1093/annonc/mdr614]

178 **Rogers JE**, Lam M, Halperin DM, Dagohoy CG, Yao JC, Dasari A. Fluorouracil, Doxorubicin with Streptozocin and Subsequent Therapies in Pancreatic Neuroendocrine Tumors. *Neuroendocrinology* 2022; **112**: 34-42 [PMID: 33434908 DOI: 10.1159/000514339]

179 **Walter T**, Malka D, Hentic O, Lombard-Bohas C, Le Malicot K, Smith D, Ferru A, Assenat E, Cadiot G, Lievre A, Kurtz JE, Dahan L, Dubreuil O, Hautefeuille V, Lepere C, Gangloff A, Elhajbi F, Coriat R, Roquin G, Bouarioua N, Granger V, Scoazec JY, Lepage C. Evaluating bevacizumab in combination with FOLFIRI after the failure of platinum-etoposide regimen in patients with advanced poorly differentiated neuroendocrine carcinoma: The PRODIGE 41-BEVANEC randomized phase II study. *Dig Liver Dis* 2018; **50**: 195-198 [PMID: 29258812 DOI: 10.1016/j.dld.2017.11.020]

180 **Kamp K**, Gumz B, Feelders RA, Kwekkeboom DJ, Kaltsas G, Costa FP, de Herder WW. Safety and efficacy of everolimus in gastrointestinal and pancreatic neuroendocrine tumors after (177)Lu-octreotate. *Endocr Relat Cancer* 2013; **20**: 825-831 [PMID: 24036133 DOI: 10.1530/ERC-13-0254]

181 **Fröss-Baron K**, Garske-Roman U, Welin S, Granberg D, Eriksson B, Khan T, Sandström M, Sundin A. 177Lu-DOTATATE Therapy of Advanced Pancreatic Neuroendocrine Tumors Heavily Pretreated with Chemotherapy: Analysis of Outcome, Safety, and Their Determinants. *Neuroendocrinology* 2021; **111**: 330-343 [PMID: 32097917 DOI: 10.1159/000506746]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 February 27; 14(2): 107-119

DOI: 10.4240/wjgs.v14.i2.107

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

# Surgical strategies for Mirizzi syndrome: A ten-year single center experience

Wei Lai, Jie Yang, Nan Xu, Jun-Hua Chen, Chen Yang, Hui-Hua Yao

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

**P-Reviewer:** Balakrishnan DS, Kotelevets SM

**Received:** September 3, 2021
**Peer-review started:** September 3, 2021
**First decision:** October 2, 2021
**Revised:** October 13, 2021
**Accepted:** January 14, 2022
**Article in press:** January 14, 2022
**Published online:** February 27, 2022

**Wei Lai, Jie Yang, Nan Xu, Jun-Hua Chen, Chen Yang, Hui-Hua Yao,** Department of Hepatobiliary-Pancreatic-Splenic Surgery, Chengdu First People's Hospital (Chengdu Integrated TCM & Western Medicine Hospital), Chengdu 610044, Sichuan Province, China

**Corresponding author:** Wei Lai, MD, Associate Professor, Attending Doctor, Department of Hepatobiliary-Pancreatic-Splenic Surgery, Chengdu First People's Hospital (Chengdu Integrated TCM & Western Medicine Hospital), No. 18 Wanxiang North Road, High Tech District, Chengdu 610044, Sichuan Province, China. laiwei119@163.com

## Abstract

### *BACKGROUND*

Mirizzi syndrome (MS) remains a challenging biliary disease, and its low rate of preoperative diagnosis should be resolved. Moreover, technological advances have not resulted in decisive improvements in the surgical treatment of MS. Complex bile duct lesions due to MS make surgery difficult, especially when the laparoscopic approach is adopted. The safety and long-term effect of MS treatment need to be guaranteed in terms of preoperative diagnosis and surgical strategy.

### *AIM*

To analyze preoperative diagnostic methods and the safety, effectiveness, prognosis and related factors of surgical strategies for different types of MS.

### *METHODS*

The clinical data of MS patients who received surgical treatment from January 1, 2010 to December 31, 2020 were retrospectively reviewed. Patients with malignancies, choledochojejunal fistula, lack of data and lost to follow-up were excluded. According to preoperative imaging examination records and documented intraoperative findings, the clinical types of MS were determined using the Csendes classification. The safety, effectiveness and long-term prognosis of surgical treatment in different types of MS, and their interactions with the clinical characteristics of patients were summarized.

### *RESULTS*

Sixty-six patients with MS were included (34 males and 32 females). Magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) showed specific imaging features of MS in 58 cases (87.9%), which was superior to ultrasound scan (USS) in the diagnosis of MS and more sensitive to subtle biliary

lesions than USS. The overall laparoscopic surgery completion rate was 53.03% (35/66), where the completion rates of MS type I, II and III were 69.05% (29/42), 42.86% (6/14) and zero (0/10), respectively. Thirty-one patients (46.97%) underwent laparotomy or conversion to laparotomy including 11 cases of iatrogenic bile duct injury which occurred in type I patients, and 25 of these patients underwent bile duct exploration, repair and T-tube drainage. In addition, 25 patients underwent intraoperative choledochoscopy and T-tube cholangiography. Overall, 21 cases (31.8%) were repaired by simple suturing, and 14 cases (21.2%) were repaired using the remaining gallbladder wall patch in the subtotal cholecystectomy. The ascendant of the Csendes classification types led to an increase in surgical complexity reflected by increased operation time, bleeding volume and cost. Gender, acute abdominal pain and measurable stone size had no effect on Csendes type of MS or final surgical approach. Age had no effect on the classification of MS, but it influenced the final surgical approach, hospital stay and cost. A total of 66 patients obtained a relatively high preoperative diagnostic rate and underwent surgery safely without serious complications, and no mortality was observed during the follow-up period of 36.5 ± 26.5 mo (range 13-76, median 22 mo).

*CONCLUSION*

MRI/MRCP can improve the preoperative diagnosis of MS. The Csendes classification can reflect the difficulty of treatment. The surgical strategies including laparoscopic surgery for MS should be formulated based on full evaluation and selection.

**Key Words:** Mirizzi syndrome; Surgical strategy; Diagnosis; Classification; Surgical approach; Laparoscope



**Core Tip:** Accurate preoperative diagnosis is a prerequisite for rational selection of surgical strategies for Mirizzi syndrome (MS). Preoperative images combined with findings during intraoperative exploration to determine the classification of MS is the basis for confirming the surgical approach. The present study revealed that magnetic resonance imaging is an effective and reliable preoperative diagnostic method for MS. Laparoscopic surgery can be used in most patients with MS type I and II following detailed evaluation, while type III and IV patients require laparotomy or conversion surgery. Our results verified that disease classification can reflect the difficulty of MS surgery.

**Citation:** Lai W, Yang J, Xu N, Chen JH, Yang C, Yao HH. Surgical strategies for Mirizzi syndrome: A ten-year single center experience. *World J Gastrointest Surg* 2022; 14(2): 107-119
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i2/107.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i2.107

## INTRODUCTION

Mirizzi syndrome (MS) is a special clinical complication of cholecystolithiasis. It refers to a series of symptoms caused by compression of the common bile duct (CBD) or hepatic duct with or without varying degrees of cholecystobiliary fistula, which results from the impaction of stones in the Hartmann pouch or cystic duct of the gallbladder and/or tissue inflammation and edema[1].

According to the clinical manifestations, pathophysiological changes and imaging features, MS is divided into different types. The Csendes classification is most commonly used in classification of clinical types of MS[2]. This classification divides MS into four main types. Type I: The Hartmann pouch or cystic duct is impacted by gallstones accompanied by compression of the CBD, without fistula formation. Type II: A fistula is formed and the eroded circumference of the CBD is less than one third of that in type I. Type III: The fistula erodes two thirds of the circumference of the CBD. Type IV: Cholecystobiliary fistula involves the whole circumference of the CBD.

Advances in medical technology, such as laparoscopy and robotic surgery, have brought hepatobiliary surgery into a new era. Even so, MS is still a dilemma for surgeons because the low incidence rate leads to difficulty in accumulating personal experience, and is associated with a high conversion rate, and a high risk of operative complications, particularly bile duct injury (BDI)[3,4].

Accurate diagnosis is a prerequisite for the correct treatment of MS. An inaccurate diagnosis usually results in misjudgment during surgery, increases the incidence of BDI, and finally leads to worse clinical consequences. MS has long been a dilemma for surgeons, especially when laparoscopic surgery is performed[5,6]. The diagnosis and management of MS are still challenging[7,8].

Even in patients with a definite diagnosis, many difficulties and risks still need to be overcome in dealing with MS. The erosion of structures, changes in anatomy, dense adhesions and fibrotic lesions caused by stone incarceration and local inflammation increase the difficulty of surgery, the risk of bleeding and the probability of BDI[9]. In view of the above reasons, it is believed that laparoscopic surgery is not the best treatment method for MS, even if it is not a contraindication[10,11].

Endoscopic retrograde cholangiopancreatography (ERCP) can provide more accurate biliary images, and establish diagnosis before operation, and intervene on the combined CBD stones simultaneously. However, its inherent disadvantages limit its application in the comprehensive treatment of MS[1,12,13], such as the treatment of the diseased gallbladder, and cholecystectomy still needs to be performed at the same time or delayed.

Due to the high cost and low popularization, requirements for the operating skills of surgeons, and complications similar to laparoscopic surgery, robotic surgery is not a practical means to treat MS[14-16]. Moreover, it is usually performed in combination with ERCP when dealing with MS, which increases the requirements for facilities and personnel[17,18].

This study retrospectively reviewed the experience of the surgical treatment of MS in our hospital over the past ten years. This experience is mainly based on the strategy that magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) is used as an essential preoperative diagnostic method, combined with the findings of intraoperative exploration to determine the surgical plan in MS patients, without ERCP preoperatively or intraoperatively. The strategy was safe and effective, even though ERCP was not routinely performed. It can be implemented in hospitals with basic facilities and medical qualifications. It is especially suitable for promotion in areas with insufficient medical resources.

## MATERIALS AND METHODS

### *Study design and setting*

We conducted a retrospective study involving patients diagnosed with MS who were treated by surgery at the Chengdu First People's Hospital. Data were collected from the case database in our hospital.

### *Patients and data collection*

All patients diagnosed with MS from January 1, 2010 to December 31, 2020 were enrolled in this study. The inclusion criteria were: (1) Over 18 years old; (2) MS patients without intrahepatic bile duct stones and choledocholithiasis; and (3) The results of related imaging and detailed intraoperative exploration were recorded. The exclusion criteria were: (1) Patients with hepatobiliary malignancies; (2) Patients complicated by choledochojejunal fistula; (3) Data were missing and could not be classified; and (4) Patients lost to follow-up.

According to preoperative imaging examination and intraoperative findings, the clinical types of MS was determined using the Csendesclassification[2].

### *Ethical concerns*

The study was reviewed and approved by the Institutional Review Board of Chengdu First People's Hospital(Chengdu Integrated TCM & Western Medicine Hospital). All patients and/or their guardians signed an informed consent before surgery, which met the ethical requirements. Due to the retrospective design of the study, informed consent was waived by the ethics committee for this study.

### *Follow-up*

All patients were followed up in the outpatient department until to June 30, 2021. At least one liver function and ultrasound scan (USS) examination of the hepatobiliary system was completed during the follow-up period after discharge. Before extubation, T-tube cholangiography was performed routinely in patients with T-tube placement, and MRI/MRCP was adopted if necessary. The patients with a percutaneous transhepatic cholangio pancreatic drainage (PTCD) tube were treated in the same way as those with a T-tube. Whether the patients would receive subsequent treatment was determined according to the review results.

### *Statistical analysis*

Continuous variables are presented as mean ± SD, and categorical variables are presented as frequencies and percentages. The comparison of rates among different groups was based on counting data $\chi^2$ test. The mean number of different groups was compared by variance analysis. Statistical analyses were performed using SPSS 19 (IBM Corp., Armonk, NY, United States). A two-sided $P < 0.05$ was considered statistically significant.

## RESULTS

### General information

Sixty-six patients with MS were included, 34 males (51.5%) and 32 females (48.5%), which is approximately 0.6% of the patients who underwent cholecystectomy in our hospital during the same period. Their age ranged from 18 to 83 years (48.1 ± 15.0, median 47 years). Forty-eight patients (72.7%) with acute abdominal pain and 18 patients (27.3%) without acute abdominal pain were admitted through different routes.

Thirty-nine patients (59.1%) had at least one previous admission according to the available medical records. The upper limit of the normal reference value for total bilirubin detection in our hospital is 28 μmol/L. According to this standard, 35 patients (53.0%) also had jaundice at the time of admission, and 6 of these patients (1 with type II and 5 with type III) underwent preoperative PTCD because of severe comorbidities (hypertension in 1, diabetes in 2 and lung disease in 3) and received general anesthesia surgery after their comorbidities were controlled. The demographic data of the MS patients included in this study are shown in Table 1.

### Imaging examinations

ERCP was not performed in any of the 66 MS patients, and USS and MRI/MRCP were performed in all the patients. USS showed bile duct dilatation in 13 cases (19.7%), bile duct compression in 11 cases (16.7%), and the others showed no specific signs. All patients underwent MRI/MRCP at the same time. The results showed that 58 cases (87.9%) had special imaging features of MS, including stones in the Hartmann pouch or cystic duct, extrinsic compression of the bile duct, dilatation of the bile duct and obvious inflammatory changes in Calot's triangle. MRI/MRCP was superior to USS in the diagnosis of MS (Fisher's exact test, $\chi^2 = 5.873$, $P = 0.023$). It seemed that serious biliary changes (type II and type III) could be easily identified by USS, especially when combined with higher bilirubin levels. MRI/MRCP was more sensitive to subtle biliary lesions than USS, even without jaundice (Table 2).

### Clinical type and surgical method, hospitalization time, treatment cost

According to preoperative imaging examinations and intraoperative findings, 42 patients were classified as Csendes type I, 14 patients were classifies as type II, and 10 patients were classified as type III. None of the patients had type IV disease. Taking laparoscopic surgery as the standard, the overall completion rate was 53.03% (35/66), where the completion rates in type I, II and III were 69.05% (29/42), 42.86% (6/14) and zero (0/10), respectively. Different Csendes types had different degrees of jaundice ($\chi^2 = 51.417$, $P = 0.000$), and the different types ultimately required different surgical methods, as laparoscopic surgery alone could not be performed in all MS patients (Table 3). The ascendant in the type of Csendes classification led to increased surgical complexity (Table 3). Thus, the higher the classification degree, the more difficult the surgery. This was reflected in increased operation time, bleeding volume and treatment cost, which were statistically significant (Table 3). The hospitalization time increased in different Csendes types, but the differences were not statistically significant.

Gender, acute abdominal pain and the measurable stone size had no effect on Csendes type of MS and final surgical method. Preoperative treatment time did not affect the final surgical method ($\chi^2 = 5.950$, $P = 0.295$). However, the longer the preoperative treatment time, the longer the overall length of hospital stay ($F = 19.70$, $P = 0.000$) and the higher the overall cost ($F = 6.778$, $P = 0.002$).

Age had no effect on the classification of MS, but it did influence the final surgical method. The laparoscopic surgery completion rates in different age groups (< 45 year, 45-60 year and > 60 year) were 58.06% (18/31), 52.94% (9/17) and 47.06% (8/17), respectively ($\chi^2 = 16.06$, $P = 0.042$). In addition, hospital stay ($F = 5.654$, $P = 0.002$) and hospitalization cost ($F = 7.400$, $P = 0.008$) in patients over 60 years old were both significantly higher than those in patients under 60 years old.

### Intraoperative data and technical details

Three-port laparoscopic surgery was used routinely. Four-port laparoscopic surgery as an alternative technique was performed when necessary. The right subcostal incision was the standard approach for laparotomy or conversion. Impacted stones varied in size from 0.5 cm to 6 cm, resulting in different fistulas accompanied by local inflammation and fibrotic adhesions. The upper and lower bile ducts of these lesions were dilated to varying degrees (Table 4). Six patients with preoperative PTCD underwent intraoperative cholangiography through the PTCD tube to achieve the correct anatomical identification. Thirty-six patients underwent retrograde cholecystectomy to obtain correct anatomical identification. Due to improper operation when separating Calot's triangle, such as vigorous tearing, 11 cases of iatrogenic BDI occurred in type I patients. Twenty-one cases (31.8%) were repaired by simple suturing, and 14 cases (21.2%) were repaired using the remaining gallbladder wall patch in subtotal cholecystectomy (STC). The excess gallbladder wall can be resected after satisfactory repair to avoid the formation of residual gallbladder. A T-tube should be placed in patients with obvious compression of the bile duct, severe scar fibrosis and unsatisfactory repair. The T-tube was generally placed below the bile duct repair site, one short arm placed upward to the repair site to play a supporting role, and the PTCD tube placed above the repair site. T-tubes were placed in 25 patients (37.9%), including 3 type III

**Table 1 Demographic data of Mirizzi syndrome patients, *n* (%), (mean ± SD), (range and median)**

| Category | | |
|---|---|---|
| Male/Female | | 34/32 |
| Age (yr) | | 48.1 ± 15.0, 18-83, 47 |
| Admission route (Emergency/Outpatient) | | 48/18 |
| Previous admissions | | 2.24 ± 0.96, 1-3, 3 |
| Months from discovery of gallstone to this admission | | 17.8 ± 4.51, 9-22, 21 |
| Confirmed episodes of abdominal pain | | 2.15 ± 1.04, 1-6, 2 |
| Total bilirubin (μmol/L) | ≤ 28 | 31 (47.0%) |
| | 28-56 | 27 (40.9%) |
| | > 56 | 8 (12.1%) |
| Postoperative pathologicalresults ofgallbladder | Acute inflammation | 24 (36.4%) |
| | Acute inflammation and gangrene | 8 (12.1%) |
| | Acute suppurative inflammation | 9 (13.6%) |
| | Chronic inflammation | 12 (18.2%) |
| | Chronic suppurative inflammation | 5 (7.6%) |
| | Xanthogranuloma | 8 (12.1%) |
| Preoperative PTCD | | 6 (9.1%) |
| Preoperative treatment time (d) | | 6.35 ± 3.28, 2-20, 6 |
| Postoperative treatment time (d) | | 7.36 ± 3.66, 3-19, 6.5 |
| Total hospitalization time (d) | | 13.76 ± 5.41, 6-31, 13 |
| Hospitalization cost (CNY Yuan) | | 24549 ± 6536, 13596-40815, 23044 |

PTCD: Percutaneous transhepatic cholangio pancreatic drainage.

**Table 2 Diagnosticclues of Mirizzi syndrome by ultrasound scan and magnetic resonance imaging/magnetic resonance cholangiopancreatography in different cases**

| Imaging examination | | Type I | Type II | Type III | Statistics | Total bilirubin (μmol/L) | | | Statistics |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | ≤ 28 | 28-56 | > 56 | |
| USS | + | 10 | 8 | 6 | $\chi^2 = 12.00$; $P = 0.002$ | 11 | 9 | 4 | $\chi^2 = 0.760$; $P = 0.684$ |
| | - | 32 | 6 | 4 | | 20 | 18 | 4 | |
| MRI/MRCP | + | 34 | 14 | 10 | $\chi^2 = 5.202$; $P = 0.074$ | 23 | 27 | 8 | $\chi^2 = 10.28$; $P = 0.006$ |
| | - | 8 | 0 | 0 | | 8 | 0 | 0 | |

USS: Ultrasound scan; MS: Mirizzi syndrome; MRI: Magnetic resonance imaging; MRCP: Magnetic resonance cholangiopancreatography.

patients through the fistula, and in the other 22 cases through the bile duct incision. Twenty-five patients underwent intraoperative choledochoscopy and T-tube cholangiography to further clarify the condition of the bile duct and ensure no residual stones before the end of surgery. A Winslow foramen drainage tube was also routinely placed in all patients before the end of surgery. The operation time varied, but the total bleeding volume was acceptable and no patients required intraoperative blood transfusion (Table 4).

### *Follow up, postoperative complications and prognosis*

A total of 66 patients were followed up for 36.5 ± 26.5 mo (range 13-76, median 22 mo). All Winslow foramen drainage tubes were removed 3-25 d after surgery according to the recovery, drainage characteristics, combined with liver function and USS results. If a T-tube was placed, it was removed 1.5 to 6 mo after cholangiography if liver function tests were normal.

**Table 3 Effects of Csendes classification on surgical methods, operative time, bleeding volume, hospitalization time and cost (*n* = 66), (mean ± SD), (range, median)**

| | | Type I | Type II | Type III | Type IV | Statistics |
|---|---|---|---|---|---|---|
| *n* (%) | | 42 (63.64%) | 14 (21.21%) | 10 (15.15%) | 0 | |
| Total bilirubin (μmol/L) | ≤ 28 | 29 | 2 | 0 | - | $\chi^2$ = 51.42; *P* = 0.000 |
| | 28-56 | 13 | 11 | 3 | - | |
| | > 56 | 0 | 1 | 7 | - | |
| Surgical methods | LC | 29 | 6[2] | 0 | - | $\chi^2$ = 29.91; *P* = 0.000 |
| | LC convert to OC | 2 | 3[2] | 0 | - | |
| | LC convert to OC + BDER + T-tube | 7[1,2] | 4[3] | 8[3] | - | |
| | OC | 0 | 1[2] | 0 | - | |
| | OC + BDER + T-tube | 4[1,2] | 0 | 2[3] | - | |
| Hospitalization time (d) | | 12.8 ± 4.8; 6-25, 12.5 | 15.1 ± 6.2; 8-26, 13.5 | 15.9 ± 6.1; 8-31, 15 | - | *F* = 1.981; *P* = 0.146 |
| Treatment cost (CNY Yuan) | | 23037 ± 5522; 13596-40815, 21963 | 24916 ± 7146; 15108-36557, 23593 | 30387 ± 6865; 17161-40568, 28624 | - | *F* = 5.909; *P* = 0.004 |
| Operative time (minutes) | | 154.4 ± 91.1; 50-395, 122.5 | 230.4 ± 133.7; 80-480, 175 | 219.0 ± 122.2; 95-520, 177.5 | - | *F* = 3.486; *P* = 0.037 |
| Bleeding volume (mL) | | 96.6 ± 81.5; 20-340, 60 | 191.4 ± 123.3; 30-390, 180 | 163.5 ± 114.3; 25-400, 140 | - | *F* = 5.919; *P* = 0.004 |

[1]Bile duct exploration and repair due to intraoperative iatrogenic bile duct injury (BDI).
[2]Simple suture due to small fistula or slight BDI.
[3]Repaired with remaining gallbladder wall patch following subtotal cholecystectomy.
LC: Laparoscopic cholecystectomy; OC: Open cholecystectomy; BDER: Bile duct exploration and repair.

Incision infection occurred in 7 patients, mainly in those who underwent open surgery or conversion. Overall, incision infection was mild and healed after local drainage and oral antibiotic treatment. Bile leakage occurred in 9 cases during the perioperative period accompanied by different degrees of localized peritonitis, which were resolved by strengthening drainage, delayed extubation and symptomatic treatment. Postoperative bleeding occurred in 4 patients, mainly manifested as bloody drainage (2 cases of abdominal bloody drainage and 2 cases of bloody bile), which lasted three to four days in the week after surgery. It was estimated that the average daily volume did not exceed 60 mL, and the patients recovered following conservative hemostasis treatment without reoperation or interventional therapy. Five patients were considered to have acute cholangitis due to abnormal liver function and fever. These patients recovered after liver protection and anti-infection treatment. Fourteen patients had a transient elevation in transaminase and/or bilirubin based on preoperative liver function, they gradually recovered and were discharged after symptomatic treatment. One patient with preoperative Csendes type III had elevated transaminase repeatedly with normal bilirubin after discharge. USS showed dilation of the right intrahepatic bile duct and MRI/MRCP showed slight constriction of the right hepatic duct with dilation of the right intrahepatic bile duct, which was considered to be compression caused by inflammation and edema. The transaminase level and imaging results gradually returned to normal after oral liver protective drug treatment. Five patients had residual or recurrent stones in the CBD during the follow-up period, and the stones were successfully removed (3 cases by choledochoscopy*via* the T-tube sinus, and 2 cases by ERCP). Postoperative pneumonia occurred in 3 patients who had preoperative lung diseases, these patients recovered after treatment according to advice provided by the Respiratory Department. Seven cases had different degrees of gastrointestinal dysfunction which normalized after symptomatic treatment.

By the end of the follow-up period, no residual gallbladder was confirmed by imaging examination and no reoperations were necessary. No patients died during the follow-up period (Table 5).

## DISCUSSION

The first accurate description and report of MS was by the Argentine surgeon Mirizzi in 1948[1]. Since

**Table 4 Intraoperative data and technical details (*n* = 66)**

| Category | | *n* = 66 |
|---|---|---|
| Final surgical approach | 3-port laparoscopic surgery | 24, 36.4% |
| | 4-port laparoscopic surgery | 11, 16.7% |
| | Right subcostal incision | 31, 46.9% |
| Maximum diameter of stone (cm) | | 2.15 ± 1.17, 0.5-6, 2 |
| Fistula size (mm) | Longitudinal diameter | 4.1 ± 1.0, 2-6, 4 |
| | Transverse diameter | 4.5 ± 1.4, 2-8, 4 |
| Diameter of extra hepatic bile duct (mm) | | Maximum 14 ± 2.8, 10-22, 14 |
| | | Minimum 8.4 ± 1.8, 6-12, 8 |
| Iatrogenic BDI | | 11, 16.7% (11 in type I) |
| Retrograde resection of gallbladder | | 36, 54.5% |
| BDER (35, 53%) | Simple suture repair | 21, 31.8% (11 in type I, 10 in type II) |
| | STC and repair using gallbladder wall | 14, 21.2% (4 in Type II,10 in type III) |
| T-tube (25, 37.9%) (14-22 Fr, 18 Fr) | | Transfistula 3 (in type III) |
| | | Transbiliary incision 22 |
| Cholangiography (25, 37.9%) | Trans-PTCD | 6[1] |
| | Trans-T-tube | 25 |
| Choledochoscopy (25, 37.9%) | Trans-fistula | 3 |
| | Trans-cystic duct | 2 |
| | Trans-biliary incision | 20 |
| Operative time (min) | | 180 ± 110, 50-520, 140 |
| Bleeding volume (mL) | | 127 ± 104, 87.5, 20-400 |

[1]At the beginning of operation, cholangiography was performed using the percutaneous transhepatic cholangio pancreatic drainage tube to confirm the anatomical structure of the biliary duct.
BDER: Bile duct exploration and repair; STC: Subtotal cholecystectomy; PTCD: Percutaneous transhepatic cholangio pancreatic drainage; BDI: Bile duct injury.

**Table 5 Postoperative complications (*n* = 66)**

| Postoperative complications | *n* (%) |
|---|---|
| Incision infection | 7 (10.6) |
| Bile leakage | 9 (13.6) |
| Bloody drainage | 4 (6.1) |
| Cholangitis | 5 (7.6) |
| Abnormal liver function | 14 (21.2) |
| Biliary stricture | 1 (1.5) |
| Residual or recurrent stone | 5 (7.6) |
| Pneumonia | 3 (4.5) |
| Gastrointestinal dysfunction | 7 (10.6) |

then, different MS classification criteria have emerged to aid surgical decision-making[3,19-23]. Among them, the Csendes classification with four types[2] is the most commonly used in clinical practice, which includes the presence or absence of gallbladder bile duct fistula and its degree.

The incidence of MS is relatively low, and usually accounts for less than 5% of gallstone patients[13,24,25]. The proportion of patients with each type of MS is also different, and gradually decreases from type I to type IV[23,26-29]. The proportion of patients with type I is 35% to 77%, and the proportion with type IV is usually less than 5%. Safioleas *et al*[26], Kwon and Inui[29] reported the diagnosis and treatment of 24 cases of MS in 8 years and 27 cases of MS in 20 years, respectively, and found no type IV patients. Cui *et al*[27] reported 198 cases of MS in 6 years, of which type I accounted for 59.1% and type IV accounted for 3.1%. Kamalesh *et al*[28] reported 20 cases in 7 years, of which type I accounted for 35% and type IV accounted for 5%.

As MS has no specific symptoms other than those observed in patients with gallstones, the preoperative diagnosis rate of MS is low, and it is confirmed by further exploration when iatrogenic BDI occurs during surgery. In various studies, the preoperative diagnosis rate of MS ranged from 30% to 83%[26,29].

At present, USS is still the first choice for the diagnosis of cholecystolithiasis, but the accuracy of USS for the diagnosis of MS is insufficient. As a basic and routine examination method, USS cannot objectively and comprehensively judge the condition of the bile duct preoperatively and most MS patients have no specific clinical manifestations other than the symptoms associated with gallstones; thus, the preoperative diagnosis of MS is not easy using USS[1,3,30]. Although Joseph *et al*[31] reported that the "Tri-duct sign" represented by the cystic duct, common hepatic duct and portal vein dilatation is helpful in the diagnosis of MS, the clinical typical "Tri-duct sign" is rare and it is affected by the experience of ultrasound examiners , limited understanding of MS and insufficient vigilance. Therefore, in order to improve the diagnostic accuracy, other methods such as CT, ERCP and MRI/MRCP are also used in the preoperative diagnosis of MS. Most studies have demonstrated that CT is not better than USS in the diagnosis of MS, and it is not a deterministic method. ERCP has been used to show the anatomical structure of the bile duct accurately, for removal of coexisting common duct stones and placement of a biliary stent, which is a great help for surgeons in managing MS. It is been considered the gold standard for MS diagnosis due to the above-mentioned advantages[32-35]. However, ERCP has certain equipment requirements and a technical threshold, and not every hospital can carry out ERCP routinely. ERCP is an invasive method of examination and treatment, and associated with some complications[1,12]. In clinical practice, ERCP is not usually performed in patients with simple gallstones, and is only performed if MS is suspected, rather than as a routine method. Therefore, a reliable routine preferred method to diagnose MS is required. As a result, ERCP cannot be popularized in the clinic, especially in hospitals with scarce resources. Due to the specific conditions of our hospital, we cannot conveniently and routinely perform ERCP; thus, ERCP was not included in the diagnosis and treatment of MS in this study. When ERCP is unavailable, the difficulties faced by surgeons cannot be reduced[13].

MRI/MRCP has beneficial characteristics such as it is noninvasive, repeatable, and provides multi-layer clear imaging. It can fully display the number, size and distribution of stones, the shape of the bile duct, the level and degree of obstruction, gallbladder lesions and other details, and help to screen tumors[12,13]. It has become the most suitable method for the preoperative diagnosis of MS, and has practical significance in helping surgeons to manage MS. In the present study, the diagnostic rate of preoperative MRI/MRCP for MS was 87.9% (58/66), while the detection rate of USS for MS was only 36.4% (24/66). However, MRI/MRCP is still insufficient in defining Csendes classification as it cannot accurately judge the presence and degree of the fistula[12,36], which should be further determined by combining with intraoperative findings.

Due to stone compression, biliary stricture, fistula formation, inflammatory edema, fibrotic adhesions, intraoperative bleeding and other difficult conditions, MS has become an important cause of BDI. It was also considered a taboo in laparoscopic surgery and open operation was suggested. In 2016, Kumar *et al*[3] reported 169 patients with MS, including 34 (20%) with type I, 97 (57%) with type II, 28 (17%) was type III and 10 (6%) with type IV MS, who were treated surgically. An open surgery was performed in 146 (86%) cases. Laparoscopic surgery was attempted in only 23 (14%) cases and was successful in only 1 patient with type II. Other scholars have also made considerable efforts to perform laparoscopic surgery for MS, but mainly for Csendes type I and type II patients[7-11]. The results of our study also showed that in most Csendes type I and in some type II MS patients, laparoscopic cholecystectomy (LC) can be completed safely with an overall success rate of 53% (35/66) under comprehensive evaluation and careful dissection. Generally, after relieving compression and inflammatory adhesion of type I MS, the diameter of the bile duct can be restored. However, BDI cannot be completely avoided. A total of 11 cases of BDI occurred in this study, all in type I patients, which may be related to the characteristics of local lesions and the failure of surgeons to treat with caution. Fortunately, BDI was not severe and did not lead to ischemia and disconnection of the bile duct. However, the occurrence of BDI will eventually lead to a change in classification, that is, patients with type I will at least upgrade to type II accompanied by an increase in the complexity of the operation. This is an important reason why our success rate of laparoscopic surgery is lower than those in other studies[7,9], even though our study had a relatively high preoperative diagnosis rate. Similarly, it is necessary to avoid fistula enlargement in Csendes type II and type III patients caused by iatrogenic injury.

From a technical perspective, small bile duct fistulas can be repaired with intermittent absorbable sutures. Such patients can usually undergo cholecystectomy and bile duct repair under complete laparoscopy without T-tube drainage. Larger fistulas can be repaired using the retained gallbladder wall patch following STC and a T-tube ought to be placed. STC is emphasized if bile duct repair is required, which can be used to repair the CBD fistula in difficult circumstances[37].

If the laparoscopic repair is not satisfactory or the operation is difficult, it should be converted to open surgery. For patients with Csendes type III MS, the surgical plan should be chosen based on the preoperative evaluation, combined with the technical level and clinical experience of the surgical team, and laparoscopic surgery should not be performed. According to our results, open surgery or timely conversion to open surgery was preferred in 31 cases (46.97%) including type I patients. Although the surgical trauma increased, the overall postoperative outcomes were good with no long-term morbidity or mortality.

Whether open or laparoscopic surgery for MS is chosen, correct anatomical identification is very important. Intraoperative biliary imaging can be used to clarify anatomy and avoid BDI[12]. We performed intraoperative cholangiography (6 of them *via* the PTCD and T tube) and choledochoscopy in 25 patients (37.9%). These methods can not only help us confirm the correct anatomical structure, but also judge whether there are complicated bile duct stones, strictures and satisfactory repair. We suggest that intraoperative cholangiography should be a mandatory adjunct in difficult situations.

In 2018, Seah *et al*[30] reported 64 patients with MS treated at Singapore General Hospital, including 43 with type I, 18 with type II, and 3 with type III. The diagnostic rate of MS was 88.9% by preoperative MRI and was 11.4% by USS, which were similar to our results (87.9% by MRI and 36.4% by USS). Our study also showed similar results to their studies in the frequency of intraoperative choledochoscopy (37.9% *vs* 44.6%) and cholangiography (37.9% *vs* 46.2%). However, in their study, 57 patients (57/64, 89.1%) chose direct open surgery or conversion surgery with a higher T-tube placement rate (63.1%) and an overall complication rate of approximately 43.8%. In addition, a total of 10 patients (10/64, 15.6%) needed hepaticoenteric anastomosis, including 3 patients with type I MS. They came to a conclusion on this basis that a trial of laparoscopic dissection with low threshold for open conversion is recommended if suspicion is high.

In our study, cholangiojejunostomy was avoided. However, according to the results of other studies [3,23,25,30], cholangiojejunostomy is still a necessary surgical method for patients with a large biliary fistula, especially those with obvious local scarring, ischemia or a large longitudinal defect. Therefore, patients who require cholangiojejunostomy are mainly some type III patients and almost all type IV patients. In addition, the surgical approach is usually open or laparoscopic converted to open surgery. Although surgical technology has made great progress in recent years, including endoscopy, minimally invasive technology and robotics, it has not directly improved the surgical treatment of type IV MS[14-16,29]. Our study did not include type IV patients; thus, we have no direct experience in the surgical treatment of type IV patients. It may take a little longer before technical progress can be routinely applied to the treatment of MS.

Thus, patients with MS should be evaluated comprehensively based on MRI/MRCP. Open surgery or timely conversion to open surgery should be selected when preoperative evaluation or LC intraoperative exploration shows that laparoscopic surgery is unsuitable. Based on this study, a flowchart of surgical strategies for MS is presented as Figure 1.

This study also found that the cost, operative time and bleeding volume in patients with Csendes type I, type II and type III showed an increasing trend with statistical significance (Table 3). Thus, the classification can reflect the difficulty of treatment, indicating that we should avoid increasing the risk to patients due to a change in classification caused by iatrogenic BDI.

Surgery for MS patients should be carried out as soon as the diagnosis and classification are determined. This study confirmed that prolonging preoperative treatment time does not increase the success rate of MS laparoscopic surgery. On the contrary, the longer the preoperative treatment time, the longer the overall length of hospital stay and the higher the overall cost. The reason for this may be that preoperative treatment cannot change the existing lesions and type of MS, and it is difficult to eliminate local inflammatory edema and fibrotic adhesions in a short time. This study also confirmed that the presence or absence of acute abdominal pain had no effect on the classification of MS and the final surgical technique, and suggested that the preoperative treatment time should not be prolonged until the symptoms disappear.This study also found that the success rate of laparoscopic surgery in elderly patients was lower and the treatment cost was higher, which may be related to the longer course of disease, more serious inflammatory scar adhesions and bile duct compression in elderly patients. In addition, it does not rule out the selection bias caused by the subjective will of both surgeons and patients in clinical practice. The size of stones has no effect on the classification of MS and the final surgical technique, which may be because the inflammation, edema, adhesions and compression induced by stones play important roles in the pathogenesis of MS.

The main limitations of our study are its retrospective nature and small sample size. The operations were completed by different surgeons, which inevitably resulted in heterogeneity of the treatment process and consequences. As the published studies adopted incompletely consistent classification standards of MS, the final conclusions have not reached a consensus. In view of this, we only provide our own experience in the surgical treatment of MS. The conclusions in our study should be confirmed

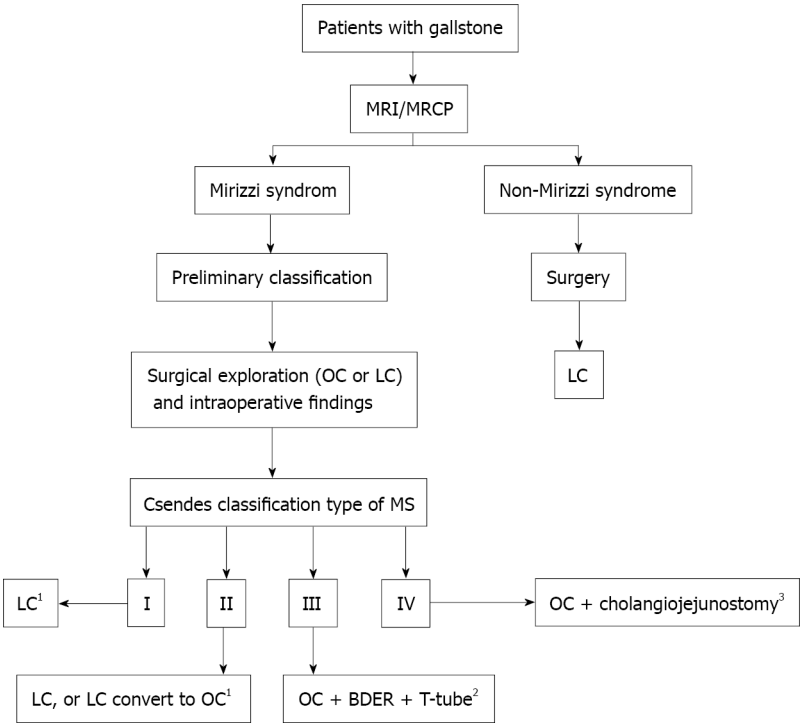



**Figure 1 Flowchart of surgical strategies for Mirizzi syndrome.** [1]If necessary, bile duct exploration and repair and T-tube drainage (BDER + T-tube) should be carried out using different methods according to different situations; [2]A part of type III patients need cholangiojejunostomy; [3]Cholangiojejunostomy is inevitable in almost all type IV patients. LC: Laparoscopic cholecystectomy; OC: Open cholecystectomy; BDER: Bile duct exploration and repair; MRI: Magnetic resonance imaging; MRCP: Magnetic resonance cholangiopancreatography; MS: Mirizzi syndrome.

by further large sample prospective research.

## CONCLUSION

In this study, a relatively high preoperative diagnosis rate was obtained in 66 patients with MS who underwent surgery safely without serious long-term complications. Based on our limited experience, we recommend that MRI/MRCP should be considered a routine and necessary examination before laparoscopic surgery for MS. On the basis of a full evaluation and careful selection, MS patients can be treated by laparoscopic surgery, especially Csendes type I and type II patients, and timely conversion to open surgery may also be necessary. For patients with Csendes type III, the surgical technique requires careful decision-making. The Csendes classification can reflect treatment difficulty in MS patients, and increased risk due to a change in type grade caused by iatrogenic BDI should be avoided. These findings also suggest that active treatment should be carried out for gallbladder stones to reduce the risk of progression to MS, and surgery should be performed as soon as possible once MS is diagnosed. Use of the above strategies can reduce surgical complications, avoid cholangiojejunostomy and obtain a better clinical prognosis.

## ARTICLE HIGHLIGHTS

### *Research background*

Mirizzi syndrome (MS) has always been a challenge for surgeons and an important cause of bile duct injury (BDI). At present, this problem has still not been resolved. If we do not accurately understand the pathological characteristics and potential surgical risks of MS, this may lead to adverse clinical consequences.

### *Research motivation*

The treatment methods and effects for MS are changeable according to the different classification types, and the risks are also variable. Whether laparoscopic surgery is suitable for the treatment of MS is also controversial.

### *Research objectives*

This study is a retrospective analysis using data accumulated over a decade that aimed to summarize preoperative diagnostic methods and the safety, effectiveness, prognosis and related factors of surgical strategies including laparoscopic surgery for different types of MS.

### *Research methods*

Sixty-six patients who met the inclusion criteria were included in the study. The diagnostic methods, clinical classification, surgical approach, complications and long-term prognosis were analyzed.

### *Research results*

Magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) is superior to ultrasound scan in the diagnosis of MS. The overall laparoscopic surgery completion rate was 53.03% (35/66). Thirty-one patients (46.97%, 31/66) underwent laparotomy or conversion to laparotomy, including 11 cases of iatrogenic BDI which occurred in type I patients. Overall, 35 patients (53.03%, 35/66) needed bile duct repair using different methods. Twenty-five patients underwent intraoperative choledochoscopy and T-tube cholangiography. A total of 66 patients obtained a relatively high preoperative diagnosis rate and underwent surgery safely without serious complications and no mortality was observed during the follow-up period.

### *Research conclusions*

MRI/MRCP can improve the preoperative diagnosis rate of MS. Laparoscopic surgery can be undertaken safely in some patients with MS, especially Csendes type I and type II patients, and the surgical technique should be carefully determined for Csendes type III patients. The Csendes classification can reflect treatment difficulty and was related to the length of hospital stay and cost. The risk to patients due to a change in Csendes classification caused by iatrogenic injury during surgery should be avoided.

### *Research perspectives*

Sixty-six patients completed diagnostic and treatment procedures by different medical groups within 10 years, which may have led to significant heterogeneity. Accurate conclusions should be confirmed by further large sample prospective studies.


## FOOTNOTES

**Author contributions:** Lai W designed the research protocol, wrote the paper analyzed the data, reviewed and revised the paper; Lai W, Yang J, Xu N, Chen JH, Yang C and Yao HH conducted the research and analyses; all authors have read and approved the final version to be submitted.

**Institutional review board statement:** The study was reviewed and approved by the Institutional Review Board of Chengdu First People's Hospital(Chengdu Integrated TCM & Western Medicine Hospital).

**Informed consent statement:** Due to the retrospective design of the study, informed consent was waived by the ethics committee for this study.

**Conflict-of-interest statement:** The authors have no conflicts of interest to report.

**Data sharing statement:** No additional data are available.

**STROBE statement:** The authors have read the STROBE Statement checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.



**Country/Territory of origin:** China

**ORCID number:** Wei Lai 0000-0002-9763-5349; Jie Yang 0000-0001-7201-1858; Nan Xu 0000-0003-3898-6381; Jun-Hua Chen 0000-0002-3813-0842; Chen Yang 0000-0003-0225-5130; Hui-Hua Yao 0000-0002-7803-8565.

**S-Editor:** Fan JR
**L-Editor:** A

**P-Editor:** Fan JR

## REFERENCES


1 **Beltrán MA**. Mirizzi syndrome: history, current knowledge and proposal of a simplified classification. *World J Gastroenterol* 2012; **18**: 4639-4650 [PMID: 23002333 DOI: 10.3748/wjg.v18.i34.4639]

2 **Csendes A**, Díaz JC, Burdiles P, Maluenda F, Nava O. Mirizzi syndrome and cholecystobiliary fistula: a unifying classification. *Br J Surg* 1989; **76**: 1139-1143 [PMID: 2597969 DOI: 10.1002/bjs.1800761110]

3 **Kumar A**, Senthil G, Prakash A, Behari A, Singh RK, Kapoor VK, Saxena R. Mirizzi's syndrome: lessons learnt from 169 patients at a single center. *Korean J Hepatobiliary Pancreat Surg* 2016; **20**: 17-22 [PMID: 26925146 DOI: 10.14701/kjhbps.2016.20.1.17]

4 **Valderrama-Treviño AI**, Granados-Romero JJ, Espejel-Deloiza M, Chernitzky-Camaño J, Barrera Mera B, Estrada-Mata AG, Ceballos-Villalva JC, Acuña Campos J, Argüero-Sánchez R. Updates in Mirizzi syndrome. *Hepatobiliary Surg Nutr* 2017; **6**: 170-178 [PMID: 28653000 DOI: 10.21037/hbsn.2016.11.01]

5 **Lai EC**, Lau WY. Mirizzi syndrome: history, present and future development. *ANZ J Surg* 2006; **76**: 251-257 [PMID: 16681544 DOI: 10.1111/j.1445-2197.2006.03690.x]

6 **Rust KR**, Clancy TV, Warren G, Mertesdorf J, Maxwell JG. Mirizzi's syndrome: a contraindication to coelioscopic cholecystectomy. *J Laparoendosc Surg* 1991; **1**: 133-137 [PMID: 1751827 DOI: 10.1089/Lps.1991.1.133]

7 **Zhao J**, Fan Y, Wu S. Safety and feasibility of laparoscopic approaches for the management of Mirizzi syndrome: a systematic review. *Surg Endosc* 2020; **34**: 4717-4726 [PMID: 32661708 DOI: 10.1007/s00464-020-07785-0]

8 **Vezakis A**, Davides D, Birbas K, Ammori BJ, Larvin M, McMahon MJ. Laparoscopic treatment of Mirizzi syndrome. *Surg Laparosc Endosc Percutan Tech* 2000; **10**: 15-18 [PMID: 10872520]

9 **Chowbey PK**, Sharma A, Mann V, Khullar R, Baijal M, Vashistha A. The management of Mirizzi syndrome in the laparoscopic era. *Surg Laparosc Endosc Percutan Tech* 2000; **10**: 11-14 [PMID: 10872519]

10 **Yeh CN**, Wang SY, Liu KH, Yeh TS, Tsai CY, Tseng JH, Wu CH, Liu NJ, Chu YY, Jan YY. Surgical outcome of Mirizzi syndrome: Value of endoscopic retrograde cholangiopancreatography and laparoscopic procedures. *J Hepatobiliary Pancreat Sci* 2021; **28**: 760-769 [PMID: 34174017 DOI: 10.1002/jhbp.1016]

11 **Clemente G**, Tringali A, De Rose AM, Panettieri E, Murazio M, Nuzzo G, Giuliante F. Mirizzi Syndrome: Diagnosis and Management of a Challenging Biliary Disease. *Can J Gastroenterol Hepatol* 2018; **2018**: 6962090 [PMID: 30159303 DOI: 10.1155/2018/6962090]

12 **Chen H**, Siwo EA, Khu M, Tian Y. Current trends in the management of Mirizzi Syndrome: A review of literature. *Medicine (Baltimore)* 2018; **97**: e9691 [PMID: 29369192 DOI: 10.1097/MD.0000000000009691]

13 **Weledji EP**, Ndono DN, Zouna F. A case of obstructive jaundice without biliary stones in a low resource setting. *Clin Case Rep* 2021; **9**: e04163 [PMID: 34194762 DOI: 10.1002/ccr3.4163]

14 **Higgins RM**, Frelich MJ, Bosler ME, Gould JC. Cost analysis of robotic versus laparoscopic general surgery procedures. *Surg Endosc* 2017; **31**: 185-192 [PMID: 27139704 DOI: 10.1007/s00464-016-4954-2]

15 **Kane WJ**, Charles EJ, Mehaffey JH, Hawkins RB, Meneses KB, Tache-Leon CA, Yang Z. Robotic compared with laparoscopic cholecystectomy: A propensity matched analysis. *Surgery* 2020; **167**: 432-435 [PMID: 31492434 DOI: 10.1016/j.surg.2019.07.020]

16 **Aguayo E**, Dobaria V, Nakhla M, Seo YJ, Hadaya J, Cho NY, Sareh S, Sanaiha Y, Benharash P. National trends and outcomes of inpatient robotic-assisted versus laparoscopic cholecystectomy. *Surgery* 2020; **168**: 625-630 [PMID: 32762874 DOI: 10.1016/j.surg.2020.06.018]

17 **Lee KF**, Chong CN, Ma KW, Cheung E, Wong J, Cheung S, Lai P. A minimally invasive strategy for Mirizzi syndrome: the combined endoscopic and robotic approach. *Surg Endosc* 2014; **28**: 2690-2694 [PMID: 24737533 DOI: 10.1007/s00464-014-3529-3]

18 **Magge D**, Steve J, Novak S, Slivka A, Hogg M, Zureikat A, Zeh HJ 3rd. Performing the Difficult Cholecystectomy Using Combined Endoscopic and Robotic Techniques: How I Do It. *J Gastrointest Surg* 2017; **21**: 583-589 [PMID: 27896657 DOI: 10.1007/s11605-016-3323-8]

19 **Beltran MA**, Csendes A. Mirizzi syndrome and gallstone ileus: an unusual presentation of gallstone disease. *J Gastrointest Surg* 2005; **9**: 686-689 [PMID: 15862264 DOI: 10.1016/j.gassur.2004.09.058]

20 **Beltran MA**, Csendes A, Cruces KS. The relationship of Mirizzi syndrome and cholecystoenteric fistula: validation of a modified classification. *World J Surg* 2008; **32**: 2237-2243 [PMID: 18587614 DOI: 10.1007/s00268-008-9660-3]

21 **Nagakawa T**, Ohta T, Kayahara M, Ueno K, Konishi I, Sanada H, Miyazaki I. A new classification of Mirizzi syndrome from diagnostic and therapeutic viewpoints. *Hepatogastroenterology* 1997; **44**: 63-67 [PMID: 9058121]

22 **Solis-Caxaj CA**. Mirizzi syndrome: diagnosis, treatment and a plea for a simplified classification. *World J Surg* 2009; **33**: 1783-4; author reply 1786 [PMID: 19225836 DOI: 10.1007/s00268-009-9929-1]

23 **Payá-Llorente C**, Vázquez-Tarragón A, Alberola-Soler A, Martínez-Pérez A, Martínez-López E, Santarrufina-Martínez S, Ortiz-Tarín I, Armañanzas-Villena E. Mirizzi syndrome: a new insight provided by a novel classification. *Ann Hepatobiliary Pancreat Surg* 2017; **21**: 67-75 [PMID: 28567449 DOI: 10.14701/ahbps.2017.21.2.67]

24 **Dorrance HR**, Lingam MK, Hair A, Oien K, O'Dwyer PJ. Acquired abnormalities of the biliary tract from chronic gallstone disease. *J Am Coll Surg* 1999; **189**: 269-273 [PMID: 10472927 DOI: 10.1016/s1072-7515(99)00126-x]

25 **Abou-Saif A**, Al-Kawas FH. Complications of gallstone disease: Mirizzi syndrome, cholecystocholedochal fistula, and gallstone ileus. *Am J Gastroenterol* 2002; **97**: 249-254 [PMID: 11866258 DOI: 10.1111/j.1572-0241.2002.05451.x]

26 **Safioleas M**, Stamatakos M, Safioleas P, Smyrnis A, Revenas C, Safioleas C. Mirizzi Syndrome: an unexpected problem of cholelithiasis. Our experience with 27 cases. *Int Semin Surg Oncol* 2008; **5**: 12 [PMID: 18495037 DOI: 10.1186/1477-7800-5-12]

27 **Cui Y**, Liu Y, Li Z, Zhao E, Zhang H, Cui N. Appraisal of diagnosis and surgical approach for Mirizzi syndrome. *ANZ J Surg* 2012; **82**: 708-713 [PMID: 22901276 DOI: 10.1111/j.1445-2197.2012.06149.x]

28 **Kamalesh NP**, Prakash K, Pramil K, George TD, Sylesh A, Shaji P. Laparoscopic approach is safe and effective in the management of Mirizzi syndrome. *J Minim Access Surg* 2015; **11**: 246-250 [PMID: 26622114 DOI: 10.4103/0972-9941.140216]

29 **Kwon AH**, Inui H. Preoperative diagnosis and efficacy of laparoscopic procedures in the treatment of Mirizzi syndrome. *J Am Coll Surg* 2007; **204**: 409-415 [PMID: 17324774 DOI: 10.1016/j.jamcollsurg.2006.12.005]

30 **Seah WM**, Koh YX, Cheow PC, Chow PKH, Chan CY, Lee SY, Ooi LLPJ, Chung AYF, Goh BKP. A Retrospective Review of the Diagnostic and Management Challenges of Mirizzi Syndrome at the Singapore General Hospital. *Dig Surg* 2018; **35**: 491-497 [PMID: 29190631 DOI: 10.1159/000484256]

31 **Joseph S**, Carvajal S, Odwin C. Sonographic diagnosis of Mirizzi's syndrome. *J Clin Ultrasound* 1985; **13**: 199-201 [PMID: 3920283 DOI: 10.1002/jcu.1870130309]

32 **Xu XQ**, Hong T, Li BL, Liu W, He XD, Zheng CJ. Mirizzi syndrome: our experience with 27 cases in PUMC Hospital. *Chin Med Sci J* 2013; **28**: 172-177 [PMID: 24074620 DOI: 10.1016/s1001-9294(13)60044-9]

33 **Yuan H**, Yuan T, Sun X, Zheng M. A Minimally Invasive Strategy for Mirizzi Syndrome Type II: Combined Endoscopic With Laparoscopic Approach. *Surg Laparosc Endosc Percutan Tech* 2016; **26**: 248-252 [PMID: 27077221 DOI: 10.1097/SLE.0000000000000260]

34 **Lee KF**. Mirizzi syndrome: a new approach to an old problem. *Hepatobiliary Surg Nutr* 2018; **7**: 56-57 [PMID: 29531948 DOI: 10.21037/hbsn.2017.12.09]

35 **Kim PN**, Outwater EK, Mitchell DG. Mirizzi syndrome: evaluation by MRI imaging. *Am J Gastroenterol* 1999; **94**: 2546-2550 [PMID: 10484023 DOI: 10.1111/j.1572-0241.1999.01313.x]

36 **Piccinni G**, Sciusco A, De Luca GM, Gurrado A, Pasculli A, Testini M. Minimally invasive treatment of Mirizzi's syndrome: is there a safe way? *Ann Hepatol* 2014; **13**: 558-564 [PMID: 25152990]

37 **Brunt LM**, Deziel DJ, Telem DA, Strasberg SM, Aggarwal R, Asbun H, Bonjer J, McDonald M, Alseidi A, Ujiki M, Riall TS, Hammill C, Moulton CA, Pucher PH, Parks RW, Ansari MT, Connor S, Dirks RC, Anderson B, Altieri MS, Tsamalaidze L, Stefanidis D; and the Prevention of Bile Duct Injury Consensus Work Group. Safe Cholecystectomy Multi-society Practice Guideline and State of the Art Consensus Conference on Prevention of Bile Duct Injury During Cholecystectomy. *Ann Surg* 2020; **272**: 3-23 [PMID: 32404658 DOI: 10.1097/SLA.0000000000003791]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 February 27; 14(2): 120-131

DOI: 10.4240/wjgs.v14.i2.120

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

**Retrospective Cohort Study**

# Long-term outcomes of postgastrectomy syndrome after total laparoscopic distal gastrectomy using the augmented rectangle technique

Suguru Yamauchi, Hajime Orita, Jun Chen, Hiroki Egawa, Yutaro Yoshimoto, Akira Kubota, Ryota Matsui, Yukinori Yube, Sanae Kaji, Shinichi Oka, Malcolm V Brock, Tetsu Fukunaga

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D, D
Grade E (Poor): 0

**P-Reviewer:** Cai ZL, Luo TH

**Received:** October 7, 2021
**Peer-review started:** October 7, 2021
**First decision:** December 4, 2021
**Revised:** December 15, 2021
**Accepted:** February 10, 2022
**Article in press:** February 10, 2022
**Published online:** February 27, 2022

**Suguru Yamauchi, Hajime Orita, Jun Chen, Hiroki Egawa, Yutaro Yoshimoto, Akira Kubota, Ryota Matsui, Yukinori Yube, Sanae Kaji, Shinichi Oka, Tetsu Fukunaga,** Department of Gastroenterology and Minimally Invasive Surgery, Juntendo University Hospital, Tokyo 113-8431, Japan

**Malcolm V Brock,** Department of Surgery, The Johns Hopkins University School of Medicine, Baltimore, MD 21205-2196, United States

**Corresponding author:** Suguru Yamauchi, MD, Doctor, Surgeon, Department of Gastroenterology and Minimally Invasive Surgery, Juntendo University Hospital, 3-1-3 Hongo, Bunkyo-ku, Tokyo 113-8431, Japan. s.yamauchi.gk@juntendo.ac.jp

## Abstract

### *BACKGROUND*

For total laparoscopic distal gastrectomies for gastric cancer, the reconstruction method is critical to the clinical outcome of the procedure. However, which reconstruction technique is optimal remains controversial. We originally reported the augmented rectangle technique (ART) as a reconstruction option for total laparoscopic Billroth I reconstructions. Still, little is known about its effect on long-term outcomes, specifically the incidence of postgastrectomy syndrome and its impact on quality of life.

### *AIM*

To analyze postgastrectomy syndrome and quality of life after ART using the Postgastrectomy Syndrome Assessment Scale-37 (PGSAS-37) questionnaire.

### *METHODS*

At Juntendo University, a total of 94 patients who underwent ART for Billroth I reconstruction with total laparoscopic distal gastrectomies for gastric cancer between July 2016 and March 2020 completed the PGSAS-37 questionnaire. Multidimensional analysis was performed, comparing those 94 ART cases from our institution (ART group) to 909 distal gastrectomy cases with a Billroth I reconstruction from other Japanese institutions who also completed the PGSAS-37 as part of a larger national database (PGSAS group).

***RESULTS***
Patients in the ART group had significantly better total symptom scores in all the symptom subscales (*i.e.*, esophageal reflux, abdominal pain, meal-related distress, indigestion, diarrhea, constipation, and dumping). The loss of body weight was marginally greater for those in the ART group than in the PGSAS group (-9.3% *vs* -7.9%, $P = 0.054$). The ART group scored significantly lower in their dissatisfaction of ongoing symptoms, during meals, and with daily life.

***CONCLUSION***
ART for Billroth I reconstruction provided beneficial long-term results for postgastrectomy syndrome and quality of life in patients undergoing total laparoscopic distal gastrectomies for gastric cancer.

**Key Words:** Laparoscopic distal gastrectomy; Postgastrectomy syndrome; Augmented rectangle technique; Billroth I; Postgastrectomy Syndrome Assessment Scale-37



**Core Tip:** Reducing the prevalence of postgastrectomy syndrome (PGS) and improving the quality of life (QOL) after gastrectomy for gastric cancer patients has become an important technical challenge for surgeons. We developed the augmented rectangle technique (ART) for Billroth I reconstruction after total laparoscopic distal gastrectomy. Our patient outcome results have been good in the short-term. Long-term patient outcomes have not been studied. Here, we evaluated PGS and QOL after gastrectomy with ART using the Postgastrectomy Syndrome Assessment Scale-37. Application of ART produced beneficial long-term PGS and QOL results in patients undergoing total laparoscopic distal gastrectomies.

**Citation:** Yamauchi S, Orita H, Chen J, Egawa H, Yoshimoto Y, Kubota A, Matsui R, Yube Y, Kaji S, Oka S, Brock MV, Fukunaga T. Long-term outcomes of postgastrectomy syndrome after total laparoscopic distal gastrectomy using the augmented rectangle technique. *World J Gastrointest Surg* 2022; 14(2): 120-131
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i2/120.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i2.120

## INTRODUCTION

The postgastrectomy syndrome (PGS) is an almost inevitable functional disorder after a radical gastrectomy for gastric cancer[1-3]. In addition to precipitating weight loss because of a reduction in the size (or loss) of the stomach, PGS can also induce systemic disturbances, such as dumping syndrome. These problems can lead to deterioration of a patient's long-term postoperative quality of life (QOL)[4, 5]. Determining if there is a correlation between an increased risk of PGS and certain gastrectomy reconstruction techniques will ensure the optimal selection of appropriate surgical approaches to prevent and treat PGS. Importantly, it is appropriate to question how widely employed contemporary minimally invasive surgeries, such as laparoscopic gastrectomy, contribute to the risk of developing PGS.

Total laparoscopic distal gastrectomy (TLDG) for gastric cancer has evolved from a conventional laparoscopic-assisted gastrectomy to a more complex procedure incorporating more sophisticated techniques and instruments. Fukunaga *et al*[6] originally described the augmented rectangle technique (ART) as a novel Billroth I reconstruction after TLDG. ART for Billroth I reconstruction has been reported to have good short-term results, but no long-term PGS and QOL results have been reported.

The Postgastrectomy Syndrome Assessment Scale-37 (PGSAS-37) was developed by the Japanese Postgastrectomy Syndrome Working Party (JPGSWP) in 2015 to serve as an integrated questionnaire designed to assess postgastrectomy-specific clinical symptoms and QOL[7]. JPGSWP also initiated a multi-institutional nationwide surveillance program to investigate medium to long-term symptoms, living status, and QOL following various types of gastrectomies. The JPGSWP felt that it was necessary to create a standard tool to assess postoperative QOL after any surgical procedure performed at any facility in Japan. This also allowed the statistical analysis of national data collected for each gastrectomy performed at numerous institutions throughout Japan. A "PGSAS statistical kit" was also created to allow free access that allowed individual institutions to compare their own patient outcomes to those PGS outcomes from patients undergoing gastrectomy procedures anywhere else in Japan.

This study investigated the impact on PGS and QOL in patients at Juntendo University in Japan who underwent ART for Billroth I reconstruction compared to a national database of patients who

underwent other reconstruction techniques from multiple institutions throughout Japan and who completed the PGSAS-37 form.

## MATERIALS AND METHODS

### Patients

From 238 patients who underwent gastrectomy for gastric cancer at Juntendo University Hospital from July 2016 to March 2020, 115 (48.3%) had received a TLDG using ART for Billroth I reconstruction. A PGSAS-37 questionnaire was administered to all patients. Completed or nearly completed questionnaires were retrieved from 94 (81.7%) patients, and these patients were selected for inclusion in this retrospective study (Figure 1). Clinical, perioperative, pathological, and PGSAS-37 questionnaire data were collected and analyzed. Clinicopathological variables included postoperative observation period, age, sex, preoperative body mass index, pathological stage, approach, extent of lymph node dissection, and combined resection. Pathological stage was described according to the Japanese Classification of Gastric Carcinoma[8]. Perioperative outcomes included operative time, intraoperative blood loss, and conversion to open surgery. Postoperative complications, stratified using the Clavien-Dindo classification system[9], included postoperative hospital stay and adjuvant chemotherapy. The study protocol was approved by the ethics committee of the Juntendo University Hospital (Approval No. 20-192). The need for informed consent was waived in view of the retrospective and observational nature of the study. An opt-out approach was used by accessing a written disclosure on the study's website (URL: https://www.gcprec.juntendo.ac.jp/kenkyu/files/6379827945f9a62a8f32ec.pdf).

### ART

ART is an anastomosis technique that uses three linear staplers (LS) for TLDG. After gastrectomy, an insertion hole is made in the duodenum and the remnant stomach stump on the greater curvature side. The thinner and thicker 60-mm jaws of the LS are inserted into the greater curvature ends of both the duodenal and remnant gastric stump. The lesser curvature end of the stapled duodenal stump is rotated externally 90°, and the device is closed and fired. After the initial suturing of the stomach and duodenum, the posterior wall and cranial wall form a V-shape. A 30-mm LS is used to close the insertion holes up to the closest side of the duodenal resection margin. This suture creates the third side, which is the caudal wall. Finally, the entire stapled duodenal resection is removed, using a 60-mm LS to create the fourth side that makes up the rectangular anterior wall. This series of operations creates an augmented rectangular gastroduodenal anastomotic stoma.

### PGS & QOL assessment

The PGSAS-37 is a multidimensional QOL questionnaire based on the Gastrointestinal Symptom Rating Scale[10,11]. The PGSAS-37 questionnaire consists of 37 questions with 15 items from the Gastrointestinal Symptom Rating Scale, and 22 clinically relevant items selected and added by the JPGSWP (Table 1). These additional items consist of eight assessing overall symptoms, two dumping syndrome, five meal quantity, three meal quality, one work status, and three life dissatisfaction. These items are aggregated into nine subscales, for a total of seventeen main assessable outcomes. Nine subscales are derived from the average score of the corresponding items and include an evaluation of esophageal reflux, abdominal pain, meal-related distress, indigestion, diarrhea, constipation, dumping, quality of ingestion, and dissatisfaction with daily life. The total symptoms score is calculated from the average of the seven symptoms subscale scores. The main outcome consists of three categories, namely symptoms, living status, and QOL (Table 2). In the PGSAS-37 questionnaire, high scores denote favorable outcomes regarding ingested amounts of food per meal, ingested amounts of food per day, appetite, hunger, satiety, the quality of food, and change in body weight. Low scores on most of the other items and for symptom subscales indicate favorable outcomes.

The questionnaire was distributed to all patients who underwent gastrectomy for gastric cancer by a doctor or nurse at the time of outpatient treatment. Questionnaires were conducted at 1 mo, 3 mo, 6 mo, 12 mo, and 24 mo after surgery. The most recent questionnaire data collected for each patient was used in this study. The questionnaire was collected and managed by a medical clerk, and the data were blindly scored.

### Study method

This is a retrospective cohort study. We compared it to a national database of 909 patients with distal gastrectomies and Billroth I reconstructions who completed the PGSAS-37 questionnaire. The primary endpoint of our study was to compare the long-term patient outcomes between the two groups in terms of prevalence of PGS and QOL.

### Statistical analysis

Continuous data are presented as average and standard deviations. Independent-sample *t*-tests were

**Table 1 Postgastrectomy Syndrome Assessment Scale-37 evaluation items**

| | Item | | Subscales |
|---|---|---|---|
| Symptom | 1 | Abdominal pains | Esophageal reflux subscale (items 2, 3, 5, 16) |
| | 2 | Heartburn | Abdominal pain subscale (items 1, 4, 20) |
| | 3 | Acid regurgitation | Meal-related distress subscale (items 17-19) |
| | 4 | Sucking sensations in the epigastrium | Indigestion subscale (items 6-9) |
| | 5 | Nausea and vomiting | Diarrhea subscale (items 11, 12, 14) |
| | 6 | Borborygmus | Constipation subscale (items 10, 13, 15) |
| | 7 | Abdominal distension | Dumping subscale (items 22, 23, 25) |
| | 8 | Eructation | |
| | 9 | Increased flatus | Total symptom score (more than seven subscale) |
| | 10 | Decreased passage of stools | |
| | 11 | Increased passage of stools | |
| | 12 | Loose stools | |
| | 13 | Hard stools | |
| | 14 | Urgent need for defecation | |
| | 15 | Feeling of incomplete evacuation | |
| | 16 | Bile regurgitation | |
| | 17 | Sense of foods sticking | |
| | 18 | Postprandial fullness | |
| | 19 | Early satiation | |
| | 20 | Lower abdominal pains | |
| | 21 | Number and type of early dumping symptoms | |
| | 22 | Early dumping, general symptoms | |
| | 23 | Early dumping, abdominal symptoms | |
| | 24 | Number and type of late dumping symptoms | |
| | 25 | Late dumping symptoms | |
| Living status | 26 | Ingested amount of food per meal[1] | |
| | 27 | Ingested amount of food per day[1] | |
| | 28 | Frequency of main meals | |
| | 29 | Frequency of additional meals | |
| | 30 | Appetite[1] | Quality of ingestion subscale (items 30-32)[1] |
| | 31 | Hunger feeling[1] | |
| | 32 | Satiety feeling[1] | |
| | 33 | Necessity for additional meals | |
| | 34 | Ability for working | |
| Quality of life | 35 | Dissatisfaction with symptoms | Dissatisfaction with daily life subscale (items 35-37) |
| | 36 | Dissatisfaction at the meal | |
| | 37 | Dissatisfaction with working | |

[1]Higher scores indicate a better condition. In items or subscale without [1], higher scores indicate a worse condition. Each subscale and total symptom score is calculated as the average of its composite items or subscale score.

**Table 2 Main outcomes consisting of three categories**

| Category | Main outcome measure |
|---|---|
| Symptoms | |
| Subscale | Esophageal reflux subscale |
| | Abdominal pain subscale |
| | Meal-related distress subscale |
| | Indigestion subscale |
| | Diarrhea subscale |
| | Constipation subscale |
| | Dumping subscale |
| Total | Total symptom score |
| Living status | |
| Body weight | Change in body weight (%)[1] |
| Meals (amount) | Amount of food ingested per meal (%)[1] |
| | Necessity of additional meals |
| Meals (quality) | Quality of ingestion subscale[1] |
| Work | Ability for working |
| Quality of life | Dissatisfaction with symptom |
| Dissatisfaction | Dissatisfaction at the meal |
| | Dissatisfaction at working |
| | Dissatisfaction with daily life subscale |

[1]Higher scores indicate a better condition. In items or subscale without [1], higher scores indicate a worse condition.

used to analyze continuous data while $\chi^2$ or Fisher's exact tests were used to assess differences in categorical data. Statistical analysis was performed using the StatMate statistical software program (version V). $P < 0.05$ was considered significant. Cohen's d was calculated to determine the effect size. The value of Cohen's d reflects the effect of each casual variable, with 0.2 to < 0.5 denoting a small but clinically meaningful effect, while 0.5 to < 0.8 and ≥ 0.8 denote medium and large effects, respectively. The PGSAS statistic kit was used to compare our experimental data with Japanese national standard values for the Billroth I method from cases obtained from the PGSAS database.

## RESULTS

### *Patient characteristics*

Table 3 shows the patients' clinicopathological characteristics. There were 94 patients in the ART group and 909 patients in the PGSAS group. The postoperative observation period was significantly longer in the PGSAS group than in the ART group (40.7 ± 30.7 mo *vs* 27.1 ± 12.2 mo, respectively; $P < 0.001$). Age was significantly higher in the ART group than in the PGSAS group (70.0 ± 11.0 *vs* 61.6 ± 9.1, respectively; $P < 0.001$). Sex and preoperative body mass index showed no significant differences between the two groups. Patients in the ART group had significantly more advanced-stage cancer than those in the PGSAS group. The mean tumor size was 30.7±15.6 mm in the ART group. Laparoscopic surgery was performed in all cases in the ART group, but in only 45.6% of patients in the PGSAS group. Patients in the PGSAS group had a significantly higher rate of combined resection than those in the ART group.

### *Perioperative outcomes*

Perioperative outcomes are shown in Table 4. The average operative time was 285 min, and the intraoperative blood loss was 21.1 mL. No cases were converted to open surgery. Postoperative complications included Clavien-Dindo ≥ 3 in 3 patients (3.1%), anastomotic leakage in 1 patient (1.0%), and anastomotic bleeding in 2 patients (2.1%). The average postoperative hospital stay was 14.5 d with adjuvant chemotherapy performed in 17 patients (18.1%).

**Table 3 Patients' clinicopathological characteristics**

| | ART group | PGSAS group | *P* value |
|---|---|---|---|
| Number of patients | 94 | 909 | |
| Postoperative period in mo | 27.1 ± 12.2 | 40.7 ± 30.7 | < 0.001 |
| Age in yr | 70.0 ± 11.0 | 61.6 ± 9.1 | < 0.001 |
| Sex | | | 0.333 |
| Male | 57 | 594 | |
| Female | 37 | 311 | |
| Preoperative BMI in kg/m$^2$ | 22.7 ± 3.4 | 22.7 ± 3.0 | 1.000 |
| Stage | | | < 0.001 |
| I | 70 | 909 | |
| II | 16 | 0 | |
| III | 8 | 0 | |
| IV | 0 | 0 | |
| Approach | | | < 0.001 |
| Open | 0 | 489 | |
| Laparoscopic | 94 | 415 | |
| Extent of lymph node dissection (D1 >/D1/D2) | | | 0.135 |
| D1 > | 0 | 4 | |
| D1 | 70 | 586 | |
| D2 | 24 | 319 | |
| Combined resection (absence/presence) | | | 0.001 |
| Absence | 89 | 743 | |
| Presence | 5 | 166 | |

ART: Augmented rectangle technique; BMI: Body mass index; PGSAS: Postgastrectomy Syndrome Assessment Scale.

### *Main outcomes*

A total of 17 main outcomes in three categories (symptoms, living status, and QOL) are shown in Tables 5 and 6, along with the results of the univariate analysis comparing the ART and the PGSAS groups. For the symptoms category, patients in the ART group had significantly lower scores (indicating a better physical condition) in all symptom subscales (esophageal reflux, abdominal pain, meal-related distress, indigestion, diarrhea, constipation, and dumping) and in the total symptoms score (1.6 ± 0.4 *vs* 2.0 ± 0.7; $P < 0.001$). Regarding the living status category, the loss of body weight was marginally greater for the ART group than the PGSAS group, (-9.3% *vs* -7.9%; $P = 0.054$). The ingested amount of food per meal was statistically lower (indicating a worse physical condition) in the ART group compared to the PGSAS group (6.3 ± 1.9 *vs* 7.1 ± 2.0; $P < 0.001$). Although the need for additional meals was not different between the two groups, the quality of ingestion subscale was significantly lower in the ART group compared to the PGSAS group (3.3 ± 1.0 *vs*3.8 ± 0.9; $P < 0.001$). Regarding the QOL category, the ART group was significantly lower (indicating a better physical condition) in the subscale of dissatisfaction with symptoms, meals, and daily life (except for the work related item). Furthermore, almost the same results were obtained if the same eligible patient criteria for PGSAS was applied (Supplementary Tables 1 and 2).

## DISCUSSION

This is the first report to evaluate PGS and QOL after a TLDG reconstructed with the novel Billroth I method of ART. Importantly, we compared our results to patients from the Japanese national PGSAS study who did not receive ART. We analyzed PGS and QOL in patients who did and did not receive an ART and found that ART was beneficial. This is important because in Japan a distal gastrectomy is the

**Table 4 Perioperative outcomes**

| | ART, *n* = 94 |
|---|---|
| Operation time in min | 285 ± 84 |
| Intraoperative blood loss in mL | 21.1 ± 16.4 |
| Conversion to open surgery | 0 (0%) |
| Postoperative complication CD ≥ 3 | 3 (3.1%) |
| Anastomotic-related complication | |
| Anastomotic leakage | 1 (1.0%) |
| Anastomotic bleeding | 2 (2.1%) |
| Anastomotic stenosis | 0 (0%) |
| Delayed gastric emptying | 0 (0%) |
| Non-anastomotic-related complication | |
| Pancreatic fistula | 4 (4.2%) |
| Surgical site infection | 4 (4.2%) |
| Pneumoniae | 1 (1.0%) |
| Postoperative hospital stay in day | 14.5 ± 14.9 |
| Adjuvant chemotherapy | 17 (18.1%) |
| Adjuvant radiation therapy | 0 (0%) |

ART: Augmented rectangle technique; CD: Clavien-Dindo.

**Table 5 Main outcomes in symptoms categories**

| | | ART group, *n* = 94 | | PGSAS group, *n* = 909 | | Cohen's d | *P* value |
|---|---|---|---|---|---|---|---|
| | | mean | SD | mean | SD | | |
| Symptom | Esophageal reflux subscale | 1.4 | 0.6 | 1.7 | 0.8 | 0.30 | < 0.001 |
| | Abdominal pain subscale | 1.5 | 0.5 | 1.7 | 0.7 | 0.26 | 0.003 |
| | Meal-related distress subscale | 1.7 | 0.7 | 2.1 | 0.9 | 0.35 | < 0.001 |
| | Indigestion subscale | 1.6 | 0.6 | 2.0 | 0.8 | 0.43 | < 0.001 |
| | Diarrhea subscale | 1.8 | 0.7 | 2.1 | 1.1 | 0.27 | 0.001 |
| | Constipation subscale | 1.9 | 0.7 | 2.2 | 1.0 | 0.32 | < 0.001 |
| | Dumping subscale | 1.5 | 0.7 | 2.0 | 1.0 | 0.41 | < 0.001 |
| | Total symptoms score | 1.6 | 0.4 | 2.0 | 0.7 | 0.45 | < 0.001 |

ART: Augmented rectangle technique; PGSAS: Postgastrectomy Syndrome Assessment Scale; SD: Standard deviation.

most commonly performed surgical procedure for gastric cancer.

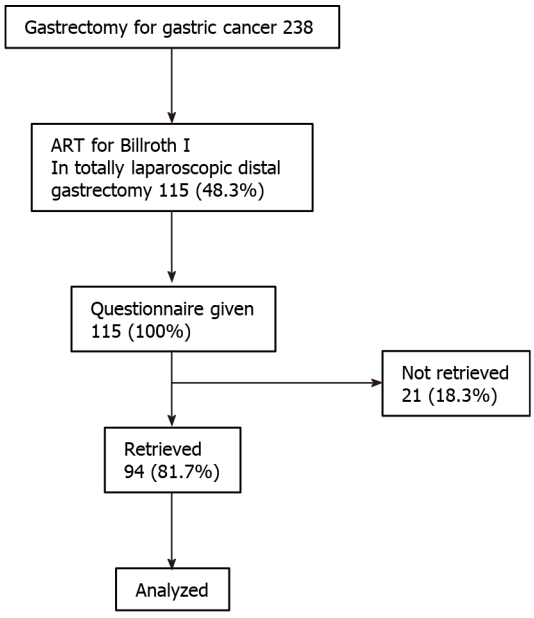
Billroth I is our preferred post-distal gastrectomy reconstruction method because of its technical simplicity and its restoration of normal anatomy[12]. Our patient questionnaire regarding reconstruction methods after distal gastrectomies in Japan showed that Billroth I was selected as the first choice in 77% of Japanese institutions[13]. In recent years, the number of laparoscopic gastrectomies performed in Japan has dramatically increased, resulting in the publication of multiple reports on various reconstruction techniques[14-17]. However, all of these reported techniques are technically challenging, requiring a certain degree of skill and experience and are associated with complications, such as obstruction due to torsion or stenosis at the anastomotic site.

In 2013, we developed ART as a simpler reconstruction technique after TLDG and currently utilize it for all Billroth I reconstruction methods. Importantly, we also reported a low rate of anastomotic-related complications in the short-term after surgery[6]. There was a concern, however, that in the long-term, there would be a high prevalence of esophageal reflux and dumping symptoms because of the large

**Table 6 Main outcomes in living status and quality of life categories**

| | | ART group, *n* = 94 | | PGSAS group, *n* = 909 | | | |
|---|---|---|---|---|---|---|---|
| | | mean | SD | mean | SD | Cohen's d | *P* value |
| Living status | Change in body weight (%)[1] | -9.3 | 6.4 | -7.9 | 8.1 | 0.17 | 0.054 |
| | Amount of food ingested per meal (%)[1] | 6.3 | 1.9 | 7.1 | 2.0 | 0.41 | < 0.001 |
| | Necessity of additional meals | 1.8 | 0.7 | 1.9 | 0.8 | 0.00 | 0.977 |
| | Quality of ingestion subscale[1] | 3.3 | 1.0 | 3.8 | 0.9 | 0.52 | < 0.001 |
| | Ability for working | 1.8 | 0.9 | 1.8 | 0.9 | 0.13 | 0.261 |
| Quality of life | Dissatisfaction with symptoms | 1.6 | 0.7 | 1.8 | 0.9 | 0.21 | 0.022 |
| | Dissatisfaction during meals | 1.8 | 0.9 | 2.2 | 1.1 | 0.29 | 0.004 |
| | Dissatisfaction during work | 1.6 | 0.7 | 1.7 | 0.9 | 0.03 | 0.774 |
| | Dissatisfaction with daily life subscale | 1.7 | 0.6 | 1.9 | 0.8 | 0.21 | 0.016 |

[1]Higher scores indicate a better condition. In items or subscale without [1], higher scores indicate a worse condition. ART: Augmented rectangle technique; PGSAS: Postgastrectomy Syndrome Assessment Scale; SD: Standard deviation.




**DOI:** 10.4240/wjgs.v14.i2.120 

**Figure 1 Flow diagram for study inclusion.** ART: Augmented rectangle technique.

rectangular anastomosis. Therefore, we evaluated long-term PGS and QOL after ART using the PGSAS-37 questionnaire and analyzed patients' postoperative functions in comparison to patients in a national database who did not receive ART. The PGSAS questionnaire, used by the national database, is designed specifically to evaluate functional parameters after gastrectomy. It is also freely accessible and is highly versatile since it observes a patient's condition during daily routine medical care.

Unexpectedly, patients in the ART group fared significantly better in all symptom subscales (esophageal reflux, abdominal pain, meal-related distress, ingestion, diarrhea, constipation, dumping) and in the total symptom scores than the patients in the PGSAS group. Symptoms such as regurgitation and dumping, presumably due to the large anastomosis, were significantly fewer than the national average. This result suggests that ART may be beneficial in reducing these symptoms after gastrectomy. It is not clear why the symptoms subscale and the total score categories both improved. Postoperative anastomotic complications cause a variety of complaints, so our low anastomotic complication rates associated with ART may have contributed to our better PGSAS-37 scores than the national average.

Moreover, the reason for this may not only be due to the anastomosis technique but also due to the fact that patients received postoperative continuous nutritional guidance (especially avoiding overeating), ready treatment for any complaint, life guidance as well as psychiatric care. At the very least, this study shows that the large rectangular anastomosis, which is a characteristic of ART, does not cause various complaints.

Focusing on the category of living status, the rate of weight loss in patients was marginally greater in the ART group than observed nationally ($P$ = 0.054). Since the data suggest no additional meals consumed, a smaller amount of food per meal in the ART group may be one of the causes of weight loss. Another reason may be related to the shorter length of the postoperative observation period in our study. The average postoperative observation period was 40.7 mo in patients in the national PGSAS database but only 27.1 mo in patients with ART. In addition, the ART group included 17 patients (18.1%) who received postoperative adjuvant chemotherapy, which is also a factor that can lead to weight loss.

There are several reports on the relationship between PGS and the size of the gastric remnant after a distal gastrectomy with a Billroth I reconstruction. Nomura *et al*[18] reported that in cases of early gastric cancer patients who maintained half of their gastric remnant showed improved food intake, little postoperative weight loss, and few abdominal symptoms, such as diarrhea and abdominal pain, compared to those who only had one-third of their gastric remnant after a distal gastrectomy with a Billroth I reconstruction. On the other hand, there are reports that there is no relationship between the size of the gastric remnant and weight loss[19].

Japanese gastric cancer guidelines recommend at least two-thirds of the stomach be removed during a distal gastrectomy. We also follow the Japanese gastric cancer treatment guidelines and perform a complete gastric dissection. Misawa *et al*[19] evaluated PGS with and without a Kocher maneuver during distal gastrectomy with a Billroth I reconstruction. They reported that the Kocher maneuver resulted in poor PGSAS scores in the quality of ingestion subscale, which evaluates appetite, hunger, and satiety. We found the same result in our study. ART also slightly mobilizes the duodenum during reconstruction, although not to the same extent as a Kocher maneuver. This may be one of the reasons why this aspect of the PGSAS score in the quality of ingestion subscale was worse than the national average. The superior score for patients in the ART group, for the subscales of dissatisfaction with symptoms, diet, and with daily life, indicates that patients are in good shape physically. This also suggests that the lack of ART post-gastrectomy symptoms contributes to maintaining a good QOL on a daily basis. It is difficult to conclude that the infrequency of post-gastrectomy symptoms was due to an anastomosis technique alone but may also reflect appropriate decision making regarding the type of surgical procedure as well as the attentive postoperative management.

This study has several limitations. Specifically, this was a retrospective study in which there were substantial differences between the two groups making some direct comparisons problematic. For example, it is not possible to accurately match patients' preoperative physical conditioning. Also, since the data published by the PGSAS database are limited, it is again not possible to analyze certain variables that may have impacted outcome. However, almost the same results were obtained if the same eligible patient criteria for PGSAS were applied (Supplementary Tables 1 and 2). Further prospective research is needed to examine the effects of preoperative factors, including age, sex, body mass index, stage, *etc.* on PGS and QOL. Another limitation is that it was difficult to provide a rational explanation for all results. PGS varies widely among individuals and is influenced by a variety of physical and functional factors. There have been no studies of a specific Billroth I technique for TLDG that have examined as many symptoms as in this study. In particular, chronological changes are thought to be the most important issue in evaluating a patient's QOL after gastrectomy. However, we mainly focused on a certain variable, QOL, at the average postoperative observation period of 27.1 mo after gastrectomy. Kobayashi *et al*[20] reported that patients rarely had any subsequent changes in their QOL more than 1 year after gastrectomy. The average observation period in our study is, by definition, appropriate. At present, PGSAS-45, which is PGSAS plus SF-8, is often used for QOL evaluations after gastrectomy. SF-8 was not measured in this study, and further follow-up studies are needed with this instrument.

## CONCLUSION

From this retrospective evaluation, we concluded that the results of an ART reconstruction produced beneficial long-term results with regards to PGS and postoperative QOL. Further investigation involving a larger number of patients comparing ART with other anastomotic techniques and evaluating long-term patient outcomes is needed to validate the benefits of ART reconstruction after TLDG.

## ARTICLE HIGHLIGHTS

### *Research background*

For total laparoscopic distal gastrectomies for gastric cancer, the reconstruction method is critical to the clinical outcome of the procedure. We originally reported the augmented rectangle technique (ART) as a reconstruction option for total laparoscopic Billroth I reconstructions. Yet, little is known about its effect on long-term outcomes, specifically the incidence of postgastrectomy syndrome (PGS) and its impact on quality of life (QOL).

### *Research motivation*

Reducing the prevalence of PGS and improving the QOL after gastrectomy for gastric cancer patients has become an important technical challenge for surgeons. ART shows good short-term results, but long-term results in terms of PGS and quality of life should be reported.

### *Research objectives*

To analyze PGS and QOL after ART using the Postgastrectomy Syndrome Assessment Scale-37 (PGSAS-37) questionnaire.

### *Research methods*

At Juntendo University, 94 patients who underwent ART for Billroth I reconstruction with total laparoscopic distal gastrectomies for gastric cancer between July 2016 to March 2020 completed questionnaires. Multidimensional analysis was performed comparing those 94 ART cases from our institution (ART group) to 909 distal gastrectomy cases with a Billroth I reconstruction from other Japanese institutions who also completed the PGSAS as part of a larger national database (PGSAS group).

### *Research results*

Patients in the ART group had significantly better total symptom scores in all the symptom subscales (esophageal reflux, abdominal pain, meal-related distress, indigestion, diarrhea, constipation, and dumping). The loss of body weight was marginally greater for those in the ART group than in the PGSAS group (-9.3% *vs* -7.9%; $P = 0.054$). The ART group scored significantly lower in their dissatisfaction of ongoing symptoms, during meals, and with daily life.

### *Research conclusions*

The use of ART for Billroth I reconstruction produced beneficial long-term results with regards to PGS and QOL in patients undergoing total laparoscopic distal gastrectomies for gastric cancer.

### *Research perspectives*

Further investigation of the mechanism underlying the usefulness of ART in terms of PGS and QOL is needed. Prospective studies are also needed on the involvement of factors other than the anastomotic method.

## FOOTNOTES

**Author contributions:** Yamauchi S, Orita H Matusi R, Yube Y, Kaji S, Orita H, Brock MV and Fukunaga T contributed to writing of the manuscript; Yamauchi S, Orita H, Jun C, Egawa H, Yoshimoto Y, Yube Y, Kaji S and Oka S contributed to performing the procedures and analyzing the data; Yamauchi S and Yoshimoto Y contributed to statistical review; Orita H, Fukunaga T and Brock MV contributed to the conception and design of this work.

**Institutional review board statement:** The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Juntendo University Hospital (Approval No. 20-192).

**Informed consent statement:** The study design was retrospective and a noninterventional study. Patients were not required to give informed consent to the study because the analysis used anonymized clinical data that were obtained after each patient agreed to treatment by written consent. We also applied an opt-out method to obtain consent for this study. The opt-out approach was used with website disclosure (URL: https://www.gcprec.juntendo.ac.jp/kenkyu/files/6379827945f9a62a8f32ec.pdf).

**Conflict-of-interest statement:** The authors declare having no conflicts of interest.

**Data sharing statement:** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. The data is not publicly available due to patient privacy and the General Data Protection Regulation.

**STROBE statement:** The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.



**Country/Territory of origin:** Japan

**ORCID number:** Suguru Yamauchi 0000-0003-3185-3333; Hajime Orita 0000-0002-8263-7069; Jun Chen 0000-0003-1127-3824; Hiroki Egawa 0000-0003-1934-9918; Yutaro Yoshimoto 0000-0003-2354-5604; Akira Kubota 0000-0002-7869-4511; Ryota Matsui 0000-0003-3185-3332; Yukinori Yube 0000-0002-0289-8892; Sanae Kaji 0000-0002-1372-4468; Shinichi Oka 0000-0002-3820-3394; Malcolm V Brock 0000-0003-2961-851X; Tetsu Fukunaga 0000-0003-4802-8945.

**S-Editor:** Wang LL
**L-Editor:** A
**P-Editor:** Wang LL

## REFERENCES

1 **Davis JL**, Ripley RT. Postgastrectomy Syndromes and Nutritional Considerations Following Gastric Surgery. *Surg Clin North Am* 2017; **97**: 277-293 [PMID: 28325187 DOI: 10.1016/j.suc.2016.11.005]
2 **Bolton JS**, Conway WC 2nd. Postgastrectomy syndromes. *Surg Clin North Am* 2011; **91**: 1105-1122 [PMID: 21889032 DOI: 10.1016/j.suc.2011.07.001]
3 **Carvajal SH**, Mulvihill SJ. Postgastrectomy syndromes: dumping and diarrhea. *Gastroenterol Clin North Am* 1994; **23**: 261-279 [PMID: 8070912]
4 **Kim AR**, Cho J, Hsu YJ, Choi MG, Noh JH, Sohn TS, Bae JM, Yun YH, Kim S. Changes of quality of life in gastric cancer patients after curative resection: a longitudinal cohort study in Korea. *Ann Surg* 2012; **256**: 1008-1013 [PMID: 23154395 DOI: 10.1097/SLA.0b013e31827661c9]
5 **Karanicolas PJ**, Graham D, Gönen M, Strong VE, Brennan MF, Coit DG. Quality of life after gastrectomy for adenocarcinoma: a prospective cohort study. *Ann Surg* 2013; **257**: 1039-1046 [PMID: 23665970 DOI: 10.1097/SLA.0b013e31828c4a19]
6 **Fukunaga T**, Ishibashi Y, Oka S, Kanda S, Yube Y, Kohira Y, Matsuo Y, Mori O, Mikami S, Enomoto T, Otsubo T. Augmented rectangle technique for Billroth I anastomosis in totally laparoscopic distal gastrectomy for gastric cancer. *Surg Endosc* 2018; **32**: 4011-4016 [PMID: 29915985 DOI: 10.1007/s00464-018-6266-1]
7 **Nakada K**, Ikeda M, Takahashi M, Kinami S, Yoshida M, Uenosono Y, Kawashima Y, Oshio A, Suzukamo Y, Terashima M, Kodera Y. Characteristics and clinical relevance of postgastrectomy syndrome assessment scale (PGSAS)-45: newly developed integrated questionnaires for assessment of living status and quality of life in postgastrectomy patients. *Gastric Cancer* 2015; **18**: 147-158 [PMID: 24515247 DOI: 10.1007/s10120-014-0344-4]
8 **Japanese Gastric Cancer Association**. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101-112 [PMID: 21573743 DOI: 10.1007/s10120-011-0041-5]
9 **Dindo D**, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205-213 [PMID: 15273542 DOI: 10.1097/01.sla.0000133083.54934.ae]
10 **Svedlund J**, Sjödin I, Dotevall G. GSRS--a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Dig Dis Sci* 1988; **33**: 129-134 [PMID: 3123181 DOI: 10.1007/BF01535722]
11 **Wiklund IK**, Junghard O, Grace E, Talley NJ, Kamm M, Veldhuyzen van Zanten S, Paré P, Chiba N, Leddin DS, Bigard MA, Colin R, Schoenfeld P. Quality of Life in Reflux and Dyspepsia patients. Psychometric documentation of a new disease-specific questionnaire (QOLRAD). *Eur J Surg* 1998; **583**: 41-49 [DOI: 10.1016/s0016-5085(98)80199-6]
12 **Kim BJ**, O'Connell T. Gastroduodenostomy after gastric resection for cancer. *Am Surg* 1999; **65**: 905-907 [PMID: 10515531]
13 **Kumagai K**, Shimizu K, Yokoyama N, Aida S, Arima S, Aikou T; Japanese Society for the Study of Postoperative Morbidity after Gastrectomy. Questionnaire survey regarding the current status and controversial issues concerning reconstruction after gastrectomy in Japan. *Surg Today* 2012; **42**: 411-418 [PMID: 22391980 DOI: 10.1007/s00595-012-0159-z]
14 **Kanaya S**, Gomi T, Momoi H, Tamaki N, Isobe H, Katayama T, Wada Y, Ohtoshi M. Delta-shaped anastomosis in totally laparoscopic Billroth I gastrectomy: new technique of intraabdominal gastroduodenostomy. *J Am Coll Surg* 2002; **195**: 284-287 [PMID: 12168979 DOI: 10.1016/s1072-7515(02)01239-5]
15 **Tanimura S**, Higashino M, Fukunaga Y, Takemura M, Nishikawa T, Tanaka Y, Fujiwara Y, Osugi H. Intracorporeal Billroth 1 reconstruction by triangulating stapling technique after laparoscopic distal gastrectomy for gastric cancer. *Surg Laparosc Endosc Percutan Tech* 2008; **18**: 54-58 [PMID: 18287984 DOI: 10.1097/SLE.0b013e3181568e63]
16 **Ikeda T**, Kawano H, Hisamatsu Y, Ando K, Saeki H, Oki E, Ohga T, Kakeji Y, Tsujitani S, Kohnoe S, Maehara Y. Progression from laparoscopic-assisted to totally laparoscopic distal gastrectomy: comparison of circular stapler (i-DST)

and linear stapler (BBT) for intracorporeal anastomosis. *Surg Endosc* 2013; **27**: 325-332 [PMID: 22733199 DOI: 10.1007/s00464-012-2433-y]

17 **Byun C**, Cui LH, Son SY, Hur H, Cho YK, Han SU. Linear-shaped gastroduodenostomy (LSGD): safe and feasible technique of intracorporeal Billroth I anastomosis. *Surg Endosc* 2016; **30**: 4505-4514 [PMID: 26895918 DOI: 10.1007/s00464-016-4783-3]

18 **Nomura E**, Lee SW, Bouras G, Tokuhara T, Hayashi M, Hiramatsu M, Okuda J, Tanigawa N. Functional outcomes according to the size of the gastric remnant and type of reconstruction following laparoscopic distal gastrectomy for gastric cancer. *Gastric Cancer* 2011; **14**: 279-284 [PMID: 21519869 DOI: 10.1007/s10120-011-0046-0]

19 **Misawa K**, Terashima M, Uenosono Y, Ota S, Hata H, Noro H, Yamaguchi K, Yajima H, Nitta T, Nakada K. Evaluation of postgastrectomy symptoms after distal gastrectomy with Billroth-I reconstruction using the Postgastrectomy Syndrome Assessment Scale-45 (PGSAS-45). *Gastric Cancer* 2015; **18**: 675-681 [PMID: 25091080 DOI: 10.1007/s10120-014-0407-6]

20 **Kobayashi D**, Kodera Y, Fujiwara M, Koike M, Nakayama G, Nakao A. Assessment of quality of life after gastrectomy using EORTC QLQ-C30 and STO22. *World J Surg* 2011; **35**: 357-364 [PMID: 21104250 DOI: 10.1007/s00268-010-0860-2]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 February 27; 14(2): 132-142

DOI: 10.4240/wjgs.v14.i2.132

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

# Choledocholithiasis characteristics with periampullary diverticulum and endoscopic retrograde cholangiopancreatography procedures: Comparison between two centers from Lanzhou and Kyoto

Ke-Xiang Zhu, Ping Yue, Hai-Ping Wang, Wen-Bo Meng, Jian-Kang Liu, Lei Zhang, Xiao-Liang Zhu, Hui Zhang, Long Miao, Zheng-Feng Wang, Wen-Ce Zhou, Azumi Suzuki, Kiyohito Tanaka, Xun Li

**Specialty type:** Surgery

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Reddy NNR

**Received:** April 20, 2021
**Peer-review started:** April 20, 2021
**First decision:** June 13, 2021
**Revised:** June 24, 2021
**Accepted:** January 27, 2022
**Article in press:** January 27, 2022
**Published online:** February 27, 2022

**Ke-Xiang Zhu, Ping Yue, Wen-Bo Meng, Lei Zhang, Xiao-Liang Zhu, Hui Zhang, Long Miao, Zheng-Feng Wang, Wen-Ce Zhou, Xun Li,** Department of General Surgery, The First Hospital of Lanzhou University, Lanzhou 730000, Gansu Province, China

**Ke-Xiang Zhu, Ping Yue, Hai-Ping Wang, Wen-Bo Meng, Lei Zhang, Xiao-Liang Zhu, Hui Zhang, Long Miao, Zheng-Feng Wang, Wen-Ce Zhou, Xun Li,** Key Laboratory of Biological Therapy and Regenerative Medicine Transformation Gansu Province, The First Hospital of Lanzhou University, Lanzhou 730000, Gansu Province, China

**Jian-Kang Liu,** Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02451, United States

**Azumi Suzuki, Kiyohito Tanaka,** Department of Gastroenterology, Kyoto Second Red Cross Hospital, Kyoto 602-8026, Japan

**Corresponding author:** Xun Li, PhD, Chief Doctor, Department of General Surgery, The First Hospital of Lanzhou University, No. 1 Donggang West Road, Chengguan District, Lanzhou 730000, Gansu Province, China. lxdr21@126.com

## Abstract

*BACKGROUND*

Most of study regarding periampullary diverticulum (PAD) impact on endoscopic retrograde cholangiopancreatography (ERCP) therapy for choledocholithiasis based on data from one endoscopy center and lacked to compare the clinical characteristic of choledocholithiasis with PAD from different geographical patients.

*AIM*

To compare the choledocholithiasis clinical characteristics between two regional endoscopy centers and analyze impacts of clinical characteristics on ERCP methods for choledocholithiasis patients with PAD.

*METHODS*

Patients seen in two endoscopy centers (The First Hospital of Lanzhou University, Lanzhou, Gansu Province, China, and Kyoto Second Red Cross Hospital, Kyoto,

Japan) underwent ERCP treatment for the first time between January 2012 and December 2017. The characteristics of choledocholithiasis with PAD were compared between the two centers, and their ERCP procedures and therapeutic outcomes were analyzed.

***RESULTS***

A total of 829 out of 3608 patients in the Lanzhou center and 241 out of 1198 in the Kyoto center had choledocholithiasis with PAD. Lots of clinical characteristics were significantly different between the two centers. The common bile duct (CBD) diameter was wider, choledocholithiasis size was lager and multiple CBD stones were more in the Lanzhou center patients than those in the Kyoto center patients (14.8 ± 5.2 mm *vs* 11.6 ± 4.2 mm, 12.2 ± 6.5 mm *vs* 8.2 ± 5.3 mm, 45.3% *vs* 20.3%, $P < 0.001$ for all). In addition, concomitant diseases, such as acute cholangitis, gallbladder stones, obstructive jaundice, cholecystectomy, and acute pancreatitis, were significantly different between the two centers ($P = 0.03$ to $< 0.001$). In the Lanzhou center, CBD diameter and choledocholithiasis size were lower, and multiple CBD stones and acute cholangitis were less in non-PAD patients than those in PAD patients (13.4 ± 5.1 mm *vs* 14.8 ± 5.2 mm, 10.3 ± 5.4 mm *vs* 12.2 ± 6.5, 39% *vs* 45.3%, 13.9% *vs* 18.5%, $P = 0.002$ to $< 0.001$). But all these characteristics were not significantly different in the Kyoto center. The proportions of endoscopic sphincterotomy (EST), endoscopic balloon dilatation (EPBD), and EST+EPBD were 50.5%, 1.7%, and 42.5% in the Lanzhou center and 90.0%, 0.0%, and 0.4% in the Kyoto center, respectively. However, the overall post-ERCP complication rate was not significantly different between the two centers (8.9% in the Lanzhou and 5.8% in the Kyoto. $P = 0.12$). In the Lanzhou center, the difficulty rate in removing CBD stones in PAD was higher than in non-PAD group (35.3% *vs* 26.0%, $P < 0.001$). But the rate was no significant difference between the two groups in Kyoto center. The residual rates of choledocholithiasis were not significantly different between the two groups in both centers. Post-ERCP complications occurred in 8.9% of the PAD patients and 8.1% of the non-PAD patients in the Lanzhou Center, and it occurred in 5.8% in PAD patients and 10.0% in non-PAD patients in the Kyoto center, all $P > 0.05$.

***CONCLUSION***

Many clinical characteristics of choledocholithiasis patients with PAD were significantly different between the Lanzhou and Kyoto centers. The patients had larger and multiple stones, wider CBD diameter, and more possibility of acute cholangitis and obstructive jaundice in the Lanzhou center than those in the Kyoto center. The ERCP procedures to manage native duodenal papilla were different depending on the different clinical characteristics while the overall post-ERCP complications were not significantly different between the two centers. The stone residual rate and post-ERCP complications were not significantly different between choledocholithiasis patients with PAD and without PAD in each center.

**Key Words:** Clinical characteristics; Periampullary diverticulum; Endoscopic retrograde cholangiopancreatography; Choledocholithisasis



**Core Tip:** There were many studies on periampullary diverticulum (PAD) association with biliary stone and endoscopic retrograde cholangiopancreatography (ERCP) therapy. But many of them were from only single endoscopy center. In this article, the data from two centers of Lanzhou and Kyoto. We focused on comparing the choledocholithiasis characteristics with PAD, ERCP procedures and efficacy between the two centers. A total of 829 cases of choledocholithiasis with PAD in Lanzhou Center and 241 cases in Kyoto Center were involved. We find there are different characteristics of choledocholithiasis with PAD and different ERCP procedures to handle duodenal papilla between Lanzhou and Kyoto, and ERCP procedure depends on its own clinical characteristics.

**Citation:** Zhu KX, Yue P, Wang HP, Meng WB, Liu JK, Zhang L, Zhu XL, Zhang H, Miao L, Wang ZF, Zhou WC, Suzuki A, Tanaka K, Li X. Choledocholithiasis characteristics with periampullary diverticulum and endoscopic retrograde cholangiopancreatography procedures: Comparison between two centers from Lanzhou and Kyoto. *World J Gastrointest Surg* 2022; 14(2): 132-142

**URL:** https://www.wjgnet.com/1948-9366/full/v14/i2/132.htm

**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i2.132

## INTRODUCTION

Choledocholithiasis is a common disease of the biliary tract system, and its causes are not completely clear, but its occurrence is closely related to periampullary diverticulum (PAD). It was reported that the incidence of bile duct stones reached 51.3%-88.0% among PAD patients[1-4]. Our previous study also revealed that PAD is an important factor for the occurrence and reoccurrence of bile duct stones[5]. Endoscopic retrograde cholangiopancreatography (ERCP) is regarded as an effective method for the treatment of choledocholithiasis. However, the anatomy of the duodenal junction may change due to the presence of PAD and possibly make ERCP cumbersome in the treatment of choledocholithiasis[6-9]. Therefore, many studies have focused on the safety and success of ERCP for PAD patients with choledocholithiasis[6,9-13]. However, there were inconsistent results regarding the impact of PAD on the safety and success of ERCP for choledocholithiasis. Some studies have shown that PAD is a challenge in ERCP[6,14]. Other studies concluded that PAD was not considered an obstacle to ERCP cannulation[4,7,9]. Regarding efficacy, some studies have reported that therapeutic outcomes are not affected by the presence of PAD, and complication rates of ERCP were similar in patients with and without PAD[9]. However, other studies suggested that a high rate of ERCP-related complications was associated with PAD[14-15], and it is unknown what caused those differences. Hypothetically, one of the reasons for these inconsistent conclusions may be associated with the discrepancies in the clinical characteristics in different studies regarding PAD patients with choledocholithiasis.

Many previous studies were based on data from only one endoscopy center and lacked a comparison of the clinical characteristics of choledocholithiasis with PAD from different regions. Thus, little is known about the difference in the clinical characteristics of choledocholithiasis with PAD patients from different regions and the impact of the clinical characteristics on ERCP methods. Therefore, in this study, we compared the clinical characteristics of PAD patients with choledocholithiasis and identified the impact of PAD on the methods and efficacy of ERCP, involving two different regional endoscopy centers (The First Hospital of Lanzhou University, a University School of Medicine of Gansu, Lanzhou, Gansu Province, China, and the Kyoto Second Red Cross Hospital, Kyoto, Japan) over the same period.

## MATERIALS AND METHODS

This study was performed in two endoscopy centers, the First Hospital of Lanzhou University, a University School of Medicine of Gansu, China, and the Kyoto Second Red Cross Hospital, Japan. PAD patients with choledocholithiasis were enrolled retrospectively from all patients with a naïve papilla who needed therapeutic ERCP between January 2012 and December 2017. Patient information included patient demographics, diagnosis with PAD or without PAD, diameter of the common bile duct (CBD), presence of choledocholithiasis, maximum diameter and number of choledocholithiasis, and concomitant diseases such as acute cholangitis, gallbladder stones, obstructive jaundice, cholecystectomy, and acute pancreatitis. The ERCP procedure, whether there was difficulty cannulating or not, the outcome of therapeutic ERCP for choledocholithiasis with PAD and the difficulty in removing the stones, residual stones in the CBD, and post-ERCP complications were all evaluated.

According to the above mentioned data, the comparative analysis was as follows: (1) comparison of the clinical characteristics of PAD patients with choledocholithiasis between the Lanzhou and Kyoto endoscopy centers and comparison of the clinical characteristics of patients with choledocholithiasis with and without PAD within each endoscopy center; (2) the ERCP procedures for PAD patients with choledocholithiasis between the two endoscopy centers and the ERCP curative efficacy with and without PAD within each center. The difficulty of removing biliary stones was defined by the presence of one or more of the following situations: the need for mechanical lithotripsy or another fragmented method; failure to remove the bile duct stones within 30 min; failure of stone extraction with a standard basket; and more than two endoscopic balloon dilatations (EPBDs). Residual stones in the common bile duct were defined as follows: Some choledocholithiasis was still in the bile duct or stones were suspected to still be in the bile duct through X-ray fluoroscopy at the end of ERCP and choledocholithiasis was again diagnosed within 3 mo after the first ERCP. Patients were placed under conscious sedation with meperidine and midazolam. ERCP was performed by experienced endoscopists who performed over 100 biliary interventions per year. Patients who initially planned to undergo diagnostic ERCP were not enrolled in this study. The follow-up was started as long as the ERCP was performed.

### *Statistical analysis*

Categorical variables were analyzed with the chi-squared or Fisher's exact test, while continuous variables were expressed as the median and interquartile range and compared with the Wilcoxon rank sum test, or expressed as the mean and standard deviation and compared with *t*-test. All statistical assessments were 2-sided, and a *P* value less than 0.05 was considered significant. Statistical analysis was performed using the SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

In the cases of choledocholithiasis with PAD, 829 of 3608 patients in the Lanzhou center, and 241 of 1198 patients in the Kyoto center were enrolled in consecutive first session ERCP. Comparing the clinical characteristics between the Lanzhou center and the Kyoto center, patient age, diameter of the CBD, stone number and size in the CBD, comorbidities such as acute cholangitis, gallstones, obstructive jaundice, acute pancreatitis, and operation history of the bile duct were all significantly different, except for sex. In detail, compared with an average diameter (11.6 ± 4.2 mm) of the CBD in patients in the Kyoto center, the average diameter of the CBD was 14.8 ± 5.2 mm in patients in the Lanzhou center. Compared with the mean diameter of choledocholithiasis that was 8.2 ± 5.3 mm in patients in the Kyoto center, the mean diameter of choledocholithiasis was 12.2 ± 6.5 mm in Lanzhou. Regarding single or multiple choledocholithiasis, 45.3% of the patients had multiple stones and 54.7% of the patients had single stones in the Lanzhou center but 20.3% and 79.7% of patients had single and multiple stones in the Kyoto center, respectively. Each of those comparisons was significantly different ($P < 0.001$). Some comorbidities were also significantly different between the Lanzhou and Kyoto centers: acute cholangitis (18.5% *vs* 9.5%, $P = 0.001$); obstructive jaundice (13.8% *vs* 0.4%, $P < 0.001$); acute pancreatitis (4.7% *vs* 1.7%, $P = 0.03$); cholecystectomy (38.4% *vs* 3.7%, $P < 0.001$); and gallbladder stones (4.7% *vs* 12.5%, $P < 0.001$) (Table 1).

The failure rate of ERCP was not different between the two endoscopy centers, but the difficulty rate of deep cannulation of the bile duct was significantly different: 9.7% in Lanzhou *vs* 24.1% in Kyoto ($P < 0.001$). The proportions of endoscopic sphincterotomy (EST), EPBD, and EST+EPBD were 50.5%, 1.7%, and 42.5% in the Lanzhou center and 90.0%, 0.0%, and 0.4% in the Kyoto center, respectively. ERCP procedures to handle the duodenal papilla were significantly different between the two centers ($P < 0.001$). Regarding ERCP-related complications, the overall complication rate was 8.9% in Lanzhou and 5.8% in Kyoto. The results showed that the overall complications were not significantly different between the Lanzhou and Kyoto centers ($P = 0.12$) (Table 2).

Comparing PAD with non-PAD in each center, the results were as follows: The mean age of the PAD group was 56 years and was 65 years for non-PAD in Lanzhou, and it was 71 years and 76 with and without PAD in Kyoto, respectively. The mean age of PAD patients was significantly older than those without PAD in each center. In the Lanzhou center, the mean diameter of the CBD was 14.8 ± 5.2 mm in the PAD group and 13.4 ± 5.1 mm in the non-PAD group. The mean diameter of the CBD in the PAD group was significantly wider than that in the non-PAD group ($P < 0.001$). In the Kyoto Center, the mean diameter of the CBD was 11.6 ± 4.2 mm in the PAD group and 10.9 ± 3.6 mm in the non-PAD group. The mean diameter of the CBD was not significantly different between the two groups in Kyoto. Likewise, the mean diameter of the CBD stones was 12.2 ± 6.5 mm and 10.3 ± 5.4 mm in PAD group and non-PAD group in Lanzhou, respectively, and was 8.2 ± 5.3 mm and 7.5 ± 5.2 mm in PAD group and non-PAD group in Kyoto, respectively. The mean diameter of the CBD stones in the PAD group was higher than that in the non-PAD group in the Lanzhou center, whereas there was no significant difference in the diameter of the CBD stones in the Kyoto Center. The cases of multiple CBD stones were 45.3% and 39% in the PAD group and non-PAD group in the Lanzhou center and 20.3% and 19% in the PAD group and non-PAD group in the Kyoto center, respectively. The percent of patients with PAD with multiple CBD stones was significantly higher in Lanzhou but not in Kyoto. Concomitant diseases such as acute cholangitis, gallstones, and obstructive jaundice were significantly different between PAD and non-PAD patients in the Lanzhou center, but those comorbidities were not different between the PAD and non-PAD groups in the Kyoto center (Table 3).

The rate in the difficulty to cannulate aim tubes was 9.7% and 8.1% in the PAD group and non-PAD group in Lanzhou center, respectively, with no significant difference between the two groups ($P = 0.19$). Furthermore, in the Kyoto center, the rates were 24.1% and 32.5% in the PAD group and non-PAD group, respectively, with a significant difference between the two groups ($P = 0.02$) (Table 4). In the Lanzhou center, EST was performed in 57.9% and EST plus EPBD was performed in 33.5% of non-PAD patients, while EST was performed in 50.5% and EST plus EPBD was performed in 42.5% of PAD patients. The ERCP procedures to handle native duodenal papilla were different between the PAD and non-PAD groups in the Lanzhou center. In the Kyoto center, EST was performed in 87.6%, EST plus EPBD was performed in 1.1% of non-PAD patients, EST was performed in 90.0%, and EST plus EPBD was performed in only 0.4% of PAD patients. There were no differences in the ERCP procedures to handle native duodenal papilla between the PAD and non-PAD groups in Kyoto (Table 4).

Regarding the rate of difficulty in removing the stones, in the Lanzhou center, the ratio reached 35.3% and 26.0% in the PAD group and non-PAD group, respectively, with a significant difference between the two groups ($P < 0.001$), while it accounted for 53.8% and 53.3% in the PAD group and non-PAD group in the Kyoto center, respectively, with no significant difference between the two groups ($P = 0.89$) (Table 4).

The residual rate of choledocholithiasis in the Lanzhou center was 7.6% and 6.6% in the PAD group and non-PAD group, respectively, and it was 24.6% and 23.4% in the PAD group and non-PAD group in the Kyoto center, respectively. The residual rate of choledocholithiasis was not significantly different between the PAD group and the non-PAD group, both in the Lanzhou center ($P = 0.39$) and in the Kyoto center ($P = 0.73$) (Table 4).

**Table 1 Comparison clinical characteristics of choledocholithiasis patient with periampullary diverticulum between Lanzhou and Kyoto**

| Clinical Item | Lanzhou (*n* = 829) | Kyoto (*n* = 241) | *P* |
|---|---|---|---|
| Age (mean ± SD, yr) | 64.6 ± 13.6 | 75.7 ± 12.1 | < 0.001 |
| Gender | | | 0.48 |
| Male | 448 (54.0) | 124 (51.5) | |
| Female | 381 (46.0) | 117 (48.6) | |
| Diameter of CBD (mean ± SD, mm) | 14.8 ± 5.2 | 11.6 ± 4.2 | < 0.001 |
| Cholecystectomy | 15.5 ± 5.2 | 13.1 ± 4.8 | 0.18 |
| Gallbladder in situ | 14.4 ± 5.1 | 11.5 ± 4.2 | < 0.001 |
| Proportion of CBD stone, *n* (%) | | | < 0.001 |
| Single-stone | 449 (54.7) | 188 (79.7) | |
| Multiple-stone | 372 (45.3) | 48 (20.3) | |
| Maximum diameter of CBD stone (mean ± SD, mm) | 12.2 ± 6.5 | 8.2 ± 5.3 | < 0.001 |
| Diameter (< 2cm), *n* (%) | 718 (86.6) | 233 (96.7) | < 0.001 |
| Diameter (≥ 2cm), *n* (%) | 111 (13.39) | 8 (3.3) | |
| Concomitant disease, *n* (%) | | | |
| Acute cholangitis | 153 (18.5) | 23 (9.5) | 0.001 |
| Gallbladder stone | 39 (4.7) | 30 (12.5) | < 0.001 |
| Obstructive jaundice | 114 (13.8) | 1 (0.4) | < 0.001 |
| Acute pancreatitis | 39 (4.7) | 4 (1.7) | 0.03 |
| Pancreatic duct stones | 1 (0.1) | 0 (0.0) | |
| Past medical history, *n* (%) | | | |
| Operation Billroth I | 0 (0.0) | 3 (1.2) | 0.01 |
| Operation Billroth II | 5 (0.6) | 1 (0.4) | 1.00 |
| Cholecystectomy | 318 (38.4) | 9 (3.7) | < 0.001 |
| Billary tract surgery | 34 (4.1) | 0 (0.0) | 0.001 |

CBD: Common bile duct.

Post-ERCP complications occurred in 8.9% of PAD patients and 8.1% of non-PAD patients in the Lanzhou center; furthermore, it was 5.8% in PAD patients and 10.0% in non-PAD patients in the Kyoto center. The post-ERCP complications between PAD and non-PAD patients in each center was not significantly different (Lanzhou, $P = 0.48$; Kyoto, $P = 0.07$) (Table 4).

## DISCUSSION

PADs are extraluminal mucosal outpouchings of the duodenum that arise within a radius of 2-3 cm from the ampulla of Vater[6]. Patients with PAD often have slow biliary excretion and bile stasis due to mechanical pressure from the PAD to the distal end of the biliary tract. Additionally, PAD is often accompanied by duodenobiliary reflux and subsequent bacterial infection because of sphincter of Oddi dysfunction. These are potential reasons that PADs are clinically associated with biliary stones in many studies[16-20]. However, it is unknown what the characteristics of choledocholithiasis with PAD are from different regions. In our study, we found that the clinical characteristics of PAD patients with choledocholithiasis were significantly different between the Lanzhou center and Kyoto center.

The results showed that comorbid diseases, such as acute cholangitis, obstructive jaundice, and acute pancreatitis, were more common in the Lanzhou center than in the Kyoto center for PAD patients with choledocholithiasis. Our study showed that the average diameter of the CBD was 14.8 ± 5.2 mm in Lanzhou and 11.6 ± 4.2 mm in Kyoto, with a significant difference ($P < 0.001$), and the reasons are not entirely clear. However, one of the reasons for these different kinds of characteristics may be attributed to the larger stone size and multiple stone numbers in the CBD in patients in the Lanzhou center

**Table 2 Comparison of endoscopic retrograde cholangiopancreatography related contents of choledocholithiasis with periampullary diverticulum between Lanzhou and Kyoto**

| ERCP Item | Lanzhou (*n* = 829) | Kyoto (*n* = 241) | *P* |
|---|---|---|---|
| Intubation failure, *n* (%) | 8 (1.0) | 1 (0.4) | 0.69 |
| Intubation difficulty, *n* (%) | 80 (9.7) | 58 (24.1) | < 0.001 |
| Difficulty to remove stone out, *n* (%) | 290 (35.3) | 127 (53.8) | < 0.001 |
| Residual stone, *n* (%) | 62 (7.6) | 58 (24.6) | < 0.001 |
| Procedure to duodenal papilla, *n* (%) | | | |
| EST Only | 419 (50.5) | 217 (90.0) | < 0.001 |
| EST + EPBD | 352 (42.5) | 1 (0.4) | < 0.001 |
| EPBD only | 14 (1.7) | 0 (0.0) | 0.049 |
| Non-EST & non-EPBD | 44 (5.3) | 23 (9.5) | 0.017 |
| Post-complication (overall), *n* (%) | 74 (8.9) | 14 (5.8) | 0.12 |
| Acute cholangitis | 22 (2.7) | 1 (0.4) | 0.035 |
| Acute pancreatitis | 49 (5.9) | 8 (3.3) | 0.11 |
| Perforation | 2 (0.2) | 0 (0.0) | 1.00 |
| Bleeding | 0 (0.0) | 5 (2.1) | < 0.001 |

ERCP: Endoscopic retrograde cholangiopancreatography; EST: Endoscopic sphincterotomy; EPBD: Endoscopic balloon dilatation.

compared to the Kyoto center. Actually, the results revealed that the mean diameter of the stone size was 12.2 ± 6.5 mm in Lanzhou and 8.2 ± 5.3 mm in Kyoto, and the rate of multiple stones was 45.3% in Lanzhou, and only 20.3% in Kyoto, both with $P < 0.001$. Therefore, larger and multiple stones in the CBD would contribute to a dilated CBD, acute cholangitis and obstructive jaundice, and even to acute pancreatitis. Also, the reasons why the CBD stones were more abundant and larger in Lanzhou Center than in Kyoto Center are unknown. However, biliary duct stones are usually associated with the environment and metabolic diseases such as being overweight, obesity, diabetes and hyperlipidemia[21-23]. There are many different characteristics in dietary habits and geographical environments, even in metabolic diseases, between the Lanzhou center in China and the Kyoto center in Japan.

Non-PAD choledocholithiasis was used as a control, and the characteristics of choledocholithiasis with PAD within each center were further analyzed. We noticed that in the Lanzhou center, the clinical characteristics, including mean age, sex, mean size of the choledocholithiasis, single or multiple choledocholithiasis, diameter of the CBD, and concomitant diseases, such as acute cholangitis, obstructive jaundice, and gallbladder stones, differed significantly between the choledocholithiasis cases with PAD and without PAD. However, in the Kyoto center, excluding the mean age, the abovementioned clinical characteristics were not significantly different between choledocholithiasis cases with PAD and without PAD. These results indicated that PADs were associated with different clinical characteristics in patients with CBD stones in the Lanzhou center, but these characteristics were not seen in the Kyoto center. It was difficult to explain the outcome, but it confirmed that there is actually a difference in the characteristics of choledocholithiasis patients with PAD and without PAD from different regions. Ham JH *et al*[24] reported that PAD induces marked postcholecystectomy CBD dilatation. Kim CW *et al*[25] suggested that acute cholangitis patients with PAD had larger CBD stones and more severe cholangitis than those without PAD. However, Lee JJ *et al*[26] demonstrated that PAD alone does not lead to abnormal biliary dilatation in age- and sex-matched control groups. Therefore, choledocholithiasis with PAD had different clinical characteristics between Lanzhou and Kyoto. The different geographical environments, lifestyles, dietary habits, and health consciousness may contribute to the clinical characteristics.

ERCP is now a well-established standard method for removing choledocholithiasis, but it carries an 8%-12% risk of early complications, such as bleeding, duodenal perforation, and pancreatitis[17-18]. If the duodenal papilla opens intra-PAD or is very close to the PAD, the appearance, shape, and orifice of the duodenal papilla will be changed anatomically[25]. This kind of change likely leads to a higher risk and is more difficult to EST because the EST direction may deviate from the long axis of the CBD and the length available for EST is not enough. Under the condition of an insufficient length for the EST, the difficulty rate of removing large choledocholithiasis and residual rate of the stone will increase, and mechanical lithotripsy will probably be needed. In 2003, Ersoz G *et al*[27] first reported that EST followed by sequential EPBD using a 12-20 mm diameter balloon may be effective for difficult removals

**Table 3 Comparison of clinical characteristics of choledocholithiasis patient with and without periampullary diverticulum in Lanzhou or Kyoto**

| Clinical Item | Lanzhou (*n* = 2702) | | | Kyoto (*n* = 613) | | |
|---|---|---|---|---|---|---|
| | Non-PAD, *n* = 1873 | PAD, *n* = 829 | *P* | Non-PAD, *n* = 372 | PAD, *n* = 241 | *P* |
| Age, (median) | 56.1 ± 16.9 | 64.6 ± 13.6 | < 0.001 | 71.0 ± 15.0 | 75.7 ± 12.1 | < 0.001 |
| Gender, *n* (%) | | | < 0.001 | | | 0.22 |
| Male | 842 (45.0) | 448 (54.0) | | 210 (56.4) | 124 (51.4) | |
| Female | 1031 (55.1) | 381 (46.0) | | 162 (43.6) | 117 (48.6) | |
| Proportion of CBD stone, *n* (%) | | | 0.002 | | | 0.69 |
| Single-stone | 1131 (61.0) | 449 (54.7) | | 298 (81.0) | 188 (79.7) | |
| Multiple-stone | 724 (39.0) | 372 (45.3) | | 70 (19.0) | 48 (20.3) | |
| Maximum diameter of CBD stone (mean ± SD, mm) | 10.3 ± 5.4 | 12.2 ± 6.5 | < 0.001 | 7.5 ± 5.2 | 8.2 ± 5.3 | 0.11 |
| Diameter of CBD (mean ± SD, mm) | 13.4 ± 5.1 | 14.8 ± 5.2 | < 0.001 | 10.9 ± 3.6 | 11.6 ± 4.2 | 0.06 |
| Cholecystectomy | 14.5 ± 5.5 | 15.5 ± 5.2 | 0.008 | 11.3 ± 2.7 | 13.1 ± 4.8 | 0.25 |
| Gallbladder in situ | 12.7 ± 4.6 | 14.4 ± 5.1 | < 0.001 | 10.9 ± 3.6 | 11.5 ± 4.2 | 0.07 |
| Concomitant disease, *n* (%) | | | | | | |
| Acute cholangitise | 260 (13.9) | 153 (18.5) | 0.002 | 39 (10.5) | 23 (9.5) | 0.71 |
| Gallbladder stone | 129 (6.9) | 39 (4.7) | 0.03 | 43 (11.6) | 30 (12.5) | 0.74 |
| Obstructive jaundice | 311 (16.6) | 114 (13.8) | 0.06 | 0 (0.0) | 1 (0.4) | |
| Past medical history, *n* (%) | | | | | | |
| Operation Billroth I | 6 (0.3) | 0 (0.0) | 0.19 | 8 (2.2) | 3 (1.2) | 0.54 |
| Operation Billroth II | 5 (0.3) | 5 (0.6) | 0.19 | 4 (1.1) | 1 (0.4) | 0.65 |
| Cholecystectomy | 738 (39.4) | 318 (38.4) | 0.61 | 16 (4.3) | 9 (3.7) | 0.73 |
| Billary tract surgery | 89 (4.8) | 34 (4.10) | 0.45 | 0 (0.0) | 0 (0.0) | |

PAD: Periampullary diverticulum.

of large bile duct stones, and the rate of early complications was acceptable. Weinberg BM *et al*[28] reported that an additional EST after EPBD was also required in 10%-19% of patients because the biliary opening was not sufficiently enlarged. After that report, several studies established that procedure as an effective and safe treatment for removing difficult-to-extract bile duct stones[29-31]. Kim HW *et al*[32] reported that the overall successful stone removal rate and the complication rate did not differ significantly between the PAD and control groups when applying limited EST plus large balloon dilation. Our previous study, a multicenter, randomized controlled trial, suggested that a balloon dilation time of 30 s for combined EST reduced the frequency of post-ERCP pancreatitis[33]. In addition, the Guideline of the European Society of Gastrointestinal Endoscopy strongly recommends EPBD as an alternative to EST for extracting choledocholithiasis < 8 mm in patients, especially in the presence of altered anatomy[34]. Therefore, there are now at least three methods (EST, EPBD, and EST plus EPBD) available to treat choledocholithiasis with PAD.

In our research, EST (50.5%), EST+EPBD (42.5%), and EPBD (1.7%) were adopted in the Lanzhou center, while EST (90.0%), EST+EPBD (0.4%), and EPBD (0.0%) were applied in the Kyoto center. Thus, the ERCP procedures were significantly different between the two centers. One of the main reasons for this distinction is the different clinical characteristics of choledocholithiasis with PAD mentioned above between Lanzhou and Kyoto. In other words, different ERCP methods are naturally based on patients' clinical characteristics.

Because of the different ERCP procedures between the Lanzhou and Kyoto centers, the efficacy of ERCP in each center needed to be compared. In the Kyoto center, owing to its own lack of different characteristics, such as the mean size of CBD stones (7.5 ± 5.2 mm, non-PAD; 8.2 ± 5.3 mm, PAD; $P$ = 0.11), multiple stones (19.0%, non-PAD; 20.3% PAD; $P$ = 0.69), there was no significant difference in efficacy between the patients with and without PAD (rate to remove choledocholithiasis difficulty, $P$ = 0.89; residual rate of bile duct stones, $P$ = 0.73). However, in the Lanzhou center, with differences in the clinical characteristics, such as the mean size of the CBD stones (10.3 ± 5.4 mm, non-PAD; 12.2 ± 6.5 mm,

**Table 4 Comparison of endoscopic retrograde cholangiopancreatography related contents of choledocholithiasis patient with and without periampullary diverticulum in Lanzhou or Kyoto**

| ERCP Item | Lanzhou (*n* = 2702) | | | Kyoto (*n* = 613) | | |
|---|---|---|---|---|---|---|
| | Non-PAD, *n* = 1873 | PAD, *n* = 829 | *P* | Non-PAD, *n* = 372 | PAD, *n* = 241 | *P* |
| ERCP method, *n* (%) | | | | | | |
| EST Only | 1084 (57.9) | 419 (50.5) | < 0.001 | 326 (87.6) | 217 (90.0) | 0.36 |
| EST and EPBD | 627 (33.5) | 352 (42.5) | < 0.001 | 4 (1.1) | 1 (0.4) | 0.65 |
| EPBD only | 47 (2.5) | 14 (1.7) | 0.19 | 4 (1.1) | 0 (0.0) | 0.16 |
| Non-EST and non-EPBD | 115 (6.1) | 44 (5.3) | 0.40 | 38 (10.2) | 23 (9.5) | 0.79 |
| Curative effect, *n* (%) | | | | | | |
| Intubation failure | 18 (1.0) | 8 (1.0) | 0.99 | 1 (0.3) | 1 (0.4) | |
| Intubation difficulty | 152 (8.1) | 80 (9.7) | 0.19 | 121 (32.5) | 58 (24.1) | 0.02 |
| Difficulty to remove stone out | 482 (26.0) | 290 (35.3) | < 0.001 | 196 (53.3) | 127 (53.8) | 0.89 |
| Residual stone | 123 (6.6) | 62 (7.6) | 0.39 | 86 (23.4) | 58 (24.6) | 0.73 |
| Post ERCP complication, *n* (%) | 152 (8.1) | 74 (8.9) | 0.48 | 37 (10.0) | 14 (5.8) | 0.07 |
| Acute cholangitis | 46 (2.5) | 22 (2.7) | 0.76 | 2 (0.5) | 1 (0.4) | 1.00 |
| Acute pancreatitis | 97 (5.2) | 49 (5.9) | 0.44 | 23 (6.2) | 8 (3.3) | 0.11 |
| Perforation | 4 (0.2) | 2 (0.2) | 1.00 | 3 (0.8) | 0 (0.0) | 0.28 |

ERCP: Endoscopic retrograde cholangiopancreatography; EPBD: Endoscopic balloon dilatation.

PAD; $P < 0.001$), multiple stones (39.0%, non-PAD; 45.3% PAD; $P = 0.002$), the difficulty rate of removing choledocholithiasis was significantly different ($P < 0.001$). However, if EST+EPBD was adopted, the residual rate of bile duct stones was not significantly different ($P = 0.39$) between choledocholithiasis patients with and without PAD. Therefore, to reach an appropriate efficacy, the ERCP procedure depends on the different clinical characteristics of choledocholithiasis patients with PAD. Interestingly, although different therapeutic ERCP procedures were employed in the Lanzhou and Kyoto centers, the overall post-ERCP complications were not significantly different for choledocholithiasis with PAD not only between Lanzhou and Kyoto centers ($P = 0.12$) but also within each center (Lanzhou, $P = 0.48$; Kyoto, $P = 0.07$). Thus, we confirmed that PAD did not increase ERCP-related complications when using an experienced endoscopist.

## CONCLUSION

In conclusion, many clinical characteristics of choledocholithiasis patients with PAD were significantly different between the Lanzhou center and Kyoto center. Choledocholithiasis with PAD had more complexity with larger and multiple stones, wider diameter of the CBD, and more biliary duct comorbidities in the Lanzhou center compared to the Kyoto center. In the internal center analysis, the clinical characteristics mentioned above were also different between the PAD and non-PAD groups in the Lanzhou center but not in the Kyoto center. Different ERCP procedures to manage native duodenal papilla were adopted naturally depending on the clinical characteristics of choledocholithiasis with PAD to approve efficacy between the Lanzhou and the Kyoto centers. Although there was increased difficulty removing stones in the Lanzhou Center and an increased difficulty in removing deep cannulates in the Kyoto centers, the stone residual rate was not significantly different within each center for choledocholithiasis with PAD, and post-ERCP complications were also not significantly different between the two centers or within each center. Nevertheless, there are some shortcomings in this study, such as the role of different ERCP procedures in the recurrence of choledocholithiasis, which needs to be confirmed by further subsequent research.

## ARTICLE HIGHLIGHTS

### *Research background*

Most of study regarding periampullary diverticulum (PAD) impact on endoscopic retrograde cholangiopancreatography (ERCP) therapy for choledocholithiasis based on data from one endoscopy center and there were inconsistent conclusions of the PAD impacts on safety and post ERCP complications for choledocholithiasis.

### *Research motivation*

What did cause the different conclusions of PAD impacts on post ERCP complications and safety for choledocholithiasis? UP to now, the real reason is little known and lacked to compare the clinical characteristic of choledocholithiasis with PAD from different geographical endoscopy centers.

### *Research objectives*

To compare the clinical characteristics of choledocholithiasis with PAD between two regional endoscopy centers and analyze the efficacy of clinical characteristics on ERCP procedures for choledocholithiasis patients with PAD.

### *Research methods*

Patients underwent ERCP treatment at first time between January 2012 and December 2017 were Involved. The clinical characteristics and ERCP related contents of choledocholithiasis with PAD were compared between Lanzhou center and Kyoto center. Furthermore, Choledocholithiasis without PAD as control, analyzed the clinical characteristic and ERCP therapy of Choledocholithiasis with PAD internal each center.

### *Research results*

829 out of 3608 patients in Lanzhou center and 241 out of 1198 in Kyoto center suffered from choledocholithiasis with PAD. The overall clinical characteristics were significantly different excepting the gender between the two centers. Non-PAD choledocholithiasis as control, in Lanzhou center, many clinical characteristics of patients were significant difference between non-PAD and PAD ($P$ = 0.03 - <0.001), but were no difference in Kyoto center (each with $P$ > 0.05).

For choledocholithiasis with PAD patients, ERCP procedures to handle the duodenal papilla were significant different Lanzhou center and Kyoto center ($P$ < 0.001). But the overall post-complication was no significant different between two centers (8.9% in Lanzhou center, 5.8% in Kyoto center. $P$ = 0.12).

The difficult rate to remove stone, in Lanzhou center, was 35.3% and 26.0% in PAD group and non-PAD group, with a significant difference between two groups ($P$ < 0.001), while it accounted for 53.8% and 53.3% in PAD group and non-PAD group in Kyoto center, with no significant difference between two groups. However, residual rate of choledocholithisasis was no significant difference between two groups in each center. Meanwhile, there were also no significant differences of post-ERCP complications between PAD and non-PAD patients within each center.

### *Research conclusions*

Many clinical characteristics of choledocholithiasis patients with PAD were significant difference between Lanzhou and Kyoto. Patients carried characteristics with larger and multiple stones, wider diameter of CBD, and more possibility of acute cholangitis and obstructive jaundice in Lanzhou center than those in Kyoto. ERCP procedures to cope with native duodenal papilla were different between Lanzhou and Kyoto, depended on its own different clinical characteristics of choledocholithiasis with PAD. The efficacy and post-ERCP complications were no significant differences for choledocholithiasis with PAD in each own center. The overall post-ERCP complication was no statistics difference between two centers as well.

### *Research perspectives*

The control study of multiple endoscopy centers from different region is worthy of conducting to uncover the characteristics of choledocholithiasis patients with PAD and their influences on therapy ERCP. The role of different ERCP procedures for recurrence of choledocholithiasis need to be confirmed through further subsequent research or prospective studies.

## FOOTNOTES

**Author contributions:** Zhu KX, Yue P, Suzuki A, Tanaka K, Li X designed the research protocol; Zhu KX, Yue P, Meng WB, Zhang L, Zhu XL, Zhang H, Miao L, Wang ZF, Zhou WC, Suzuki A, Tanaka K, Li X were responsible for patient enrollment and data acquisition; Zhu KX, Yue P, Wang HP, Tanaka K contributed to data analysis and interpretation; Zhu KX, Yue P wrote the original manuscript; Zhu KX, Yue P, Meng WB, Liu JK, Li X contributed to critical revision

of the manuscript for important content; Wang HP, Liu JK contributed to statistical analysis for this study; Li X contributed to final approval of the article.

**Institutional review board statement:** The study was reviewed and approved by the First Hospital of Lanzhou University Institutional Review Board (Approval No. LDYYLL 2021-192).

**Conflict-of-interest statement:** The authors declare that they have no conflicts of interest to disclose.

**Data sharing statement:** No additional data are available.



**Country/Territory of origin:** China

**ORCID number:** Ke-Xiang Zhu 0000-0003-4272-5221; Ping Yue 0000-0001-8736-949X; Hai-Ping Wang 0000-0003-2055-8936; Wen-Bo Meng 0000-0002-9355-0225; Jian-Kang Liu 0000-0003-2454-8209; Lei Zhang 0000-0001-9320-304X; Xiao-Liang Zhu 0000-0002-5697-9583; Hui Zhang 0000-0003-0728-9188; Long Miao 0000-0002-7861-6134; Zheng-Feng Wang 0000-0002-4556-9247; Wen-Ce Zhou 0000-0002-0529-7777; Azumi Suzuki 0000-0002-6041-7719; Kiyohito Tanaka 0000-0002-9189-1755; Xun Li 0000-0001-6862-7692.

**S-Editor:** Chang KL
**L-Editor:** A
**P-Editor:** Chang KL

## REFERENCES

1 **Wu SD**, Su Y, Fan Y, Zhang ZH, Wang HL, Kong J, Tian Y. Relationship between intraduodenal peri-ampullary diverticulum and biliary disease in 178 patients undergoing ERCP. *Hepatobiliary Pancreat Dis Int* 2007; **6**: 299-302 [PMID: 17548255 DOI: 10.1111/j.1523-5378.2007.00502.x]
2 **Tzeng JJ**, Lai KH, Peng NJ, Lo GH, Lin CK, Chan HH, Hsu PI, Cheng JS, Wang EM. Influence of juxtapapillary diverticulum on hepatic clearance in patients after endoscopic sphincterotomy. *J Gastroenterol Hepatol* 2005; **20**: 772-776 [PMID: 15853993 DOI: 10.1111/j.1440-1746.2005.03782.x]
3 **Christoforidis E**, Goulimaris I, Kanellos I, Tsalis K, Dadoukis I. The role of juxtapapillary duodenal diverticula in biliary stone disease. *Gastrointest Endosc* 2002; **55**: 543-547 [PMID: 11923769 DOI: 10.1067/mge.2002.122615]
4 **Panteris V**, Vezakis A, Filippou G, Filippou D, Karamanolis D, Rizos S. Influence of juxtapapillary diverticula on the success or difficulty of cannulation and complication rate. *Gastrointest Endosc* 2008; **68**: 903-910 [PMID: 18635174 DOI: 10.1016/j.gie.2008.03.1092]
5 **Li X**, Zhu K, Zhang L, Meng W, Zhou W, Zhu X, Li B. Periampullary diverticulum may be an important factor for the occurrence and recurrence of bile duct stones. *World J Surg* 2012; **36**: 2666-2669 [PMID: 22911215 DOI: 10.1007/s00268-012-1716-8]
6 **Lobo DN**, Balfour TW, Iftikhar SY. Periampullary diverticula: consequences of failed ERCP. *Ann R Coll Surg Engl* 1998; **80**: 326-331 [PMID: 9849331 DOI: 10.1007/BF02303652]
7 **Boix J**, Lorenzo-Zúñiga V, Añaños F, Domènech E, Morillas RM, Gassull MA. Impact of periampullary duodenal diverticula at endoscopic retrograde cholangiopancreatography: a proposed classification of periampullary duodenal diverticula. *Surg Laparosc Endosc Percutan Tech* 2006; **16**: 208-211 [PMID: 16921297 DOI: 10.1097/00129689-200608000-00002]
8 **Ko KS**, Kim SH, Kim HC, Kim IH, Lee SO. Juxtapapillary duodenal diverticula risk development and recurrence of biliary stone. *J Korean Med Sci* 2012; **27**: 772-776 [PMID: 22787373 DOI: 10.3346/jkms.2012.27.7.772]
9 **Altonbary AY**, Bahgat MH. Endoscopic retrograde cholangiopancreatography in periampullary diverticulum: The challenge of cannulation. *World J Gastrointest Endosc* 2016; **8**: 282-287 [PMID: 27014423 DOI: 10.4253/wjge.v8.i6.282]
10 **Guo SB**, Meng H, Duan ZJ, Li CY. Small sphincterotomy combined with endoscopic papillary large balloon dilation *vs* sphincterotomy alone for removal of common bile duct stones. *World J Gastroenterol* 2014; **20**: 17962-17969 [PMID: 25548495 DOI: 10.3748/wjg.v20.i47.17962]
11 **Harada H**, Suehiro S, Shimizu T, Katsuyama Y, Hayasaka K. Submucosal injection can facilitate biliary access in patients with periampullary diverticula. *Gastrointest Endosc* 2016; **84**: 185-186 [PMID: 26772894 DOI: 10.1016/j.gie.2016.01.002]
12 **Rustagi T**, Jamidar PA. Endoscopic retrograde cholangiopancreatography (ERCP)-related adverse events: post-ERCP pancreatitis. *Gastrointest Endosc Clin N Am* 2015; **25**: 107-121 [PMID: 25442962 DOI: 10.1016/j.giec.2014.09.006]
13 **Major P**, Dembiński M, Winiarski M, Pędziwiatr M, Rubinkiewicz M, Stanek M, Dworak J, Pisarska M, Rembiasz K, Budzyński A. A Periampullary Duodenal Diverticula in Patient with Choledocholithiasis - Single Endoscopic Center Experience. *Pol Przegl Chir* 2016; **88**: 328-333 [PMID: 28141552 DOI: 10.1515/pjs-2016-0072]
14 **Karaahmet F**, Kekilli M. The presence of periampullary diverticulum increased the complications of endoscopic retrograde cholangiopancreatography. *Eur J Gastroenterol Hepatol* 2018; **30**: 1009-1012 [PMID: 29864066 DOI: 10.1097/MEG.0000000000001172]

15 **Zoepf T**, Zoepf DS, Arnold JC, Benz C, Riemann JF. The relationship between juxtapapillary duodenal diverticula and disorders of the biliopancreatic system: analysis of 350 patients. *Gastrointest Endosc* 2001; **54**: 56-61 [PMID: 11427842 DOI: 10.1067/mge.2001.115334]

16 **Park M**, Song DY, Je Y, Lee JE. Body mass index and biliary tract disease: a systematic review and meta-analysis of prospective studies. *Prev Med* 2014; **65**: 13-22 [PMID: 24721739 DOI: 10.1016/j.ypmed.2014.03.027]

17 **Watanabe H**, Yoneda M, Tominaga K, Monma T, Kanke K, Shimada T, Terano A, Hiraishi H. Comparison between endoscopic papillary balloon dilatation and endoscopic sphincterotomy for the treatment of common bile duct stones. *J Gastroenterol* 2007; **42**: 56-62 [PMID: 17322994 DOI: 10.1007/s00535-006-1969-9]

18 **Boender J**, Nix GA, de Ridder MA, van Blankenstein M, Schütte HE, Dees J, Wilson JH. Endoscopic papillotomy for common bile duct stones: factors influencing the complication rate. *Endoscopy* 1994; **26**: 209-216 [PMID: 8026367 DOI: 10.1055/s-2007-1008945]

19 **Ozogul B**, Ozturk G, Kisaoglu A, Aydinli B, Yildirgan M, Atamanalp SS. The clinical importance of different localizations of the papilla associated with juxtapapillary duodenal diverticula. *Can J Surg* 2014; **57**: 337-341 [PMID: 25265108 DOI: 10.1503/cjs.021113]

20 **Elmunzer BJ**, Boetticher NC. Reverse guidewire anchoring of the papilla for difficult cannulation due to a periampullary diverticulum. *Gastrointest Endosc* 2015; **82**: 957 [PMID: 26142553 DOI: 10.1016/j.gie.2015.05.054]

21 **Pacchioni M**, Nicoletti C, Caminiti M, Calori G, Curci V, Camisasca R, Pontiroli AE. Association of obesity and type II diabetes mellitus as a risk factor for gallstones. *Dig Dis Sci* 2000; **45**: 2002-2006 [PMID: 11117574 DOI: 10.1023/a:1005544009372]

22 **Shebl FM**, Andreotti G, Rashid A, Gao YT, Yu K, Shen MC, Wang BS, Li Q, Han TQ, Zhang BH, Fraumeni JF Jr, Hsing AW. Diabetes in relation to biliary tract cancer and stones: a population-based study in Shanghai, China. *Br J Cancer* 2010; **103**: 115-119 [PMID: 20517308 DOI: 10.1038/sj.bjc.6605706]

23 **Stender S**, Frikke-Schmidt R, Benn M, Nordestgaard BG, Tybjærg-Hansen A. Low-density lipoprotein cholesterol and risk of gallstone disease: a Mendelian randomization study and meta-analyses. *J Hepatol* 2013; **58**: 126-133 [PMID: 22922093 DOI: 10.1016/j.jhep.2012.08.013]

24 **Ham JH**, Yu JS, Choi JM, Cho ES, Kim JH, Chung JJ. Peri-ampullary duodenal diverticulum: effect on extrahepatic bile duct dilatation after cholecystectomy. *Clin Radiol* 2019; **74**: 735.e15-735.e22 [PMID: 31256908 DOI: 10.1016/j.crad.2019.05.031]

25 **Kim CW**, Chang JH, Kim JH, Kim TH, Lee IS, Han SW. Size and type of periampullary duodenal diverticula are associated with bile duct diameter and recurrence of bile duct stones. *J Gastroenterol Hepatol* 2013; **28**: 893-898 [PMID: 23432035 DOI: 10.1111/jgh.12184]

26 **Lee JJ**, Brahm G, Bruni SG, Thipphavong S, Sreeharsha B. Biliary dilatation in the presence of a periampullary duodenal diverticulum. *Br J Radiol* 2015; **88**: 20150149 [PMID: 26133074 DOI: 10.1259/bjr.20150149]

27 **Ersoz G**, Tekesin O, Ozutemiz AO, Gunsar F. Biliary sphincterotomy plus dilation with a large balloon for bile duct stones that are difficult to extract. *Gastrointest Endosc* 2003; **57**: 156-159 [PMID: 12556775 DOI: 10.1067/mge.2003.52]

28 **Weinberg BM**, Shindy W, Lo S. Endoscopic balloon sphincter dilation (sphincteroplasty) *vs* sphincterotomy for common bile duct stones. *Cochrane Database Syst Rev* 2006; CD004890 [PMID: 17054222 DOI: 10.1002/14651858.CD004890.pub2]

29 **Kim KH**, Kim TN. Endoscopic papillary large balloon dilation in patients with periampullary diverticula. *World J Gastroenterol* 2013; **19**: 7168-7176 [PMID: 24222962 DOI: 10.3748/wjg.v19.i41.7168]

30 **Misra SP**, Dwivedi M. Large-diameter balloon dilation after endoscopic sphincterotomy for removal of difficult bile duct stones. *Endoscopy* 2008; **40**: 209-213 [PMID: 18264886 DOI: 10.1055/s-2007-967040]

31 **Rouquette O**, Bommelaer G, Abergel A, Poincloux L. Large balloon dilation post endoscopic sphincterotomy in removal of difficult common bile duct stones: a literature review. *World J Gastroenterol* 2014; **20**: 7760-7766 [PMID: 24976713 DOI: 10.3748/wjg.v20.i24.7760]

32 **Kim HW**, Kang DH, Choi CW, Park JH, Lee JH, Kim MD, Kim ID, Yoon KT, Cho M, Jeon UB, Kim S, Kim CW, Lee JW. Limited endoscopic sphincterotomy plus large balloon dilation for choledocholithiasis with periampullary diverticula. *World J Gastroenterol* 2010; **16**: 4335-4340 [PMID: 20818818 DOI: 10.3748/wjg.v16.i34.4335]

33 **Meng W**, Leung JW, Zhang K, Zhou W, Wang Z, Zhang L, Sun H, Xue P, Liu W, Wang Q, Zhang J, Wang X, Wang M, Shao Y, Cai K, Hou S, Li Q, Zhu K, Yue P, Wang H, Zhang M, Sun X, Yang Z, Tao J, Wen Z, Chen B, Shao Q, Zhao M, Zhang R, Jiang T, Liu K, Chen K, Zhu X, Zhang H, Miao L, Li J, Yan X, Wang F, Suzuki A, Tanaka K, Nur U, Weiderpass E, Li X. Optimal dilation time for combined small endoscopic sphincterotomy and balloon dilation for common bile duct stones: a multicentre, single-blinded, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2019; **4**: 425-434 [PMID: 31003961 DOI: 10.1016/S2468-1253(19)30075-5]

34 **Testoni PA**, Mariani A, Aabakken L, Arvanitakis M, Bories E, Costamagna G, Devière J, Dinis-Ribeiro M, Dumonceau JM, Giovannini M, Gyokeres T, Hafner M, Halttunen J, Hassan C, Lopes L, Papanikolaou IS, Tham TC, Tringali A, van Hooft J, Williams EJ. Papillary cannulation and sphincterotomy techniques at ERCP: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2016; **48**: 657-683 [PMID: 27299638 DOI: 10.1055/s-0042-108641]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 February 27; 14(2): 143-160

DOI: 10.4240/wjgs.v14.i2.143

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

# Nomograms predicting prognosis of patients with pathological stages T1N2-3 and T3N0 gastric cancer

Yu-Fei Wang, Xin Yin, Tian-Yi Fang, Yi-Min Wang, Dao-Xu Zhang, Yao Zhang, Xi-Bo Wang, Hao Wang, Ying-Wei Xue

**Specialty type:** Oncology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

**P-Reviewer:** Kotelevets SM, Xue M

**Received:** June 6, 2021
**Peer-review started:** June 6, 2021
**First decision:** July 16, 2021
**Revised:** July 24, 2021
**Accepted:** January 6, 2022
**Article in press:** January 6, 2022
**Published online:** February 27, 2022

**Yu-Fei Wang, Xin Yin, Tian-Yi Fang, Yi-Min Wang, Dao-Xu Zhang, Yao Zhang, Xi-Bo Wang, Hao Wang, Ying-Wei Xue,** Department of Gastroenterological Surgery, Harbin Medical University Cancer Hospital, Harbin 150081, Heilongjiang Province, China

**Corresponding author:** Ying-Wei Xue, PhD, Chief Doctor, Professor, Department of Gastroenterological Surgery, Harbin Medical University Cancer Hospital, No. 150 Haping Road, Harbin 150081, Heilongjiang Province, China. xueyingwei@hrbmu.edu.cn

## Abstract

### *BACKGROUND*

Patients with pathological stages T1N2-3 (pT1N2-3) and pT3N0 gastric cancer (GC) have not been routinely included in the target population for postoperative chemotherapy according to the Japanese Gastric Cancer Treatment Guideline, and their prognosis is significantly different.

### *AIM*

To identify the high-risk patients after radical surgery by analyzing biomarkers and clinicopathological features and construct prognostic models for them.

### *METHODS*

A total of 459 patients with pT1N2-3/pT3N0 GC were retrospectively selected for the study. The Chi-square test was used to analyze the differences in the clinicopathological features between the pT1N2-3 and pT3N0 groups. The Kaplan–Meier analysis and log-rank test were used to analyze overall survival (OS). The independent risk factors for patient prognosis were analyzed by univariate and multivariate analyses based on the Cox proportional hazards regression model. The cutoff values of continuous variables were identified by receiver operating characteristic curve. The nomogram models were constructed with R studio.

### *RESULTS*

There was no statistically significant difference in OS between the pT1N2-3 and pT3N0 groups ($P$ = 0.374). Prealbumin ($P$ = 0.040), carcino-embryonic antigen (CEA) ($P$ = 0.021), and metastatic lymph node ratio (mLNR) ($P$ = 0.035) were independent risk factors for prognosis in the pT1N2-3 group. Age ($P$ = 0.039), body mass index (BMI) ($P$ = 0.002), and gastrectomy ($P$ < 0.001) were independent

risk factors for prognosis in the pT3N0 group. The area under the curve values of the nomogram models for predicting the 5-year prognosis of the pT1N2-3 group and pT3N0 group were 0.765 and 0.699, respectively.

***CONCLUSION***

Nomogram model combining prealbumin, CEA, and mLNR levels can be used to predict the prognosis of pT1N2-3 GC. Nomogram model combining age, BMI, and gastrectomy can be used to predict the prognosis of pT3N0 GC.

**Key Words:** Gastric cancer; Biomarker; Clinicopathological feature; Adjuvant chemotherapy; Prognosis; Nomogram



**Core Tip:** Patients with pathological stage T1N2-3 (pT1N2-3) and pT3N0 gastric cancer (GC) have not been routinely included in the target population for postoperative chemotherapy, and their prognosis is significantly different. The study aimed to identify the high-risk patients after radical surgery by analyzing biomarkers and clinicopathological features and construct prognostic models for them. Our results showed that the predictive models constructed by peripheral blood biomarkers and clinicopathological features can evaluate the prognosis of patients with pT1N2-3 and pT3N0 GC, which is worthy of further validation and promotion in clinical practice.

**Citation:** Wang YF, Yin X, Fang TY, Wang YM, Zhang DX, Zhang Y, Wang XB, Wang H, Xue YW. Nomograms predicting prognosis of patients with pathological stages T1N2-3 and T3N0 gastric cancer. *World J Gastrointest Surg* 2022; 14(2): 143-160

**URL:** https://www.wjgnet.com/1948-9366/full/v14/i2/143.htm

**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i2.143

## INTRODUCTION

Gastric cancer (GC) is the sixth most common cancer and the third leading cause of cancer-related death, with more than 860000 deaths annually[1]. The TNM staging system based on tumor infiltration, regional lymph node metastasis, and distant metastasis is considered as the conventional criterion for predicting prognosis and guiding treatment[2]. Adjuvant chemotherapy is recommended for patients with pathological stage II or III GC after radical resection to reduce recurrence probability. However, based on the results of the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC)[3], the Japanese Gastric Cancer Treatment Guidelines[4] recommend stage II/III disease as the standard target of adjuvant chemotherapy after surgery, with the exception of pathological stage T1N2-3 (pT1N2-3) and pT3N0. But, in these two groups, there is still a portion of high-risk patients with a poor prognosis. Therefore, the research of pT1N2-3 and pT3N0 GC patients with a poor prognosis may help clinicians carry out targeted and individualized treatment.

Although previous studies have discussed independent prognostic factors among patients with pT1N2-3 and pT3N0 GC, relevant results have not been consistent. Yura *et al*[5] suggested that pT1N2-3 patients with stage N3 or tumor diameter < 30 mm had a relatively poor prognosis, while pT3N0 patients had a good prognosis. Terada *et al*[6] suggested that patients with pT3N0/pT1N2-3 complicated with vascular infiltration might be at a high risk for disease recurrence and might be candidates for adjuvant chemotherapy. Other relevant studies have shown that lymphatic infiltration is an independent risk factor for poor prognosis in pT3N0 GC patients[7,8]. The above studies showed that the high heterogeneity of the same stage GC patients leads to significant differences in the risk for recurrence and death. Therefore, the search for effective diagnostic and monitoring tools for GC patients is a critical clinical goal. Many studies have shown that peripheral blood biomarkers and clinicopathological features can play an effective complementary role and have been widely used for the early diagnosis, therapeutic effect monitoring, and prognostic prediction of GC patients[9-11]. However, previous studies evaluated the prognostic value of only a limited number of clinicopathological features, and the results of these studies inevitably have some limitations. Therefore, this study aimed to determine peripheral blood biomarkers and clinicopathological features that influence the prognosis of patients with pT1N2-3 and pT3N0 GC, thereby more comprehensively identifying patients who may benefit from adjuvant chemotherapy.

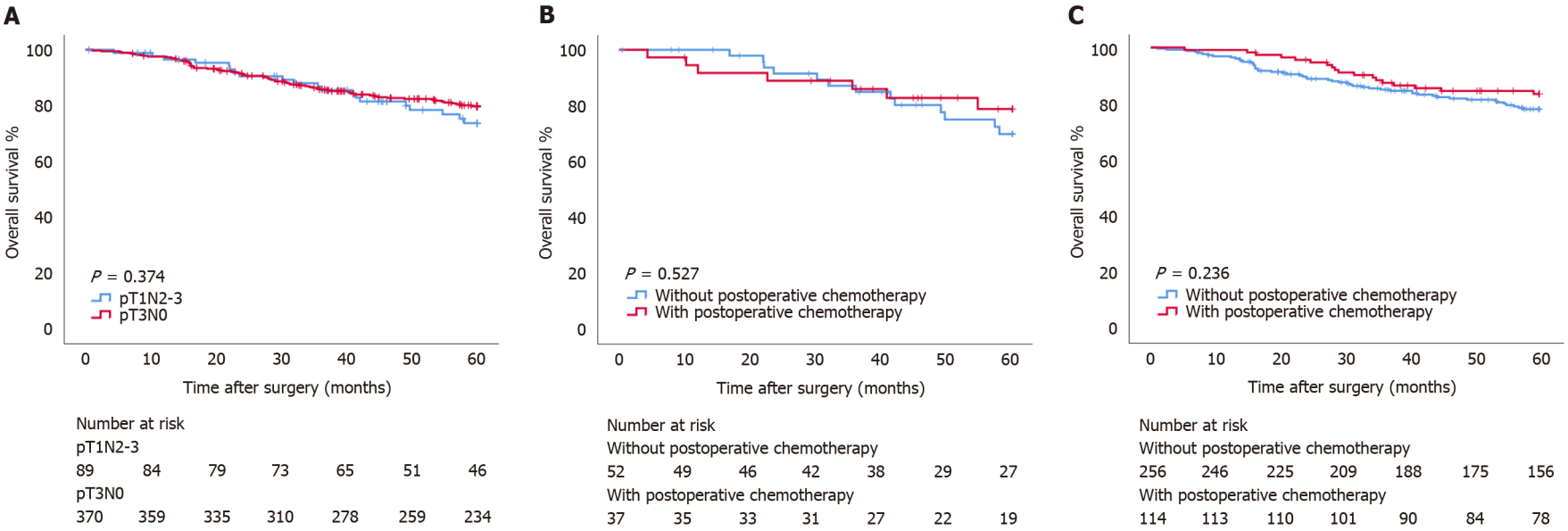



**Figure 1 Survival curve analyses for patients with pT1N2-3 and pT3N0 GC.** A: Overall survival curves for all patients; B: Overall survival curves for pT1N2-3 patients with and without postoperative chemotherapy; C: Overall survival curves for pT3N0 patients with and without postoperative chemotherapy.

In this study, we retrospectively analyzed patients who underwent radical gastrectomy at the Harbin Medical University Cancer Hospital between January 2000 and April 2016. The predictive models were constructed by combining the peripheral blood biomarkers and clinicopathological features which influence the prognosis of pT1N2-3b and pT3N0 GC patients.

## MATERIALS AND METHODS

### *Patients*

A total of 459 patients with pT1N2-3/pT3N0 GC were continuously selected for the study. All GC patients underwent radical gastrectomy according to the respective conditions[4]. The diagnosis of GC was based on tissue samples obtained during gastroscopy and further confirmed by pathologists through examination of postoperative pathological tissue. During hospitalization, the patients underwent routine preoperative examinations, including magnetic resonance imaging/gastric computed tomography (CT), abdominal ultrasonography, chest radiography, electrocardiography, hematological examination, and tumor marker examination. Some patients underwent positron emission tomography (PET)/CT if necessary. The patients were followed until the date of death or for 5

years, whichever came first.

The exclusion criteria were as follows: (1) Preoperative chemotherapy; (2) severe heart disease; (3) remnant gastric cancer; (4) postoperative confirmation of stage IV disease; (5) history of partial resection; (6) history of other malignant tumors; (7) esophagogastric junction tumor; and (8) endocrine carcinoma.

Postoperative chemotherapy regimens were based on the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology[12]. Oxaliplatin + capecitabine (XELOX) or oxaliplatin + S-1 (SOX) are the main treatment options for patients with stage II or III GC. To ensure the accuracy of the study, we included 166 patients who received complete postoperative chemotherapy at our institution. We did not include patients who did not undergo treatment at our institution or who returned to the local hospital after surgery and had incomplete chemotherapy records.

### Clinicopathological data

Clinicopathological data of the patients were saved in the Gastric Cancer Information Management System v1.2 of the Harbin Medical University Cancer Hospital (Copyright No. 2013SR087424, http://www.sgihmu.com), including sex, age, body mass index (BMI), tumor diameter, tumor location, gastrectomy, histological type, metastatic lymph node ratio (mLNR), pT stage, pN stage, Borrmann type, vascular infiltration, nerve infiltration, postoperative chemotherapy, and laboratory examination. pTNM stage was consistent with the eighth edition of the American Joint Commission on Cancer (AJCC). Tumor marker or radiographic examinations (ultrasound, CT, and gastroscopy) were performed on all patients every 3-6 mo postoperatively. In addition, PET/CT examinations were performed as needed.

### Blood sample collection

Blood samples were taken on an empty stomach the day after admission. Venous blood (2 mL) was collected from the cubital vein and sent to the blood laboratory to separate the serum and calculate the corresponding blood indexes.

### Statistical analysis

The chi–square test was used to analyze the differences in clinicopathological factors between the two groups. Overall survival (OS) was defined as the date from surgery to death or the date of the last follow-up. The OS was shown as the mean and 95% confidence interval (CI). According to the receiver operating characteristic curve (ROC), the "Youden index" was calculated by sensitivity- (1-specificity). The maximum value of the Youden index was the optimal cutoff value for continuous variables. The log-rank test and Kaplan–Meier method were used to analyze survival curves. Univariate and multivariate analyses based on the Cox proportional hazards regression model were used to analyze the independent risk factors for prognosis. Hazard ratios (HRs) and 95%CIs were estimated for each factor. The nomogram models were drawn through R studio using the “SvyNom” and “rms” packages. Calibration plots were used to show the relationship between predicted probabilities and the actual outcome by using the Hosmer goodness-of-fit test. SPSS version 25.0 (SPSS Inc., Chicago, IL, United States) was used for statistical analyses, and $P < 0.05$ was considered statistically significant.

## RESULTS

### Clinicopathological characteristics

According to the postoperative pathology report, there were 89 and 370 patients in the pT1N2-3 group and pT3N0 group, respectively. In the pT1N2-3 group, the age range was 28-81 years (median, 55 years), and the male:female ratio was 44:45. In the pT3N0 group, the age range was 24-87 years (median, 58 years), and the male:female ratio was 269:101. There were statistically significant differences in the clinicopathological features between the two groups, including sex ($P < 0.001$), tumor diameter ($P = 0.002$), tumor location ($P = 0.007$), gastrectomy ($P = 0.001$), histological type ($P = 0.043$), vascular infiltration ($P = 0.021$), nerve infiltration ($P < 0.001$), and postoperative chemotherapy ($P < 0.001$). Table 1 shows the clinicopathological features of the two groups.

### Comparison of prognosis between the two groups

The OS of patients with pT1N2-3 GC was 53.34 (95%CI: 50.369-56.317) mo, and the 5-year OS rate was 73.7%. The OS of patients with pT3N0 GC was 53.66 (95%CI: 52.179-55.149) mo, and the 5-year OS rate was 79.7%. There was no statistically significant difference in OS between the two groups ($P$=0.374) (Figure 1A). In the pT1N2-3 group, there was no significant difference in OS between patients with and without postoperative chemotherapy (OS: 53.20 mo *vs* 53.40 mo, $P = 0.527$; HR: 0.744, 95%CI: 0.297-1.865) (Figure 1B). Similarly, in the pT3N0 group, there was no significant difference in OS between patients with and without postoperative chemotherapy (OS: 55.08 mo *vs* 53.03 mo, $P = 0.236$; HR: 0.774, 95%CI: 0.430-1.393) (Figure 1C).

**Table 1 Baseline characteristics of patients with pT1N2-3 and pT3N0 GC, *n* (%)**

| Characteristic | pT1N2-3b (*n* = 89) | pT3N0 (*n* = 370) | *P* value |
|---|---|---|---|
| Sex | | | **< 0.001** |
| Male | 44 (49.4) | 269 (72.7) | |
| Female | 45 (50.6) | 101 (27.3) | |
| Age (yr) | | | 0.071 |
| ≤ 60 | 58 (65.2) | 219 (59.2) | |
| > 60 | 25 (34.8) | 151 (40.8) | |
| BMI (kg/m$^2$) | | | 0.964 |
| < 24 | 63 (70.8) | 261 (70.5) | |
| ≥ 24 | 26 (29.2) | 109 (29.5) | |
| Borrmann type | | | **< 0.001** |
| 0 | 89 (100.0) | 0 (0.0) | |
| 1 | 0 (0.0) | 23 (6.2) | |
| 2 | 0 (0.0) | 126 (34.1) | |
| 3 | 0 (0.0) | 195 (52.7) | |
| 4 or 5 | 0 (0.0) | 26 (7.0) | |
| Tumor diameter (mm) | | | **0.002** |
| ≤ 50 | 74 (83.1) | 245 (66.2) | |
| > 50 | 15 (16.9) | 125 (33.8) | |
| Tumor location | | | **0.007** |
| Upper | 4 (4.5) | 53 (14.3) | |
| Middle | 11 (12.4) | 66 (17.8) | |
| Lower | 74 (83.1) | 243 (65.7) | |
| Total | 0 (0.0) | 8 (2.2) | |
| Gastrectomy | | | **0.001** |
| Partial gastrectomy | 83 (93.3) | 289 (78.1) | |
| Total gastrectomy | 6 (6.7) | 81 (21.9) | |
| Histological type | | | **0.043** |
| Differentiated | 32 (36.0) | 177 (47.8) | |
| Undifferentiated | 57 (64.0) | 193 (52.2) | |
| pT stage | | | **< 0.001** |
| T1a | 18 (20.2) | 0 (0.0) | |
| T1b | 71 (79.8) | 0 (0.0) | |
| T3 | 0 (0.0) | 370 (100.0) | |
| pN stage | | | **< 0.001** |
| N0 | 0 (0.0) | 370 (100.0) | |
| N2 | 70 (78.7) | 0 (0.0) | |
| N3a | 18 (20.2) | 0 (0.0) | |
| N3b | 1 (1.1) | 0 (0.0) | |
| Vascular infiltration | | | **0.021** |
| No | 64 (71.9) | 306 (82.7) | |
| Yes | 25 (28.1) | 64 (17.3) | |

| | | | |
|---|---|---|---|
| Nerve infiltration | | | **< 0.001** |
| No | 82 (92.1) | 224 (60.5) | |
| Yes | 7 (7.9) | 146 (39.5) | |
| Postoperative chemotherapy | | | **< 0.001** |
| Yes | 52 (58.4) | 114 (30.8) | |
| No | 37 (41.6) | 256 (69.2) | |

Tumor location, histological type, pT stage, pN stage, pTNM stage, vascular infiltration, and nerve infiltration were according to the postoperative pathology report. Statistically significant *P* values are in bold ($P < 0.05$). BMI: Body mass index.

### *Prognosis of the pT1N2-3 group*

Univariate and multivariate analyses based on the Cox proportional hazards regression model were performed to identify independent risk factors associated with the prognosis of patients with pT1N2-3 GC. Univariate analysis showed that age ($P = 0.044$), prealbumin ($P = 0.003$), carcino-embryonic antigen (CEA) ($P = 0.004$), and mLNR ($P < 0.001$) were statistically significant. Multivariate analysis showed that prealbumin ($P = 0.040$), CEA ($P = 0.021$), and mLNR ($P = 0.035$) were independent risk factors associated with prognosis (Table 2).

Subgroup analysis of independent risk factors associated with the prognosis of pT1N2-3 patients was performed. According to the Youden index, 222.35, 3.17, and 0.28 were the optimal cutoff values for prealbumin, CEA, and mLNR to evaluate the prognosis of patients with pT1N2-3 disease (Figure 2A). Subgroup analysis showed that there was a statistically significant difference in OS between patients with prealbumin > 222.35 mg/L and those with prealbumin ≤ 222.35 mg/L (OS: 57.11 mo *vs* 42.82 mo, $P < 0.001$; HR: 5.972, 95%CI: 2.430-14.681), between patients with CEA ≤ 3.17 ng/mL and those with CEA > 3.17 ng/mL (OS: 55.34 mo *vs* 43.19 mo, $P = 0.008$; HR: 3.497, 95%CI: 1.391-8.792), and between patients with mLNR ≤ 0.28 and those with mLNR > 0.28 (OS: 55.07 mo *vs* 45.72 mo, $P = 0.001$; HR: 4.430, 95%CI: 1.825-10.750). In addition, the combination of independent risk factors associated with the prognosis of pT1N2-3 patients was analyzed for survival. Patients with 0, 1, and 2-3 risk factors were defined as the low-risk group, moderate-risk group, and high-risk group, respectively, and there were statistically significant differences in OS among these groups (OS: 58.95 mo *vs* 48.91 mo *vs* 38.36 mo, respectively, $P < 0.001$) (Figure 3A-D).

### *Prognosis of the pT3N0 group*

Univariate and multivariate analyses based on the Cox proportional hazards regression model were performed to identify independent risk factors associated with the prognosis of patients with pT3N0 disease. Univariate analysis showed that age ($P = 0.019$), BMI ($P = 0.004$), tumor diameter ($P = 0.003$), Borrmann type ($P = 0.018$), and gastrectomy ($P < 0.001$) were statistically significant. Multivariate analysis showed that age ($P = 0.039$), BMI ($P = 0.002$), and gastrectomy ($P < 0.001$) were independent risk factors associated with prognosis (Table 3).

Subgroup analysis of independent risk factors associated with pT3N0 patient prognosis was performed. According to the Youden index, 60.5 and 22.48 were the optimal cutoff values for age and BMI to evaluate the prognosis of patients with pT1N2-3 (Figure 2B). Subgroup analysis showed that there was a statistically significant difference in OS between patients aged ≤ 60 years and those aged > 60 years (OS: 55.07 mo *vs* 51.66 mo, $P = 0.003$; HR: 2.010, 95%CI: 1.252-3.228), between patients with BMI > 22.48 kg/m$^2$ and those with BMI ≤ 22.48 kg/m$^2$ (OS: 55.80 mo *vs* 51.81 mo, $P = 0.002$; HR: 2.165, 95%CI: 1.299-3.611), and between patients who underwent partial gastrectomy and those who underwent total gastrectomy (OS: 55.19 mo *vs* 47.92 mo, $P < 0.001$; HR: 3.378, 95%CI: 2.105-5.421). In addition, the combination of independent risk factors associated with the prognosis of pT3N0 patients was analyzed for survival. Patients with 0, 1, and 2-3 risk factors were defined as the low-risk group, moderate-risk group, and high-risk group, respectively, and there were statistically significant differences in OS among these groups (OS: 57.42 mo *vs* 55.02 mo *vs* 49.45 mo, respectively, $P < 0.001$) (Figure 3E-H).

### *Nomogram models*

We combined the independent risk factors associated with prognosis to construct nomograms that were used to evaluate the prognosis of patients in the pT1N2-3 and pT3N0 groups (Figure 4A and D). The area under the curve (AUC) of the nomogram model in predicting the 3-year and 5-year prognosis of pT1N2-3 patients was 0.772 (95%CI: 0.617-0.926) and 0.765 (95%CI: 0.639-0.891), respectively; the sensitivity was 81.8% and 75.0%, respectively, and the specificity was 73.1% and 73.9%, respectively (Figure 4B and C). The AUC of the nomogram model for predicting the 3-year and 5-year prognosis of pT3N0 patients was 0.632 (95%CI: 0.547-0.837) and 0.699 (95%CI: 0.629-0.768), respectively; the sensitivity was 52.9% and 64.3%, respectively, and the specificity was 69.9% and 67.3%, respectively (Figure 4E and F). In addition, the calibration plots showed that the nomogram performed well for

**Table 2 Univariate and multivariate analyses of clinicopathological factors of patients with pT1N2-3b GC**

| Characteristic | pT1N2-3b | | | |
|---|---|---|---|---|
| | Univariate analysis | | Multivariate analysis | |
| | HR (95%CI) | *P* value | HR (95%CI) | *P* value |
| Sex | | 0.870 | - | - |
| Male | 1.000 | | | |
| Female | 0.929 (0.387-2.233) | | | |
| Age (yr) | 1.044 (1.001-1.089) | **0.044** | 1.022 (0.978-1.069) | 0.335 |
| BMI (kg/m$^2$) | 0.924 (0.815-1.047) | 0.216 | - | - |
| Neutrophils (10$^9$/L) | 1.034 (0.795-1.345) | 0.802 | - | - |
| Lymphocytes (10$^9$/L) | 0.616 (0.297-1.278) | 0.193 | - | - |
| Platelets (10$^9$/L) | 0.999 (0.992-1.006) | 0.692 | - | - |
| Fibrinogen (g/L) | 1.277 (0.723-2.256) | 0.399 | - | - |
| ALT (U/L) | 1.000 (0.973-1.029) | 0.972 | - | - |
| AST (U/L) | 1.016 (0.968-1.067) | 0.521 | - | - |
| Albumin (g/L) | 0.926 (0.833-1.028) | 0.150 | - | - |
| Prealbumin (mg/L) | 0.986 (0.977-0.995) | **0.003** | 0.990 (0.981-1.000) | **0.040** |
| CEA (ng/mL) | 1.254 (1.074-1.464) | **0.004** | 1.199 (1.028-1.399) | **0.021** |
| CA19-9 (U/mL) | 1.000 (0.972-1.028) | 0.992 | - | - |
| Tumor diameter (mm) | 0.986 (0.961-1.013) | 0.307 | - | - |
| Gastrectomy | | 0.683 | - | - |
| Partial gastrectomy | 1.000 | | | |
| Total gastrectomy | 1.356 (0.314-5.851) | | | |
| Histological type | | 0.324 | - | - |
| Differentiated | 1.000 | | | |
| Undifferentiated | 1.665 (0.605-4.581) | | | |
| pN stage | | 0.251 | - | - |
| N2 | 1.000 | | | |
| N3 | 1.752 (0.673-4.562) | | | |
| mLNR | 47.797 (5.421-421.417) | **< 0.001** | 17.488 (1.215-251.748) | **0.035** |
| Vascular infiltration | | 0.187 | - | - |
| No | 1.000 | | | |
| Yes | 1.865 (0.738-4.708) | | | |
| Nerve infiltration | | 0.989 | - | - |
| No | 1.000 | | | |
| Yes | 1.010 (0.234-4.359) | | | |
| Postoperative chemotherapy | | 0.528 | - | - |
| Yes | 1.000 | | | |
| No | 0.744 (0.297-1.865) | | | |

CEA and CA19-9 were according to the tumor marker examination. Tumor location, histological type, mLNR, pTstage, pNstage, vascular infiltration, and nerve infiltration were according to the postoperative pathology report. Statistically significant *P* values are in bold ($P < 0.05$). HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index; ALT: Alanine transaminase; AST: A CEA: Carcino-embryonic antigen; CA19-9: Carbohydrate antigen 19-9; mLNR: Metastatic lymph node ratio.

**Table 3 Univariate and multivariate analyses of clinicopathological factors of patients with pT3N0 GC**

| Characteristic | pT3N0 | | | |
|---|---|---|---|---|
| | Univariate analysis | | Multivariate analysis | |
| | HR (95%CI) | *P* value | HR (95%CI) | *P* value |
| Sex | | 0.087 | - | - |
| Male | 1.000 | | | |
| Female | 1.533 (0940-2.500) | | | |
| Age (yr) | 1.029 (1.005-1.054) | **0.019** | 1.025 (1.001-1.049) | **0.039** |
| BMI (kg/m$^2$) | 0.890 (0.822-0.964) | **0.004** | 0.881 (0.812-0.955) | **0.002** |
| Neutrophils (10$^9$/L) | 0.947 (0.829-1.082) | 0.421 | - | - |
| Lymphocytes (10$^9$/L) | 0.966 (0.719-1.298) | 0.819 | - | - |
| Platelets (10$^9$/L) | 1.000 (0.997-1.003) | 0.914 | - | - |
| Fibrinogen (g/L) | 1.048 (0.974-1.129) | 0.210 | - | - |
| ALT (U/L) | 0.992 (0.969-1.015) | 0.469 | - | - |
| AST (U/L) | 1.012 (0.986-1.037) | 0.369 | - | - |
| Albumin (g/L) | 0.991 (0.949-1.034) | 0.670 | - | - |
| Prealbumin (mg/L) | 1.657 (0.954-2.005) | 0.087 | - | - |
| CEA (ng/mL) | 1.007 (0.985-1.030) | 0.535 | - | - |
| CA19-9 (U/mL) | 1.002 (0.999-1.004) | 0.214 | - | - |
| Tumor diameter (mm) | 1.011 (1.004-1.019) | **0.003** | 1.000 (0.990-1.010) | 0.981 |
| Borrmann type | | **0.018** | | 0.282 |
| 1 | 1.000 | | 1.000 | |
| 2 | 0.368 (0.159-0.853) | **0.020** | 0.473 (0.195-1.150) | 0.099 |
| 3 | 0.520 (0.242-1.119) | 0.095 | 0.620 (0.279-1.377) | 0.240 |
| 4 or 5 | 1.110 (0.428-2.879) | 0.830 | 1.051 (0.379-2.911) | 0.924 |
| Gastrectomy | | **< 0.001** | | **< 0.001** |
| Partial gastrectomy | 1.000 | | 1.000 | |
| Total gastrectomy | 3.378 (2.105-5.421) | | 3.222 (1.945-5.338) | |
| Histological type | | 0.380 | - | - |
| Differentiated | 1.000 | | | |
| Undifferentiated | 1.236 (0.771-1.980) | | | |
| Vascular infiltration | | 0.237 | - | - |
| No | 1.000 | | | |
| Yes | 1.142 (0.798-2.499) | | | |
| Nerve infiltration | | 0.373 | - | - |
| No | 1.000 | | | |
| Yes | 1.240 (0772-1.991) | | | |
| Postoperative chemotherapy | | 0.238 | - | - |
| Yes | 1.000 | | | |
| No | 0.774 (0.430-1.393) | | | |

CEA and CA19-9 were according to the tumor marker examination. Tumor location, histological type, mLNR, pTstage, pNstage, vascular infiltration, and nerve infiltration were according to the postoperative pathology report. Statistically significant *P* values are in bold ($P < 0.05$). HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index; ALT: Alanine transaminase; AST: A CEA: Carcino-embryonic antigen; CA19-9: Carbohydrate antigen 19-9;

mLNR: Metastatic lymph node ratio.

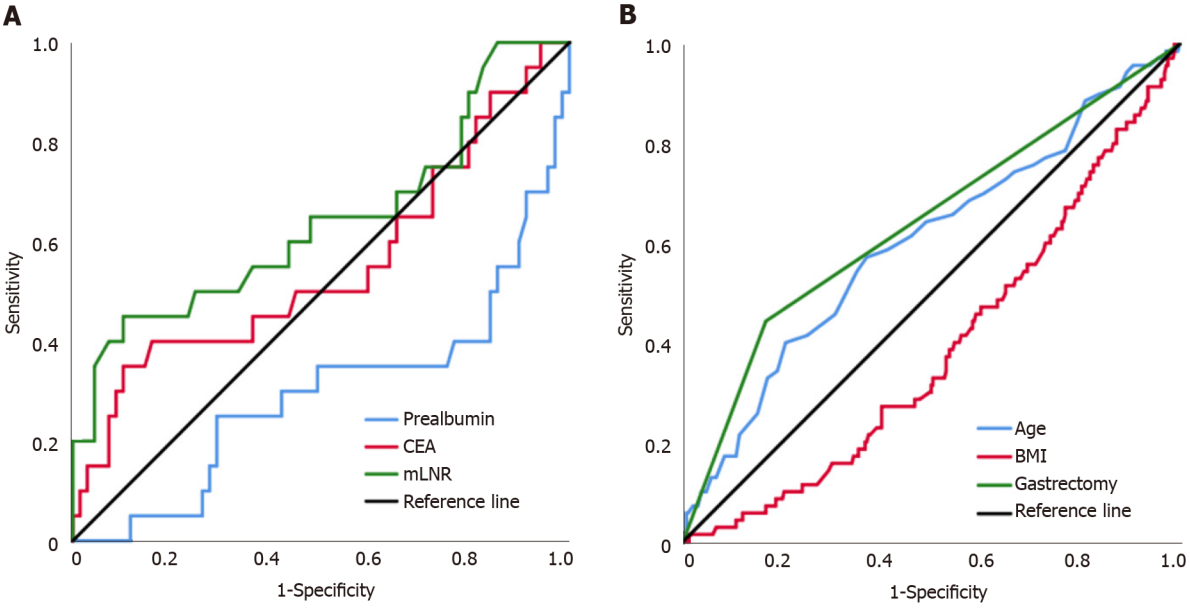


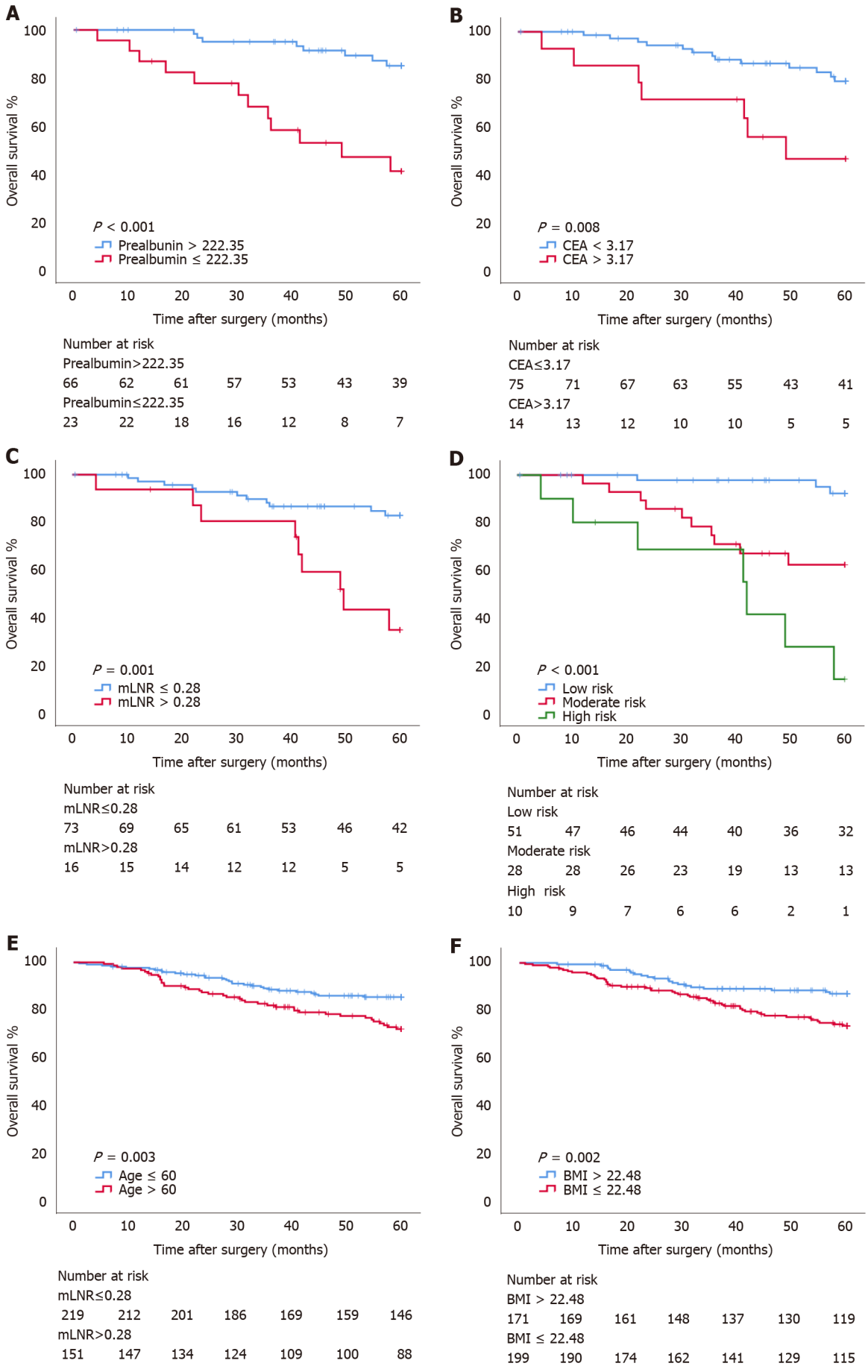

**Figure 2 Receiver operating characteristic curves of clinicopathological factors of patients with pT1N2-3 and pT3N0 GC.** A: Assessing the prognosis of patients with pT1N2-3 GC; B: Assessing the prognosis of patients with pT3N0 GC. CEA: Carcino-embryonic antigen; mLNR: Metastatic lymph node ratio; BMI: Body mass index.

predicting the 3-year OS of the pT1N2-3 group and the 3- and 5-year OS of the pT3N0 group but did not perform well for predicting the 5-year OS of the pT1N2-3 group (Figure 5).

## DISCUSSION

To date, much evidence has been found indicating that appropriate postoperative adjuvant chemotherapy can improve the survival probability after radical resection[3,13-15]. According to the results of the ACTS-GC trial[3], the indications for postoperative chemotherapy excluded pT1N2-3 patients who were classified as stage II/III due to pT1 and pT3N0 patients who were classified as stage IB based on the 13th edition of the Japanese Classification of Gastric Carcinoma[16]. And in the current 14th edition, pT3N0 patients were classified as stage IIA[6]. However, there are still patients with pTIN2-3 and pT3N0 GC who have a poor prognosis, and identifying them through a clinical retrospective study is of substantial value.

Based on the Cox hazards regression model, our study identified prealbumin, CEA, and mLNR as independent prognostic factors for pT1N2-3 patients, while age, BMI, and gastrectomy were independent prognostic factors for pT3N0 patients. Some studies have shown that, as an important indicator of nutritional assessment, prealbumin plays a key role in the complicated link among systemic inflammation, malnutrition, and the tumor immune microenvironment[17,18]. Our study showed that low preoperative prealbumin levels may cause immunodeficiency in patients with stage T1 disease accompanied by extensive lymph node metastasis, leading to tumor progression[19]. Consistent with the results of Qiao *et al*[20], we found that high preoperative CEA level was associated with positive lymph node metastasis in patients with pT1 disease and predicted a poor prognosis. This is related to the function of CEA as an isotype of intercellular adhesion molecule that can promote the aggregation and distant metastasis of tumor cells[21]. In addition, we found that advanced age, low preoperative BMI, and total gastrectomy, as independent prognostic risk factors for pT3N0 patients, were closely related to postoperative malnutrition, which was consistent with the results of the previous studies[22,23]. Short- to medium-term postoperative malnutrition might weaken immune function throughout the body, resulting in an increased risk for cancer recurrence, infectious disease, and death[19]. The mechanism by which immune function is weakened in malnourished individuals involves cytoplasmic nutrient sensors affecting T lymphocyte metabolism and intestinal dysfunction changing the pathway of nutrient sensing[24,25]. Additionally, surgical stress compromises the activity of natural killer (NK) cells and causes immune dysfunction, which is associated with high cancer recurrence and mortality rates[26,27]. Therefore, immune dysfunction due to surgical stress and malnutrition may increase the risk for


A
Overall survival %
P < 0.001
Prealbunin > 222.35
Prealbumin ≤ 222.35
Time after surgery (months)
Number at risk
Prealbumin>222.35
66 62 61 57 53 43 39
Prealbumin≤222.35
23 22 18 16 12 8 7
B
Overall survival %
P = 0.008
CEA < 3.17
CEA > 3.17
Time after surgery (months)
Number at risk
CEA≤3.17
75 71 67 63 55 43 41
CEA>3.17
14 13 12 10 10 5 5
C
Overall survival %
P = 0.001
mLNR ≤ 0.28
mLNR > 0.28
Time after surgery (months)
Number at risk
mLNR≤0.28
73 69 65 61 53 46 42
mLNR>0.28
16 15 14 12 12 5 5
D
Overall survival %
P < 0.001
Low risk
Moderate risk
High risk
Time after surgery (months)
Number at risk
Low risk
51 47 46 44 40 36 32
Moderate risk
28 28 26 23 19 13 13
High risk
10 9 7 6 6 2 1
E
Overall survival %
P = 0.003
Age ≤ 60
Age > 60
Time after surgery (months)
Number at risk
mLNR≤0.28
219 212 201 186 169 159 146
mLNR>0.28
151 147 134 124 109 100 88
F
Overall survival %
P = 0.002
BMI > 22.48
BMI ≤ 22.48
Time after surgery (months)
Number at risk
BMI > 22.48
171 169 161 148 137 130 119
BMI ≤ 22.48
199 190 174 162 141 129 115

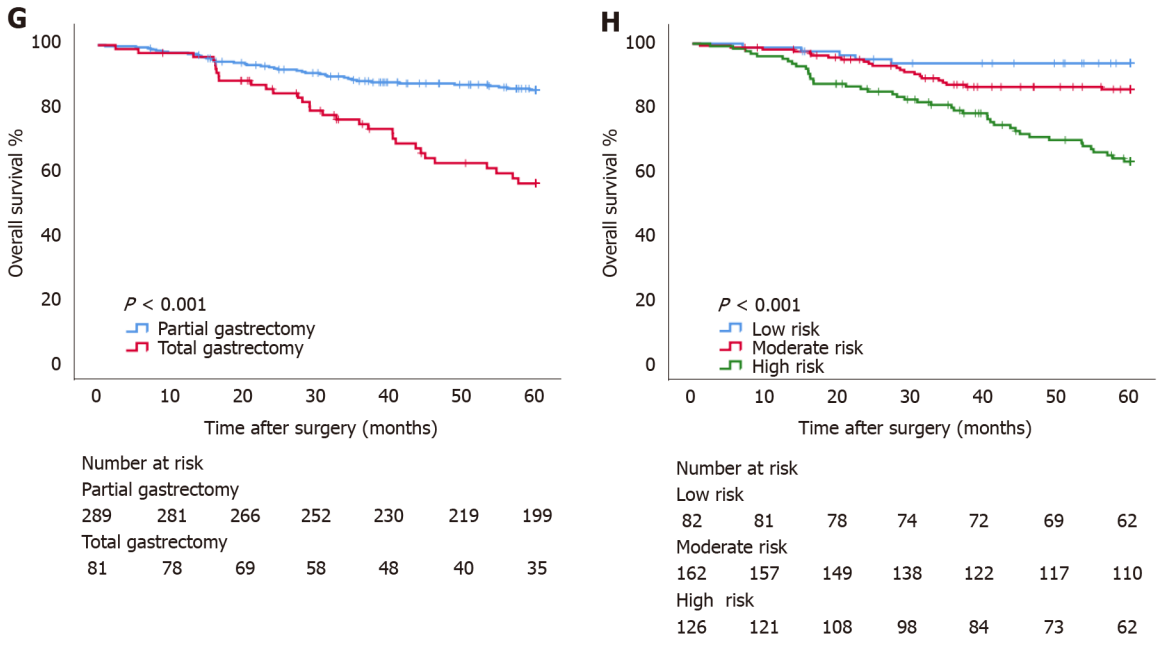
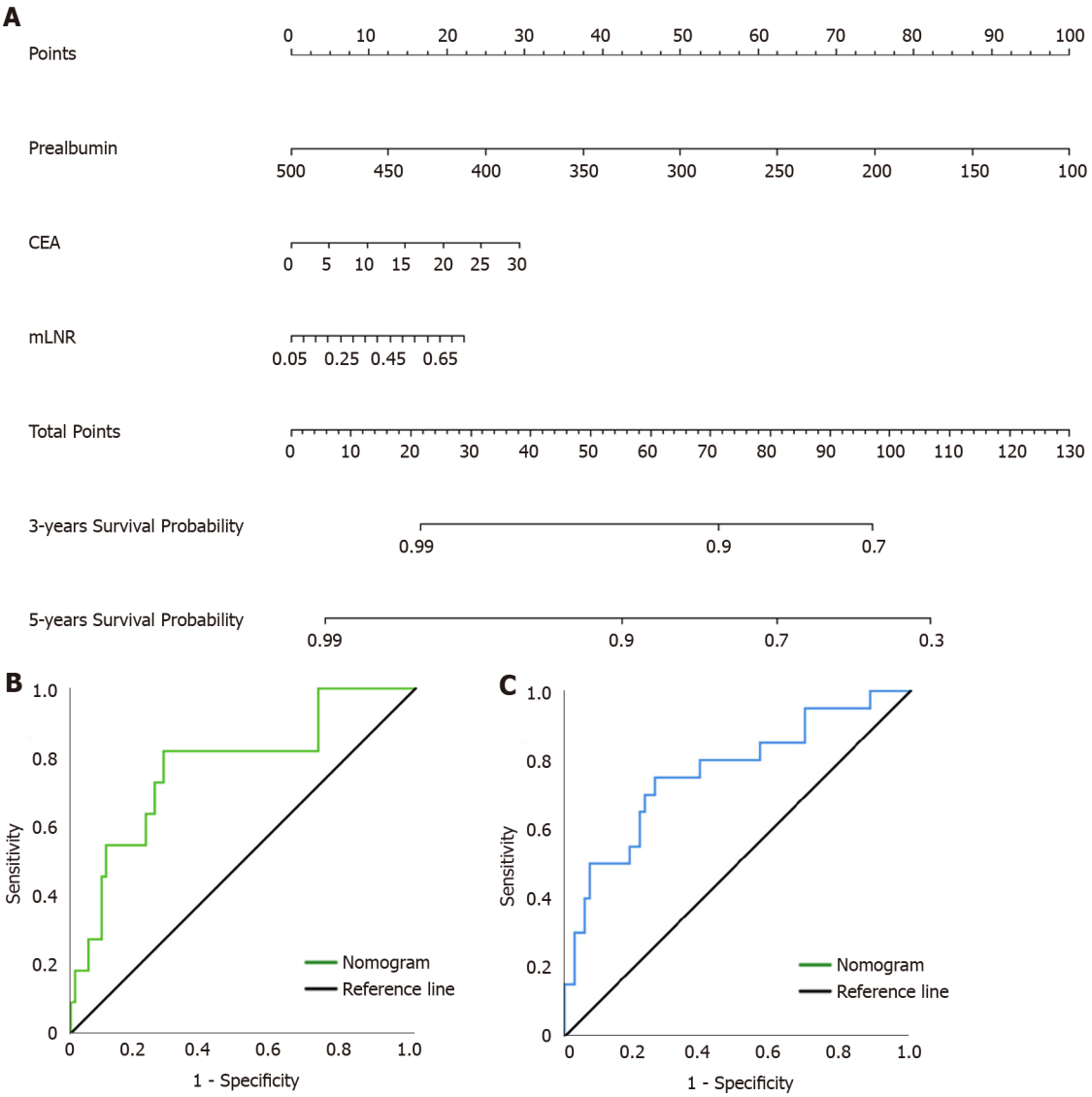


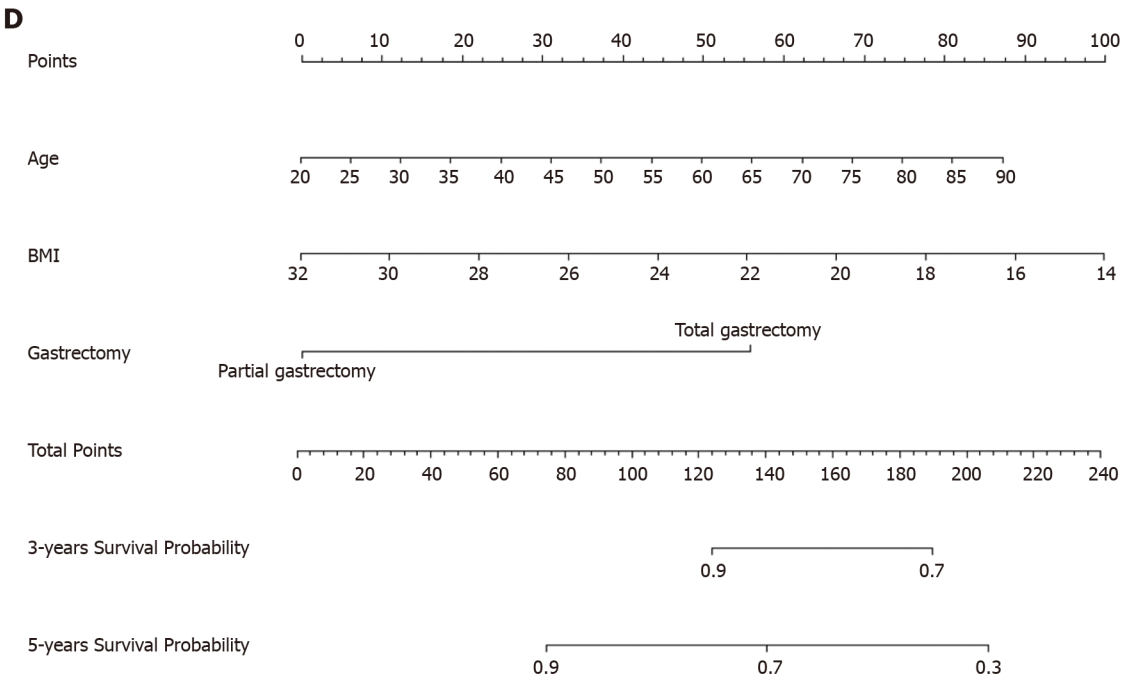

**Figure 3 Survival curve subgroup analyses of patients.** A: Overall survival curves for patients with prealbumin ≤ 222.35 mg/L and prealbumin > 222.35 mg/L in the pT1N2-3 group; B: Overall survival curves for patients with carcino-embryonic antigen (CEA) ≤ 3.17 ng/mL and CEA > 3.17 ng/mL in the pT1N2-3 group; C: Overall survival curves for patients with metastatic lymph node ratio (mLNR) ≤ 0.28 and mLNR > 0.28 in the pT1N2-3 group; D: Overall survival curves for patients with low risk, moderate risk, and high risk in the pT1N2-3 group; E: Overall survival curves for patients aged ≤ 60 years and aged > 60 years in the pT3N0 group; F: Overall survival curves for patients with body mass index (BMI) ≤ 22.48 kg/m$^2$ and BMI > 22.48 kg/m$^2$ in the pT3N0 group; G: Overall survival curves for patients with partial gastrectomy and total gastrectomy in the pT3N0 group; H: Overall survival curves for patients with low risk, moderate risk, and high risk in the pT3N0 group. CEA: Carcino-embryonic antigen; mLNR: Metastatic lymph node ratio; BMI: Body mass index.

early cancer recurrence after surgery.

However, contrary to the findings of Yura *et al*[5], our findings suggested that mLNR is an independent prognostic factor for patients with pT1N2-3, rather than N stage. Schwarz *et al*[28] found that the prediction of survival based on N stage depended on the total number of lymph nodes resected and the quantity of negative nodes. However, there is considerable heterogeneity in the number of recovered lymph nodes due to differences in the skill level of the surgeons and the experience of the pathologists. Some researchers suggested that variability due to the difference in the number of recovered lymph nodes might be eliminated by mLNR, and they also found that mLNR was an independent prognostic factor[29,30]. Therefore, we believe that for evaluating the prognosis of pT1N2-3 GC patients, mLNR is more suitable than N stage. Furthermore, we found that tumor diameter was not an independent prognostic factor for pT1N2-3 patients. Tumor diameter was included by Yura *et al*[5] as a categorical variable, and the *P* value became significant only when the optimal cutoff value of tumor diameter was 30 mm. We included the tumor diameter as a continuous variable, which improved the reliability of the results. Previous studies have revealed that pT3N0 GC patients with vascular infiltration have a higher risk of tumor recurrence[6-8], indicating a poor prognosis, which was not consistent with our findings. In fact, determination of the presence or absence of postoperative vascular infiltration may vary due to different staining methods and diagnostic criteria between single centers[31]. Therefore, in the future, a multicenter study that uses unified methods and standards is needed to more accurately determine the prognostic value of vascular infiltration in pT3N0 patients.

Our study showed that whether patients with pT1N2-3b and pT3N0 receive postoperative adjuvant chemotherapy has no significant effect on the OS, which was consistent with the results of previous studies[3,32]. The JCOG8801 phase III trial compared adjuvant chemotherapy with mitomycin and fluorouracil to surgery alone. They found that for patients with pT1N+ or pT2-3N0 GC, adjuvant chemotherapy did not provide additional survival benefits compared with surgery alone and excluded pT1N2-3 and pT3N0 from the indications for postoperative adjuvant chemotherapy. In that trial, the subgroups of pT1N2-3 and pT3N0 were not examined. It was not known whether all patients with pT1N2-3 and pT3N0 who receive surgical treatment alone have a good prognosis. In this study, we evaluated the independent risk factors that affected the prognosis of patients in both groups and attempted to identify patients who would potentially benefit from adjuvant chemotherapy based on peripheral blood biomarkers and clinicopathological features. Our study found that pT1N2-3 patients with high-risk factors, such as low preoperative prealbumin level, high preoperative CEA level, and high mLNR, would potentially benefit from postoperative adjuvant chemotherapy, while surgical treatment alone was not guaranteed to improve prognosis. Therefore, appropriate use of adjuvant chemotherapy after surgery, as well as regular reexamination and close follow-up, is recommended.


A
Points
0 10 20 30 40 50 60 70 80 90 100
Prealbumin
500 450 400 350 300 250 200 150 100
CEA
0 5 10 15 20 25 30
mLNR
0.05 0.25 0.45 0.65
Total Points
0 10 20 30 40 50 60 70 80 90 100 110 120 130
3-years Survival Probability
0.99 0.9 0.7
5-years Survival Probability
0.99 0.9 0.7 0.3
B
Sensitivity
1 - Specificity
Nomogram
Reference line
C
Sensitivity
1 - Specificity
Nomogram
Reference line


D
Points
0 10 20 30 40 50 60 70 80 90 100
Age
20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
BMI
32 30 28 26 24 22 20 18 16 14
Gastrectomy
Total gastrectomy
Partial gastrectomy
Total Points
0 20 40 60 80 100 120 140 160 180 200 220 240
3-years Survival Probability
0.9 0.7
5-years Survival Probability
0.9 0.7 0.3

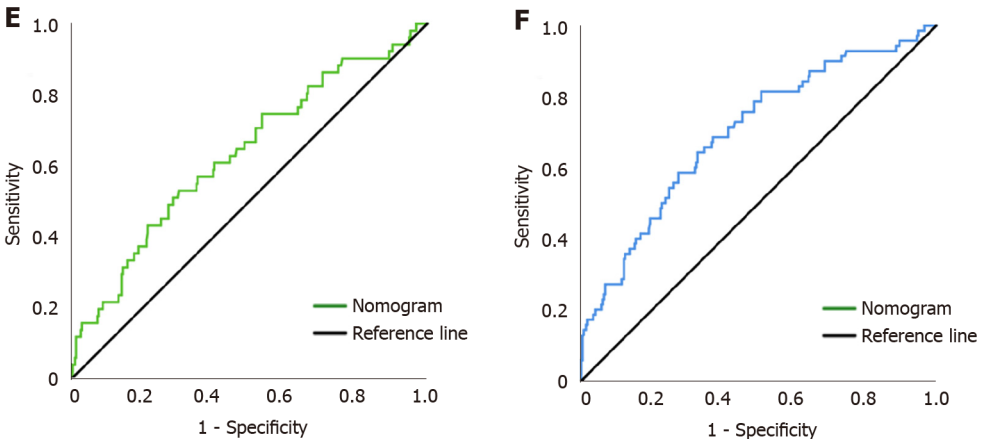



**Figure 4 Nomogram models for predicting the survival of patients with pT1N2-3 and pT3N0 GC.** A: Nomogram model predicting the 3- and 5-year survival of patients with pT1N2-3 GC; B: Receiver operating characteristic curve (ROC) of the nomogram model for predicting the 3-year survival of patients with pT1N2-3 GC; C: ROC of the nomogram model for predicting the 5-year survival of patients with pT1N2-3 GC; D: Nomogram model for predicting the 3- and 5-year survival of patients with pT3N0 GC; E: ROC of the nomogram model for predicting the 3-year survival of patients with pT3N0 GC; F: ROC of the nomogram model for predicting the 5-year survival of patients with pT3N0 GC. CEA: Carcino-embryonic antigen; mLNR: Metastatic lymph node ratio; BMI: Body mass index.

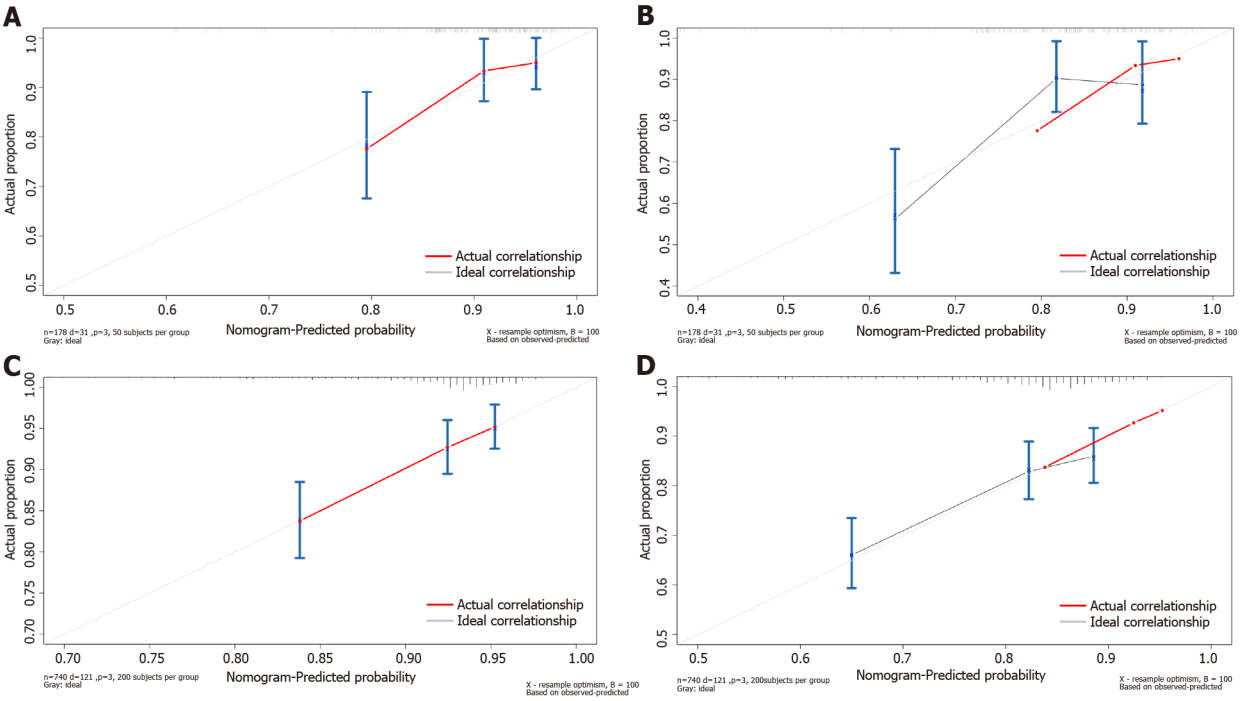



**Figure 5 Calibration plots for the nomograms.** Correlation between the predicted probabilities based on the nomograms and actual values is shown. A: 3-year survival of patients with pT1N2-3 GC; B: 5-year survival of patients with pT1N2-3 GC; C: 3-year survival of patients with pT3N0; D: 5-year survival of patients with pT3N0 GC.

However, considering that independent risk factors for prognosis in pT3N0 patients, such as advanced age, preoperative low BMI, and total gastrectomy, are strongly associated with postoperative malnutrition, we recommend pT3N0 patients whose indicators mentioned above indicate a poor prognosis as candidates for active nutritional intervention. Furthermore, their tolerance to postoperative adjuvant chemotherapy is poor, and postoperative adjuvant chemotherapy may increase the risk for malnutrition among these patients[23]. Therefore, postoperative adjuvant chemotherapy is not a preferred treatment strategy. Clinicians should pay more attention to the postoperative nutritional condition, complications, and infections of these patients, and select the appropriate time for postoperative adjuvant chemotherapy based on these factors.

Clinically, some experts have found that pTNM stage based on postoperative pathology can provide effective but incomplete information for treatment. Patients at the same stage show significant individual differences in prognosis. Many studies have shown that peripheral blood biomarkers and clinicopathological features can play effective complementary roles and are widely used in the early

detection, clinical staging, treatment response monitoring, and prognosis prediction of GC. For example, Liu *et al*[33] constructed a nomogram based on inflammatory biomarkers and mLNR to predict the survival of patients with radical gastrectomy. Therefore, the predictive models constructed by combining peripheral blood biomarkers with clinicopathological features have the advantages of more accurate and individualized evaluation of patient prognosis and reducing the differences caused by heterogeneity. Based on the Cox hazards regression model, we found that prealbumin, CEA, and mLNR were independent risk factors associated with the prognosis of pT1N2-3 GC patients, and age, BMI, and gastrectomy were independent risk factors associated with the prognosis of pT3N0 GC patients. Then, we constructed nomogram models to predict the prognosis of patients with pT1N2-3 and pT3N0. ROC analysis showed that the AUC of the nomogram model in predicting the 3-year and 5-year prognosis of pT1N2-3 patients was 0.772 (95%CI: 0.617-0.926) and 0.765 (95%CI: 0.639-0.891), respectively; the sensitivity was 81.8% and 75.0%, respectively, and the specificity was 73.1% and 73.9%, respectively. The AUC of the nomogram model in predicting the 3-year and 5-year prognosis of pT3N0 patients was 0.632 (95%CI: 0.547-0.837) and 0.699 (95%CI: 0.629-0.768), respectively; the sensitivity was 52.9% and 64.3%, respectively, and the specificity was 69.9% and 67.3%, respectively. The lower AUC may be related to the fact that patients with pT3N0 tend to have a good prognosis and fewer significant clinicopathological factors. In addition, the calibration plots showed that the nomogram performed well for predicting the 3-year OS of the pT1N2-3 group and the 3- and 5-year OS of the pT3N0 group but did not perform well in predicting the 5-year OS of the pT1N2-3 group. This may be due to the small number of patients in the pT1N2-3 group included in our study. Our results showed that the predictive model constructed by peripheral blood biomarkers and clinicopathological features can evaluate the prognosis of patients with pT1N2-3 and pT3N0, which is worthy of further validation and promotion in clinical practice.

There were some limitations in this study. First, this was a retrospective study, and the sample size in the pT1N2-3 group was small. The results of this study need to be verified by more prospective studies. Second, this was a single-center study, focusing only on Asian populations. Whether these results are widely applicable to both White and Black populations needs to be further studied by enlarging the sample size. Third, because pT1N2-3 and pT3N0 GC patients are too rare, there is a lack of sufficient sample size for internal and external validation of nomogram model, which is also the direction of our further study in the future.

## CONCLUSION

The nomogram model based on prealbumin, CEA, and mLNR can be used to predict the prognosis of pT1N2-3 GC patients. The nomogram model based on age, BMI, and gastrectomy can be used to predict the prognosis of pT3N0 GC patients.

## ARTICLE HIGHLIGHTS

### *Research background*

Gastric cancer (GC) is an important public health burden worldwide. The TNM staging system based on tumor infiltration, regional lymph node metastasis, and distant metastasis is considered as the conventional criterion for evaluating prognosis and guiding treatment after surgery. Adjuvant chemotherapy can effectively reduce the disease recurrence. Based on the results of the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC), stage II/III disease as the standard target of adjuvant chemotherapy after surgery, with the exception of pathological stages T1N2-3 (pT1N2-3) and pT3N0. However, in these two groups, there is still a portion of high-risk patients with a poor prognosis.

### *Research motivation*

Analyzing the independent risk factors for the prognosis of pT1N2-3 and pT3N0 GC patients will provide a basis for clinicians to treat and predict the prognosis of these patients in the future.

### *Research objectives*

To identify the high-risk group among these patients after radical surgery by analyzing biomarkers and clinicopathological features and construct prognostic models for them.

### *Research methods*

This retrospective study analyzed the clinicopathological characteristics and long-term survival data of 459 patients with pT1N2-3/pT3N0 GC, all of whom underwent radical gastrectomy at the Harbin Medical University Cancer Hospital between January 2000 and April 2016. The chi–square test was used to analyze the differences in the clinicopathological features between the pT1N2-3 and pT3N0 groups.

The Kaplan–Meier analysis and log-rank test were used to analyze overall survival (OS). The independent risk factors for patient prognosis were analyzed by univariate and multivariate analyses based on the Cox proportional hazards regression model. The cutoff values of continuous variables were analyzed by receiver operating characteristic curve. The nomogram models were constructed with R studio.

### Research results

According to the postoperative pathology report, there were 89 and 370 patients in the pT1N2-3 group and pT3N0 group, respectively. There was no statistically significant difference in OS between the pT1N2-3 and pT3N0 groups ($P$ = 0.374). Prealbumin ($P$ = 0.040), carcino-embryonic antigen (CEA) ($P$ = 0.021), and metastatic lymph node ratio (mLNR) ($P$ = 0.035) were independent risk factors for prognosis in the pT1N2-3b group. Age ($P$ = 0.039), body mass index (BMI) ($P$ = 0.002), and gastrectomy ($P$ < 0.001) were independent risk factors for prognosis in the pT3N0 group. The area under the curve values of the nomogram models predicting the 5-year prognosis of the pT1N2-3 group and pT3N0 group were 0.765 and 0.699, respectively.

### Research conclusions

The nomogram model based on peripheral blood biomarkers and clinicopathological features, including prealbumin, CEA, and mLNR, can be used to predict the prognosis of pT1N2-3 GC patients. Age, BMI, and gastrectomy can be used to predict the prognosis of pT3N0 GC patients.

### Research perspectives

Further multicentric studies are needed to expand the sample size and external validation of the nomogram models will be performed to determine their predictive ability.

## FOOTNOTES

**Author contributions:** Wang YF and Yin X designed and conceived this study, and they contributed equally to this work; Wang YF, Yin X, Fang TY, and Wang YM interpreted and analyzed the data; Xue YW revised the manuscript for important intellectual content; Wang YF, Yin X, Fang TY, Wang YM, Zhang DX, Zhang Y, Wang XB, and Wang H participated in the patient information collection; all authors read and approved the final manuscript.

**Supported by** Nn10 Program of Harbin Medical University Cancer Hospital, China, No. Nn10 PY 2017-03.

**Institutional review board statement:** The study was approved by the Ethics Committee of the Affiliated Tumor Hospital of Harbin Medical University.

**Informed consent statement:** All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

**Conflict-of-interest statement:** All the authors have no conflict of interest related to the manuscript.

**Data sharing statement:** Patients' data were saved in the Gastric Cancer Information Management System v1.2 of Harbin Medical University Cancer Hospital (Copyright No. 2013SR087424, http//:www.sgihmu.com).



**Country/Territory of origin:** China

**ORCID number:** Yu-Fei Wang 0000-0002-1410-2716; Xin Yin 0000-0003-3587-371X; Tian-Yi Fang 0000-0002-5015-4898; Yi-Min Wang 0000-0002-9824-4097; Dao-Xu Zhang 0000-0002-2202-7437; Yao Zhang 0000-0002-3405-570X; Xi-Bo Wang 0000-0002-4141-8134; Hao Wang 0000-0003-4909-8937; Ying-Wei Xue 0000-0003-4525-8163.

**S-Editor:** Gong ZM
**L-Editor:** Wang TQ
**P-Editor:** Wu RR

## REFERENCES

1 **Global Burden of Disease Cancer Collaboration**, Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, Abdel-Rahman O, Abdelalim A, Abdoli A, Abdollahpour I, Abdulle ASM, Abebe ND, Abraha HN, Abu-Raddad LJ, Abualhasan A, Adedeji IA, Advani SM, Afarideh M, Afshari M, Aghaali M, Agius D, Agrawal S, Ahmadi A, Ahmadian E, Ahmadpour E, Ahmed MB, Akbari ME, Akinyemiju T, Al-Aly Z, AlAbdulKader AM, Alahdab F, Alam T, Alamene GM, Alemnew BTT, Alene KA, Alinia C, Alipour V, Aljunid SM, Bakeshei FA, Almadi MAH, Almasi-Hashiani A, Alsharif U, Alsowaidi S, Alvis-Guzman N, Amini E, Amini S, Amoako YA, Anbari Z, Anber NH, Andrei CL, Anjomshoa M, Ansari F, Ansariadi A, Appiah SCY, Arab-Zozani M, Arabloo J, Arefi Z, Aremu O, Areri HA, Artaman A, Asayesh H, Asfaw ET, Ashagre AF, Assadi R, Ataeinia B, Atalay HT, Ataro Z, Atique S, Ausloos M, Avila-Burgos L, Avokpaho EFGA, Awasthi A, Awoke N, Ayala Quintanilla BP, Ayanore MA, Ayele HT, Babaee E, Bacha U, Badawi A, Bagherzadeh M, Bagli E, Balakrishnan S, Balouchi A, Bärnighausen TW, Battista RJ, Behzadifar M, Bekele BB, Belay YB, Belayneh YM, Berfield KKS, Berhane A, Bernabe E, Beuran M, Bhakta N, Bhattacharyya K, Biadgo B, Bijani A, Bin Sayeed MS, Birungi C, Bisignano C, Bitew H, Bjørge T, Bleyer A, Bogale KA, Bojia HA, Borzì AM, Bosetti C, Bou-Orm IR, Brenner H, Brewer JD, Briko AN, Briko NI, Bustamante-Teixeira MT, Butt ZA, Carreras G, Carrero JJ, Carvalho F, Castro C, Castro F, Catalá-López F, Cerin E, Chaiah Y, Chanie WF, Chattu VK, Chaturvedi P, Chauhan NS, Chehrazi M, Chiang PP, Chichiabellu TY, Chido-Amajuoyi OG, Chimed-Ochir O, Choi JJ, Christopher DJ, Chu DT, Constantin MM, Costa VM, Crocetti E, Crowe CS, Curado MP, Dahlawi SMA, Damiani G, Darwish AH, Daryani A, das Neves J, Demeke FM, Demis AB, Demissie BW, Demoz GT, Denova-Gutiérrez E, Derakhshani A, Deribe KS, Desai R, Desalegn BB, Desta M, Dey S, Dharmaratne SD, Dhimal M, Diaz D, Dinberu MTT, Djalalinia S, Doku DT, Drake TM, Dubey M, Dubljanin E, Duken EE, Ebrahimi H, Effiong A, Eftekhari A, El Sayed I, Zaki MES, El-Jaafary SI, El-Khatib Z, Elemineh DA, Elkout H, Ellenbogen RG, Elsharkawy A, Emamian MH, Endalew DA, Endries AY, Eshrati B, Fadhil I, Fallah Omrani V, Faramarzi M, Farhangi MA, Farioli A, Farzadfar F, Fentahun N, Fernandes E, Feyissa GT, Filip I, Fischer F, Fisher JL, Force LM, Foroutan M, Freitas M, Fukumoto T, Futran ND, Gallus S, Gankpe FG, Gayesa RT, Gebrehiwot TT, Gebremeskel GG, Gedefaw GA, Gelaw BK, Geta B, Getachew S, Gezae KE, Ghafourifard M, Ghajar A, Ghashghaee A, Gholamian A, Gill PS, Ginindza TTG, Girmay A, Gizaw M, Gomez RS, Gopalani SV, Gorini G, Goulart BNG, Grada A, Ribeiro Guerra M, Guimaraes ALS, Gupta PC, Gupta R, Hadkhale K, Haj-Mirzaian A, Hamadeh RR, Hamidi S, Hanfore LK, Haro JM, Hasankhani M, Hasanzadeh A, Hassen HY, Hay RJ, Hay SI, Henok A, Henry NJ, Herteliu C, Hidru HD, Hoang CL, Hole MK, Hoogar P, Horita N, Hosgood HD, Hosseini M, Hosseinzadeh M, Hostiuc M, Hostiuc S, Househ M, Hussen MM, Ileanu B, Ilic MD, Innos K, Irvani SSN, Iseh KR, Islam SMS, Islami F, Jafari Balalami N, Jafarinia M, Jahangiry L, Jahani MA, Jahanmehr N, Jakovljevic M, James SL, Javanbakht M, Jayaraman S, Jee SH, Jenabi E, Jha RP, Jonas JB, Jonnagaddala J, Joo T, Jungari SB, Jürisson M, Kabir A, Kamangar F, Karch A, Karimi N, Karimian A, Kasaeian A, Kasahun GG, Kassa B, Kassa TD, Kassaw MW, Kaul A, Keiyoro PN, Kelbore AG, Kerbo AA, Khader YS, Khalilarjmandi M, Khan EA, Khan G, Khang YH, Khatab K, Khater A, Khayamzadeh M, Khazaee-Pool M, Khazaei S, Khoja AT, Khosravi MH, Khubchandani J, Kianipour N, Kim D, Kim YJ, Kisa A, Kisa S, Kissimova-Skarbek K, Komaki H, Koyanagi A, Krohn KJ, Bicer BK, Kugbey N, Kumar V, Kuupiel D, La Vecchia C, Lad DP, Lake EA, Lakew AM, Lal DK, Lami FH, Lan Q, Lasrado S, Lauriola P, Lazarus JV, Leigh J, Leshargie CT, Liao Y, Limenih MA, Listl S, Lopez AD, Lopukhov PD, Lunevicius R, Madadin M, Magdeldin S, El Razek HMA, Majeed A, Maleki A, Malekzadeh R, Manafi A, Manafi N, Manamo WA, Mansourian M, Mansournia MA, Mantovani LG, Maroufizadeh S, Martini SMS, Mashamba-Thompson TP, Massenburg BB, Maswabi MT, Mathur MR, McAlinden C, McKee M, Meheretu HAA, Mehrotra R, Mehta V, Meier T, Melaku YA, Meles GG, Meles HG, Melese A, Melku M, Memiah PTN, Mendoza W, Menezes RG, Merat S, Meretoja TJ, Mestrovic T, Miazgowski B, Miazgowski T, Mihretie KMM, Miller TR, Mills EJ, Mir SM, Mirzaei H, Mirzaei HR, Mishra R, Moazen B, Mohammad DK, Mohammad KA, Mohammad Y, Darwesh AM, Mohammadbeigi A, Mohammadi H, Mohammadi M, Mohammadian M, Mohammadian-Hafshejani A, Mohammadoo-Khorasani M, Mohammadpourhodki R, Mohammed AS, Mohammed JA, Mohammed S, Mohebi F, Mokdad AH, Monasta L, Moodley Y, Moosazadeh M, Moossavi M, Moradi G, Moradi-Joo M, Moradi-Lakeh M, Moradpour F, Morawska L, Morgado-da-Costa J, Morisaki N, Morrison SD, Mosapour A, Mousavi SM, Muche AA, Muhammed OSS, Musa J, Nabhan AF, Naderi M, Nagarajan AJ, Nagel G, Nahvijou A, Naik G, Najafi F, Naldi L, Nam HS, Nasiri N, Nazari J, Negoi I, Neupane S, Newcomb PA, Nggada HA, Ngunjiri JW, Nguyen CT, Nikniaz L, Ningrum DNA, Nirayo YL, Nixon MR, Nnaji CA, Nojomi M, Nosratnejad S, Shiadeh MN, Obsa MS, Ofori-Asenso R, Ogbo FA, Oh IH, Olagunju AT, Olagunju TO, Oluwasanu MM, Omonisi AE, Onwujekwe OE, Oommen AM, Oren E, Ortega-Altamirano DDV, Ota E, Otstavnov SS, Owolabi MO, P A M, Padubidri JR, Pakhale S, Pakpour AH, Pana A, Park EK, Parsian H, Pashaei T, Patel S, Patil ST, Pennini A, Pereira DM, Piccinelli C, Pillay JD, Pirestani M, Pishgar F, Postma MJ, Pourjafar H, Pourmalek F, Pourshams A, Prakash S, Prasad N, Qorbani M, Rabiee M, Rabiee N, Radfar A, Rafiei A, Rahim F, Rahimi M, Rahman MA, Rajati F, Rana SM, Raoofi S, Rath GK, Rawaf DL, Rawaf S, Reiner RC, Renzaho AMN, Rezaei N, Rezapour A, Ribeiro AI, Ribeiro D, Ronfani L, Roro EM, Roshandel G, Rostami A, Saad RS, Sabbagh P, Sabour S, Saddik B, Safiri S, Sahebkar A, Salahshoor MR, Salehi F, Salem H, Salem MR, Salimzadeh H, Salomon JA, Samy AM, Sanabria J, Santric Milicevic MM, Sartorius B, Sarveazad A, Sathian B, Satpathy M, Savic M, Sawhney M, Sayyah M, Schneider IJC, Schöttker B, Sekerija M, Sepanlou SG, Sepehrimanesh M, Seyedmousavi S, Shaahmadi F, Shabaninejad H, Shahbaz M, Shaikh MA, Shamshirian A, Shamsizadeh M, Sharafi H, Sharafi Z, Sharif M, Sharifi A, Sharifi H, Sharma R, Sheikh A, Shirkoohi R, Shukla SR, Si S, Siabani S, Silva DAS, Silveira DGA, Singh A, Singh JA, Sisay S, Sitas F, Sobngwi E, Soofi M, Soriano JB, Stathopoulou V, Sufiyan MB, Tabarés-Seisdedos R, Tabuchi T, Takahashi K, Tamtaji OR, Tarawneh MR, Tassew SG, Taymoori P, Tehrani-Banihashemi A, Temsah MH, Temsah O, Tesfay BE, Tesfay FH, Teshale MY, Tessema GA, Thapa S, Tlaye KG, Topor-Madry R, Tovani-Palone MR, Traini E, Tran BX, Tran KB, Tsadik AG, Ullah I, Uthman OA, Vacante M, Vaezi M, Varona Pérez P, Veisani Y, Vidale S, Violante FS, Vlassov V, Vollset SE, Vos T, Vosoughi K, Vu GT, Vujcic IS, Wabinga H, Wachamo TM, Wagnew FS, Waheed Y, Weldegebreal F, Weldesamuel GT, Wijeratne T, Wondafrash DZ, Wonde TE, Wondmieneh AB, Workie HM, Yadav R, Yadegar A, Yadollahpour A, Yaseri M, Yazdi-Feyzabadi V, Yeshaneh A, Yimam MA, Yimer EM, Yisma E, Yonemoto N, Younis MZ, Yousefi B, Yousefifard M, Yu C, Zabeh E, Zadnik V, Moghadam TZ, Zaidi Z, Zamani M, Zandian H, Zangeneh A, Zaki L, Zendehdel K, Zenebe ZM, Zewale TA, Ziapour A, Zodpey S, Murray CJL. Global, Regional, and

National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol* 2019; **5**: 1749-1768 [PMID: 31560378 DOI: 10.1001/jamaoncol.2019.2996]

2 **In H**, Solsky I, Palis B, Langdon-Embry M, Ajani J, Sano T. Validation of the 8th Edition of the AJCC TNM Staging System for Gastric Cancer using the National Cancer Database. *Ann Surg Oncol* 2017; **24**: 3683-3691 [PMID: 28895113 DOI: 10.1245/s10434-017-6078-x]

3 **Sakuramoto S**, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K; ACTS-GC Group. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007; **357**: 1810-1820 [PMID: 17978289 DOI: 10.1056/NEJMoa072252]

4 **Japanese Gastric Cancer Association**. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer* 2021; **24**: 1-21 [PMID: 32060757 DOI: 10.1007/s10120-020-01042-y]

5 **Yura M**, Yoshikawa T, Otsuki S, Yamagata Y, Morita S, Katai H, Nishida T. Is surgery alone sufficient for treating T1 gastric cancer with extensive lymph node metastases? *Gastric Cancer* 2020; **23**: 349-355 [PMID: 31512081 DOI: 10.1007/s10120-019-01006-x]

6 **Terada M**, Kinoshita T, Kaito A, Sugita S, Watanabe M, Hayashi R. Evaluation of the prognostic factors in patients with pT3N0 or pT1N2-3 gastric cancer: a single institutional retrospective cohort study. *Surg Today* 2018; **48**: 325-332 [PMID: 28993997 DOI: 10.1007/s00595-017-1592-9]

7 **Imamura T**, Komatsu S, Ichikawa D, Kubota T, Okamoto K, Konishi H, Shiozaki A, Fujiwara H, Morimura R, Murayama Y, Kuriu Y, Ikoma H, Nakanishi M, Sakakura C, Otsuji E. Poor prognostic subgroup in T3N0 stage IIA gastric cancer, suggesting an indication for adjuvant chemotherapy. *J Surg Oncol* 2015; **111**: 221-225 [PMID: 25327711 DOI: 10.1002/jso.23796]

8 **Saito H**, Murakami Y, Miyatani K, Kuroda H, Matsunaga T, Fukumoto Y, Osaki T, Ikeguchi M. Predictive factors for recurrence in T2N0 and T3N0 gastric cancer patients. *Langenbecks Arch Surg* 2016; **401**: 823-828 [PMID: 27460840 DOI: 10.1007/s00423-016-1480-6]

9 **Li TT**, Liu H, Yu J, Shi GY, Zhao LY, Li GX. Prognostic and predictive blood biomarkers in gastric cancer and the potential application of circulating tumor cells. *World J Gastroenterol* 2018; **24**: 2236-2246 [PMID: 29881233 DOI: 10.3748/wjg.v24.i21.2236]

10 **Fang T**, Wang Y, Yin X, Zhai Z, Zhang Y, Yang Y, You Q, Li Z, Ma Y, Li C, Song H, Shi H, Yu X, Gao H, Sun Y, Xie R, Xue Y. Diagnostic Sensitivity of NLR and PLR in Early Diagnosis of Gastric Cancer. *J Immunol Res* 2020; **2020**: 9146042 [PMID: 32211444 DOI: 10.1155/2020/9146042]

11 **Selcukbiricik F**, Buyukunal E, Tural D, Ozguroglu M, Demirelli F, Serdengecti S. Clinicopathological features and outcomes of patients with gastric cancer: a single-center experience. *World J Gastroenterol* 2013; **19**: 2154-2161 [PMID: 23599641 DOI: 10.3748/wjg.v19.i14.2154]

12 **National Comprehensive Cancer Network**. NCCN clinical practice guildlines in oncology: Gastric cancer. 2018. Available from: URL: https://www.nccn.org/

13 **Takahari D**, Hamaguchi T, Yoshimura K, Katai H, Ito S, Fuse N, Kinoshita T, Yasui H, Terashima M, Goto M, Tanigawa N, Shirao K, Sano T, Sasako M. Feasibility study of adjuvant chemotherapy with S-1 plus cisplatin for gastric cancer. *Cancer Chemother Pharmacol* 2011; **67**: 1423-1428 [PMID: 20809123 DOI: 10.1007/s00280-010-1432-8]

14 **Yoshida K**, Kodera Y, Kochi M, Ichikawa W, Kakeji Y, Sano T, Nagao N, Takahashi M, Takagane A, Watanabe T, Kaji M, Okitsu H, Nomura T, Matsui T, Yoshikawa T, Matsuyama J, Yamada M, Ito S, Takeuchi M, Fujii M. Addition of Docetaxel to Oral Fluoropyrimidine Improves Efficacy in Patients With Stage III Gastric Cancer: Interim Analysis of JACCRO GC-07, a Randomized Controlled Trial. *J Clin Oncol* 2019; **37**: 1296-1304 [PMID: 30925125 DOI: 10.1200/JCO.18.01138]

15 **Noh SH**, Park SR, Yang HK, Chung HC, Chung IJ, Kim SW, Kim HH, Choi JH, Kim HK, Yu W, Lee JI, Shin DB, Ji J, Chen JS, Lim Y, Ha S, Bang YJ; CLASSIC trial investigators. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; **15**: 1389-1396 [PMID: 25439693 DOI: 10.1016/S1470-2045(14)70473-5]

16 **Japanese Gastric Cancer Association**. Japanese Classification of Gastric Carcinoma - 2nd English Edition - Gastric Cancer 1998; 1: 10-24 [PMID: 11957040 DOI: 10.1007/s101209800016]

17 **Chertow GM**, Ackert K, Lew NL, Lazarus JM, Lowrie EG. Prealbumin is as important as albumin in the nutritional assessment of hemodialysis patients. *Kidney Int* 2000; **58**: 2512-2517 [PMID: 11115085 DOI: 10.1046/j.1523-1755.2000.00435.x]

18 **Alifano M**, Mansuet-Lupo A, Lococo F, Roche N, Bobbio A, Canny E, Schussler O, Dermine H, Régnard JF, Burroni B, Goc J, Biton J, Ouakrim H, Cremer I, Dieu-Nosjean MC, Damotte D. Systemic inflammation, nutritional status and tumor immune microenvironment determine outcome of resected non-small cell lung cancer. *PLoS One* 2014; **9**: e106914 [PMID: 25238252 DOI: 10.1371/journal.pone.0106914]

19 **Bourke CD**, Berkley JA, Prendergast AJ. Immune Dysfunction as a Cause and Consequence of Malnutrition. *Trends Immunol* 2016; **37**: 386-398 [PMID: 27237815 DOI: 10.1016/j.it.2016.04.003]

20 **Qiao YF**, Chen CG, Yue J, Ma MQ, Ma Z, Yu ZT. Prognostic significance of preoperative and postoperative CK19 and CEA mRNA levels in peripheral blood of patients with gastric cardia cancer. *World J Gastroenterol* 2017; **23**: 1424-1433 [PMID: 28293089 DOI: 10.3748/wjg.v23.i8.1424]

21 **Kuespert K**, Pils S, Hauck CR. CEACAMs: their role in physiology and pathophysiology. *Curr Opin Cell Biol* 2006; **18**: 565-571 [PMID: 16919437 DOI: 10.1016/j.ceb.2006.08.008]

22 **Fujiya K**, Kawamura T, Omae K, Makuuchi R, Irino T, Tokunaga M, Tanizawa Y, Bando E, Terashima M. Impact of Malnutrition After Gastrectomy for Gastric Cancer on Long-Term Survival. *Ann Surg Oncol* 2018; **25**: 974-983 [PMID: 29388124 DOI: 10.1245/s10434-018-6342-8]

23 **Park JH**, Kim E, Seol EM, Kong SH, Park DJ, Yang HK, Choi JH, Park SH, Choe HN, Kweon M, Park J, Choi Y, Lee HJ. Prediction Model for Screening Patients at Risk of Malnutrition After Gastric Cancer Surgery. *Ann Surg Oncol* 2021; **28**: 4471-4481 [PMID: 33481124 DOI: 10.1245/s10434-020-09559-3]

24 **Ramsay G**, Cantrell D. Environmental and metabolic sensors that control T cell biology. *Front Immunol* 2015; **6**: 99 [PMID: 25852681 DOI: 10.3389/fimmu.2015.00099]

25 **Yu J**, Ordiz MI, Stauber J, Shaikh N, Trehan I, Barnell E, Head RD, Maleta K, Tarr PI, Manary MJ. Environmental Enteric Dysfunction Includes a Broad Spectrum of Inflammatory Responses and Epithelial Repair Processes. *Cell Mol Gastroenterol Hepatol* 2016; **2**: 158-174.e1 [PMID: 26973864 DOI: 10.1016/j.jcmgh.2015.12.002]

26 **Pollock RE**, Lotzová E, Stanford SD. Surgical stress impairs natural killer cell programming of tumor for lysis in patients with sarcomas and other solid tumors. *Cancer* 1992; **70**: 2192-2202 [PMID: 1394051 DOI: 10.1002/1097-0142(19921015)70:8<2192::aid-cncr2820700830>3.0.co;2-6]

27 **Tartter PI**, Steinberg B, Barron DM, Martinelli G. The prognostic significance of natural killer cytotoxicity in patients with colorectal cancer. *Arch Surg* 1987; **122**: 1264-1268 [PMID: 3675190 DOI: 10.1001/archsurg.1987.01400230050009]

28 **Schwarz RE**, Smith DD. Clinical impact of lymphadenectomy extent in resectable gastric cancer of advanced stage. *Ann Surg Oncol* 2007; **14**: 317-328 [PMID: 17094022 DOI: 10.1245/s10434-006-9218-2]

29 **Lee SR**, Kim HO, Son BH, Shin JH, Yoo CH. Prognostic significance of the metastatic lymph node ratio in patients with gastric cancer. *World J Surg* 2012; **36**: 1096-1101 [PMID: 22382768 DOI: 10.1007/s00268-012-1520-5]

30 **Wang J**, Dang P, Raut CP, Pandalai PK, Maduekwe UN, Rattner DW, Lauwers GY, Yoon SS. Comparison of a lymph node ratio-based staging system with the 7th AJCC system for gastric cancer: analysis of 18,043 patients from the SEER database. *Ann Surg* 2012; **255**: 478-485 [PMID: 22330040 DOI: 10.1097/SLA.0b013e31824857e2]

31 **Gresta LT**, Rodrigues-Júnior IA, de Castro LP, Cassali GD, Cabral MM. Assessment of vascular invasion in gastric cancer: a comparative study. *World J Gastroenterol* 2013; **19**: 3761-3769 [PMID: 23840114 DOI: 10.3748/wjg.v19.i24.3761]

32 **Nakajima T**, Nashimoto A, Kitamura M, Kito T, Iwanaga T, Okabayashi K, Goto M. Adjuvant mitomycin and fluorouracil followed by oral uracil plus tegafur in serosa-negative gastric cancer: a randomised trial. Gastric Cancer Surgical Study Group. *Lancet* 1999; **354**: 273-277 [PMID: 10440302 DOI: 10.1016/s0140-6736(99)01048-x]

33 **Liu J**, Geng Q, Chen S, Liu X, Kong P, Zhou Z, Zhan Y, Xu D. Nomogram based on systemic inflammatory response markers predicting the survival of patients with resectable gastric cancer after D2 gastrectomy. *Oncotarget* 2016; **7**: 37556-37565 [PMID: 27121054 DOI: 10.18632/oncotarget.8788]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 February 27; 14(2): 161-173

DOI: 10.4240/wjgs.v14.i2.161

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

# Laparoscopic *vs* open total gastrectomy for advanced gastric cancer following neoadjuvant therapy: A propensity score matching analysis

Hai-Tao Hu, Fu-Hai Ma, Jian-Ping Xiong, Yang Li, Peng Jin, Hao Liu, Shuai Ma, Wen-Zhe Kang, Yan-Tao Tian

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Kawabata H, Masaki S, Taira K

**Received:** July 15, 2021
**Peer-review started:** July 15, 2021
**First decision:** November 8, 2021
**Revised:** December 13, 2021
**Accepted:** February 10, 2022
**Article in press:** February 10, 2022
**Published online:** February 27, 2022

**Hai-Tao Hu, Fu-Hai Ma, Jian-Ping Xiong, Yang Li, Peng Jin, Hao Liu, Shuai Ma, Wen-Zhe Kang, Yan-Tao Tian,** Department of Pancreatic and Gastric Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, Beijing Province, China

**Corresponding author:** Yan-Tao Tian, MD, Chief Doctor, Department of Pancreatic and Gastric Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17, Panjiayuan Nanli, Chaoyang District, Beijing 100021, Beijing Province, China.
tianyantao@cicams.ac.cn

## Abstract

### *BACKGROUND*

Laparoscopic total gastrectomy (LTG) has drawn increasing attention over the years. Although LTG has shown surgical benefits compared to open TG (OTG) in early stage gastric cancer (GC), little is known about the surgical and oncological outcomes of LTG for advanced GC following neoadjuvant therapy (NAT).

### *AIM*

To compare the long- and short-term outcomes of advanced GC patients who underwent LTG *vs* OTG following NAT.

### *METHODS*

Advanced GC patients who underwent TG following NAT between April 2011 and May 2018 at the Cancer Hospital of the Chinese Academy of Medical Sciences were enrolled and stratified into two groups: LTG and OTG. Propensity score matching analysis was performed at a 1:1 ratio to overcome possible bias.

### *RESULTS*

In total, 185 patients were enrolled (LTG: 78; OTG: 109). Of these, 138 were paired after propensity score matching. After adjustment for propensity score matching, baseline parameters were similar between the two groups. Compared to OTG, LTG was associated with a significantly shorter length of hospital stay ($P$ = 0.012). The rates of R0 resection, lymph node harvest, and postoperative morbidity did not significantly differ between the two groups. Overall survival (OS) outcomes were comparable between the two groups. Pathological T and N stages were

found to be independent risk factors for OS.

***CONCLUSION***
LTG can be a feasible method for advanced GC patients following NAT, as it appears to be associated with better short- and comparable long-term outcomes compared to OTG.

**Key Words:** Gastric cancer; Laparoscopic total gastrectomy; Open total gastrectomy; Neoadjuvant therapy; Propensity score matching



**Core Tip:** Laparoscopic total gastrectomy (LTG) is known to have better short-term outcomes and prognosis than open TG (OTG) in early gastric cancer (GC). However, its application in advanced GC remains controversial. In this study, we evaluated both long- and short-term outcomes of LTG compared to those of OTG in 185 patients with advanced GC who had received neoadjuvant therapy (NAT). Our results indicate that LTG is associated with better short-term and comparable long-term outcomes compared to the traditional OTG surgery. Therefore, it can be a feasible surgical treatment for advanced GC patients following NAT.

**Citation:** Hu HT, Ma FH, Xiong JP, Li Y, Jin P, Liu H, Ma S, Kang WZ, Tian YT. Laparoscopic *vs* open total gastrectomy for advanced gastric cancer following neoadjuvant therapy: A propensity score matching analysis. *World J Gastrointest Surg* 2022; 14(2): 161-173
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i2/161.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i2.161

## INTRODUCTION

According to the latest data from the Global Cancer Statistics 2020 report, gastric cancer (GC) is the fifth most common cancer and the fifth leading cause of cancer-related deaths worldwide[1]. Despite a slight drop in mortality rates, a considerable number of patients with GC have locally advanced disease at first diagnosis. Since the MAGIC trial[2], neoadjuvant therapy (NAT) has played a significant role in the comprehensive treatment of advanced GC (AGC). Numerous prospective studies have been carried out in Western and Eastern Asian countries, and although the efficacy of NAT has been validated, chemotherapy regimens are quite different between Western and Eastern Asian countries.

After NAT, patients generally undergo D2 gastrectomy with curative intent. Laparoscopic gastrectomy (LG) has gained popularity in the management of early GC (EGC) because of its minimal invasiveness and similar long-term outcomes compared to those of conventional open gastrectomy (OG)[3]. Although its use is still under debate, the application of LG in AGC has drawn increasing attention over the years. The available evidence from the CLASS-01 and KLASS-02 trials suggests that laparoscopy-assisted distal gastrectomy is safe and provides faster postoperative recovery than open distal gastrectomy (ODG) does for patients with AGC[4]. Moreover, the CLASS-01 trial demonstrated that laparoscopic distal gastrectomy (LDG) did not lead to inferior disease-free survival at 3 years compared to ODG for patients with AGC[5].

Since there has been a recent increase in the prevalence of adenocarcinoma of the esophagogastric junction (AEG), total gastrectomy (TG) constitutes an increasing proportion of all gastric operations[6]. Laparoscopic TG (LTG) has been confirmed to have better short-term outcomes and prognosis than those of open TG (OTG) in EGC; however, its application in AGC remains controversial[7,8]. Some retrospective studies and meta-analyses have shown that LTG has lower rates of complications and amount of blood loss; however, there is still a need for high-volume research to validate its efficacy and safety compared to those of OTG[9,10].

Chemotherapy-induced tissue fibrotic changes and edema provide new technical challenges for LG, and the effect of NAT on LG compared to that on OG remains unclear. A randomized controlled trial conducted by Li *et al*[11] (2019) reported the safety and efficacy of LDG with D2 lymphadenectomy following neoadjuvant chemotherapy (NAC) for AGC. The STOMACH trial also published preliminary results for LTG after NAC, showing that LTG is not inferior to OTG in short-term outcomes[12]. However, the rate of D2 lymphadenectomy was quite low in both groups-49% for OTG and 36.2% for LTG-and it is still doubtful whether LTG is safe in clinical oncology practice. To the best of our knowledge, only two studies with small sample sizes have investigated the long-term survival of LG following NAC, and no previous study has examined the long-term survival of patients who received LTG[13,14].

Therefore, we conducted this study to evaluate the long- and short-term outcomes of LTG for AGC following NAT and to determine the surgical and oncological safety of LTG as an acceptable alternative to OTG.

## MATERIALS AND METHODS

### Patients

We retrospectively screened our database of patients with GC and identified those with preoperative and pathological diagnoses of AGC who received LTG or OTG with lymphadenectomy after NAT from April 2011 to May 2018 at the Cancer Hospital of the Chinese Academy of Medical Sciences. The inclusion criteria were as follows: (1) Gastric adenocarcinoma; (2) Clinical stages cT2-4a, N-/+, and M0; and (3) Received chemotherapy or chemoradiotherapy before surgery. The exclusion criteria were as follows: (1) Remnant GC; (2) Siewert type I AEG; (3) Emergent gastrectomy; (4) Other simultaneous malignant diseases; and (5) Missing clinical data. In total, 185 patients were included, of whom 107 had undergone LTG, and 78 had undergone OTG. This study was approved by the Ethics Committee of the Cancer Hospital of the Chinese Academy of Medical Sciences and the requirement was waived.

### Administration of NAT

NAC regimens were divided into three categories: (1) Platinum-based doublets (SOX, XELOX, CS, FOLFOX, and TP); (2) Epirubicin-based triplets (ECF); or (3) Taxane-based triplets (DCF, DCX). As neoadjuvant chemoradiotherapy (NCRT), patients received concurrent chemoradiotherapy with tegafur/gimeracil/oteracil (S-1). The planned dose of total radiotherapy was 45 Gy with a daily fraction of 1.8 Gy for 5 wk. S-1 was administered orally twice daily when receiving radiotherapy. After evaluation by experienced oncologists and surgeons, surgery was performed approximately 4-6 wk after the completion of NAT.

### Surgical procedure

Approximately 2-4 wk after the end of NAT, patients underwent TG with standard D2 lymphadenectomy following the Japanese Gastric Cancer Treatment Guidelines[15]. A total of 5 trocars were used in the LTG surgery. The resection margins were examined intraoperatively in the frozen sections. Reconstruction of the gastrointestinal passage is typically accomplished using the Roux-en-Y gastric bypass. All operations were performed by a lead surgeon who had performed at least 60 OG or LG operations and two or three assistants. Intraoperative and postoperative complications and corresponding outcomes were documented.

### Definitions

Clinical and pathological data were collected from medical records. Clinical staging was assessed using the 8$^{th}$ American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) classification through biopsy, endoscopic ultrasonography, and computed tomography (CT) data. Enlarged lymph nodes > 8 mm along their longest axis or those with necrosis were classified as cN+. Postoperative complications included pancreatic fistula, abdominal bleeding, anastomotic leakage, wound infection, lymphorrhagia, intestinal obstruction, abdominal infection, duodenal fistula, and gastroparesis. These were considered surgical and other medical complications and graded according to the Clavien-Dindo system[16]. The response to NAT was evaluated using the Mandard tumor regression grading (TRG) system[17]. Pathological T status, N status, and ypTNM stage were also determined using the 8$^{th}$ AJCC/UICC staging system. Overall survival (OS) was measured from the day of surgery.

### Follow-up

In the first 2 years, patients were followed-up every 3 mo, then every 6 mo for the next 3 years, and yearly thereafter. Any loss to follow-up was censored. The final follow-up was completed in October 2020.

### Propensity score matching and statistical analysis

We performed propensity score matching (PSM) to minimize bias between the baseline of the two groups. Propensity scores were calculated using a logistic regression model and the following variables: Sex, age, American Society of Anesthesiologists physical status classification (ASA), body mass index (BMI), tumor size, histological differentiation, ypT, ypN, and ypTNM status. Patients were then individually matched using the 1:1 nearest neighbor matching method with a caliper width of 0.05. This method randomly ordered the case (LTG) and control (OTG) subjects based on the propensity score and matched the control subject with the closest comparison from the first case subject[18].

Categorical values are presented as percentages and continuous values are presented as mean ± SEM. Clinical and pathological variables were analyzed using the chi-squared test, Fisher's exact test and

**Table 1 Patients and tumors' clinical and pathological characteristics before and after propensity score matching**

| Variable | All patients | | *P* value | Matched patients | | *P* value |
|---|---|---|---|---|---|---|
| | LTG (*n* = 78) | OTG (*n* = 107) | | LTG (*n* = 69) | OTG (*n* = 69) | |
| Age (yr) | 52.7 ± 16.1 | 56.0 ± 12.0 | 0.120 | 53.42 ± 13.4 | 53.9 ± 12.7 | 0.828 |
| Gender *n* (%) | | | | | | |
| Male | 61 (78.2) | 78 (72.9) | 0.409 | 53 (76.8) | 52 (75.4) | 0.842 |
| Female | 17 (21.8) | 29 (27.1) | | 16 (23.2) | 17 (24.6) | |
| BMI (kg/m$^2$) | 22.6 ± 3.1 | 23.7 ± 3.7 | 0.028 | 22.6 ± 3.1 | 22.8 ± 3.3 | 0.750 |
| ASA *n* (%) | | | | | | |
| 1-2 | 74 (94.9) | 99 (92.5) | 0.522 | 65 (94.2) | 64 (92.8) | 1.000 |
| 3 | 4 (5.1) | 8 (7.5) | | 4 (5.8) | 5 (7.2) | |
| The history of abdominalsurgery *n* (%) | | | | | | |
| Yes | 10 (12.8) | 19 (17.8) | 0.362 | 8 (11.6) | 13 (18.8) | 0.236 |
| No | 68 (87.2) | 88 (82.2) | | 61 (88.4) | 56 (81.2) | |
| Tumor location *n* (%) | | | 0.775 | | | 0.698 |
| Upper | 30 (38.5) | 35 (37.6) | | 28 (25.0) | 22 (25.0) | |
| Middle | 25 (32.1) | 42 (39.3) | | 23 (33.3) | 26 (37.7) | |
| Lower | 9 (11.5) | 12 (11.2) | | 7 (10.1) | 10 (14.5) | |
| More than two position or total | 14 (17.9) | 18 (16.8) | | 11 (15.9) | 11 (15.9) | |
| Clinical T stage *n* (%) | | | 0.402 | | | 0.784 |
| 2 | 3 (3.8) | 1 (0.9) | | 3 (4.3) | 1 (1.4) | |
| 3 | 19 (24.4) | 26 (24.3) | | 17 (24.6) | 18 (26.1) | |
| 4 | 56 (71.8) | 80 (74.8) | | 49 (71.0) | 50 (72.5) | |
| Clinical N stage *n* (%) | | | 0.404 | | | 0.619 |
| 0 | 1 (1.3) | 5 (4.7) | | 1 (1.4) | 3 (4.3) | |
| 1-3 | 77 (98.7) | 102 (95.3) | | 68 (98.6) | 66 (95.7) | |
| Clinical TNM stage *n* (%) | | | 0.966 | | | 1.000 |
| II | 4 (5.1) | 6 (5.6) | | 4 (5.8) | 4 (5.8) | |
| III | 73 (93.6) | 100 (93.5) | | 64 (92.8) | 65 (94.2) | |
| IVA | 1 (1.3) | 1 (0.9) | | 1 (1.4) | 0 (0) | |
| Tumor size (cm) | 5.2 ± 3.1 | 6.0 ± 3.4 | 0.126 | 5.4 ± 3.3 | 5.4 ± 3.1 | 0.953 |
| Nerve invasion *n* (%) | | | 1.000 | | | 0.394 |
| Yes | 43 (55.1) | 59 (55.1) | | 38 (55.1) | 33 (47.8) | |
| No | 35 (44.9) | 48 (44.9) | | 31 (44.9) | 36 (52.2) | |
| Lymph-vascular invasion *n* (%) | | | 0.410 | | | 1.000 |
| Yes | 43 (55.1) | 59 (55.1) | | 23 (33.3) | 23 (33.3) | |
| No | 35 (44.9) | 48 (44.9) | | 46 (66.7) | 46 (66.7) | |
| Differentiation *n* (%) | | | 0.360 | | | 0.780 |
| Well | 4 (5.1) | 3 (2.8) | | 1 (1.4) | 2 (2.9) | |
| Moderate | 24 (30.8) | 25 (23.4) | | 22 (31.9) | 19 (27.5) | |
| Poor | 50 (64.1) | 79 (73.8) | | 46 (66.7) | 48 (69.6) | |
| Pathological T stage *n* (%) | | | 0.254 | | | 0.282 |
| ypT0-1 | 8 (10.3) | 8 (7.5) | | 6 (8.7) | 7 (10.1) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| ypT2 | 11 (14.1) | 7 (6.5) | | 11 (15.9) | 4 (5.8) | |
| ypT3 | 23 (29.5) | 31 (29.0) | | 17 (24.6) | 21 (30.4) | |
| ypT4a/4b | 36 (46.2) | 61 (57.0) | | 35 (50.7) | 37 (53.6) | |
| Pathological N stage *n* (%) | | | 0.168 | | | 0.443 |
| ypN0 | 26 (33.3) | 26 (24.3) | | 23 (33.3) | 18 (26.1) | |
| ypN1 | 12 (15.4) | 23 (21.5) | | 11 (15.9) | 18 (26.1) | |
| ypN2 | 16 (20.5) | 14 (13.1) | | 14 (20.3) | 11 (15.9) | |
| ypN3 | 24 (30.8) | 44 (41.1) | | 21 (30.4) | 22 (31.9) | |
| Distant metastasis *n* (%) | | | 0.531 | | | 1.000 |
| Yes | 6 (7.7) | 5 (4.7) | | 4 (5.8) | 3 (4.3) | |
| No | 72 (92.3) | 102 (95.3) | | 65 (94.2) | 66 (95.7) | |
| Pathological TNM stage *n* (%) | | | 0.576 | | | 0.781 |
| IIA | 12 (15.4) | 13 (12.1) | | 10 (14.5) | 9 (13.0) | |
| IIB | 17 (55.1) | 20 (64.5) | | 17 (24.6) | 13 (18.8) | |
| III | 43 (55.1) | 69 (64.5) | | 38 (55.1) | 44 (63.8) | |
| IV | 6 (7.7) | 5 (4.7) | | 4 (5.8) | 3 (4.3) | |
| Adjuvant chemotherapy *n* (%) | | | 0.824 | | | 0.848 |
| Yes | 58 (74.4) | 78 (72.9) | | 50 (72.5) | 51 (73.9) | |
| No | 20 (25.6) | 29 (27.1) | | 19 (27.5) | 18 (26.1) | |

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; BMI: Body mass index; ASA: Anesthesiologists physical status classification.

Student's *t*-test, depending on the distribution of the parameters. We used the Kaplan-Meier survival analysis and the log-rank test to estimate OS and compare the survival distributions. Multivariate Cox regression analysis was used to adjust for confounding factors and non-balanced between-group variables in univariate analysis. Statistical significance was set at $P < 0.05$. All analyses were performed using SPSS statistical software (version 26.0; IBM Corp., Armonk, New York, United States).

## RESULTS

### Clinicopathologic characteristics of patients

Table 1 shows the clinical data, clinical staging, tumor status, and pathological staging of the patients before PSM ($n = 185$) and after PSM ($n = 138$). Before PSM, there was a significant difference between the two groups in terms of BMI ($P = 0.028$). Compared to the OTG group, the average age was younger ($P = 0.120$), tumor size was smaller ($P = 0.126$), and occurrence of yN stage ($P = 0.168$) was lower in the LTG group; however, the differences were not statistically significant. Distant metastasis was confirmed by operative pathological examination in all 11 patients (LTG: 6, OTG: 5). In the LTG and OTG groups, distant metastasis occurred in the peritoneum of five and four patients and in the liver of one and one patients, respectively. After PSM, all clinicopathological characteristics were comparable between the LTG and OTG groups.

### NAT and response

There was no significant difference in the type of NAT between the two groups neither before nor after PSM. A total of 17 patients received NCRT, and the remaining received NAC. For NAC regimens, there was no significant difference between the groups with respect to the use of platinum-based doublets or epirubicin/taxane-based triplets, although the former was more common. The mean cycles of the groups after PSM were not statistically significantly different (3.3 *vs* 3.6, $P = 0.300$). There was no significant difference between the two groups in terms of clinical response and TRG scores before and after PSM (Table 2).

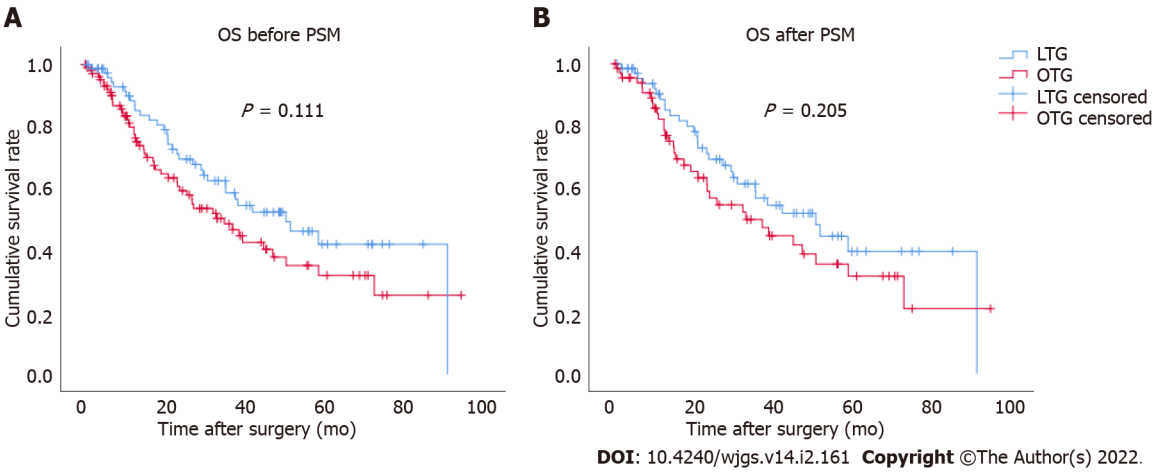
### Intraoperative and recovery outcomes

In total, 4 patients in the OTG group and none in the LTG group underwent combined resection. Before and after PSM, the LTG group showed significant differences in the following characteristics:

**Table 2 Neoadjuvant therapy and response before and after propensity score matching**

| Variable | All patients | | *P* value | Matched patients | | *P* value |
|---|---|---|---|---|---|---|
| | LTG (*n* = 78) | OTG (*n* = 107) | | LTG (*n* = 69) | OTG (*n* = 69) | |
| Type *n* (%) | | | 0.345 | | | 0.784 |
| NAC | 69 (88.5) | 99 (92.5) | | 61 (88.4) | 62 (89.9) | |
| NCRT | 9 (11.5) | 8 (7.5) | | 8 (11.6) | 7 (10.1) | |
| NAC regimens *n* (%) | | | 0.491 | | | 0.659 |
| Platinum-based doublets | 41 (59.4) | 64 (64.6) | | 36 (59.0) | 39 (62.9) | |
| Epirubicin/taxane-based triplets | 28 (40.6) | 35 (35.4) | | 25 (41.0) | 23 (37.1) | |
| Cycles | 3.3 ± 1.3 | 3.8 ± 1.8 | 0.086 | 3.3 ± 1.3 | 3.6 ± 1.6 | 0.300 |
| Clinical response *n* (%) | | | 0.939 | | | 0.859 |
| PR | 50 (64.1) | 68 (63.6) | | 44 (63.8) | 45 (65.2) | |
| SD | 28 (35.9) | 39 (36.4) | | 25 (36.2) | 24 (34.8) | |
| Mandard TRG score *n* (%) | | | 0.316 | | | 0.654 |
| 1 | 26 (33.3) | 52 (48.6) | | 22 (31.9) | 29 (42.0) | |
| 2 | 4 (5.1) | 4 (3.7) | | 4 (5.8) | 2 (2.9) | |
| 3 | 30 (38.5) | 34 (31.8) | | 26 (37.7) | 25 (36.2) | |
| 4 | 5 (6.4) | 5 (4.7) | | 5 (7.2) | 5 (7.2) | |
| 5 | 13 (16.7) | 12 (11.2) | | 12 (17.4) | 8 (11.6) | |

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; NAC: Neoadjuvant chemotherapy; NCRT: Neoadjuvant chemoradiotherapy; PR: Partial response; SD: Stable disease; TRG: Tumor regression grading.



DOI: 10.4240/wjgs.v14.i2.161 

**Figure 1 Comparison of cumulative survival rates between laparoscopic total gastrectomy and open total gastrectomy.** A: Before propensity score matching (PSM); B: After PSM. There was no statistically significant difference in overall survival between the two groups before (*P* = 0.111) and after PSM (*P* = 0.205). LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; OS: Overall survival; PSM: Propensity score matching.

Postoperative hospital days (11.5 ± 7.1 *vs* 16.0 ± 12.8 d, *P* = 0.012), time to removal of gastric tube (5.1 ± 2.0 *vs* 6.8 ± 5.2, *P* = 0.013), and length of incision (10.4 ± 4.6 *vs* 21.9 ± 3.8, *P* < 0.001). Although the difference was not statistically significant, we found that blood loss during surgery in the LTG group was less than that in the OTG group (200.6 ± 162.0 *vs* 237.1 ± 194.9, *P* = 0.116). The R0 resection rates of the LTG and OTG groups were 95.7% and 97.1%, respectively, and the numbers of dissected lymph nodes were 37.3 ± 14.2 and 35.5 ± 15.9, respectively, which were not significantly different (Table 3).

### *Postoperative complications*

The overall postoperative complication rates of the LTG and OTG groups were 19.2% and 29.9%,

**Table 3 Description of intraoperative and recovery features before and after propensity score matching**

| Variable | All patients | | *P* value | Matched patients | | *P* value |
|---|---|---|---|---|---|---|
| | LTG (*n* = 78) | OTG (*n* = 107) | | LTG (*n* = 69) | OTG (*n* = 69) | |
| Operation time (min) | 207.6 ± 49.3 | 205.2 ± 52.1 | 0.744 | 204.0 ± 45.8 | 207.1 ± 53.1 | 0.713 |
| Blood loss (mL) | 197.2 ± 162.4 | 228.1 ± 193.4 | 0.252 | 200.6 ± 162.0 | 237.1 ± 194.9 | 0.116 |
| Combined resection *n* (%) | | | 0.139 | | | 0.245 |
| Yes | 0 (0) | 4 (3.7) | | 0 (0) | 3 (4.3) | |
| No | 78 (100) | 107 (96.3) | | 69 (100) | 66 (95.7) | |
| Resection *n* (%) | | | 0.651 | | | 1.000 |
| R0 | 75 (96.2) | 105 (98.1) | | 66 (95.7) | 67 (97.1) | |
| R1/R2 | 3 (3.8) | 2 (1.9) | | 3 (4.3) | 2 (2.9) | |
| Blood transfusion *n* (%) | | | 0.608 | | | 0.507 |
| Yes | 13 (16.7) | 21 (80.4) | | 11 (15.9) | 14 (20.3) | |
| No | 65 (83.3) | 86 (19.6) | | 58 (84.1) | 55 (79.7) | |
| Length of incision (cm) | 10.29 ± 4.4 | 21.6 ± 3.8 | < 0.001 | 10.4 ± 4.6 | 21.9 ± 3.8 | < 0.001 |
| Postoperative hospital stay (d) | 11.6 ± 7.0 | 15.1 ± 10.9 | 0.015 | 11.5 ± 7.1 | 16.0 ± 12.8 | 0.012 |
| Dissected lymph nodes | 37.7 ± 14.5 | 37.8 ± 17.6 | 0.950 | 37.3 ± 14.2 | 35.5 ± 15.9 | 0.465 |
| Time to ambulation (d) | 3.0 ± 1.2 | 3.4 ± 2.4 | 0.130 | 3.0 ± 1.3 | 3.4 ± 2.3 | 0.229 |
| Time to first flatus (d) | 4.8 ± 1.7 | 5.2 ± 2.3 | 0.235 | 4.9 ± 1.7 | 5.1 ± 1.8 | 0.381 |
| Time to first liquid intake (d) | 9.2 ± 5.6 | 10.1 ± 7.8 | 0.404 | 9.1 ± 5.6 | 10.7 ± 8.7 | 0.201 |
| Time to removal of gastric tube (d) | 5.0 ± 2.0 | 6.5 ± 5.0 | 0.008 | 5.1 ± 2.0 | 6.8 ± 5.2 | 0.013 |
| Time to removal of all drainage tubes | 9.7 ± 10.1 | 11.1 ± 11.1 | 0.391 | 9.7 ± 10.5 | 10.9 ± 10.3 | 0.488 |

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy.

respectively, before PSM, and 20.3% and 29.0%, respectively, after PSM. The overall postoperative complications had no significant difference between the two groups before and after PSM. The most common surgical complications after LTG include abdominal infection, anastomotic leakage and wound infection. For OTG, the most common surgical complications include wound infection, anastomotic leakage, abdominal infection, and gastroparesis. Notably, 8 patients in the OTG group developed medical complications, including pulmonary infection, arterial catheter-related infection, and renal failure, whereas none in the LTG group did. There were no significant differences in terms of minor complications (Grades I-II according to the Clavien-Dindo classification) and severe complications (Grade III-V) between the two groups before and after PSM (Table 4). None of the patients in either group died within the first 30 d after surgery.

### *Long-term oncological outcomes*

The Kaplan-Meier survival curve for OS between the LTG and OTG groups was plotted (Figure 1). The median follow-up period was 45 mo (range, 3-94 mo). There were no significant differences between the two groups before ($P$ = 0.111) and after PSM ($P$ = 0.205). After PSM, the calculated 5-year cumulative survival rates of the LTG and OTG groups were 39.4% and 31.4%, respectively.

To identify prognostic factors, univariate and multivariate Cox regression analyses were performed after PSM (Table 5). In the univariate analysis, ypT ($P$ = 0.002), ypN ($P$ = 0.004), metastasis ($P$ = 0.103), nerve invasion ($P$ = 0.064), lymph-vascular invasion ($P$ = 0.005), Mandard TRG scores ($P$ = 0.007), type of NAT ($P$ = 0.083), and R0 ($P$ = 0.109) were closely associated with OS. These variables were entered into the multivariate analysis and revealed that ypT0–3 ($P$ = 0.014) and ypN0 ($P$ = 0.010) were independently associated with OS (Figure 2).

## DISCUSSION

Recently, LTG has been widely performed in many high-volume hospitals and has gradually expanded

**Table 4 Postoperative complications before and after propensity score matching**

| Variable | All patients | | *P* value | Matched patients | | *P* value |
|---|---|---|---|---|---|---|
| | LTG (*n* = 78) | OTG (*n* = 107) | | LTG (*n* = 69) | OTG (*n* = 69) | |
| Complications, *n* (%) | | | | | | |
| Overall | | | 0.100 | | | 0.236 |
| Yes | 15 (19.2) | 32 (29.9) | | 14 (20.3) | 20 (29.0) | |
| No | 63 (80.8) | 75 (70.1) | | 55 (79.7) | 49 (71.0) | |
| Surgical complications | | | | | | |
| Pancreatic fistula | 0 (0) | 1 (0.9) | 1.000 | 0 (0) | 1 (1.4) | 1.000 |
| Abdominal bleeding | 1 (1.3) | 0 (0) | 0.422 | 1 (1.4) | 0 (0) | 1.000 |
| Anastomotic leakage | 5 (6.4) | 6 (5.6) | 1.000 | 4 (5.8) | 3 (4.3) | 1.000 |
| Wound infection | 4 (5.1) | 5 (4.7) | 1.000 | 4 (5.8) | 4 (5.8) | 1.000 |
| Lymphorrhagia | 1 (1.3) | 0 (0) | 0.422 | 1 (1.4) | 0 (0) | 1.000 |
| Intestinal obstruction | 0 (0) | 2 (1.9) | 0.510 | 0 (0) | 1 (1.4) | 1.000 |
| Abdominal infection | 5 (6.4) | 9 (8.4) | 0.611 | 5 (7.2) | 2 (2.9) | 0.441 |
| Duodenal fistula | 0 (0) | 1 (0.9) | 1.000 | 0 (0) | 0 (0) | NA |
| Gastroparesis | 0 (0) | 3 (2.8) | 0.264 | 0 (0) | 3 (4.3) | 0.245 |
| Medical complications | | | | | | |
| Pulmonary infection | 0 (0) | 6 (5.6%) | 0.04 | 0 | 5 (7.2) | 0.058 |
| Arterial catheter-related infection | 0 (0) | 1 (0.9) | 1.000 | 0 (0) | 1 (1.4) | 1.000 |
| Renal failure | 0 (0) | 1 (0.9) | 1.000 | 0 (0) | 1 (1.4) | 1.000 |
| Clavien-Dindo classification *n* (%) | | | 0.331 | | | 1.000 |
| Grade I-II | 12 (80.0) | 20 (64.5) | | 11 (78.6) | 14 (73.7) | |
| Grade III-V | 3 (20.0) | 11 (35.5) | | 3 (21.4) | 5 (26.3) | |

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy.

the indications for surgery from EGC to AGC[19,20]. However, only one study to date has confirmed the non-inferiority of LTG compared to OTG after NAC in short-term outcomes[12]. To the best of our knowledge, our study is the first to report the long- and short-term outcomes of LTG. Moreover, we found that LTG offered significant advantages in terms of shorter postoperative hospital days and earlier gastric tube removal and had similar postoperative complication rates and OS to those of OTG for patients with GC treated with NAT.

Although NAT is regarded as a key step in the comprehensive treatment of GC, the difference in NAC regimens between Western and Eastern Asian countries should be considered. Three or four-drug NAC regimens have been proved effective in AGC[2,21-24]; however, NAC clinical trials based on two-drug regimens have been exten-sively undertaken in Eastern Asian countries, including JCOG 0210[25], JCOG 0405[26], JCOG 0501[27] in Japan, the NEO-CLASSIC study[28] and the RESOLVE trial (NCT01534546) in China. The optimal NAC regimen for treating AGC remains controversial worldwide, and the differences between Eastern and Western treatment regimens in GC cannot be neglected[29]. In our study, over 60% of all patients received platinum-based doublets, and the overall response rate was more than 60%. Over 80% of all cases were TRG 1-3, which was proved to be an independent prognostic factor[30].

Previous studies have confirmed the oncological and surgical safety of LDG after NAC. Studies by Li *et al*[11] demonstrated that compared to open surgery, LDG has an advantage in postoperative rehabilitation and complications. A number of meta-analyses and retrospective studies have shown that although there is no significant difference between LTG and OTG in the number of lymph node dissections and the rate of radical surgery, LTG has a lower amount of intraoperative bleeding, lower rate of postoperative complications, and faster postoperative rehabilitation[9,10,31-33]. However, none of these studies specifically focused on the influence of NAT on TG. In our study, we found that in addition to the advantage in incision length, the LTG group had a faster postoperative recovery than that of the OTG group after NAT, which was mainly reflected in the postoperative hospital stay.

**Table 5 Univariate and multivariate analysis of overall survival after propensity score matching**

| Variables | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95%CI | *P* value | Hazard ratio | 95%CI | *P* value |
| Age (yr): < 60 *vs* ≥ 60 | 0.806 | 0.491-1.323 | 0.393 | | | |
| Sex: Female *vs* Male | 1.244 | 0.711-2.177 | 0.444 | | | |
| ASA: 1-2 *vs* 3 | 0.978 | 0.355-2.696 | 0.965 | | | |
| Surgery: LTG *vs* OTG | 0.729 | 0.446-1.192 | 0.207 | | | |
| BMI: < 28 *vs* ≥ 28 | 1.608 | 0.504-5.133 | 0.422 | | | |
| Differentiation: Well/moderate *vs* Poor | 0.713 | 0.416-1.224 | 0.220 | | | |
| ypT stage: T0-3 *vs* T4 | 0.446 | 0.267-0.746 | 0.002 | 0.520 | 0.308-0.877 | 0.014 |
| ypN stage: N0 *vs* N1-3 | 0.401 | 0.217-0.741 | 0.004 | 0.431 | 0.227-0.821 | 0.010 |
| Metastasis: M0 *vs* M1 | 0.425 | 0.152-1.188 | 0.103 | 0.529 | 0.185-1.510 | 0.234 |
| Nerve invasion: Yes *vs* No | 1.601 | 0.973-2.635 | 0.064 | 0.930 | 0.531-1.628 | 0.799 |
| Lymph-vascular invasion: Yes *vs* No | 2.046 | 1.236-3.388 | 0.005 | 1.155 | 0.623-2.140 | 0.647 |
| Mandard TRG: ≤ 3 *vs* > 3 | 0.510 | 0.312-0.833 | 0.007 | 0.666 | 0.390-1.136 | 0.136 |
| Postoperative complication: Yes *vs* No | 0.635 | 0.338-1.193 | 0.158 | | | |
| Type of NAT: NAC *vs* NCRT | 2.248 | 0.900-5.619 | 0.083 | 1.647 | 0.619-4.382 | 0.317 |
| Resection: R0 *vs* R1/R2 | 0.385 | 0.120-1.237 | 0.109 | 0.357 | 0.110-1.154 | 0.085 |

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; CI: Confidence interval; ASA: American Society of Anesthesiologist; BMI: Body mass index; TRG: Tumor regression grading; NAT: Neoadjuvant therapy; NAC: Neoadjuvant chemotherapy; NCRT: Neoadjuvant chemoradiotherapy.

Compared to a previous study[19], the mean postoperative hospital stay in the LTG group (11.5 d) was slightly longer, which was possibly attributed to the NAT. The number of dissected lymph nodes can be considered an indicator to evaluate the quality of gastrectomy, and is positively correlated with the prognosis of GC[34-36]. The number of dissected lymph nodes between the LTG and OTG groups was not significantly different, and the mean number in LTG (37.3 ± 14.2) was similar to that observed in a previous study[37].

Whether NAT will negatively influence the incidence of postoperative morbidities is of great concern to oncologists and surgeons. A few prospective studies have indicated that NAT does not significantly increase postoperative morbidity in patients with GC[2,22,38]. In the present study, morbidity rates were in accordance with those observed in previous studies, which ranged from 9.6% to 23.8% in LTG, and from 15.6% to 68% in OTG[10,39-41]. To fully elucidate the influence of NAT, large-sample multicenter studies are needed. As for the specific complications, we noticed that both groups had comparable numbers of cases of anastomotic leakage. Moreover, pulmonary infection occurred in 6 patients in the OTG group and none in the LTG group, which was in accordance with a previous study [10]. This rather intriguing finding might be a result of minimally invasive techniques which avoid unnecessary trauma while detaching the cardia region[42].

Whether LTG can achieve the same oncologic outcomes as those of OTG is still debatable. Although LTG is minimally invasive and offers quicker rehabilitation, it also allows a limited visual field and poses challenges to prognosis. Current guidelines only recommend attempting LTG with caution[15, 43]. Several retrospective studies showed that there is no significant difference between LTG and OTG in oncological results[44]; however, none of these studies focused on the prognosis of patients treated with NAT. In our study, we found a comparable OS between the LTG and OTG groups, which showed that LTG is non-inferior to OTG after NAT in long-term oncologic outcomes. By using a univariate and multivariate Cox regression analysis, we further found that pathological T stage and N stage were independent risk factors for OS and that the type of TG did not influence the prognosis. With the development of the concept of comprehensive treatment for GC, patients are expected to have a better prognosis.

The major limitation of our study is that it was a single retrospective study. To reduce sample bias and balance the baseline, PSM was performed, which decreased the sample size. In our study, we excluded the missing data instead of multiple imputation, which may bring less statistical power and bias. Therefore, further high-volume, prospective, and multi-center clinical trials are required to

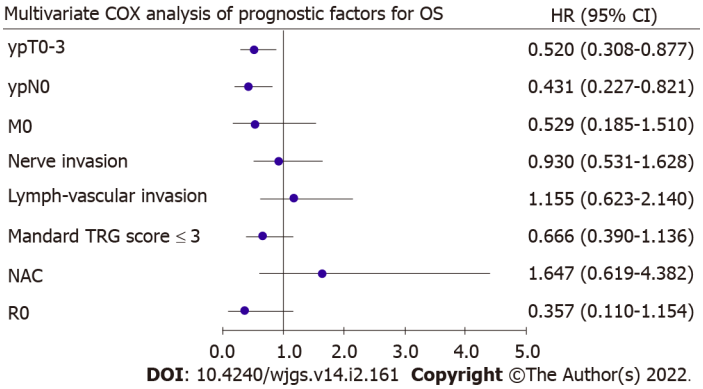



**Figure 2 Forest graph of multivariate COX analysis of prognostic factors for overall survival.** Pathological T stage and N stage were found as independent risk factors for overall survival. OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; TRG: Tumor regression grading; NAC: Neoadjuvant chemotherapy.

evaluate the surgical and oncological outcomes of LTG after NAT.

## CONCLUSION

In conclusion, LTG is considered advantageous in the postoperative rehabilitation of AGC patients treated with NAT and can achieve similar long-term outcomes compared to those of OTG.

## ARTICLE HIGHLIGHTS

### *Research background*

Laparoscopic total gastrectomy (LTG) has been widely used these days. Its surgical and oncological outcomes following neoadjuvant therapy (NAT) is still unkown.

### *Research motivation*

To compare the long- and short-term outcomes between LTG and open TG (OTG) following NAT.

### *Research objectives*

Advanced gastric cancer (GC) patients who underwent TG following NAT.

### *Research methods*

Patients were divided into two groups: LTG and OTG. Propensity score matching analysis was performed to minimize possible bias.

### *Research results*

LTG had advantages in short-term outcomes, such as shorter length of hospital stay ($P$ = 0.012), and the oncological outcomes were close to OTG. Overall survival (OS) outcomes were comparable between the two groups. Pathological T and N stages were independent risk factors for OS.

### *Research conclusions*

LTG can be a safe and effective method for advanced GC patients following NAT.

### *Research perspectives*

Further high-volume, prospective, and multi-center clinical trials are required to evaluate the surgical and oncological outcomes of LTG.

## FOOTNOTES

**Author contributions:** Hu HT contributed to the design of the study, collected data and drafted the manuscript; Ma FH and Xiong JP performed the data analyses and revised the manuscript; Li Y, Jin P and Liu H helped perform the analysis with constructive discussions; Ma S and Kang WZ contributed to manuscript preparation data for the work;

Tian YT conceived the work that led to the submission and approved the final version; and all authors issued final approval for the version to be submitted.

**Supported by** National Natural Science Foundation of China, No. 81772642.

**Institutional review board statement:** This study was approved by the Ethics Committee of the Cancer Hospital of the Chinese Academy of Medical Sciences (No.14-067/857).

**Informed consent statement:** This study obtained informed consent exemptions approved by the Ethics Committee of the Cancer Hospital of the Chinese Academy of Medical Sciences.

**Conflict-of-interest statement:** All authors declare no conflicts of interest related to this article.

**Data sharing statement:** No additional data are available.



**Country/Territory of origin:** China

**ORCID number:** Hai-Tao Hu 0000-0003-0585-6070; Fu-Hai Ma 0000-0003-2437-6881; Jian-Ping Xiong 0000-0001-6593-6377; Yang Li 0000-0002-4549-1087; Peng Jin 0000-0001-8179-6191; Hao Liu 0000-0001-5809-6824; Shuai Ma 0000-0003-1738-6651; Wen-Zhe Kang 0000-0001-9965-8109; Yan-Tao Tian 0000-0001-6479-7547.

**S-Editor:** Wang JJ
**L-Editor:** A
**P-Editor:** Wang JJ

## REFERENCES

1 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]

2 **Cunningham D**, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355**: 11-20 [PMID: 16822992 DOI: 10.1056/NEJMoa055531]

3 **Kim HH**, Han SU, Kim MC, Kim W, Lee HJ, Ryu SW, Cho GS, Kim CY, Yang HK, Park DJ, Song KY, Lee SI, Ryu SY, Lee JH, Hyung WJ; Korean Laparoendoscopic Gastrointestinal Surgery Study (KLASS) Group. Effect of Laparoscopic Distal Gastrectomy vs Open Distal Gastrectomy on Long-term Survival Among Patients With Stage I Gastric Cancer: The KLASS-01 Randomized Clinical Trial. *JAMA Oncol* 2019; **5**: 506-513 [PMID: 30730546 DOI: 10.1001/jamaoncol.2018.6727]

4 **Hu Y**, Huang C, Sun Y, Su X, Cao H, Hu J, Xue Y, Suo J, Tao K, He X, Wei H, Ying M, Hu W, Du X, Chen P, Liu H, Zheng C, Liu F, Yu J, Li Z, Zhao G, Chen X, Wang K, Li P, Xing J, Li G. Morbidity and Mortality of Laparoscopic Versus Open D2 Distal Gastrectomy for Advanced Gastric Cancer: A Randomized Controlled Trial. *J Clin Oncol* 2016; **34**: 1350-1357 [PMID: 26903580 DOI: 10.1200/JCO.2015.63.7215]

5 **Yu J**, Huang C, Sun Y, Su X, Cao H, Hu J, Wang K, Suo J, Tao K, He X, Wei H, Ying M, Hu W, Du X, Hu Y, Liu H, Zheng C, Li P, Xie J, Liu F, Li Z, Zhao G, Yang K, Liu C, Li H, Chen P, Ji J, Li G; Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) Group. Effect of Laparoscopic vs Open Distal Gastrectomy on 3-Year Disease-Free Survival in Patients With Locally Advanced Gastric Cancer: The CLASS-01 Randomized Clinical Trial. *JAMA* 2019; **321**: 1983-1992 [PMID: 31135850 DOI: 10.1001/jama.2019.5359]

6 **Liu K**, Yang K, Zhang W, Chen X, Zhang B, Chen Z, Chen J, Zhao Y, Zhou Z, Chen L, Hu J. Changes of Esophagogastric Junctional Adenocarcinoma and Gastroesophageal Reflux Disease Among Surgical Patients During 1988-2012: A Single-institution, High-volume Experience in China. *Ann Surg* 2016; **263**: 88-95 [PMID: 25647058 DOI: 10.1097/SLA.0000000000001148]

7 **Katai H**, Mizusawa J, Katayama H, Morita S, Yamada T, Bando E, Ito S, Takagi M, Takagane A, Teshima S, Koeda K, Nunobe S, Yoshikawa T, Terashima M, Sasako M. Survival outcomes after laparoscopy-assisted distal gastrectomy versus open distal gastrectomy with nodal dissection for clinical stage IA or IB gastric cancer (JCOG0912): a multicentre, non-inferiority, phase 3 randomised controlled trial. *Lancet Gastroenterol Hepatol* 2020; **5**: 142-151 [PMID: 31757656 DOI: 10.1016/S2468-1253(19)30332-2]

8 **Liu F**, Huang C, Xu Z, Su X, Zhao G, Ye J, Du X, Huang H, Hu J, Li G, Yu P, Li Y, Suo J, Zhao N, Zhang W, Li H, He H, Sun Y; Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) Group. Morbidity and Mortality of Laparoscopic vs Open Total Gastrectomy for Clinical Stage I Gastric Cancer: The CLASS02 Multicenter Randomized Clinical Trial. *JAMA Oncol* 2020; **6**: 1590-1597 [PMID: 32815991 DOI: 10.1001/jamaoncol.2020.3152]

9 **Straatman J**, van der Wielen N, Cuesta MA, de Lange-de Klerk ES, Jansma EP, van der Peet DL. Minimally Invasive Versus Open Total Gastrectomy for Gastric Cancer: A Systematic Review and Meta-analysis of Short-Term Outcomes and Completeness of Resection : Surgical Techniques in Gastric Cancer. *World J Surg* 2016; **40**: 148-157 [PMID: 26350821 DOI: 10.1007/s00268-015-3223-1]

10 **Haverkamp L**, Weijs TJ, van der Sluis PC, van der Tweel I, Ruurda JP, van Hillegersberg R. Laparoscopic total gastrectomy versus open total gastrectomy for cancer: a systematic review and meta-analysis. *Surg Endosc* 2013; **27**: 1509-1520 [PMID: 23263644 DOI: 10.1007/s00464-012-2661-1]

11 **Li Z**, Shan F, Ying X, Zhang Y, E JY, Wang Y, Ren H, Su X, Ji J. Assessment of Laparoscopic Distal Gastrectomy After Neoadjuvant Chemotherapy for Locally Advanced Gastric Cancer: A Randomized Clinical Trial. *JAMA Surg* 2019; **154**: 1093-1101 [PMID: 31553463 DOI: 10.1001/jamasurg.2019.3473]

12 **van der Wielen N**, Straatman J, Daams F, Rosati R, Parise P, Weitz J, Reissfelder C, Diez Del Val I, Loureiro C, Parada-González P, Pintos-Martínez E, Mateo Vallejo F, Medina Achirica C, Sánchez-Pernaute A, Ruano Campos A, Bonavina L, Asti ELG, Alonso Poza A, Gilsanz C, Nilsson M, Lindblad M, Gisbertz SS, van Berge Henegouwen MI, Fumagalli Romario U, De Pascale S, Akhtar K, Jaap Bonjer H, Cuesta MA, van der Peet DL. Open versus minimally invasive total gastrectomy after neoadjuvant chemotherapy: results of a European randomized trial. *Gastric Cancer* 2021; **24**: 258-271 [PMID: 32737637 DOI: 10.1007/s10120-020-01109-w]

13 **Fujisaki M**, Mitsumori N, Shinohara T, Takahashi N, Aoki H, Nyumura Y, Kitazawa S, Yanaga K. Short- and long-term outcomes of laparoscopic versus open gastrectomy for locally advanced gastric cancer following neoadjuvant chemotherapy. *Surg Endosc* 2021; **35**: 1682-1690 [PMID: 32277356 DOI: 10.1007/s00464-020-07552-1]

14 **Wang N**, Zhou A, Jin J, Huang H, Zhang Y, Chen Y, Zhao D. Open vs. laparoscopic surgery for locally advanced gastric cancer after neoadjuvant therapy: Short-term and long-term survival outcomes. *Oncol Lett* 2020; **20**: 861-867 [PMID: 32566013 DOI: 10.3892/ol.2020.11626]

15 **Japanese Gastric Cancer Association**. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer* 2021; **24**: 1-21 [PMID: 32060757 DOI: 10.1007/s10120-020-01042-y]

16 **Dindo D**, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205-213 [PMID: 15273542 DOI: 10.1097/01.sla.0000133083.54934.ae]

17 **Langer R**, Becker K. Tumor regression grading of gastrointestinal cancers after neoadjuvant therapy. *Virchows Arch* 2018; **472**: 175-186 [PMID: 28918544 DOI: 10.1007/s00428-017-2232-x]

18 **D'Agostino RB Jr**. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998; **17**: 2265-2281 [PMID: 9802183 DOI: 10.1002/(sici)1097-0258(19981015)17:19<2265::aid-sim918>3.0.co;2-b]

19 **Huang CJ**, Zhang RC, Mou YP, Zhou YC, Wang YY, Lu C, Xu XW. Short and long-term outcomes of laparoscopic total gastrectomy for gastric cancer: A single-center experience (retrospective cohort study). *Int J Surg* 2018; **51**: 109-113 [PMID: 29367040 DOI: 10.1016/j.ijsu.2018.01.027]

20 **Komatsu S**, Kosuga T, Kubota T, Okamoto K, Konishi H, Shiozaki A, Fujiwara H, Ichikawa D, Otsuji E. Comparison of short- and long-term outcomes following laparoscopy and open total gastrectomy for gastric cancer: a propensity score-matched analysis. *Am J Transl Res* 2020; **12**: 2225-2233 [PMID: 32509214]

21 **Ychou M**, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, Ducourtieux M, Bedenne L, Fabre JM, Saint-Aubert B, Genève J, Lasser P, Rougier P. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011; **29**: 1715-1721 [PMID: 21444866 DOI: 10.1200/JCO.2010.33.0597]

22 **Al-Batran SE**, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, Kopp HG, Mayer F, Haag GM, Luley K, Lindig U, Schmiegel W, Pohl M, Stoehlmacher J, Folprecht G, Probst S, Prasnikar N, Fischbach W, Mahlberg R, Trojan J, Koenigsmann M, Martens UM, Thuss-Patience P, Egger M, Block A, Heinemann V, Illerhaus G, Moehler M, Schenk M, Kullmann F, Behringer DM, Heike M, Pink D, Teschendorf C, Löhr C, Bernhard H, Schuch G, Rethwisch V, von Weikersthal LF, Hartmann JT, Kneba M, Daum S, Schulmann K, Weniger J, Belle S, Gaiser T, Oduncu FS, Güntner M, Hozaeel W, Reichart A, Jäger E, Kraus T, Mönig S, Bechstein WO, Schuler M, Schmalenberg H, Hofheinz RD; FLOT4-AIO Investigators. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet* 2019; **393**: 1948-1957 [PMID: 30982686 DOI: 10.1016/S0140-6736(18)32557-1]

23 **Al-Batran SE**, Hofheinz RD, Pauligk C, Kopp HG, Haag GM, Luley KB, Meiler J, Homann N, Lorenzen S, Schmalenberg H, Probst S, Koenigsmann M, Egger M, Prasnikar N, Caca K, Trojan J, Martens UM, Block A, Fischbach W, Mahlberg R, Clemens M, Illerhaus G, Zirlik K, Behringer DM, Schmiegel W, Pohl M, Heike M, Ronellenfitsch U, Schuler M, Bechstein WO, Königsrainer A, Gaiser T, Schirmacher P, Hozaeel W, Reichart A, Goetze TO, Sievert M, Jäger E, Mönig S, Tannapfel A. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. *Lancet Oncol* 2016; **17**: 1697-1708 [PMID: 27776843 DOI: 10.1016/S1470-2045(16)30531-9]

24 **Cunningham D**, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J, Norman AR; Upper Gastrointestinal Clinical Studies Group of the National Cancer Research Institute of the United Kingdom. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008; **358**: 36-46 [PMID: 18172173 DOI: 10.1056/NEJMoa073149]

25 **Iwasaki Y**, Sasako M, Yamamoto S, Nakamura K, Sano T, Katai H, Tsujinaka T, Nashimoto A, Fukushima N, Tsuburaya A; Gastric Cancer Surgical Study Group of Japan Clinical Oncology Group. Phase II study of preoperative chemotherapy with S-1 and cisplatin followed by gastrectomy for clinically resectable type 4 and large type 3 gastric cancers (JCOG0210). *J Surg Oncol* 2013; **107**: 741-745 [PMID: 23400787 DOI: 10.1002/jso.23301]

26 **Tsuburaya A**, Mizusawa J, Tanaka Y, Fukushima N, Nashimoto A, Sasako M; Stomach Cancer Study Group of the Japan

Clinical Oncology Group. Neoadjuvant chemotherapy with S-1 and cisplatin followed by D2 gastrectomy with para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis. *Br J Surg* 2014; **101**: 653-660 [PMID: 24668391 DOI: 10.1002/bjs.9484]

27 **Terashima M**, Iwasaki Y, Mizusawa J, Katayama H, Nakamura K, Katai H, Yoshikawa T, Ito Y, Kaji M, Kimura Y, Hirao M, Yamada M, Kurita A, Takagi M, Boku N, Sano T, Sasako M; Stomach Cancer Study Group, Japan Clinical Oncology Group. Randomized phase III trial of gastrectomy with or without neoadjuvant S-1 plus cisplatin for type 4 or large type 3 gastric cancer, the short-term safety and surgical results: Japan Clinical Oncology Group Study (JCOG0501). *Gastric Cancer* 2019; **22**: 1044-1052 [PMID: 30827001 DOI: 10.1007/s10120-019-00941-z]

28 **Yu Y**, Fang Y, Shen Z, Wang Y, Yan M, Cao H, Liu Y, Wang X, Cui Y, Liu F, Chen W, Li W, Li Q, Jiang H, Sun Y, Liu T. Oxaliplatin plus Capecitabine in the Perioperative Treatment of Locally Advanced Gastric Adenocarcinoma in Combination with D2 Gastrectomy: NEO-CLASSIC Study. *Oncologist* 2019; **24**: 1311-e989 [PMID: 31239311 DOI: 10.1634/theoncologist.2019-0416]

29 **Chan WL**, Lam KO, Lee VHF, Davidson M, So TH, Li JS, Chau I, Kwong DLW. Gastric Cancer - From Aetiology to Management: Differences Between the East and the West. *Clin Oncol (R Coll Radiol)* 2019; **31**: 570-577 [PMID: 31178345 DOI: 10.1016/j.clon.2019.05.012]

30 **Mandard AM**, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, Roussel A, Jacob JH, Segol P, Samama G. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer* 1994; **73**: 2680-2686 [PMID: 8194005 DOI: 10.1002/1097-0142(19940601)73:11<2680::aid-cncr2820731105>3.0.co;2-c]

31 **Kawamura H**, Yokota R, Homma S, Kondo Y. Comparison of invasiveness between laparoscopy-assisted total gastrectomy and open total gastrectomy. *World J Surg* 2009; **33**: 2389-2395 [PMID: 19760315 DOI: 10.1007/s00268-009-0208-y]

32 **Kim MG**, Kim BS, Kim TH, Kim KC, Yook JH. The effects of laparoscopic assisted total gastrectomy on surgical outcomes in the treatment of gastric cancer. *J Korean Surg Soc* 2011; **80**: 245-250 [PMID: 22066043 DOI: 10.4174/jkss.2011.80.4.245]

33 **Shim JH**, Oh SI, Yoo HM, Jeon HM, Park CH, Song KY. Short-term outcomes of laparoscopic versus open total gastrectomy: a matched-cohort study. *Am J Surg* 2013; **206**: 346-351 [PMID: 23642650 DOI: 10.1016/j.amjsurg.2012.11.011]

34 **Yamashita K**, Hosoda K, Ema A, Watanabe M. Lymph node ratio as a novel and simple prognostic factor in advanced gastric cancer. *Eur J Surg Oncol* 2016; **42**: 1253-1260 [PMID: 27017273 DOI: 10.1016/j.ejso.2016.03.001]

35 **Fujiwara Y**, Fukuda S, Tsujie M, Ishikawa H, Kitani K, Inoue K, Yukawa M, Inoue M. Effects of age on survival and morbidity in gastric cancer patients undergoing gastrectomy. *World J Gastrointest Oncol* 2017; **9**: 257-262 [PMID: 28656076 DOI: 10.4251/wjgo.v9.i6.257]

36 **Marchet A**, Mocellin S, Ambrosi A, Morgagni P, Garcea D, Marrelli D, Roviello F, de Manzoni G, Minicozzi A, Natalini G, De Santis F, Baiocchi L, Coniglio A, Nitti D; Italian Research Group for Gastric Cancer (IRGGC). The ratio between metastatic and examined lymph nodes (N ratio) is an independent prognostic factor in gastric cancer regardless of the type of lymphadenectomy: results from an Italian multicentric study in 1853 patients. *Ann Surg* 2007; **245**: 543-552 [PMID: 17414602 DOI: 10.1097/01.sla.0000250423.43436.e1]

37 **Lin JX**, Huang CM, Zheng CH, Li P, Xie JW, Wang JB, Jun L, Chen QY, Lin M, Tu R. Evaluation of laparoscopic total gastrectomy for advanced gastric cancer: results of a comparison with laparoscopic distal gastrectomy. *Surg Endosc* 2016; **30**: 1988-1998 [PMID: 26208499 DOI: 10.1007/s00464-015-4429-x]

38 **Téoule P**, Trojan J, Bechstein W, Woeste G. Impact of Neoadjuvant Chemotherapy on Postoperative Morbidity after Gastrectomy for Gastric Cancer. *Dig Surg* 2015; **32**: 229-237 [PMID: 25966823 DOI: 10.1159/000381884]

39 **Li SS**, Costantino CL, Mullen JT. Morbidity and Mortality of Total Gastrectomy: a Comprehensive Analysis of 90-Day Outcomes. *J Gastrointest Surg* 2019; **23**: 1340-1348 [PMID: 31062268 DOI: 10.1007/s11605-019-04228-7]

40 **Selby LV**, Vertosick EA, Sjoberg DD, Schattner MA, Janjigian YY, Brennan MF, Coit DG, Strong VE. Morbidity after Total Gastrectomy: Analysis of 238 Patients. *J Am Coll Surg* 2015; **220**: 863-871.e2 [PMID: 25842172 DOI: 10.1016/j.jamcollsurg.2015.01.058]

41 **Jeong O**, Jung MR, Kim GY, Kim HS, Ryu SY, Park YK. Comparison of short-term surgical outcomes between laparoscopic and open total gastrectomy for gastric carcinoma: case-control study using propensity score matching method. *J Am Coll Surg* 2013; **216**: 184-191 [PMID: 23211117 DOI: 10.1016/j.jamcollsurg.2012.10.014]

42 **Cho H**, Tsuchida K, Iwasaki K, Maezawa Y. Risk factors of post-operative pneumonia in elderly patients with gastric cancer: a retrospective cohort study. *Jpn J Clin Oncol* 2021; **51**: 1044-1050 [PMID: 33744955 DOI: 10.1093/jjco/hyab032]

43 **Smyth EC**, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D; ESMO Guidelines Committee. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016; **27**: v38-v49 [PMID: 27664260 DOI: 10.1093/annonc/mdw350]

44 **Tsumura T**, Kuroda S, Nishizaki M, Kikuchi S, Kakiuchi Y, Takata N, Ito A, Watanabe M, Kuwada K, Kagawa S, Fujiwara T. Short-term and long-term comparisons of laparoscopy-assisted proximal gastrectomy with esophagogastrostomy by the double-flap technique and laparoscopy-assisted total gastrectomy for proximal gastric cancer. *PLoS One* 2020; **15**: e0242223 [PMID: 33180871 DOI: 10.1371/journal.pone.0242223]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 February 27; 14(2): 174-184

DOI: 10.4240/wjgs.v14.i2.174

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

# Impact of parenchyma-preserving surgical methods on treating patients with solid pseudopapillary neoplasms: A retrospective study with a large sample size

Yu-Qiong Li, Shu-Bo Pan, Shu-Shu Yan, Zhen-Dong Jin, Hao-Jie Huang, Li-Qi Sun

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

**P-Reviewer:** Ashihara N, Isaji S

**Received:** October 7, 2021
**Peer-review started:** October 7, 2021
**First decision:** December 4, 2021
**Revised:** December 9, 2021
**Accepted:** January 25, 2022
**Article in press:** January 25, 2022
**Published online:** February 27, 2022

**Yu-Qiong Li, Shu-Bo Pan, Zhen-Dong Jin, Hao-Jie Huang, Li-Qi Sun,** Department of Gastroenterology, Changhai Hospital, Shanghai 200433, China

**Shu-Bo Pan,** Department of Gastroenterology, Suzhou Science and Technology Town Hospital, Suzhou 215000, Jiangsu Province, China

**Shu-Shu Yan,** Department of Anesthesiology, Changhai Hospital, Shanghai 200433, China

**Li-Qi Sun,** Department of Gastroenterology, 72nd Group Army Hospital, Huzhou University, Huzhou 313000, Zhejiang Province, China

**Corresponding author:** Li-Qi Sun, MD, Assistant Professor, Department of Gastroenterology, Changhai Hospital, No. 168 Changhai Road, Yangpu District, Shanghai 200433, China. zjhzslqsmmu@qq.com

## Abstract

*BACKGROUND*

Solid pseudopapillary neoplasm of the pancreas (SPN) is a rare neoplasm that mainly affects young women.

*AIM*

To evaluate the impact of parenchyma-preserving surgical methods (PPMs, including enucleation and central pancreatectomy) in the treatment of SPN patients.

*METHODS*

From 2013 to 2019, patients who underwent pancreatectomy for SPNs were retrospectively reviewed. The baseline characteristics, intraoperative index, pathological outcomes, short-term complications and long-term follow-up data were compared between the PPM group and the conventional method (CM) group.

*RESULTS*

In total, 166 patients were included in this study. Of them, 33 patients (19.9%) underwent PPM. Most of the tumors (104/166, 62.7%) were found accidentally. Comparing the parameters between groups, the hospital stay d (12.35 *vs* 13.5 d, *P*

= 0.49), total expense (44213 *vs* 54084 yuan, $P$ = 0.21), operation duration (135 *vs* 120 min, $P$ = 0.71), and intraoperative bleeding volume (200 *vs* 100 mL, $P$ = 0.49) did not differ between groups. Regarding pathological outcomes, tumor size (45 *vs* 32 mm, $P$ = 0.07), Ki67 index ($P$ = 0.53), peripheral tissue invasion (11.3% *vs* 9.1%, $P$ = 0.43) and positive margin status (7.5% *vs* 6%, $P$ = 0.28) also did not differ between groups. Moreover, PPM did not increase the risk of severe postoperative pancreatic fistula (3.8% *vs* 3.0%, $P$ = 0.85) or tumor recurrence (3.0% *vs* 6.0%, $P$ = 0.39). However, the number of patients who had exocrine insufficiency during follow-up was significantly lower in the PPM group (21.8% *vs* 3%, $P$ = 0.024). CM was identified as an independent risk factor for pancreatic exocrine insufficiency (odds ratio = 8.195, 95% confident interval: 1.067-62.93).

***CONCLUSION***

PPM for SPN appears to be feasible and safe for preserving the exocrine function of the pancreas.

**Key Words:** Solid pseudopapillary neoplasm; Surgical resection; Parenchyma-preserving method; Pancreatic exocrine insufficiency



**Core Tip:** Solid pseudopapillary neoplasm of the pancreas (SPN) is a rare neoplasm that mainly affects young women. The prognosis of SPN is excellent following complete surgical resection. However, the conventional surgical method is associated with a high rate of morbidity and a high rate of long-term endocrine/exocrine insufficiency due to the loss of pancreatic parenchyma. Our study identified a parenchyma-preserving surgical method (PPM) for SPN that appears to be feasible and safe for preserving the exocrine function of the pancreas. The risk of PPM did not increase the risk of severe postoperative pancreatic fistula or tumor recurrence. PPM should be taken into consideration in SPN patients with a long life expectancy.

**Citation:** Li YQ, Pan SB, Yan SS, Jin ZD, Huang HJ, Sun LQ. Impact of parenchyma-preserving surgical methods on treating patients with solid pseudopapillary neoplasms: A retrospective study with a large sample size. *World J Gastrointest Surg* 2022; 14(2): 174-184

**URL:** https://www.wjgnet.com/1948-9366/full/v14/i2/174.htm

**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i2.174

## INTRODUCTION

Solid pseudopapillary neoplasms (SPNs) are exceptionally rare. These tumors account for approximately 0.9%-2.7% of all exocrine pancreatic neoplasms[1,2] and approximately 3%-5% of pancreatic cystic neoplasms[3,4]. Although these tumors occur among a wide age range from children to elderly individuals, the mean age at presentation is 28.5 years[5]. SPNs occur predominantly in young women with a female-male ratio of 9.8:1[1]. Moreover, SPN is reported to be the most common pancreatic neoplasm among young females under the age of 40 years[6]. However, the tumor is an epithelial-originated low-grade malignant neoplasm with the possibility of locally advanced, recurrent, and metastatic disease[7]. Complete surgical resection is recommended as the main treatment for SPN[6].

Conventional pancreatic resection (pancreatoduodenectomy (PD), total pancreatectomy (TP) and distal pancreatectomy (DP)) is associated with a high rate of morbidity (40%-50%)[8] and a high rate of long-term endocrine/exocrine insufficiency (8-20% and 20-50%, respectively)[9] due to the loss of pancreatic parenchyma. However, the prognosis of SPN is excellent with a cure rate of approximately 98% following surgical resection[10]. Thus, approximately half of young SPN patients will suffer from lifelong complications.

In addition to drug therapies, improved surgical approaches are one way to address the issue.

The parenchyma preserving surgical methods (*i.e.*, enucleation or central pancreatectomy (CP)) have been explicitly advocated to be used for some benign or low-grade pancreatic neoplasms[11-13]. Parenchyma-sparing surgical approaches decrease the risk of developing endocrine and exocrine dysfunction postoperatively[14], and the subsequent quality of life is significantly higher than that of patients who underwent conventional resection. Recently, a parenchyma-sparing surgical approach was reported to be used for SPN in some retrospective studies with small-sized samples. The increased rate of postoperative pancreatic fistula (POPF) may hinder the utilization of this approach[15,16]. Moreover, although rare, SPN is associated with local recurrence or metastasis after surgery. The long-term

outcomes after the parenchyma-sparing surgical approach for SPN remain unclear.

Due to the unsolved issues noted above, we conducted this retrospective study with a large sample size. Our study aimed to compare the intraoperative, short-term, and long-term outcomes in SPN patients who underwent a parenchyma-sparing surgical approach *vs* conventional pancreatic resection with detailed surgical-related parameters included.

## MATERIALS AND METHODS

### Study population

We conducted a retrospective study at Changhai Hospital affiliated with Navy/Second Medical University and Suzhou Science and Technology Town Hospital, Suzhou. The Institutional Review Board of both hospitals approved the study. Patients who underwent surgical resection from January 2013 to December 2018 for pathologically identified SPN were included in our study. The following inclusion criteria were applied: (1) Patients pathologically diagnosed with SPN; (2) Patients whose full electronic medical records could be obtained; and (3) Patients whose follow-up data could be obtained. Exclusion criteria included: (1) Specimens obtained from reresections; (2) Concomitant other neoplasms on final pathology (*e.g.*, neuroendocrine tumor, cholangiocarcinoma); and (3) Patients with unavailable pathological and follow-up data. The selection procedure of the study participants is presented in Figure 1.

The decision on surgical treatment was made by our multidisciplinary hepatopancreatobiliary team. If the lesion was diagnosed as a pancreatic cystic lesion by imaging modality, the surgery indications would follow the International Consensus Guideline[17]. If diagnosed as invasive cancer, the surgery indications would follow the European Society for Medical Oncology guidelines[18]. The choices of surgical procedures depended on the location, degree, extent of diseases and experiences of the surgeons. The surgeons who were qualified to perform pancreatic surgery in our centers had at least 15 years of operation experience with an average of 100 operations per year.

### Perioperative management

The operations for SPN were performed by experienced surgeons in our center. We performed

Roux-Y loop in patients with a suspicious injury of the main pancreatic duct or a wide wounded area (diameter > 3 cm) of the pancreatic parenchyma.

After surgery, amylase analysis from drainage fluid was performed to determine whether POPF existed. Routine blood examinations were performed to determine whether infection existed and whether antibiotics were used. Plain CT was performed to determine whether pancreatic fluid collection existed and to detect the causes of infection. If any clinically significant complications occurred, further treatments were needed.

### The definition of included parameters

The parameters included in our study were composed of five parts: baseline characteristics, intraoperative index, pathological outcomes, short-term complications and long-term follow-up data.

The baseline characteristics included age, gender, symptoms, hospital stay d and total expense.

The intraoperative indices included surgical method, surgical approaches, operation duration, and intraoperative bleeding volume. The surgical methods included conventional methods (PD, TP and DP) and parenchyma-preserving methods (enucleation and CP). Surgical approaches include opening, laparoscopy and robotics. Intraoperative bleeding was noted as dark red liquid aspirated during the operation.

The pathological outcomes were tumor location, tumor size, Ki-67 index, margin status, and peripheral tissue invasion status. The tumor might be located in multiple head/body/tail sites of the pancreas. If multiple tumors occurred, only the size of the largest tumor was measured. The Ki-67 index of the tumor was divided into 3 grades: < 3%, 3%-20% and > 20%[19]. Positive margin status was defined as a tumor component ≤ 5 mm from the incisal margin. Peripheral tissue invasion status consisted of perineural invasion, vascular invasion, cancerization of ducts, lymphatic metastasis, common bile duct invasion, peripancreatic fat invasion, spleen invasion and duodenum invasion.

Short-term complications were adverse events that occurred within 30 d, including POPF, delayed gastric emptying, postoperative hemorrhage, postoperative infection and bile leakage. The grade of complications was based on the Claviene-Dindo score. Complications that scored Claviene Dindo grade III or greater were considered severe complications.

The long-term follow-up data included exocrine insufficiency, endocrine insufficiency, alimentary stricture due to the surgery and whether recurrence occurred. Follow-up data were obtained from telephone interviews and/or outpatient interviews in this study. Endocrine insufficiency was defined as a fasting plasma glucose level > 7.0 mmol/L and/or the need for diet modification, oral medication, or insulin use to control blood. Exocrine insufficiency was defined as symptoms (steatorrhea or weight loss) resolving after pancreatic enzyme supplementation[15]. Recurrence was defined as a local or a metastatic tumor confirmed by radiology or histology during postoperative follow-up.

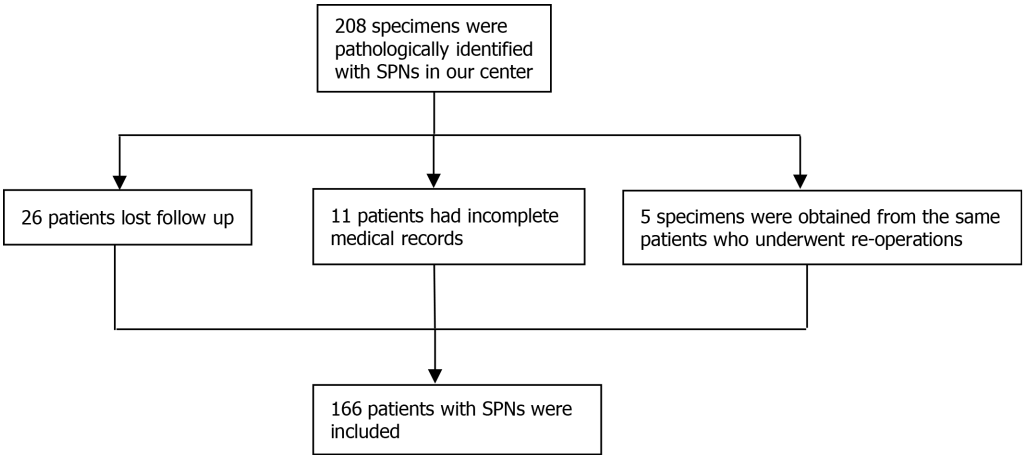



**Figure 1 Patient selection flowchart.** SPN: Solid pseudopapillary neoplasm.

### *Statistical analysis*

The patients were divided into 2 groups according to their surgical methods: conventional method (CM) group and parenchyma preserving method (PPM) group. The parameters were compared between the 2 groups. Quantitative parameters were expressed as the medians and range. Continuous data are reported as the mean ± standard deviation (SD) or as the median and range. Categorical parameters were compared between the CM group and the PPM group using $\chi^2$ or Fisher's exact test. The nonparametric Mann–Whitney U test was used to compare differences between groups for quantitative parameters. A Kaplan–Meier survival curve was established to estimate the recurrence-free survival (RFS) rate. Statistical analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, United States). All tests were two-sided, and a $P$ value < 0.05 was considered statistically significant.

## RESULTS

### *Patient characteristics*

From January 2013 to June 2019, 166 patients who underwent pancreatic surgery were included in our study. All tumors were confirmed as SPNs according to the final histology examination. Among them, 33 patients (19.9%) underwent PPM, and 133 patients (80.1%) underwent CM. In the PPM group, 13 patients underwent enucleation and 20 patients underwent CP. The median age of the overall study cohort was 32.5 years (range, 10-68 years), and most of the participants were females (129/166, 77.7%). The majority of the tumors were incidentally found (104/166,62.7%). In the patients who were symptomatic, abdominal pain was the most common symptom (53/62.85.5%) followed by abdominal distension (6/62, 9.7%), nausea and vomiting (2/62, 3.2%) and jaundice (1/62, 1.6%). The mean hospital stay was 12.53 d (SD ± 6.87 d), and no difference was noted between the CM group and the PPM group ($t$ = 0.692, $P$ = 0.49). The mean total expense during hospitalization was 46248 Chinese yuan (SD ± 25414 yuan), and no difference was noted between the 2 groups ($t$ = 1.284, $P$ = 0.21). The baseline characteristics of the study cohort are shown in Table 1.

### *Intraoperative index*

In the CM group, 44 patients (33.1%) underwent PD, 81 patients (60.9%) underwent DP, and 8 patients (6.0%) underwent TP. Moreover, 108 (81.2%) patients underwent laparotomy, 11 (8.3%) underwent laparoscopic surgery, and 14 (10.5%) underwent robot surgery. The average operation experiences for surgeons were 19 years. The median operation duration was 135 min (27-381 min), and the median intraoperative bleeding volume was 200 mL (0-2000 mL).

In the PPM group, 11 patients (33.3%) underwent enucleation, and 22 patients (66.6%) underwent CP. Moreover, 31 (93.3%) patients underwent laparotomy, 2 (6.7%) underwent laparoscopic surgery, and no patient underwent robot surgery. The average operation experiences for surgeons were 19.5 years. The median operation duration was 120 min (50-301 min), and the median intraoperative bleeding volume was 100 mL (50-600 mL).

Comparing the intraoperative index between the 2 groups, the surgical approach was not different between the 2 groups ($\chi^2$ = 4.15, $P$ = 0.126), and the surgeon experiences, operation duration and intraoperative bleeding volume were also not different between the 2 groups ($t$ = 0.85, 0.385 and 0.695, $P$ = 0.71 and 0.488) (Table 2).

**Table 1 Characteristics of the study cohort stratified by surgical method**

| | Total (*n* = 166) | CM (*n* = 133) | PPM (*n* = 33) | *P* value |
|---|---|---|---|---|
| Female, *n* (%) | 129 (77.7) | 106 (77.4) | 23 (69.7) | 0.16 |
| Age (yr), median (range) | 32.5 (10-68) | 32.0 (10-68) | 33 (13-51) | 0.85 |
| Symptoms, *n* (%) | | | | |
| Accidentally found | 104 (62.7) | 83 (62.4) | 21 (63.6) | 0.84 |
| Abdominal pain | 53 (31.9) | 43 (32.3) | 10 (30.3) | 0.75 |
| Abdominal distension | 6 (3.6) | 5 (3.8) | 1 (3.0) | 0.8 |
| Nausea and vomiting | 2 (1.2) | 1 (0.8) | 1 (3.0) | 0.49 |
| Jaundice | 1 (0.6) | 1 (0.8) | 0 (0) | 0.32 |
| Hospital stay (d) ± SD | 12.53 ± 6.87 | 12.35 ± 6.21 | 13.3 ± 9.14 | 0.49 |
| Total expense (yuan) ± SD | 46248 ± 25414 | 44213 ± 20487 | 54084 ± 38551 | 0.21 |

SD: Standard deviation; CM: Conventional method; PPM: Parenchyma preserving method.

### *Pathological outcomes*

Regarding the pathological specimens, the median size of tumors in the CM group was 45 mm (3.5-140 mm), with 46 tumors (34.6%) located in the pancreatic head, 15 tumors (11.3%) located in the pancreatic body, 17 tumors (12.8%) located in the pancreatic tail and 55 tumors (41.4%) involving multiple sites. Grade I Ki67 was identified in 115 tumors (86.5%), Grade II Ki67 was identified in 16 tumors (12.0%) and Grade III Ki67 was identified in 2 tumors (1.5%). Positive margin status was observed in 10 patients (7.5%), and peripheral tissue invasion was observed in 15 patients (11.3%).

The median size of tumors in the PPM group was 32 mm (17-140 mm) with 23 tumors (69.7%) located in pancreatic head, 4 tumors (12.1%) located in pancreatic body, no tumors (0%) located in pancreatic tail and 6 tumors (18.2%) involving multiple sites. Grade I Ki67 was identified in 26 tumors (78.8%), Grade II Ki67 was identified in 6 tumors (18.2%), and Grade III Ki67 was identified in 1 tumor (3%). Positive margin status was observed in 2 patients (6%), and peripheral tissue invasion was observed in 3 patients (9.1%).

Comparing the pathological outcomes between the 2 groups, the tumor size was not significantly larger in the CM group compared with the PMM group with a borderline *P* value ($t$ = 1.832, $P$ = 0.069). Tumors involved in multiple sites were more common in the CM group ($\chi^2$ = 15.9, $P$ = 0.001). The Ki67 grade was not different between the 2 groups ($\chi^2$ = 1.182, $P$ = 0.53), indicating that the degree of malignancy was not different between the groups. The positive margin status and peripheral tissue invasion were also not different between the 2 groups ($\chi^2$ = 1.155 and 0.832, $P$ = 0.283 and 0.425) (Table 2).

### *Short-term complications*

In the CM group, perioperative complications occurred in 27 patients (20.3%). POPF grade II or greater developed in 5 patients (5/27, 18.5%), delayed gastric emptying developed in 4 patients (4/27, 14.8%), abdominal infection developed in 12 patients (12/27, 44.4%), bleeding developed in 3 patients (3/27, 11.1%), pancreatitis developed in 2 patients (2/27, 7.4%), and 1 patient (1/27, 3.7%) developed both delayed gastric emptying and abdominal infection. Seven complications (7/27, 25.9%) scored Claviene Dindo grade III or above and were considered severe complications (Table 3).

In the PPM group, perioperative complications occurred in 6 patients (18.2%). One patient (1/6, 16.7%) developed severe POPF, 1 patient developed abdominal infection (1/6, 16.7%), 2 patients developed bleeding (2/6, 33.3%) and 2 patients (2/6, 33.3%) developed severe POPF, abdominal infection and bleeding. Two complications (2/6, 33.3%) scored Claviene Dindo grade III or greater and were considered severe complications.

The overall perioperative complication rate and severe complication rate were comparable between the groups ($\chi^2$ = 0.075 and 0.00, $P$ = 0.79 and 1.0). For each complications, the difference of incidences were not observed, either.

### *Long-term follow-up data*

The final follow-up date was June 30, 2021. The median follow-up period was 49 mo (24-102 mo). Only 1 patient died due to perioperative complications, and the 3-, 5-, and 10-year overall survival (OS) rates were estimated to be 99.4%, 99.4%, and 99.4%, respectively. In total, 6 patients (3.6%) developed recurrence in the overall study cohort with 4 patients (3 Local recurrence and 1 Liver metastasis) in the CM group and 2 patients (1 Local recurrence and 1 Liver metastasis) in the PPM group. The median

**Table 2 Intraoperative index and pathological outcomes of the study cohort stratified by surgical method**

| | Total (*n* = 166) | CM (*n* = 133) | PPM (*n* = 33) | *P* value |
|---|---|---|---|---|
| Intraoperative index | | | | |
| Surgical approach, *n* (%) | | | | 0.126 |
| laparotomy | 139 (80.1) | 108 (81.2) | 31 (93.9) | |
| laparoscopic | 13 (7.8) | 11 (8.3) | 2 (6.1) | |
| Robot | 14 (8.4) | 14 (10.5) | 0 (0) | |
| Surgeon experiences, mean (yr) | 19.3 | 19.0 | 19.5 | 0.85 |
| Operation duration, median (range) | 135 (27-381) | 135 (27-381) | 120 (50-301) | 0.71 |
| Intraoperative bleeding volume, median (± SD) | 200 (0-2000) | 200 (0-2000) | 100 (50-600) | 0.488 |
| Pathological outcomes | | | | |
| Median size (mm), median (range) | 40 (3.5-140) | 45 (3.5-140) | 32 (17-140) | 0.069 |
| Tumor location, *n* (%) | | | | 0.001[a] |
| Head | 69 (41.6) | 46 (34.6) | 23 (69.7) | |
| Body | 19 (11.4) | 15 (11.3) | 4 (12.1) | |
| Tail | 17 (10.2) | 17 (12.8) | 0 (0) | |
| Multiple sites | 64 (38.6) | 55 (41.4) | 6 (18.2) | |
| Ki67 index, *n* (%) | | | | 0.53[a] |
| I | 141 (84.9) | 115 (86.5) | 26 (78.8) | |
| II | 22 (13.3) | 16 (12.0) | 6 (18.2) | |
| III | 3 (1.8) | 2 (1.5) | 1 (3.0) | |
| Peripheral tissue invasion, *n* (%) | 18 (10.8) | 15 (11.3) | 3 (9.1) | 0.426 |
| Positive margin status, *n* (%) | 12 (7.2) | 10 (7.5) | 2 (6.0) | 0.283 |

[a]The *P* value was based on overall comparison between 2 groups. SD: Standard deviation; CM: Conventional method; PPM: Parenchyma preserving method.

time to recurrence was 48 mo (range 6–84 mo). The 3-, 5-, and 10-year RFS rates were estimated at 98.8%, 97.0%, and 96.4% for the study cohort, respectively. The 3-, 5-, and 10-year RFS rates for the CM group were 99.2%, 97.7%, and 96.9%, respectively. The 3-, 5-, and 10-year RFS rates for the PPM group were 97.0%, 93.9%, and 93.9%, respectively. Kaplan–Meier analysis and the log-rank test showed that the recurrence rate was not significantly different between the groups ($P = 0.39$) (Figure 2).

The long-term complications were also evaluated. In the CM group, alimentary strictures were observed in 5 patients (3.0%), 3 of whom were treated by digestive tract bypass operations, and the other two were treated by duodenal stents. Six patients (4.5%) experienced pancreatic endocrine insufficiency, and 29 patients (21.8%) experienced exocrine insufficiency. In the PPM group, alimentary strictures were observed in 1 patient (3.0%) and treated by bypass operation. One patient (3.0%) experienced both pancreatic exocrine insufficiency and endocrine insufficiency. No other pancreatic exocrine insufficiency or endocrine insufficiency was observed in the PPM group. The incidence rates of alimentary stricture and pancreatic endocrine insufficiency were comparable between groups (both $\chi^2 = 0.00$ and both $P = 1.0$). However, the incidence of pancreatic exocrine insufficiency was significantly higher in the CM group compared with the PPM group ($\chi^2 = 5.09$, $P = 0.024$). Based on multivariate analysis, CM was identified as an independent risk factor for pancreatic exocrine insufficiency (odds ratio = 8.195, 95% confidence interval (CI): 1.067-62.93) after adjusting for age and sex.

## DISCUSSION

Since it was first described in 1959, SPN has been widely acknowledged as a low-grade malignant neoplasm with a favorable prognosis after complete resection. If completely resected, the OS rate reached greater than 95% in previous studies[1,5]. Even in aggressive SPNs, the 5- and 10-year OS rates reached 71.1% and 65.5%, respectively[20]. In our study, only 1 patient died due to perioperative

**Table 3 Short-term and long-term outcomes of the study cohort stratified by surgical method**

| | Total (*n* = 166) | CM (*n* = 133) | PPM (*n* = 33) | *P* value |
|---|---|---|---|---|
| Short-term complications | | | | |
| Overall perioperative complication, *n* (%) | 33 (19.9) | 27 (20.3) | 6 (18.2) | 0.79 |
| Severe POPF | 6 (3.6) | 5 (3.8) | 1 (3.0) | 0.85 |
| delayed gastric emptying | 3 (1.8) | 3 (2.3) | 0 (0) | 0.56 |
| abdominal infection | 13 (7.8) | 12 (9.0) | 1 (3.0) | 0.43 |
| Bleeding | 5 (3.0) | 3 (2.3) | 2 (6.0) | 0.26 |
| Pancreatitis | 2 (1.2) | 2 (1.5) | 0 (0) | 0.49 |
| Multiple complications | 4 (2.4) | 2 (1.5) | 2 (6.0) | 0.18 |
| Severe perioperative complication, *n* (%) | 9 (5.4) | 7 (5.3) | 2 (6.0) | 1.0 |
| Long-term follow-up data | | | | |
| Recurrence, *n* (%) | 6 (3.6) | 4 (3.0) | 2 (6.0) | 0.39 |
| Local | 4 (2.4) | 3 (2.3) | 1 (3.0) | |
| Distant | 2 (1.2) | 1 (0.8) | 1 (3.0) | |
| Alimentary stricture, *n* (%) | 6 (3.6) | 5 (3.7) | 1 (3.0) | 1.0 |
| Endocrine insufficiency, *n* (%) | 7 (4.2) | 6 (4.5) | 1 (3.0) | 1.0 |
| Exocrine insufficiency, *n* (%) | 30 (18.1) | 29 (21.8) | 1 (3.0) | 0.024 |

CM: Conventional method; PPM: Parenchyma preserving method; POPF: Postoperative pancreatic fistula.

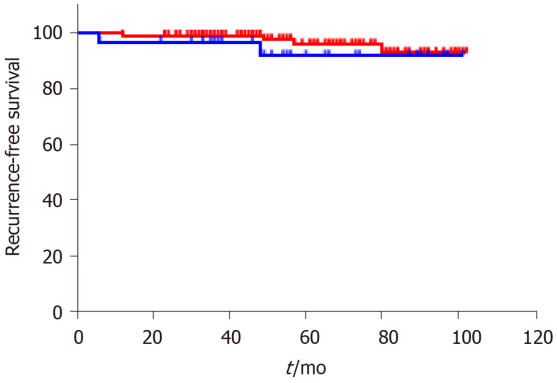



**Figure 2 Kaplan–Meier curves of recurrence-free survival.** The red line represents the conventional method group, and the blue line represents the parenchyma-preserving method.

complications, and the 10-year OS rate reached greater than 99%, indicating that SPNs have very low malignant potential. However, the tumor often occurs in young females whose life expectancy is very long. In our study, the median age of the included patients was 32.5 years. These consistent data highlight the crucial importance of standardizing treatment procedures to guarantee improved quality of life for this small but challenging subset of patients.

According to the current guidelines, complete resection with a negative surgical margin is suggested to be curative for SPN[21,22]. However, the CM (including PD, TP and DP) might bring a negative surgical margin but be accompanied by wide resection of the pancreatic parenchyma. The loss of pancreatic parenchyma may affect the quality of life of young SPN patients. The proper treatment for SPN should balance curative resection and adverse events related to surgery. PPM is increasingly used for low-grade or benign pancreatic neoplasms[23,24]. However, research regarding PPM of SPN is limited and mainly based on case reports and retrospective studies with small sample sizes[25-27] due to the rarity of the disease. However, the results were inconsistent. Christine *et al*[26] concluded that PPM harbors a significant risk for tumor recurrence. However, only 8 patients who underwent PPM were included in this study. Wang *et al*[26] found that enucleation for SPNs is feasible and safe for preserving exocrine and endocrine function of the gland, and they concluded that enucleation with a

negative surgical margin is adequate with no increased risk of tumor recurrence. In their study, 31 patients who underwent enucleation were included. Yao *et al*[27] concluded that CP was associated with a lower RFS rate than enucleation. However, only 11 patients were included in this case series, and only 5 of them were diagnosed with SPNs.

Due to the inconsistent data, we conducted a large series retrospective study to evaluate the efficacy of PPM in SPNs with various parameters included. Our results identified that PPM for SPNs had comparable intraoperative indices, pathological outcomes, and short-term complications to CM. The OS and RFS rates were also not different between groups. Long-term exocrine insufficiency was significantly lower ($P$ = 0.024) in the PPM group, and CM was an independent risk factor for exocrine insufficiency. The OR was 8.2 (95%CI: 1.067-62.93). To avoid bias, the baseline characteristics were also compared between groups, and no difference was observed. The baseline characteristics of the patients included in our study were similar to those of resected SPNs previously reported[28], which included young age at diagnosis (mean 32.5 years), female predominance (129/166, 77.7%) and relatively large tumors (median 40 mm). Moreover, SPNs were mostly detected by accident (62.7%). However, the pancreatic head appeared to be the most common site of SPNs in our study. Actually, the body and tail were still the most common location sites because almost all of the SPNs located in multiple sites involved the body and tail of the pancreas (62/64, 96.9%).

The main complication after PPM was POPF, especially after enucleation. The POPF rates after enucleation in previously reported studies were 36-67%[29]. However, the POPF rates in our study were low (3%) because only clinically significant POPF was included in our study. Moreover, we tended to perform pancreaticojejunostomy if the main duct was injured during the operation. Therefore, we deemed PPM to be performed with no significantly increased risk of POPF in specialized centers, which was consistent with the results of Hüttner *et al*[16]. Moreover, the overall rate of severe complications (Claviene Dindo grade III and above, 6.0%) after PPM of SPN was consistent with other recent studies involving a large series of PPMs (6-18%)[15,16,29].

The intraoperative index was not different in our study, which was inconsistent with previous studies [26,30]. The reason may be due to the high pancreatic surgery volume in our center. The operation duration (median, 135 min) and intraoperative bleeding volume (median, 200 mL) had already reached a very low level. In the meta-analysis by Chua *et al*[30], the mean operation duration for CM was 325 min, and the mean blood loss was 300 mL. In the study by Wang *et al* [25], the median operation duration was 245 min, and the median blood loss was 380 mL for CM. Therefore, the benefit of PPM during operations was not identified by our study.

Avoiding tumor recurrence is another important endpoint for the management of SPNs. In addition to the efficacy and safety of PPM for SPNs identified in our study, our results also indicated that PPM did not result in an increased rate of tumor recurrence or metastasis compared with CM ($P$ = 0.39). The risk factors associated with recurrence were not analyzed in our study due to the adequate evidence reported before. The main risk factors were large tumor size, lymphovascular invasion, positive margin status, Ki-67 index and synchronous metastasis[31,32]. However, the influence of these factors on the OS rate was not concluded[28,33]. As the overall prognosis is favorable for SPNs, the factors that worsen the OS rate should be clarified in future studies.

Our study had several limitations worth discussing. First, its retrospective nature prevented us from making stronger conclusions. The second limitation was the small sample size. Due to the rarity of SPNs, SPN cases were not common in our center. Moreover, the patients were often transferred from other referral institutions. Their initial medical records and follow-up data were not fully presented in our medical system.

The 2 factors greatly limited the size of the single institution series. More multicenter prospective studies with large sample sizes are necessary to better understand SPNs.

## CONCLUSION

This retrospective study identified SPN as a rare pancreatic tumor with excellent prognosis after surgical resection. PPM for SPN appears to be feasible and safe for preserving exocrine function of the gland. The risk of recurrence or metastasis did not increase in patients who underwent PPM. PPM can be taken into consideration in SPN patients whose life expectancy is long.

## ARTICLE HIGHLIGHTS

### *Research background*

Conventional surgical methods (CM) including pancreatoduodenectomy (PD), total pancreatectomy (TP) and distal pancreatectomy are standard surgical methods in the treatment of patients with Solid pseudopapillary neoplasm (SPN). CM is associated with a high rate of morbidity. However, the tumor mainly affects young women and the prognosis of the tumor is excellent.

### Research motivation
The parenchyma-preserving surgical methods (PPM, including enucleation and central pancreatectomy ) are more and more often applied in clinical practice. The role of PPM in treating SPN remains clarified.

### Research objectives
To evaluate the impact of PPM in the treatment of SPN patients.

### Research methods
Patients who underwent surgical resection for a pathological identified SPN were included in this study. Patients were divided into 2 groups: PPM group and CM group. The baseline characteristics, intraoperative index, pathological outcomes, short-term complications and long-term follow-up data were compared between the 2 groups.

### Research results
Patients with SPN had an excellent prognosis. PPM did not increase the surgical risks. After long-term follow-up, we identified PPM did not worsen the prognosis of patients with SPN. However, PPM is suitable for preserving the exocrine function of pancreas in young patients.

### Research conclusions
PPM can be taken into consideration in SPN patients whose life expectancy is long.

### Research perspectives
More multicenter prospective studies with large sample sizes are necessary to better understand the best surgical method for patients with SPN.

## FOOTNOTES

**Author contributions:** Li YQ, Pan SB and Yan SS contributed equally to this study and are co-first authors, were responsible for study design/planning, study conduct, data analysis and writing and revising the paper; Huang HJ and Sun LQ designed the study and they shared senior authorship; all authors have read and approve the final manuscript.

**Institutional review board statement:** The study was reviewed and approved by the Shanghai Changhai Hospital Ethics Committee (CHEC No. 2019-091).

**Conflict-of-interest statement:** The authors declare no conflicts of interest.

**Data sharing statement:** No additional data are available.



**Country/Territory of origin:** China

**ORCID number:** Yu-Qiong Li 0000-0002-4227-2923; Shu-Bo Pan 0000-0003-1863-5146; Shu-Shu Yan 0000-0002-0846-3718; Zhen-Dong Jin 0000-0002-9358-7351; Hao-Jie Huang 0000-0002-3100-5301; Li-Qi Sun 0000-0002-1151-3931.

**S-Editor:** Wang LL
**L-Editor:** A
**P-Editor:** Wang LL

## REFERENCES

1 **Papavramidis T**, Papavramidis S. Solid pseudopapillary tumors of the pancreas: review of 718 patients reported in English literature. *J Am Coll Surg* 2005; **200**: 965-972 [PMID: 15922212 DOI: 10.1016/j.jamcollsurg.2005.02.011]
2 **Machado MC**, Machado MA, Bacchella T, Jukemura J, Almeida JL, Cunha JE. Solid pseudopapillary neoplasm of the pancreas: distinct patterns of onset, diagnosis, and prognosis for male *vs* female patients. *Surgery* 2008; **143**: 29-34 [PMID: 18154930 DOI: 10.1016/j.surg.2007.07.030]
3 **Scholten L**, van Huijgevoort NCM, van Hooft JE, Besselink MG, Del Chiaro M. Pancreatic Cystic Neoplasms: Different Types, Different Management, New Guidelines. *Visc Med* 2018; **34**: 173-177 [PMID: 30182024 DOI: 10.1159/000489641]

4 **Stark A**, Donahue TR, Reber HA, Hines OJ. Pancreatic Cyst Disease: A Review. *JAMA* 2016; **315**: 1882-1893 [PMID: 27139061 DOI: 10.1001/jama.2016.4690]

5 **Law JK**, Ahmed A, Singh VK, Akshintala VS, Olson MT, Raman SP, Ali SZ, Fishman EK, Kamel I, Canto MI, Dal Molin M, Moran RA, Khashab MA, Ahuja N, Goggins M, Hruban RH, Wolfgang CL, Lennon AM. A systematic review of solid-pseudopapillary neoplasms: are these rare lesions? *Pancreas* 2014; **43**: 331-337 [PMID: 24622060 DOI: 10.1097/MPA.0000000000000061]

6 **Lubezky N**, Papoulas M, Lessing Y, Gitstein G, Brazowski E, Nachmany I, Lahat G, Goykhman Y, Ben-Yehuda A, Nakache R, Klausner JM. Solid pseudopapillary neoplasm of the pancreas: Management and long-term outcome. *Eur J Surg Oncol* 2017; **43**: 1056-1060 [PMID: 28238521 DOI: 10.1016/j.ejso.2017.02.001]

7 **Nagtegaal ID**, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, Washington KM, Carneiro F, Cree IA; WHO Classification of Tumours Editorial Board. The 2019 WHO classification of tumours of the digestive system. *Histopathology* 2020; **76**: 182-188 [PMID: 31433515 DOI: 10.1111/his.13975]

8 **Müller MW**, Friess H, Kleeff J, Hinz U, Wente MN, Paramythiotis D, Berberat PO, Ceyhan GO, Büchler MW. Middle segmental pancreatic resection: An option to treat benign pancreatic body lesions. *Ann Surg* 2006; **244**: 909-18; discussion 918 [PMID: 17122616 DOI: 10.1097/01.sla.0000247970.43080.23]

9 **Falconi M**, Mantovani W, Crippa S, Mascetta G, Salvia R, Pederzoli P. Pancreatic insufficiency after different resections for benign tumours. *Br J Surg* 2008; **95**: 85-91 [PMID: 18041022 DOI: 10.1002/bjs.5652]

10 **Yao J**, Song H. A Review of Clinicopathological Characteristics and Treatment of Solid Pseudopapillary Tumor of the Pancreas with 2450 Cases in Chinese Population. *Biomed Res Int* 2020; **2020**: 2829647 [PMID: 32685461 DOI: 10.1155/2020/2829647]

11 **Divarcı E**, Dökümcü Z, Çetingül N, Nart D, Barbet FY, Ergün O, Çelik A. Radical resection of the pancreas should not always be necessary in the surgical management of pancreatic solid pseudopapillary tumor in children. *Turk J Gastroenterol* 2017; **28**: 214-218 [PMID: 28336499 DOI: 10.5152/tjg.2017.16713]

12 **Cauley CE**, Pitt HA, Ziegler KM, Nakeeb A, Schmidt CM, Zyromski NJ, House MG, Lillemoe KD. Pancreatic enucleation: improved outcomes compared to resection. *J Gastrointest Surg* 2012; **16**: 1347-1353 [PMID: 22528577 DOI: 10.1007/s11605-012-1893-7]

13 **Briggs CD**, Mann CD, Irving GR, Neal CP, Peterson M, Cameron IC, Berry DP. Systematic review of minimally invasive pancreatic resection. *J Gastrointest Surg* 2009; **13**: 1129-1137 [PMID: 19130151 DOI: 10.1007/s11605-008-0797-z]

14 **Crippa S**, Boninsegna L, Partelli S, Falconi M. Parenchyma-sparing resections for pancreatic neoplasms. *J Hepatobiliary Pancreat Sci* 2010; **17**: 782-787 [PMID: 19865792 DOI: 10.1007/s00534-009-0224-1]

15 **Faitot F**, Gaujoux S, Barbier L, Novaes M, Dokmak S, Aussilhou B, Couvelard A, Rebours V, Ruszniewski P, Belghiti J, Sauvanet A. Reappraisal of pancreatic enucleations: A single-center experience of 126 procedures. *Surgery* 2015; **158**: 201-210 [PMID: 25956743 DOI: 10.1016/j.surg.2015.03.023]

16 **Hüttner FJ**, Koessler-Ebs J, Hackert T, Ulrich A, Büchler MW, Diener MK. Meta-analysis of surgical outcome after enucleation *vs* standard resection for pancreatic neoplasms. *Br J Surg* 2015; **102**: 1026-1036 [PMID: 26041666 DOI: 10.1002/bjs.9819]

17 **Tanaka M**, Fernández-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, Kimura W, Levy P, Pitman MB, Schmidt CM, Shimizu M, Wolfgang CL, Yamaguchi K, Yamao K; International Association of Pancreatology. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology* 2012; **12**: 183-197 [PMID: 22687371 DOI: 10.1016/j.pan.2012.04.004]

18 **Ducreux M**, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goéré D, Seufferlein T, Haustermans K, Van Laethem JL, Conroy T, Arnold D; ESMO Guidelines Committee. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; **26** Suppl 5: v56-v68 [PMID: 26314780 DOI: 10.1093/annonc/mdv295]

19 **Inzani F**, Petrone G, Rindi G. The New World Health Organization Classification for Pancreatic Neuroendocrine Neoplasia. *Endocrinol Metab Clin North Am* 2018; **47**: 463-470 [PMID: 30098710 DOI: 10.1016/j.ecl.2018.04.008]

20 **Hao EIU**, Hwang HK, Yoon DS, Lee WJ, Kang CM. Aggressiveness of solid pseudopapillary neoplasm of the pancreas: A literature review and meta-analysis. *Medicine (Baltimore)* 2018; **97**: e13147 [PMID: 30544374 DOI: 10.1097/MD.0000000000013147]

21 **Tanaka M**, Fernández-Del Castillo C, Kamisawa T, Jang JY, Levy P, Ohtsuka T, Salvia R, Shimizu Y, Tada M, Wolfgang CL. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. *Pancreatology* 2017; **17**: 738-753 [PMID: 28735806 DOI: 10.1016/j.pan.2017.07.007]

22 **Elta GH**, Enestvedt BK, Sauer BG, Lennon AM. ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts. *Am J Gastroenterol* 2018; **113**: 464-479 [PMID: 29485131 DOI: 10.1038/ajg.2018.14]

23 **Strobel O**, Cherrez A, Hinz U, Mayer P, Kaiser J, Fritz S, Schneider L, Klauss M, Büchler MW, Hackert T. Risk of pancreatic fistula after enucleation of pancreatic tumours. *Br J Surg* 2015; **102**: 1258-1266 [PMID: 26109380 DOI: 10.1002/bjs.9843]

24 **Pärli MS**, Müller PC, Müller SA, Ruzza CM, Z'graggen K. Posterior enucleation of the pancreatic head: an alternative route of access for parenchyma-sparing pancreatic resection. *Langenbecks Arch Surg* 2019; **404**: 1023-1028 [PMID: 31712896 DOI: 10.1007/s00423-019-01835-5]

25 **Wang X**, Chen YH, Tan CL, Zhang H, Xiong JJ, Chen HY, Ke NW, Liu XB. Enucleation of pancreatic solid pseudopapillary neoplasm: Short-term and long-term outcomes from a 7-year large single-center experience. *Eur J Surg Oncol* 2018; **44**: 644-650 [PMID: 29525465 DOI: 10.1016/j.ejso.2018.01.085]

26 **Tjaden C**, Hassenpflug M, Hinz U, Klaiber U, Klauss M, Büchler MW, Hackert T. Outcome and prognosis after pancreatectomy in patients with solid pseudopapillary neoplasms. *Pancreatology* 2019; **19**: 699-709 [PMID: 31227367 DOI: 10.1016/j.pan.2019.06.008]

27 **Yao L**, Xie ZB, Jin C, Jiang YJ, Li J, Yang F, Lin QJ, Fu DL. Radical resection and enucleation in Chinese adolescents with pancreatic tumors: A 15-year case series. *Medicine (Baltimore)* 2017; **96**: e6438 [PMID: 28328854 DOI: 10.1097/MD.0000000000006438]

28 **Jutric Z**, Rozenfeld Y, Grendar J, Hammill CW, Cassera MA, Newell PH, Hansen PD, Wolf RF. Analysis of 340 Patients with Solid Pseudopapillary Tumors of the Pancreas: A Closer Look at Patients with Metastatic Disease. *Ann Surg Oncol* 2017; **24**: 2015-2022 [PMID: 28299507 DOI: 10.1245/s10434-017-5772-z]

29 **Zhang T**, Xu J, Wang T, Liao Q, Dai M, Zhao Y. Enucleation of pancreatic lesions: indications, outcomes, and risk factors for clinical pancreatic fistula. *J Gastrointest Surg* 2013; **17**: 2099-2104 [PMID: 24101446 DOI: 10.1007/s11605-013-2355-6]

30 **Chua TC**, Yang TX, Gill AJ, Samra JS. Systematic Review and Meta-Analysis of Enucleation Versus Standardized Resection for Small Pancreatic Lesions. *Ann Surg Oncol* 2016; **23**: 592-599 [PMID: 26307231 DOI: 10.1245/s10434-015-4826-3]

31 **Lee G**, Sung YN, Kim SJ, Lee JH, Song KB, Hwang DW, Kim J, Lee SS, Kim SC, Hong SM. Large tumor size, lymphovascular invasion, and synchronous metastasis are associated with the recurrence of solid pseudopapillary neoplasms of the pancreas. *HPB (Oxford)* 2021; **23**: 220-230 [PMID: 32654914 DOI: 10.1016/j.hpb.2020.05.015]

32 **Yang F**, Wu W, Wang X, Zhang Q, Bao Y, Zhou Z, Jin C, Ji Y, Windsor JA, Lou W, Fu D. Grading Solid Pseudopapillary Tumors of the Pancreas: the Fudan Prognostic Index. *Ann Surg Oncol* 2021; **28**: 550-559 [PMID: 32424583 DOI: 10.1245/s10434-020-08626-z]

33 **Chen H**, Huang Y, Yang N, Yan W, Yang R, Zhang S, Yang P, Li N, Feng Z. Solid-Pseudopapillary Neoplasm of the Pancreas: A 63-Case Analysis of Clinicopathologic and Immunohistochemical Features and Risk Factors of Malignancy. *Cancer Manag Res* 2021; **13**: 3335-3343 [PMID: 33883945 DOI: 10.2147/CMAR.S304981]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 February 27; 14(2): 185-199

DOI: 10.4240/wjgs.v14.i2.185

ISSN 1948-9366 (online)

SYSTEMATIC REVIEWS

# Status of bariatric endoscopy–what does the surgeon need to know? A review

Diogo Turiani Hourneaux de Moura, Anna Carolina Batista Dantas, Igor Braga Ribeiro, Thomas R McCarty, Flávio Roberto Takeda, Marco Aurelio Santo, Sergio Carlos Nahas, Eduardo Guimarães Hourneaux de Moura

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Cabezuelo AS, Zhang H

**Received:** July 29, 2021
**Peer-review started:** July 29, 2021
**First decision:** October 3, 2021
**Revised:** October 14, 2021
**Accepted:** February 12, 2022
**Article in press:** February 12, 2022
**Published online:** February 27, 2022

**Diogo Turiani Hourneaux de Moura, Igor Braga Ribeiro, Eduardo Guimarães Hourneaux de Moura,** Departamento de Gastroenterologia, Faculdade de Medicina, Universidade de Sao Paulo, Serviço de Endoscopia Gastrointestinal do Hospital das Clínicas HCFMUSP, Sao Paulo 05403-010, Brazil

**Anna Carolina Batista Dantas, Flávio Roberto Takeda, Marco Aurelio Santo, Sergio Carlos Nahas,** Departamento de Gastroenterologia, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Unidade de Cirurgia Bariátrica e Metabólica, Disciplina de Cirurgia do Aparelho Digestivo e Coloproctologia, Sao Paulo 05403-010, Brazil

**Thomas R McCarty,** Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, Boston, MA 021115, United States

**Corresponding author:** Igor Braga Ribeiro, MD, Doctor, Research Assistant, Research Scientist, Surgeon, Departamento de Gastroenterologia, Faculdade de Medicina, Universidade de Sao Paulo, Serviço de Endoscopia Gastrointestinal do Hospital das Clínicas HCFMUSP, Av. Dr En éas de Carvalho Aguiar, 225, 6o andar, bloco 3, Cerqueira Cesar, Sao Paulo 05403-010, Brazil. igorbraga1@gmail.com

## Abstract

*BACKGROUND*

Obesity is a chronic and multifactorial disease with a variety of potential treatment options available. Currently, there are several multidisciplinary therapeutic options for its management, including conservative, endoscopic, and surgical treatment.

*AIM*

To clarify indications, technical aspects, and outcomes of bariatric endoscopy.

*METHODS*

Narrative review of current literature based on electronic databases including MEDLINE (PubMed), Cochrane Library, and SciELO.

*RESULTS*

Bariatric endoscopy is in constant development and comprises primary and revisional treatment options as well as management of surgical complications. Various devices act upon different mechanisms of action, which may be individualized to each patient. Despite favorable results for the endoscopic treatment of

obesity, prospective randomized studies with long-term follow-up are required to fully validate primary and revisional endoscopic therapies. Regarding the management of bariatric surgery complications, endoscopic therapy may be considered the procedure of choice in a variety of situations. Still, as there is no standardized algorithm, local experience should be considered in decision-making.

*CONCLUSION*
The treatment of patients with obesity is complex, and a multidisciplinary approach is essential. Bariatric endoscopy has shown impressive results both in the treatment of obesity and its surgical complications, and therefore, must be part of the armamentarium in the fight against this disease.

**Key Words:** Endoscopy; Gastrointestinal; Surgery; Obesity; Bariatric; Weight regain



**Core Tip:** Obesity is a chronic and recurrent disease with multiple treatment options available. Currently, there are several multidisciplinary therapeutic options for its management, including conservative, endoscopic, and surgical treatment. This study aims to clarify indications, technical aspects, and results of bariatric endoscopy based upon a detailed literature review and individual authors' experience.

**Citation:** de Moura DTH, Dantas ACB, Ribeiro IB, McCarty TR, Takeda FR, Santo MA, Nahas SC, de Moura EGH. Status of bariatric endoscopy–what does the surgeon need to know? A review. *World J Gastrointest Surg* 2022; 14(2): 185-199
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i2/185.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i2.185

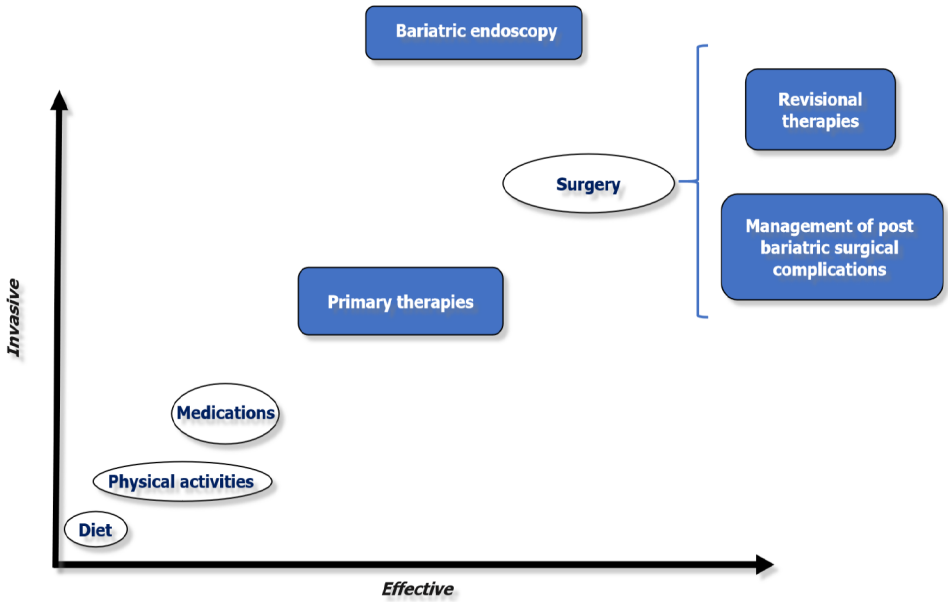
## INTRODUCTION

Obesity is defined as a body weight disorder resulting from a long-term positive energy balance and is characterized by excess adiposity. This disorder significantly increases the risk for developing many obesity-associated co-morbidities. It is a chronic, multifactorial disease resulting in a global pandemic associated with several comorbidities–most notably type 2 diabetes and hypertension–and an increase in all-cause mortality. Data from the Centers for Disease Control and Prevention (CDC) illustrates that the prevalence of obesity in the United States is 42.4%[1]. In Latin America, more specifically in Brazil, recent data from the National Health Survey (PNS) released by the Brazilian Institute of Geography and Statistics (IBGE) demonstrates that six out of 10 Brazilian adults are overweight, representing approximately 96 million individuals. If we exclusively consider those with body mass index (BMI) greater than 30 kg/m$^2$, one in every four Brazilians has obesity[2].

Treatment for obesity includes lifelong lifestyle modifications including behavioral, dietary, and exercise changes, pharmacotherapy, endoscopic therapies, and surgery. The treatment of obesity should be individualized and tailored to specific patients, taking into account several factors such as the degree of obesity (*i.e.*, class of obesity), individual associated comorbid conditions (*i.e.*, health risks), psychobehavioral and metabolic characteristics, as well as proper assessment of previous weight loss strategies. As obesity is a multifactorial disease, treatment must also be multidisciplinary[3].

Although diet, exercise, and pharmacotherapy are the least invasive and most widely utilized methods, it is clear that long-term results are unsatisfactory. Surgery, on the other hand, is proven to be the most effective and durable method for sustained weight loss and control of obesity-associated comorbidities[4]. However, while surgery is highly effective, this strategy is the most invasive option and may be associated with perioperative complications in about 0.5% to 9.6% of patients[5,6]. Additionally, approximately 50% of patients will develop some degree of long-term weight regain, requiring complex clinical management[7].

In this sense, the treatment for obesity and its associated comorbidities have recently expanded into the field of bariatric endoscopy: (1) *via* primary therapies, bridging a gap between less invasive therapies (lifestyle modification and/or pharmacological therapy) and bariatric surgery; (2) By optimizing the treatment of weight regain after bariatric surgery through revision therapies; and (3) Or in the management of postoperative bariatric surgery complications (Figure 1). In this review, we discuss the current state of bariatric endoscopy and highlight currently available treatments, including primary and revisional therapies




DOI: 10.4240/wjgs.v14.i2.185 

**Figure 1 The role of bariatric endoscopy.**

## MATERIALS AND METHODS

This is a narrative review including all available literature data obtained through electronic databases including MEDLINE (*via* PUBMED), Cochrane Library, and SciELO. This study was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The search study time period was from inception until January 15, 2022, using the search "bariatric endoscopy" AND "obesity".

## RESULTS

### *Primary therapies*

Primary therapies include intragastric balloons (IGBs), endoscopic suturing, and botulinum toxin injection.

**IGBs:** IGBs are indicated for patients with a BMI > 27 kg/m$^2$ who have not achieved or maintained weight loss with conservative measures. Other qualifying patients include those with a BMI > 35 kg/m$^2$ with comorbidities or > 40 kg/m$^2$ in patients who have contraindications or do not wish to undergo bariatric surgery. Additional indications include patients with BMI > 50 kg/m$^2$ as a bridge therapy for surgery. Absolute contraindications include active peptic ulcer disease, previous gastric surgery, large hiatal hernia, and patients with underlying eating disorders.

IGB models approved for use in most countries include "traditional" fluid filled (6 mo and one year), adjustable fluid filled (one year), and air filled (6 mo). The mechanism of action of IGBs is not yet fully established; however, it is believed that it is related to three factors: (1) Mechanical restriction, decreasing gastric capacity and leading to an increase in gastric emptying time, resulting in early satiety; (2) Hormonal changes due to direct contact with the gastric fundus, leading to a decrease in ghrelin and an increase in cholecystokinin, altering appetite and gastric emptying; and (3) Neurogenic, *via* central stimulation of the paraventricular nucleus of the solitary tract through vagal stimulation[8].

The IGB is the most widely adopted endoscopic method with proven efficacy and safety[9,10]. In a meta-analysis including only randomized studies evaluating fluid filled IGBs, the average difference in BMI loss was 1.41 kg/m$^2$ with an absolute weight loss of 3.55 kg between the IGB group *vs* the control group[10]. However, most studies do not support the effectiveness of IGBs in long-term follow-up[11]. Despite being considered a safe method, close monitoring of the patient is essential to avoid serious adverse events (AEs), such as gastrointestinal obstruction, digestive hemorrhage, pancreatitis, gastric necrosis, and perforation[9-12].

Fluid filled IGB ("Traditional"): The "traditional" IGB should be filled with 400 to 750 mL of saline and methylene blue (to alert the patient when their urine appears greenish in case of leak or rupture of the IGB). In addition to the efficacy known in the short-term follow-up, this type of IGB has the advantage of a low rate of AEs. It should be noted; however, that fluid filled IGBs possess a higher rate of early withdrawal since the initial volume cannot be changed and patients may be unable to tolerate the

balloon due to nausea and vomiting, especially within three days after placement[9-11].

Fluid filled adjustable balloon: The adjustable IGB (aIGB) may be filled up to 900 mL of fluid, having the advantage of adjusting the volume of liquid contained in the balloon. This may result in a lower rate of early withdrawal due to patient intolerance and supposedly greater weight loss after adjustment with increasing volume after initial implantation. However, due to the presence of the catheter used for the adjustment, this IGB is associated with a higher rate of ulcerations and abdominal discomfort. In a randomized study comparing the aIGB with lifestyle intervention *vs* lifestyle intervention alone, the aIGB group presented a mean total weight loss (TWL) at 32 wk of 15% compared to 3.3% of the control group. Adjustments to the aIGB occurred among 80% of patients for weight loss plateau or intolerance. Upward volume adjustment facilitated an additional mean of 5.2% TWL. Downward volume adjustment allowed 75% of patients in the aIGB group to complete the full duration of therapy. Intolerance caused early removal of the device in 17% of patients. Severe AEs were observed in 4% of patients[12].

Air balloon: The air IGB is traditionally known for being well tolerated and associated with fewer AEs including nausea and vomiting. However, air IGBs are also associated with less %TWL compared to the fluid filled IGBs, and air filled IGB removal is often challenging as these balloons may more rigid than the other types of IGBs[13,14].

**Endoscopic suturing (endoscopic sleeve gastroplasty):** Endoscopic sleeve gastroplasty (ESG) aims to restrict gastric volume by performing full-thickness sutures in the gastric body. At this time, there are several suture patterns which have been performed; however, the most commonly utilized pattern is the "U" stitch pattern. This pattern is characterized by suturing initially along the anterior wall towards the greater curvature and the posterior wall, with the turn through the posterior wall along the greater curvature and ending at the anterior wall. Often 6 to 8 sutures are performed in the "U" pattern. With this endoscopic technique, the gastric fundus is not sutured, maintaining a reservoir that contributes to the promotion of early satiety. Although the mechanism of action of ESG is not fully understood, circumferential and longitudinal reduction in the size of the stomach as well as delayed gastric emptying time are believed to promote early satiety[15-18].

ESG has been shown to be highly effective and safe in the management of patients with a BMI classified > 25 kg/m$^2$ (overweight) and > 30 kg/m$^2$ (obesity). A recent meta-analysis demonstrated a %TWL of 16.1% and 16.8% and an %EWL of 60% and 73% at 1-year and 18 mo follow-up, respectively [16]. Currently, there are still many unknowns regarding the long-term efficacy of primary endoscopic therapies, especially ESG[15-17]; however, a recent study showed satisfactory results during 5-year follow-up after ESG[18]. ESG has also been shown to be superior to IGB in terms of weight loss and side effect profile, solidifying this treatment strategy as an effective and safe option for individuals who do not quality for surgery or among patients who wish to avoid a traditional surgical approach. In a recent systematic review comparing ESG and IGB strategies, %TWL was superior in the ESG group (%TWL: 15.34% at 6 mo; 17.51% at 12 mo, and 17.85% at 24 mo) compared to the IGB group (%TWL: 12.16% at 6 mo; 10.35% at 12 mo; and 6.89% at 24 mo)[19]. This suggests improved initial weight loss as well as an improved ability to maintain that weight loss. While additional long-term data is needed, these results suggest a promising role for ESG in the management of obesity.

Unlike IGB, which is associated with nausea and vomiting in immediate post-procedure setting, post-ESG patients may experience abdominal pain as a primary symptom. However, like the initial symptoms of IGB, symptoms associated with ESG rapidly improve within three to five days post-procedure[19]. The safety of ESG has also been confirmed in a meta-analysis, demonstrating the rate of severe AEs to be 0.8%, and the rate of total AEs to be 2.3%[16]. Although safe, care during the procedure is essential to minimize complication. Therefore, we recommend use of CO2 for insufflation, general anesthesia with endotracheal intubation, proper patient positioning in the left lateral position, and specialized training to ensure adequate provider knowledge of the device, technique, and understanding of anatomy[15].

**Botulinum toxin injection:** Botulinum toxin injection of the gastric wall works *via* the inhibition of acetylcholine in the cholinergic neuromuscular endings, promoting delay in gastric emptying, thereby leading to early satiety. However, most randomized studies and meta-analyses have not demonstrated the effectiveness of the method in the treatment of obesity[20].

### *Revisional therapies*

Weight recidivism (more commonly described as weight regain) does not have a standardized definition. The most widely accepted definition is considered regain of 50% of the weight loss with initial bariatric surgery (*i.e.*, increase from the nadir weight) or regain of 20% of the nadir weight associated with the recurrence or development of an obesity-associated comorbidity. Weight regain is a multifactorial condition, including hormonal factors, the balance between expenditure and caloric intake, as well as behavioral, genetic, and anatomical factors[21,22]. While all of these factors are essential to providing complete care and ensuring success after bariatric surgery, bariatric endoscopy seeks to primarily alleviate or treat factors related to anatomical changes after bariatric surgery[21-23].

Among the currently available revisional therapies, endoscopic bariatric treatments include use of argon plasma coagulation (APC) and endoscopic suturing[24,25]. These two treatment modalities are typically used in the management of those who have undergone prior Roux-en-Y Gastric Bypass (RYGB) and aim to achieve reduction of the gastric pouch, gastrojejunal anastomosis (GJA), and in some cases, successful closure of gastrogastric fistulas (GGFs) when present. Furthermore, endoscopic suturing has recently been used to treat patients with weight regain after sleeve gastrectomy (sometimes referred to as a sleeve-in-sleeve procedure).

**Reduction of the gastric pouch and gastrojejunal anastomosis after RYGB**: APC: APC is performed circumferentially around the edge of the GJA (gastric face-about 1 to 1.5 cm). As a result, scarring and fibrosis of this area occurs, resulting in a reduction in the diameter of the GJA. In some cases, more than one session may be necessary to achieve the goal of reducing the diameter of the GJA to approximately 10 to 12 mm. A recent randomized study demonstrated no superiority of the group that underwent APC + suturing compared APC alone in terms of weight loss or complications between the techniques at one-year follow-up[25].

Endoscopic suturing (transoral outlet reduction): Endoscopic suturing for patients with a history of RYGB is typically undertaken using a transoral outlet reduction (TORe) technique. The reduction in the diameter of the GJA may also be performed using an endoscopic suturing technique–often performed after APC of the GJA since the combination of methods may result in better weight loss results compared to a suturing alone[24]. The APC technique alone is more widely used due to shorter procedure times, decreased need for deep sedation or endotracheal intubation, and cost-savings. However, endoscopic suturing also allows for the possibility of reducing the gastric pouch, which in selected cases may help to promote better weight loss results. Additionally, pursestring suturing of the GJA is likely a superior strategy to APC alone. Despite limited data at this time, TORe appears to be a highly effective and safe procedure[24].

Modified endoscopic submucosal dissection + APC + endoscopic suturing: Another strategy, based upon TORe as described above, is a modified endoscopic submucosal dissection (ESD)-TORe procedure. This treatment involves making a modified submucosal dissection around the circumference of the GJA, to expose the muscular propria. Once this accomplished, traditional APC is performed around the GJA and a pursestring, endoscopic suture pattern is made around the outlet with bites taken through the exposed muscle layer (minimizing the drawbacks of a non-full thickness or superficial bite that may occur with a traditional TORe technique). This technique was recently described and demonstrated encouraging results in a retrospective study, where the association of a modified ESD technique with APC and endoscopic suturing was superior to APC and suturing alone. In this study, both in the 6-mo follow-up (13.4% *vs* 8.5%; $P = 0.045$) and 1 year follow-up (12.1% *vs* 7.5%; $P = 0.036$) demonstrated greater %TWL in the modified ESD-TORe cohort[26]. However, the increase in costs and procedure time, as well as the need of previous experience in submucosal dissection may limit more widespread adoption of this technique. As such, this technique is likely to continue to only be available at highly specialized centers.

**Treatment of gastrogastric fistula:** Common endoscopic therapies such as APC, clips, and endoscopic suturing are associated with a low clinical success rate in the treatment of GGF. In a study including 29 patients with GGF, despite 100% technical success, clinical success after 1 year was only 17.1%[27]. The use of the cardiac septal defect occluder (CSDO) for the treatment of GGF has also been described. However, more studies are needed to prove the effectiveness and safety profile of this novel approach. In our experience, endoscopic management of GGF may be effective only in GGF smaller than 10 mm.

**Reduction of gastric volume after sleeve gastrectomy:** After sleeve gastrectomy, the ability to perform endoscopic suturing *via* a modified ESG technique is a promising method in the management of patients with postoperative weight regain. In a multicenter study, this technique demonstrated results similar to primary ESG, with %TWL in one year of 14.2%, 19.3%, 17.5%, and 20.4%, for overweight and patients with obesity class I, II, and III, respectively. Perhaps most importantly, in this study, no AEs were reported[28]. The use of a plication device *via* a USGI platform has also been described with promising results[29].

**Complications of revisional therapies:** Adverse effects after revisional endoscopic therapies are uncommon, occurring in approximately 3% to 7% of cases. The most common events reported include nausea and vomiting, abdominal discomfort, post-procedure bleeding, and the development of intraluminal strictures[22]. Additionally, a reverse Barrett´s esophagus, characterized as receding of the squamous columnar junction into the gastric pouch among patients with RYGB has also been described [30]. While the mechanism of action is not fully understood, management of these patients is typically conservative and a vast majority of other complications are managed endoscopically[22,24,31].

### *Management of complications after bariatric surgery*

Endoscopic treatment of bariatric surgery complications is considered by many as the gold standard due to its high efficacy and minimally invasive nature with a low rate of AEs. Endoscopic treatment can be used for treating intraluminal bleeding, leaks, fistulas, and stenoses. Despite the fear of anastomotic

and staple line dehiscence during an endoscopic exam in the very early post-operative period, endoscopic techniques are safe and have been well-documented to be effective in the literature[32-35].

**Hemorrhage:** In patients with early bleeding after bariatric surgery, initial supportive measures such as volume resuscitation, temporary cessation of anticoagulation, and blood transfusion when necessary, should be performed. While highly effective, it should be noted that endoscopic management is only plausible in cases of intraluminal bleeding, especially along gastric suture lines. The main signs of intraluminal hemorrhage include hematemesis, enterorrhagia, or melena. In addition to assistance with diagnosis, endoscopy may provide therapy through a variety of mechanisms–*via* injection, mechanical, thermal, and topical therapies. If endoscopic treatment fails, angiography therapy or emergency surgery may be indicated[34,35]. The proposed algorithm for the management of early bleeding after bariatric surgery is described in Figure 2.

**Treatment of postoperative leaks and fistulas:** The endoscopic treatment of postoperative leaks and fistulas includes a wide variety of techniques and devices, with therapeutic options that aim to close (glues, clips, and sutures), cover (stents and CSDO), and drain [double-pigtails stents (DPS)], septotomy, and endoscopic vacuum therapy (EVT)[32,35] (Tables 1 and 2). It is imperative to understand that early treatment is the key to success. Additionally, basic surgical principles such as drainage of associated collections (by endoscopic, radiologic, or surgical approaches) and treatment of related factors such as distal strictures as well as removal of foreign bodies (preferably by endoscopic techniques), are essential for the successful treatment of postoperative leaks and fistulas[32,35]. These therapies are described individually below, and a proposed algorithm for the management of leaks and fistulas after bariatric surgery is highlighted in Figure 3.

Endoscopic glue: The use of "glue" such as cyanoacrylate, tissue adhesive, or sealants and the acellular fibrogenic matrix is unpopular in Brazil due to its high associated cost and heterogeneous results in the literature. Additionally, multiple sessions are typically required, further making this a less than ideal strategy for many patients. The best results for endoscopic glue use are described in chronic fistulas, typically smaller than 10 mm, with low drain output (traditionally < 200 mL in 24 h), and when used in conjunction with other therapeutic options (*i.e.*, use with endoscopic suturing for oversewing marginal ulcerations). In a national study, the clinical success of the acellular fibrogenic matrix was 80%; however, this was a combined percentage accounting for a 30% success with the initial session, 55% success with the second treatment, and 15% success for patients requiring a third session[36].

Clips: The use of conventional clips are not indicated for the treatment of surgical leaks or fistulas, as this material does not have adequate tension to approximate tissue in these conditions[32]. However, cap-mounted clips can be effective as these devices approximate transmural defects with more tension than the conventional clips and have been proven to adequate close mucosal defects in longer term studies. In a recent systematic review, the effectiveness of the cap-mounted clip was 72.6% for anastomotic leaks and 55.8% for fistulas. It is important to understand that this device can only be used in fistulous orifices up to 20 mm due to its size, being best situated and utilized for small transmural defects not associated with intracavitary collections[37].

Endoscopic suturing: Endoscopic suturing is another strategy that allows for closure of leaks or fistulas *via* the use of transmural sutures, typically using a running mattress pattern to provide successful closure and reduce the risk or recurrent leak. However, despite the high technical success and safety, the clinical success is less than ideal, especially when adapted to fistula close. In a study including 56 patients with fistula, clinical success after one year was 17.1% for GGFs and 31.4% for other types of fistulas. Thus, due to the high cost of the device and unsatisfactory results, its use has been limited for this indication at this time in most countries[27,32,38].

Stents: Esophageal stents are traditionally used with satisfactory closure rates. However, these conventional (esophageal) stents have been associated with some AEs, ranging from symptoms such as pain, reflux, and nausea, to more severe complications such as perforation and migration[32,39]. In a meta-analysis including only post-bariatric surgery leaks and fistulas, clinical success was 72.8% and migration rate was 28.2%[40]. Due to the high rate of AEs, stents specifically designed for leaks and fistulas after bariatric surgery (*i.e.*, sleeve gastrectomy) have been developed. In a multicenter study, including 37 patients, the clinical success rate with these novel stents was 78.27% (similar to the conventional stents), but the rate of the complications including migrations and perforations remained high. Therefore, based upon the literature and our own experience, these novel stents do not appear to be superior to conventional (esophageal) stents and should be utilized with caution–utilized mostly in centers with expertise in the management of this condition[41]. A recent meta-analysis also did not show any advantage of these customized stents when compared to conventional stents for the treatment of sleeve leaks and fistulas[42].

Cardiac septal defect occluder: The CSDO is a shape-memory, self-expanding double-disc closure device composed of nitinol and polyester, with impressive expansion force[43]. Traditionally used to provide closure for atrial or ventricular septal cardiac defects, off-label use has expanded to the realm of gastroenterology. In a multicenter study evaluating its off-label use in fistulas after bariatric surgery, the rate of clinical success in late and chronic fistulas was 97.1%[44]. At present, the use of CSDO devices is recommended for chronic fistulas due to the presence of an epithelialized tract; however, it is important

**Table 1 Endoscopic closure and occlusion techniques for the treatment of leaks and fistulas after bariatric surgery**

| Endoscopic technique | Indications/advantages | Not indicated/disadvantages | Our experience |
|---|---|---|---|
| Glues (Closure) | (1) Acute/early/late/chronic; (2) Low-debit (< 200 mL/24 h); (3) Diameter < 10 mm; and (4) Safe | (1) Multiple sessions are usually required; (2) High costs; (3) Need for external drainage; and (4) Variable efficacy | (1) Low efficacy; (2) Multiple sessions; (3) High costs; (4) Late/chronic; (5) Combined approach; and (6) Can be used in select cases |
| Cap-mounted clips (Closure) | (1) Acute/early/late/chronic; (2) Small orifices (< 2 cm); and (3) Safe | (1) > 2 cm orifice; (2) Need for external drainage; and (3) Variable efficacy | (1) Low efficacy; (2) Late/chronic; and (3) Can be used in select cases |
| Suturing (Closure) | (1) Acute/early/late/chronic; and (2) Safe | (1) Need for external drainage; (2) Challenging-need previous experience with the device; (3) Low efficacy; and (4) High cost | (1) High cost; (2) Very poor long-term clinical success; and (3) We do not recommend it! |
| Stents (conventional esophageal or specific design for LSG) (over) | (1) Acute and early; (2) Very popular; (3) Efficacy > 70%; (4) Conventional = bariatric stent; (5) Early oral intake; and (6) Lower number of repeat procedures | (1) High rates of migration (up to 30%); (2) Need for external drainage; (3) Symptoms related to the stent; (4) Late and Chronic; and (5) You may have a "surprise" when remove it | (1) High rates of migration; (2) Partially covered > fully-covered (challenging to remove-do not keep it for more than 3 wk!); and (3) Bariatric stents: Similar efficacy, more SAE; Symptoms related to the stent (pre pyloric); More migration (post pyloric); We´re avoiding stents, specially Bariatric Stents |
| Cardiac septal defect occlude (Cover) | (1) Late and chronic; (2) Efficacy > 95%; and (3) Safe | (1) Off-label use; (2) Acute and Early; (3) High cost; and (4) Need for external drainage | (1) High efficacy in late/chronic fistulas with epithelialized tract without associated collection; (2) Safe; and (3) Good option after failure of conventional techniques |

**Table 2 Endoscopic drainage techniques for the treatment of leaks and fistulas after bariatric surgery**

| Endoscopic technique | Indications/advantages | Not indicated/disadvantages | Our experience |
|---|---|---|---|
| Septotomy | (1) You must do it when a septum is identified; (2) Early, late and chronic; (3) High efficacy: 80%-100%; and (4) Safe | It is just performed when a septum is identified! | (1) Very high clinical success rates; and (2) Septum is the cause of most late and chronic leaks/fistulas treated in a center without experience |
| EVT | (1) Acute, early, late and chronic; (2) High efficacy (> 90%) in leaks with or without associated collection; (3) No need of external drainage; and (4) Superior to stent in upper GI tract | (1) Patient discomfort related to NGT; (2) Usually repeat procedures are needed (sponge); (3) Respiratory/Cutaneous fistula; (4) Longer hospital stay (?); and (5) High costs (?) | (1) Very high clinical success rates; (2) Modified EVT: Easy placement, reduction in procedure time and need for repeat procedures, lower costs and Aes; and (3) Modified trelumina EVT: Drainage and nutrition with one tube through the nares |
| DPS | (1) Acute, early, late and chronic; (2) High efficacy (> 85%) in leaks/fistulas with associated collection; (3) Easy placement (7fr-gastroscope); (4) No need of external drainage; and (5) Short hospital stay | (1) Longer period for complete healing; (2) Risk of migration and bleeding; (3) No place to accommodate the stent in small collections; and (4) Usually fluoroscopy is needed | (1) Very high clinical success rates; (2) Shorter hospital stay; (3) Faster oral intake (clear liquids); and (4) Better patient acceptance–no symptoms |

EVT: Endoscopic vacuum therapy; DPS: Double-pigtails stents; SAE: Severe adverse events; Aes: Adverse events.

to understand that CSDO device should not be used in acute and early leaks or fistulas as these can increase the size of the orifice due to the significant expansion force[43,44].

Endoscopic internal drainage with double pigtail plastic stents: Endoscopic internal drainage with DPS of perigastric collections after bariatric surgery has also been widely employed. This technique has demonstrated satisfactory results associated with less need for prolonged hospital stay and few AEs. The principles of the DPS method are similar to that of transgastric drainage of pancreatic pseudocysts,

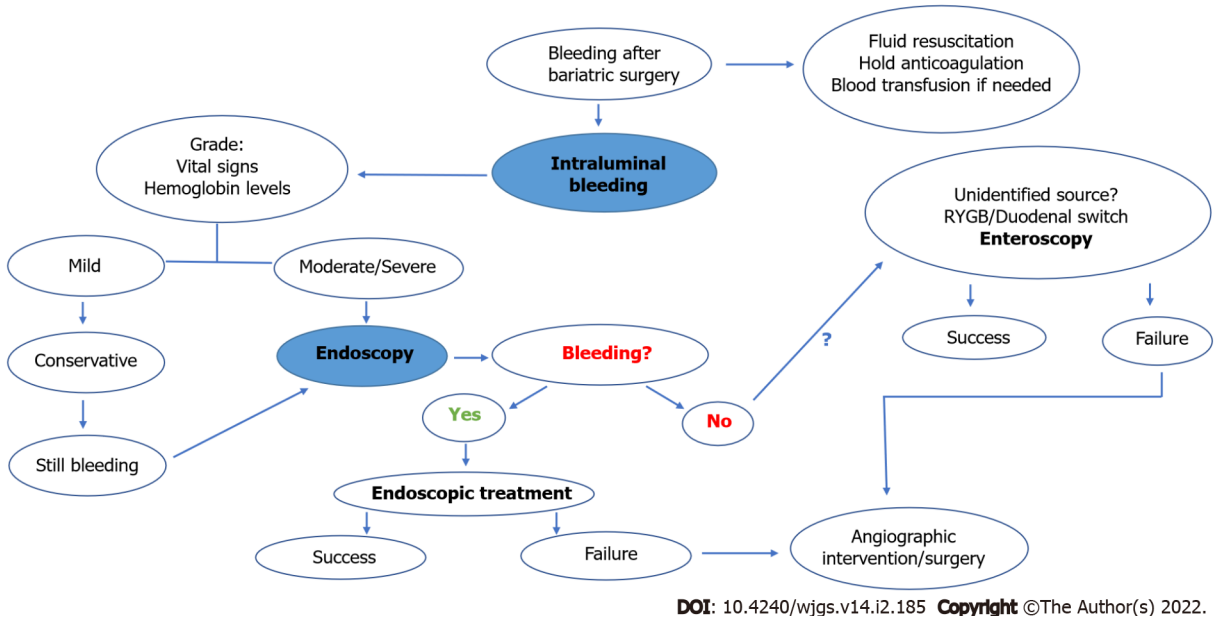



**Figure 2 Proposed algorithm for the endoscopic management of bleeding after bariatric surgery.**

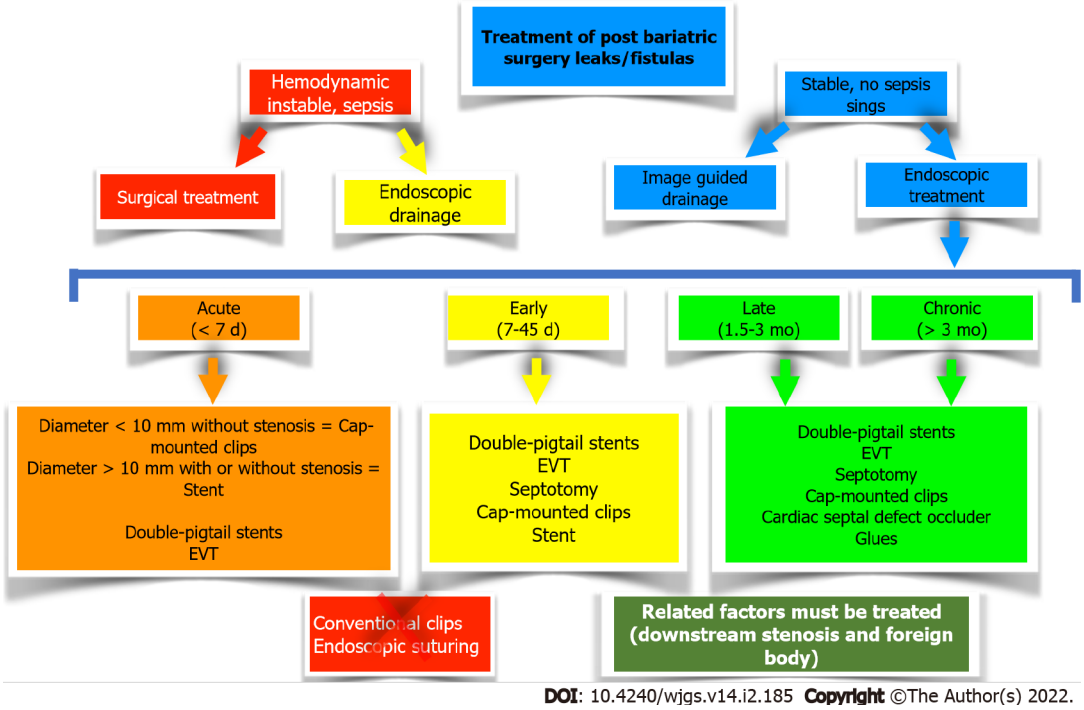



**Figure 3 Proposed algorithm for the treatment of leaks and fistulas after bariatric surgery.** EVT: Endoscopic vacuum therapy.

providing adequate internal drainage and closure of the tract around the pigtail catheter[45]. The vast majority of current studies have shown an efficacy greater than 85% and endoscopic drainage with DPSs have been associated with a low rate of AEs, including stent migration, bleeding, and perforation[46,47].

Septotomy: Endoscopic septotomy is another technique that is currently used worldwide and has a similar principle to the treatment of Zenker's diverticulum. When most helpful, the septotomy technique is beneficial where the septum must be sectioned to match the pressure of the leak or fistula site within the gastric chamber[48]. The septotomy must be performed up to the depth of the suture line, but not exceed this limit to avoid perforation. In a study involving 27 patients after bariatric surgery, including patients with RYGB, sleeve gastrectomy, and duodenal switch, the clinical success rate after septotomy was 100%, with an average treatment time of 18.11 days and the need for one to six procedures[48]. As such, this septotomy strategy can be highly effective when individual patient factors warrant this technique.

Endoscopic vacuum therapy: EVT is traditional strategy used in Europe, though its use and adoption has more recently spread across the world. The technique is performed by placing a sponge (or gauze covered by surgical adhesive when using a modified technique) on the distal end of a nasogastric tube, which is positioned in the perigastric collection (intracavitary) or in the lumen (intraluminal). Next, this nasogastric tube is connected to a vacuum machine or wall suction with continuous negative pressure (between-125 and -175 mmHg). The EVT system positioning is based on endoscopic findings, and the intracavitary position should be used whenever there is an associated collection. Mechanisms of action include microdeformation and macrodeformation, improvement of perfusion (angiogenesis), control of local edema, and bacterial clearance[49-51].

Several studies have reported high efficacy and low AE rates associated with EVT. Nonetheless, the need for repeated procedures, every seven days for traditional (polyurethane) EVT sponge, and patient discomfort due to continuous and prolonged use of a nasogastric tube are considered limiting factors by some centers. The advantages of the recently described low-cost modified EVT system includes easy placement (through nares), decreased procedure time, longer interval between EVT system exchanges, and decreased AEs[49,50]. In a meta-analysis comparing EVT *vs* stent placement for the treatment of upper gastrointestinal transmural defects, EVT was superior in closing transmural defects, associated with decreased treatment time, and found to have a lower associated mortality rate[52].

**Treatment of stenoses:** Stenosis after RYGB: Dilation with a hydrostatic balloon for stenoses after RYGB is a well-established method, with clinical success rates up to 100% after one to five treatment sessions. In addition to its effectiveness, balloon dilation is considered safe with low rates of AEs–perforation (4.9% of cases) is the most common[53]. It is important to acknowledge that the presence of an ischemic segment is associated with therapeutic failure and an increased risk of complications[53,54]. In recent years, metallic stents with lumen apposition (lumen apposing metal stents) have been used for cases refractory to dilation–with technical success rates of 100%, high clinical success rates in the short follow-up, and infrequent AEs compared to esophageal stent placement, including decreased migration, pain, recurrent stenosis, and bleeding. However, the need for re-intervention in long-term follow-up continues to be considered high[54]. In addition to the use of self-expandable metallic stents for refractory cases, incisional therapy and corticosteroid injection are less expensive options and may be performed in specialized centers.

Ring slippage after RYGB: Slipping of the ring may cause stenosis of the gastric pouch or even in the jejunal limb, leading to food intolerance. The endoscopic treatment of this condition can be carried out through pneumatic balloon dilation (using an achalasia balloon) or self-expandable stent (plastic or metal) placement. Patients who underwent pneumatic balloon dilation, aiming to stretch or rupture the ring, achieved high rates of clinical success after one to four sessions, usually with no recurrence of symptoms or perioperative complications[55]. Likewise, in a study evaluating the use of self-expandable stents in 41 patients, removal of the ring was possible in all cases. However, it should be noted that 22% of patients developed post-procedure stenosis due to local fibrosis, requiring endoscopic balloon dilation[56]. Despite these complications, reoperation or deaths are extremely rare after these approaches[55,56]. Due to the higher rate of stenosis after using self-expandable stents, we recommend treatment with pneumatic dilation as a first-line strategy whenever possible.

Erosion of the ring after RYGB: Ring erosion after RYGB is traditionally treated by endoscopy due to its ease and minimally invasive nature. Endoscopic removal of the ring is indicated with minimal intraluminal extrusion of 30%. This can be performed through the ring section, either with endoscopic scissors (silastic ring) or with APC [polypropylene (marlex) ring], followed by ring removal using a foreign body forceps or a polypectomy snare[56].

Erosion of the gastric band: Erosion of the gastric band has been noted to less frequently occur due to the more recent shift away from this surgical technique in clinical practice. Endoscopic band cutting is performed by passing a guidewire through the intragastric fragment of the band, followed by cutting using a lithotripter device. Then, with a polypectomy snare, the device is removed. The subcutaneous port must be removed before the endoscopic removal. Technical and clinical success rates are extremely high, with a low rate of AEs, mainly pneumoperitoneum. Most of these cases may be treated conservatively through decompression with an abdominal puncture[57,58]. While less individuals are undergoing the laparoscopic adjustable gastric band procedure, provider knowledge of potential complications and appropriate understanding of endoscopic treatment remain critically important.

Treatment of stenosis after sleeve gastrectomy: Several algorithms for the management of stenosis after sleeve gastrectomy have been described. Our experience is similar to the results of a recent meta-analysis, where conservative management in the first two to three weeks is recommended, with improvement in obstructive symptoms in 68.8% of cases. If patients remain symptomatic and are refractory to conservative management, endoscopic treatment is therefore recommended, with success rates approaching 82%, *via* dilation with a pneumatic balloon (one to three sessions), starting with dilation up to 30 mm, followed by dilation up to 35 mm. Dilatation up to 40 mm can be performed; however, this is not usually recommended due to the high risk of complications. Some groups report success using hydrostatic balloons (up to 20 mm) in selected cases, but it is rarely used in our practice due to limited long-term relief and symptom and stenosis recurrence.

Another endoscopic option is the use of self-expanding metal stents; however, these are indicated mainly for patients that remain refractory to pneumatic dilation. Primary surgical treatment may also be performed, but it is more invasive and results are not superior to endoscopy. In cases refractory to endoscopic therapy, surgical treatment is traditionally indicated, with a 98% success rate[59]. Recently, the endoscopic tunneled stricturotomy technique has been described with promising results in refractory cases, becoming another minimally invasive alternative to surgery[60]. The algorithm proposed by our group is shown in Figure 4.

## DISCUSSION

The exponential growth of bariatric surgery in the last decades has evolved inseparably from the advances in the field of endoscopy. In this article, we have reviewed the main therapeutic options of bariatric endoscopy that should be known by general, digestive, and bariatric surgeons. These have been summarized above and divided into three main areas: Primary treatments for obesity, revisional therapies, as well as the management of complications after bariatric surgery.

Among the primary treatments, the IGB is the most widely used, with satisfactory results in the short-term when appropriately indicated. Endoscopic suturing has been utilized with promising results and considerable weight loss; however, the evidence with long-term follow-up remains scarce. When a patient seeks a surgeon in demand for these techniques, we must emphasize that these procedures are not a substitute for bariatric surgery, and we should highlight three aspects: Adequate indication; expectation of realistic results within the BMI profile and associated comorbidities; and safety and quality of the procedure when performed by a specialized endoscopist in an appropriate medical facility. Furthermore, like other treatments for obesity, the support of a specialized multidisciplinary team and regular adherence to follow-up is necessary to ensure an optimal long-term result.

Weight regain has become a challenge due to the cumulative increase in the number of patients undergoing bariatric surgery. Mechanisms for weight regain are complex and again require a multidisciplinary approach–taking into account factors outside of just anatomic changes. In most cases mechanism of weight regain are multifactorial. Therefore, the initial step in treating these patients is a comprehensive assessment of the patient by a multidisciplinary team. For individuals with appropriate indications, endoluminal therapies are safe, reproducible and effective in treating patients with weight regain and as a less invasive therapy then revisional surgery. Therefore, endoscopic bariatric treatment should be utilized as a first line intervention to manage this condition.

When considering surgical complications, the management of postoperative bariatric surgery patients is challenging and, to achieve a positive outcome, again requires a multidisciplinary approach. Didactic knowledge, technical mastery, and good communication between the surgery, endoscopy, and interventional radiology teams remains essential. In this manner, it is also key to have a collaborative hospital structure and environment since minimally invasive treatment by endoscopic therapy may be used as first-line therapy to avoid more invasive procedures in the treatment of acute postoperative complications.

When diagnosing a leak or fistula, endoscopic treatment may be considered an early therapeutic option. As shown in Figure 3 and Table 2, the surgeon may rely upon endoscopic treatment even for severe cases. Endoscopic adjuncts to traditional surgical cases, such as peritonitis and sepsis, may include placement of an enteral feeding tube or, more recently, endoscopic internal drainage therapies such as EVT intraoperatively. Regarding late complications, bariatric endoscopy should be considered a first-line strategy for diagnosis and treatment along with an upper gastrointestinal series. This is essential for assessing patients with recurrent nausea, vomiting, reflux, or regurgitation. Additionally, endoscopy may often be used as an option for the treatment of stenosis and ring/band erosions, avoiding reoperations which include greater complexity and risk, since these are patients with long-standing surgeries, many by open access, and presenting with malnutrition due to recurrent vomiting.

As obesity treatment algorithms evolve, bariatric endoscopy procedures and their devices have been gradually adopted. However, it is important to note that there are still significant limitations due to its high associated costs and even restrictions for authorization and/or importation of these devices.

Despite being a comprehensive review of the literature, this article is not without limitations. As this is a recent topic, most studies are small or uncontrolled series, and more prospective and randomized studies are needed to establish the best therapeutic options for each situation. Also, many of these studies were carried out in large referral centers, with a team and structure dedicated to this patient profile. In this manner, not all the therapeutic options reviewed here can be applied to the reality of all services and hospitals.

## CONCLUSION

Obesity and weight regain are multifactorial disorders, and, therefore, multidisciplinary treatment is essential. Bariatric and metabolic endoscopic therapies are in constant development, including devices

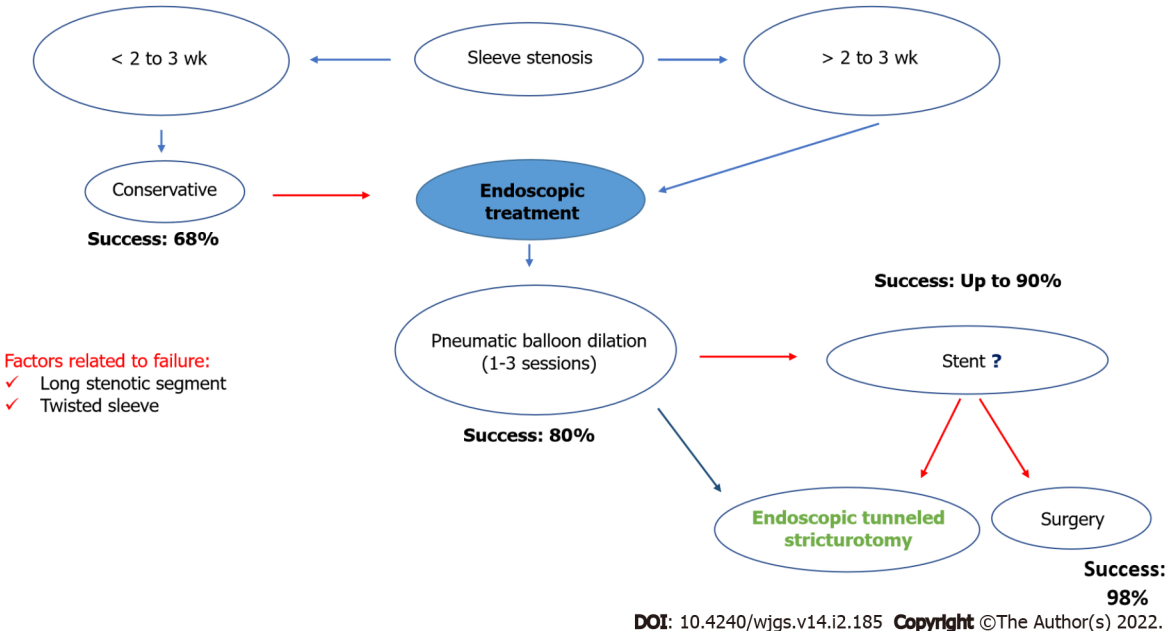



**Figure 4 Proposed algorithm for the endoscopic management of stenosis after sleeve gastrectomy.**

with a wide variety of mechanisms of action. Available endoscopic approaches have been shown to be effective and safe in the management of obesity and in patients with weight regain. However, as there is no gold standard method for managing these patients, the assessment must be individualized. Despite the favorable results, randomized studies with long-term follow-up are still required for complete validation of primary and revisional endoscopic bariatric therapies.

Regarding the management of complications after bariatric surgery, it is essential to underscore the complexity of patient care, where follow-up with a multidisciplinary team is critical. Endoscopic therapies are associated with high rates of clinical success in the management of intraluminal bleeding conditions, stenoses, leaks and fistulas, especially when performed early in the post-operative period. To date, there is no precise algorithm for the management of these patients, and therefore, local experience and device availability should be considered when choosing a therapy. Institutions without specialized staff should consider referring these patients to a center of excellence.

## ARTICLE HIGHLIGHTS

### *Research background*

Obesity is a chronic and recurrent disease resulting in a global pandemic associated with several associated comorbidities. Current treatments include lifestyle modifications including behavioral, dietary, exercise changes, and medications which are associated with less than ideal long-term outcomes. Bridging the gap between these therapies and traditional bariatric surgery is the field of bariatric endoscopy, which seeks to provide less invasive therapies to treat primary obesity, treat weight regain after bariatric surgery, and manage complications of bariatric surgery.

### *Research motivation*

To review the current literature of bariatric endoscopy and highlight the field of to colleagues from other disciplines such as surgeons, endocrinologists, and primary care physicians.

### *Research objectives*

Discuss the current state of bariatric endoscopy, including primary therapies, endoscopic management of weight regain, and the management of complications after bariatric surgery including hemorrhage, stenoses, and leaks and fistulas.

### *Research methods*

Narrative review including available literature data obtained through electronic databases and authors' experience.

### *Research results*

Bariatric endoscopy is in constantly evolving field which comprises primary and revisional treatment as well as the management of surgical complications. While longer-term, randomized studies are still warranted to fully validate primary and revisional endoscopic therapies, the field provides a high effective and safe means to treat patients with obesity and associated comorbid conditions. Regarding endoscopic treatment of post bariatric surgery complications, endoscopic management remains a first-line strategy to avoid the morbidity and mortality associated with repeat surgical operations.

### *Research conclusions*

Bariatric and metabolic endoscopic therapies are in constant development, including devices with a wide variety of mechanisms of action. Available endoscopic approaches have proved to be effective and safe for a variety of obesity associated treatments. In this manuscript, we have highlighted these indications, provided a detailed review of the literature, and summarized our own experience to improve the management and care of patients with obesity.

### *Research perspectives*

The advances in the bariatric endoscopy field have the unique opportunity to improve the quality of life and health outcomes for patients with obesity and associated comorbid conditions. The field as a whole as the ability to bridge the gap between lifestyle modifications and conventional surgery to provide treatment to a wide range of individuals, offering a minimally invasive approach for conditions and complications that previously required surgery.

## FOOTNOTES

**Author contributions:** All authors performed the conception and design of the work; de Moura DTH, Dantas ACB and Ribeiro IB drafted the manuscript; all authors contributed to the critical review of the manuscript for important intellectual contents; McCarty TR, Santo MA, Nahas SC, and de Moura EGH contributed to the manuscript supervision; all authors contributed to the approval of the version to be published, have participated in conceptualizing the research or content of the manuscript, in writing or critically editing the manuscript, and/or in analysis of data presented in the manuscript; Consent to submit has been received from all co-authors.

**Conflict-of-interest statement:** Dr. Eduardo Guimarães Hourneaux de Moura reports personal fees from Boston Scientific, personal fees from Olympus, outside the submitted work; Dr. Diogo Turiani Hourneaux de Moura reports personal fees from Bariatek, outside the submitted work; The others authors reported no potential conflict of interest.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.



**Country/Territory of origin:** Brazil

**ORCID number:** Diogo Turiani Hourneaux de Moura 0000-0002-7446-0355; Anna Carolina Batista Dantas 0000-0001-9505-6784; Igor Braga Ribeiro 0000-0003-1844-8973; Thomas R McCarty 0000-0003-4517-5261; Flávio Roberto Takeda 0000-0001-7338-922X; Marco Aurelio Santo 0000-0002-7813-6210; Sergio Carlos Nahas 0000-0002-2268-4146; Eduardo Guimarães Hourneaux de Moura 0000-0003-1215-5731.

**S-Editor:** Fan JR
**L-Editor:** Filipodia
**P-Editor:** Fan JR

## REFERENCES

1 **(CDC) C for DC and P**. Overweight & Obesity - Adult Obesity Facts [Internet]. 2021. [cited 4 January 2021]. Available from: https://www.cdc.gov/obesity/data/adult.html
2 **IBGE**. Um em cada quatro adultos do país estava obeso em 2019; Atenção Primária foi bem avaliada [Internet]. [cited 4 January 2021]. Available from: https://agenciadenoticias.ibge.gov.br/agencia-noticias/2012-agencia-de-noticias/noticias/29204-um-em-cada-quatro-adultos-do-pais-estava-obeso-em-2019
3 **Santo MA**, Pajecki D, Riccioppo D, Cleva R, Kawamoto F, Cecconello I. Early complications in bariatric surgery:

incidence, diagnosis and treatment. *Arq Gastroenterol* 2013; **50**: 50-55 [PMID: 23657307 DOI: 10.1590/S0004-28032013000100010]
4 **Zilberstein B**, Santo MA, Carvalho MH. Critical analysis of surgical treatment techniques of morbid obesity. *Arq Bras Cir Dig* 2019; **32**: e1450 [PMID: 31644670 DOI: 10.1590/0102-672020190001e1450]
5 **Elias AA**, Roque-de-Oliveira M, Campos JM, Sasake WT, Bandeira ÁA, Silva LB, Ferreira B, Ito RM, Shirozaki HY, Benetti FA, Paiva LDS, Garrido Júnior AB. Robotic-assisted bariatric surgery: case series analysis and comparison with the laparoscopic approach. *Rev Col Bras Cir* 2018; **45**: e1806 [PMID: 30043900 DOI: 10.1590/0100-6991e-20181806]
6 **Ferraz ÁAB**, Vasconcelos CFM, Santa-Cruz F, Aquino MAR, Buenos-Aires VG, Siqueira LT. Surgical site infection in bariatric surgery: results of a care bundle. *Rev Col Bras Cir* 2019; **46**: e2252 [PMID: 31508737 DOI: 10.1590/0100-6991e-20192252]
7 **Pajecki D**, Kawamoto F, Dantas ACB, Andrade PC, Brasil NC, Junqueira SM, Oliveira FMP, Ribeiro RA, Santo MA. Real-world evidence of health outcomes and medication use 24 mo after bariatric surgery in the public healthcare system in Brazil: a retrospective, single-center study. *Clinics (Sao Paulo)* 2020; **75**: e1588 [PMID: 32294671 DOI: 10.6061/clinics/2020/e1588]
8 **Kotzampassi K**, Shrewsbury AD. Intragastric balloon: ethics, medical need and cosmetics. *Dig Dis* 2008; **26**: 45-48 [PMID: 18600015 DOI: 10.1159/000109386]
9 **Cho JH**, Bilal M, Kim MC, Cohen J; Study Group for Endoscopic Bariatric and Metabolic Therapies of the Korean Society of Gastrointestinal Endoscopy. The Clinical and Metabolic Effects of Intragastric Balloon on Morbid Obesity and Its Related Comorbidities. *Clin Endosc* 2021; **54**: 9-16 [PMID: 33684281 DOI: 10.5946/ce.2020.302]
10 **Moura D**, Oliveira J, De Moura EG, Bernardo W, Galvão Neto M, Campos J, Popov VB, Thompson C. Effectiveness of intragastric balloon for obesity: A systematic review and meta-analysis based on randomized control trials. *Surg Obes Relat Dis* 2016; **12**: 420-429 [PMID: 26968503 DOI: 10.1016/j.soard.2015.10.077]
11 **Sander BQ**, Alberti LR, Moura DTH, Scarparo JIB, Arantes VN. "Analysis of Long-Term Weight Regain in Obese Patients Treated with Intragastric Balloon". *Acta Sci Gastro Dis* 2019; 08-10 [DOI: 10.31080/ASGIS.2019.02.0094]
12 **Abu Dayyeh BK**, Maselli DB, Rapaka B, Lavin T, Noar M, Hussan H, Chapman CG, Popov V, Jirapinyo P, Acosta A, Vargas EJ, Storm AC, Bazerbachi F, Ryou M, French M, Noria S, Molina D, Thompson CC. Adjustable intragastric balloon for treatment of obesity: a multicentre, open-label, randomised clinical trial. *Lancet* 2021; **398**: 1965-1973 [PMID: 34793746 DOI: 10.1016/S0140-6736(21)02394-1]
13 **Caglar E**, Dobrucali A, Bal K. Gastric balloon to treat obesity: filled with air or fluid? *Dig Endosc* 2013; **25**: 502-507 [PMID: 23369002 DOI: 10.1111/den.12021]
14 **Borges AC**, Almeida PC, Furlani SMT, Cury MS, Gaur S. Intragastric balloons in high-risk obese patients in a Brazilian center: initial experience. *Rev Col Bras Cir* 2018; **45**: e1448 [PMID: 29451645 DOI: 10.1590/0100-6991e-20181448]
15 **de Moura DTH**, de Moura EGH, Thompson CC. Endoscopic sleeve gastroplasty: From whence we came and where we are going. *World J Gastrointest Endosc* 2019; **11**: 322-328 [PMID: 31205593 DOI: 10.4253/wjge.v11.i5.322]
16 **de Miranda Neto AA**, de Moura DTH, Ribeiro IB, Khan A, Singh S, da Ponte Neto AM, Madruga Neto AC, do Monte Junior ES, Tustumi F, Bernardo WM, de Moura EGH. Efficacy and Safety of Endoscopic Sleeve Gastroplasty at Mid Term in the Management of Overweight and Obese Patients: a Systematic Review and Meta-Analysis. *Obes Surg* 2020; **30**: 1971-1987 [PMID: 32107706 DOI: 10.1007/s11695-020-04449-9]
17 **Itani MI**, Farha J, Sartoretto A, Abbarh S, Badurdeen D, de Moura DTH, Kumbhari V. Endoscopic sleeve gastroplasty with argon plasma coagulation: A novel technique. *J Dig Dis* 2020; **21**: 664-667 [PMID: 32916766 DOI: 10.1111/1751-2980.12939]
18 **Sharaiha RZ**, Hajifathalian K, Kumar R, Saunders K, Mehta A, Ang B, Skaf D, Shah S, Herr A, Igel L, Dawod Q, Dawod E, Sampath K, Carr-Locke D, Brown R, Cohen D, Dannenberg AJ, Mahadev S, Shukla A, Aronne LJ. Five-Year Outcomes of Endoscopic Sleeve Gastroplasty for the Treatment of Obesity. *Clin Gastroenterol Hepatol* 2021; **19**: 1051-1057.e2 [PMID: 33011292 DOI: 10.1016/j.cgh.2020.09.055]
19 **Singh S**, de Moura DTH, Khan A, Bilal M, Chowdhry M, Ryan MB, Bazarbashi AN, Thompson CC. Intragastric Balloon Versus Endoscopic Sleeve Gastroplasty for the Treatment of Obesity: a Systematic Review and Meta-analysis. *Obes Surg* 2020; **30**: 3010-3029 [PMID: 32399847 DOI: 10.1007/s11695-020-04644-8]
20 **Vargas EJ**, Bazerbachi F, Calderon G, Prokop LJ, Gomez V, Murad MH, Acosta A, Camilleri M, Abu Dayyeh BK. Changes in Time of Gastric Emptying After Surgical and Endoscopic Bariatrics and Weight Loss: A Systematic Review and Meta-Analysis. *Clin Gastroenterol Hepatol* 2020; **18**: 57-68.e5 [PMID: 30954712 DOI: 10.1016/j.cgh.2019.03.047]
21 **Berti LV**, Campos J, Ramos A, Rossi M, Szego T, Cohen R. POSITION OF THE SBCBM - NOMENCLATURE AND DEFINITION OF OUTCOMES OF BARIATRIC AND METABOLIC SURGERY. *Arq Bras Cir Dig* 2015; **28** Suppl 1: 2 [PMID: 26537262 DOI: 10.1590/S0102-6720201500S100002]
22 **Hourneaux De Moura DT**, Thompson CC. Endoscopic management of weight regain following Roux-en-Y gastric bypass. *Expert Rev Endocrinol Metab* 2019; **14**: 97-110 [PMID: 30691326 DOI: 10.1080/17446651.2019.1571907]
23 **Staudenmann DA**, Sui Z, Saxena P, Kaffes AJ, Marinos G, Kumbhari V, Aepli P, Sartoretto A. Endoscopic bariatric therapies for obesity: a review. *Med J Aust* 2021; **215**: 183-188 [PMID: 34333788 DOI: 10.5694/mja2.51179]
24 **Dhindsa BS**, Saghir SM, Naga Y, Dhaliwal A, Ramai D, Cross C, Singh S, Bhat I, Adler DG. Efficacy of transoral outlet reduction in Roux-en-Y gastric bypass patients to promote weight loss: a systematic review and meta-analysis. *Endosc Int Open* 2020; **8**: E1332-E1340 [PMID: 33015335 DOI: 10.1055/a-1214-5822]
25 **Brunaldi VO**, Farias GFA, de Rezende DT, Cairo-Nunes G, Riccioppo D, de Moura DTH, Santo MA, de Moura EGH. Argon plasma coagulation alone *vs* argon plasma coagulation plus full-thickness endoscopic suturing to treat weight regain after Roux-en-Y gastric bypass: a prospective randomized trial (with videos). *Gastrointest Endosc* 2020; **92**: 97-107.e5 [PMID: 32217111 DOI: 10.1016/j.gie.2020.03.3757]
26 **Jirapinyo P**, de Moura DTH, Thompson CC. Endoscopic submucosal dissection with suturing for the treatment of weight regain after gastric bypass: outcomes and comparison with traditional transoral outlet reduction (with video). *Gastrointest Endosc* 2020; **91**: 1282-1288 [PMID: 32007520 DOI: 10.1016/j.gie.2020.01.036]
27 **Mukewar S**, Kumar N, Catalano M, Thompson C, Abidi W, Harmsen W, Enders F, Gostout C. Safety and efficacy of

fistula closure by endoscopic suturing: a multi-center study. *Endoscopy* 2016; **48**: 1023-1028 [PMID: 27576179 DOI: 10.1055/s-0042-114036]

28 **de Moura DTH**, Barrichello S Jr, de Moura EGH, de Souza TF, Dos Passos Galvão Neto M, Grecco E, Sander B, Hoff AC, Matz F, Ramos F, de Lima JHF, Teixeira L, Dib V, Falcão M, Potti H, Baretta G, Jirapinyo P, Thompson CC. Endoscopic sleeve gastroplasty in the management of weight regain after sleeve gastrectomy. *Endoscopy* 2020; **52**: 202-210 [PMID: 31940667 DOI: 10.1055/a-1086-0627]

29 **Jirapinyo P**, de Moura DTH, Thompson CC. Sleeve in sleeve: endoscopic revision for weight regain after sleeve gastrectomy. *VideoGIE* 2019; **4**: 454-457 [PMID: 31709328 DOI: 10.1016/j.vgie.2019.07.003]

30 **Hourneaux de Moura DT**, Hathorn KE, Thompson CC. You Just Got Burned! What Is Wrong With This Gastric Pouch? *Gastroenterology* 2019; **156**: 2139-2141 [PMID: 30716322 DOI: 10.1053/j.gastro.2019.01.255]

31 **de Moura DTH**, Sachdev AH, Lu PW, Ribeiro IB, Thompson CC. Acute bleeding after argon plasma coagulation for weight regain after gastric bypass: A case report. *World J Clin Cases* 2019; **7**: 2038-2043 [PMID: 31423435 DOI: 10.12998/wjcc.v7.i15.2038]

32 **de Moura DTH**, Sachdev AH, Thompson CC. Endoscopic Full-Thickness Defects and Closure Techniques. *Curr Treat Options Gastroenterol* 2018; **16**: 386-405 [PMID: 30382572 DOI: 10.1007/s11938-018-0199-6]

33 **García-García ML**, Martín-Lorenzo JG, Torralba-Martínez JA, Lirón-Ruiz R, Miguel Perelló J, Flores Pastor B, Pérez Cuadrado E, Aguayo Albasini JL. Emergency endoscopy for gastrointestinal bleeding after bariatric surgery. Therapeutic algorithm. *Cir Esp* 2015; **93**: 97-104 [PMID: 25438773 DOI: 10.1016/j.ciresp.2014.05.002]

34 **Susmallian S**, Danoch R, Raskin B, Raziel A, Barnea R, Dvora P. Assessing Bleeding Risk in Bariatric Surgeries: A Retrospective Analysis Study. *Dig Dis* 2020; **38**: 449-457 [PMID: 32053819 DOI: 10.1159/000506456]

35 **Kumbhari V**, Cummings DE, Kalloo AN, Schauer PR. AGA Clinical Practice Update on Evaluation and Management of Early Complications After Bariatric/Metabolic Surgery: Expert Review. *Clin Gastroenterol Hepatol* 2021; **19**: 1531-1537 [PMID: 33741500 DOI: 10.1016/j.cgh.2021.03.020]

36 **Maluf-Filho F**, Lima MS, Hondo F, Giordano-Nappi JH, Garrido T, Sakai P. [Endoscopic placement of a "plug" made of acellular biomaterial: a new technique for the repair of gastric leak after Roux-en-Y gastric bypass]. *Arq Gastroenterol* 2008; **45**: 208-211 [PMID: 18852948 DOI: 10.1590/s0004-28032008000300008]

37 **Bartell N**, Bittner K, Kaul V, Kothari TH, Kothari S. Clinical efficacy of the over-the-scope clip device: A systematic review. *World J Gastroenterol* 2020; **26**: 3495-3516 [PMID: 32655272 DOI: 10.3748/wjg.v26.i24.3495]

38 **Chan SM**, Auyeung KKY, Lam SF, Chiu PWY, Teoh AYB. Current status in endoscopic management of upper gastrointestinal perforations, leaks and fistulas. *Dig Endosc* 2022; **34**: 43-62 [PMID: 34115407 DOI: 10.1111/den.14061]

39 **Nedelcu M**, Manos T, Noel P, Gagner M, Palermo M, Danan M, Nedelcu A, Vilallonga R. Aortic Injuries Following Stent Deployments in Bariatric Surgery-Review of Literature. *J Laparoendosc Adv Surg Tech A* 2021; **31**: 171-175 [PMID: 33351718 DOI: 10.1089/lap.2020.0731]

40 **Okazaki O**, Bernardo WM, Brunaldi VO, Junior CCC, Minata MK, de Moura DTH, de Souza TF, Campos JM, Santo MA, de Moura EGH. Efficacy and Safety of Stents in the Treatment of Fistula After Bariatric Surgery: a Systematic Review and Meta-analysis. *Obes Surg* 2018; **28**: 1788-1796 [PMID: 29654447 DOI: 10.1007/s11695-018-3236-6]

41 **de Moura DTH**, de Moura EGH, Neto MG, Jirapinyo P, Teixeira N, Orso I, Quadros LG, Amorim A, Medeiros F, Neto DR, de Siqueira Neto J, Albano A, de Sousa LH, Almeida D, Marchetti IA, Ivano F, de Lima JHF, Falcão M, Thompson CC. Outcomes of a novel bariatric stent in the management of sleeve gastrectomy leaks: a multicenter study. *Surg Obes Relat Dis* 2019; **15**: 1241-1251 [PMID: 31262650 DOI: 10.1016/j.soard.2019.05.022]

42 **Hamid HKS**, Emile SH, Saber AA, Dincer M, de Moura DTH, Gilissen LPL, Almadi MA, Montuori M, Vix M, Perisse LGS, Quezada N, Garofalo F, Pescarus R. Customized bariatric stents for sleeve gastrectomy leak: are they superior to conventional esophageal stents? *Surg Endosc* 2021; **35**: 1025-1038 [PMID: 33159298 DOI: 10.1007/s00464-020-08147-6]

43 **De Moura DTH**, Baptista A, Jirapinyo P, De Moura EGH, Thompson C. Role of Cardiac Septal Occluders in the Treatment of Gastrointestinal Fistulas: A Systematic Review. *Clin Endosc* 2020; **53**: 37-48 [PMID: 31286746 DOI: 10.5946/ce.2019.030]

44 **Baptista A**, Hourneaux De Moura DT, Jirapinyo P, Hourneaux De Moura EG, Gelrud A, Kahaleh M, Salinas A, Sabagh LC, Ospina A, Rincones VZ, Doval R, Bandel JW, Thompson CC. Efficacy of the cardiac septal occluder in the treatment of post-bariatric surgery leaks and fistulas. *Gastrointest Endosc* 2019; **89**: 671-679.e1 [PMID: 30529441 DOI: 10.1016/j.gie.2018.11.034]

45 **Farias GFA**, Bernardo WM, De Moura DTH, Guedes HG, Brunaldi VO, Visconti TAC, Gonçalves CVT, Sakai CM, Matuguma SE, Santos MELD, Sakai P, De Moura EGH. Endoscopic *vs* surgical treatment for pancreatic pseudocysts: Systematic review and meta-analysis. *Medicine (Baltimore)* 2019; **98**: e14255 [PMID: 30813129 DOI: 10.1097/MD.0000000000014255]

46 **Fuentes-Valenzuela E**, García-Alonso FJ, Tejedor-Tejada J, Nájera-Muñoz R, de Benito Sanz M, Sánchez-Ocaña R, de la Serna Higuera C, Pérez-Miranda M. Endoscopic internal drainage using transmural double-pigtail stents in leaks following upper gastrointestinal tract surgery. *Rev Esp Enferm Dig* 2021; **113**: 698-703 [PMID: 33371700 DOI: 10.17235/reed.2020.7514/2020]

47 **Sánchez-Luna SA**, Guimãraes Hourneaux De Moura E, Sena de Medeiros F, Turiani Hourneaux De Moura D. Does it matter which plastic stents we use for the treatment of post-surgical leaks? *Rev Esp Enferm Dig* 2021 [PMID: 34781688 DOI: 10.17235/reed.2021.8433/2021]

48 **Baretta G**, Campos J, Correia S, Alhinho H, Marchesini JB, Lima JH, Neto MG. Bariatric postoperative fistula: a life-saving endoscopic procedure. *Surg Endosc* 2015; **29**: 1714-1720 [PMID: 25294547 DOI: 10.1007/s00464-014-3869-z]

49 **de Moura DTH**, de Moura BFBH, Manfredi MA, Hathorn KE, Bazarbashi AN, Ribeiro IB, de Moura EGH, Thompson CC. Role of endoscopic vacuum therapy in the management of gastrointestinal transmural defects. *World J Gastrointest Endosc* 2019; **11**: 329-344 [PMID: 31205594 DOI: 10.4253/wjge.v11.i5.329]

50 **de Moura DTH**, Hirsch BS, Do Monte Junior ES, McCarty TR, de Medeiros FS, Thompson CC, de Moura EGH. Cost-effective modified endoscopic vacuum therapy for the treatment of gastrointestinal transmural defects: step-by-step process of manufacturing and its advantages. *VideoGIE* 2021; **6**: 523-528 [PMID: 34917860 DOI: 10.1016/j.vgie.2021.08.002]

51 **Markus A**, Henrik BJ, Benedikt R, Alexander H, Thomas B, Clemens S, Jan-Hendrik E. Endoscopic vacuum therapy in salvage and standalone treatment of gastric leaks after bariatric surgery. *Langenbecks Arch Surg* 2021 [PMID: 34787705 DOI: 10.1007/s00423-021-02365-9]

52 **do Monte Junior ES**, de Moura DTH, Ribeiro IB, Hathorn KE, Farias GFA, Turiani CV, Medeiros FS, Bernardo WM, de Moura EGH. Endoscopic vacuum therapy *vs* endoscopic stenting for upper gastrointestinal transmural defects: Systematic review and meta-analysis. *Dig Endosc* 2021; **33**: 892-902 [PMID: 33300634 DOI: 10.1111/den.13813]

53 **Ukleja A**, Afonso BB, Pimentel R, Szomstein S, Rosenthal R. Outcome of endoscopic balloon dilation of strictures after laparoscopic gastric bypass. *Surg Endosc* 2008; **22**: 1746-1750 [PMID: 18347868 DOI: 10.1007/s00464-008-9788-0]

54 **Bazerbachi F**, Heffley JD, Abu Dayyeh BK, Nieto J, Vargas EJ, Sawas T, Zaghlol R, Buttar NS, Topazian MD, Wong Kee Song LM, Levy M, Keilin S, Cai Q, Willingham FF. Safety and efficacy of coaxial lumen-apposing metal stents in the management of refractory gastrointestinal luminal strictures: a multicenter study. *Endosc Int Open* 2017; **5**: E861-E867 [PMID: 28924591 DOI: 10.1055/s-0043-114665]

55 **Joo MK**. Endoscopic Approach for Major Complications of Bariatric Surgery. *Clin Endosc* 2017; **50**: 31-41 [PMID: 28008162 DOI: 10.5946/ce.2016.140]

56 **Marins Campos J**, Moon RC, Magalhães Neto GE, Teixeira AF, Jawad MA, Bezerra Silva L, Neto MG, Ferraz ÁA. Endoscopic treatment of food intolerance after a banded gastric bypass: inducing band erosion for removal using a plastic stent. *Endoscopy* 2016; **48**: 516-520 [PMID: 26981619 DOI: 10.1055/s-0042-103418]

57 **Klimczak T**, Szewczyk T, Janczak P, Jurałowicz P. Laparoscopic Adjustable Gastric Band (LAGB) Migration - Endoscopic Treatment Modalities. *Pol Przegl Chir* 2016; **88**: 299-304 [PMID: 28141557 DOI: 10.1515/pjs-2016-0068]

58 **Dellaportas D**, Nastos C, Theodosopoulos T, Fragulidis G, Polydorou A, Vezakis A. Novel Endoscopic Management of Eroding Laparoscopic Adjustable Gastric Band: A Case Series. *Case Rep Gastrointest Med* 2018; **2018**: 2747852 [PMID: 30693117 DOI: 10.1155/2018/2747852]

59 **Brunaldi VO**, Galvao Neto M, Zundel N, Abu Dayyeh BK. Isolated sleeve gastrectomy stricture: a systematic review on reporting, workup, and treatment. *Surg Obes Relat Dis* 2020; **16**: 955-966 [PMID: 32331996 DOI: 10.1016/j.soard.2020.03.006]

60 **de Moura DTH**, Jirapinyo P, Aihara H, Thompson CC. Endoscopic tunneled stricturotomy in the treatment of stenosis after sleeve gastrectomy. *VideoGIE* 2019; **4**: 68-71 [PMID: 30766946 DOI: 10.1016/j.vgie.2018.09.013]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 February 27; 14(2): 200-210

DOI: 10.4240/wjgs.v14.i2.200

ISSN 1948-9366 (online)

CASE REPORT

# Surgery for Cronkhite-Canada syndrome complicated with intussusception: A case report and review of literature

Jie Dong, Tian-Shi Ma, Jiang-Feng Tu, You-Wei Chen

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Elghali MA

**Received:** August 18, 2021
**Peer-review started:** August 18, 2021
**First decision:** October 2, 2021
**Revised:** October 15, 2021
**Accepted:** January 20, 2022
**Article in press:** January 20, 2022
**Published online:** February 27, 2022

**Jie Dong, Jiang-Feng Tu, You-Wei Chen,** Cancer Center, Department of Gastroenterology, Zhejiang Provincial People's Hospital (Affiliated People's Hospital, Hangzhou Medical College), Hangzhou 310014, Zhejiang Province, China

**Tian-Shi Ma,** Cancer Center, Department of Pathology, Zhejiang Provincial People's Hospital (Affiliated People's Hospital, Hangzhou Medical College), Hangzhou 310014, Zhejiang Province, China

**Corresponding author:** You-Wei Chen, MSc, Associate Chief Physician, Cancer Center, Department of Gastroenterology, Zhejiang Provincial People's Hospital (Affiliated People's Hospital, Hangzhou Medical College), No. 158 Shangtang Road, Hangzhou 310014, Zhejiang Province, China. cyw@zju.edu.cn

## Abstract

*BACKGROUND*

Cronkhite-Canada syndrome (CCS) is a rare nonhereditary disease with a syndrome of multiple gastrointestinal polyps, skin pigmentation, hair loss, and fingernail/toenail dystrophy. Intussusception is a serious condition with an occurrence rate of 5% in adults, which is mainly caused by intestinal tumors or other intestinal occupations.

*CASE SUMMARY*

A 57-year-old woman was admitted to our hospital due to abdominal distension and pain for the past year. Her nausea and vomiting symptoms had been aggravated for the past month. Previous transoral enteroscopy results one year prior showed chronic erosive gastritis protuberans, duodenitis, and jejunitis. She had sparse body hair and brown pigmentation on the skin of her hands and bilateral anterior tibias. The nails of both hands were pale and lacked luster, and the fingernail of her ring finger was longitudinally cracked. Gastroscopy showed extensive diffuse polypoid lump changes in the gastric body and antrum, of 0.5-3 cm in size. Colonoscopy showed multiple polypoid mucosal bulges in the terminal ileum and multiple polyps (0.3-5 cm) throughout the colon. The patient was diagnosed with CCS and underwent partial excision of the polyps, but she refused hormone therapy. One month later, the patient complained of nausea and vomiting, accompanied by abdominal pain and inability to pass gas or stool. Contrast-enhanced computed tomography of the abdomen showed gastrointestinal polyposis and ileocecal intussusception. She underwent stomach and bowel surgery.

*CONCLUSION*
CCS, as a rare disease with poor prognosis, should be treated aggressively. Systematic steroids, immunosuppressive agents, and biological agents were not applied; thus, the patient's symptoms quickly progressed, and intussusception occurred. She had to undergo surgery. Improved compliance may lead to a better prognosis.

**Key Words:** Cronkhite-Canada syndrome; Intussusception; Treatment; Prognosis; Surgery; Case report



**Core Tip:** Cronkhite-Canada syndrome (CCS), a syndrome of multiple gastrointestinal polyps, skin pigmentation, hair loss, and fingernail/toenail dystrophy, is a rare nonhereditary disease. We report a case of CCS that quickly progressed, and intussusception occurred, which eventually led to surgery because systematic steroids, immunosuppressive agents, and biological agents were not applied. As a rare disease with poor prognosis, CCS should be treated aggressively. Meanwhile, improved compliance may lead to a better prognosis.

**Citation:** Dong J, Ma TS, Tu JF, Chen YW. Surgery for Cronkhite-Canada syndrome complicated with intussusception: A case report and review of literature. *World J Gastrointest Surg* 2022; 14(2): 200-210
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i2/200.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i2.200

## INTRODUCTION

Cronkhite-Canada syndrome (CCS) is a rare nonhereditary disease with multiple gastrointestinal polyps, skin pigmentation, hair loss, and fingernail/toenail dystrophy. The disease was first reported in 1955[1]. More than 500 confirmed cases have been reported worldwide to date, resulting in an incidence of approximately 1 *per* million[2,3]. Approximately 75% of the existing reports are from Japan, where the incidence is approximately 3.7 *per* million[4].

Intussusception is a common complication in children, while in adults, the incidence of intussusception is only approximately 5% and is mainly caused by occupations, such as tumors[5].

## CASE PRESENTATION

### *Chief complaints*

A 57-year-old woman was admitted to our hospital due to abdominal distension and pain for 1 year, which had been aggravated with nausea and vomiting for 1 mo.

### *History of present illness*

The patient experienced abdominal distension and pain accompanied by the absence of exhaust defecation without obvious inducement 1 year prior. She was evaluated in a local hospital before admission to our hospital. Abdominal computed tomography (CT) (July 14, 2019) showed edema and thickening of the duodenal wall, with mild dilation of some parts of the small intestine with effusion. Transoral enteroscopy showed chronic erosive gastritis protuberans, duodenitis, and jejunitis. She was treated by fasting, gastrointestinal decompression, antibiotics, a proton pump inhibitor (PPI), and fluid supplementation, and then she was discharged after relief of abdominal distension and pain and restoration of anal gas evacuation. The patient had cracked fingernails, accompanied by hair loss, weakened sense of taste, and repeated abdominal distension and abdominal pain starting 10 mo prior. One month prior, the patient had nausea and vomiting with aggravated abdominal distension, and diarrhea consisting of yellow-green loose stools. She experienced anorexia and fatigue. In the previous month, her weight loss was approximately 5-6 kg.

### *History of past illness*

The patient was healthy overall except for a 5-year history of hypertension. She had brown pigmentation on the anterior tibia skin of her lower limbs for more than 10 years, and the pigmentation size varied from a coin-sized area when the condition was relieved to an area extending from above the ankle to below the knee when the condition was more severe. The lesion produced itching and

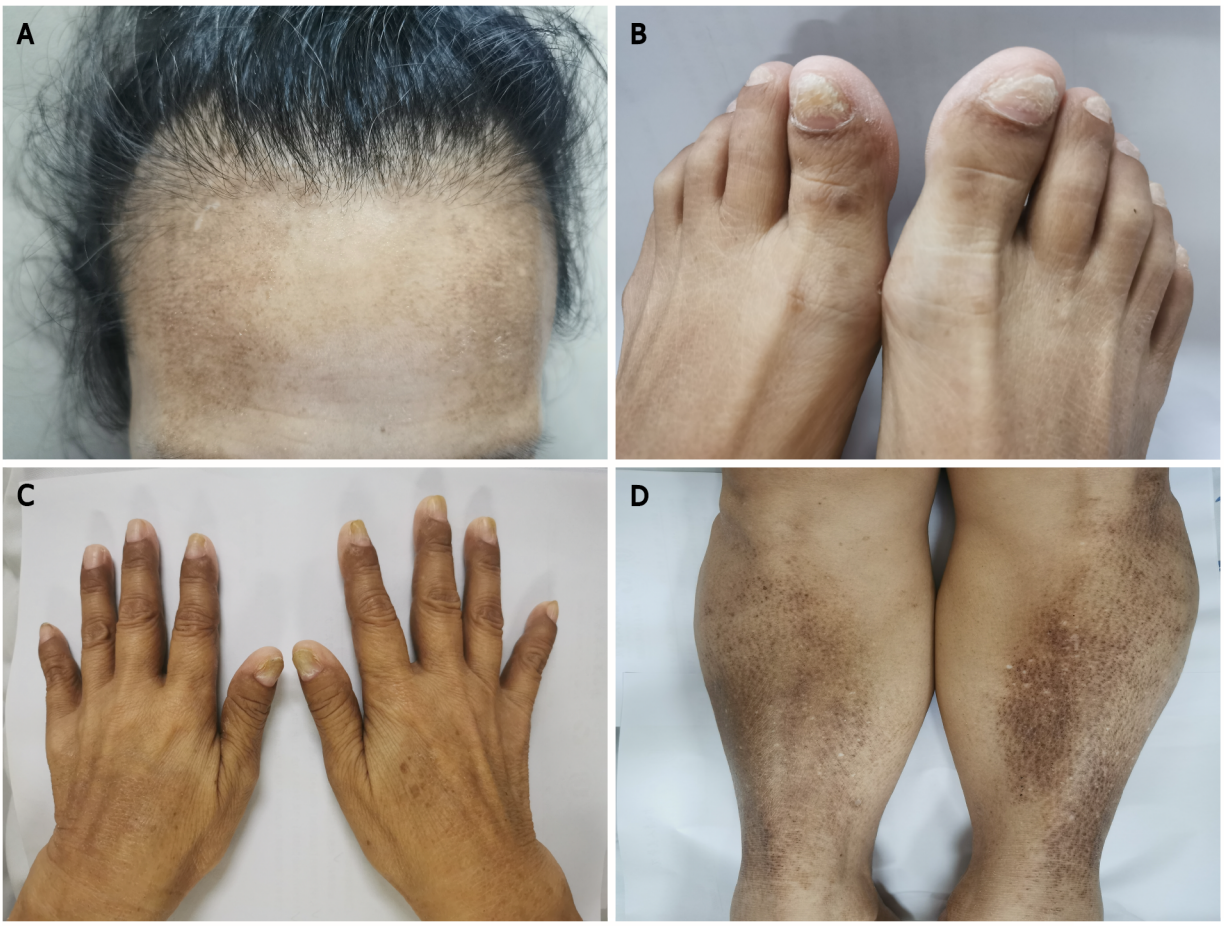



**Figure 1 Physical examination.** A: Sparse hair; B: Nail dystrophy; C: Skin pigmentation of the hands; D: Skin pigmentation of the legs.

discomfort but did not exhibit redness, swelling, or ulceration. The patient had sparse body hair since childhood and had no history of oral steroids or long-term medication use.

### *Personal and family history*

She had no infectious disease, drug or food allergy, surgery, or blood transfusion. She also had no family history of gastrointestinal polyposis or other genetic diseases.

### *Physical examination*

Height: 157 cm; weight: 36 kg; body mass index: 14.6 kg/m$^2$; ear temperature: 36.2 °C; breaths: 18/min; pulse: 118 beats/min; blood pressure: 110/78 mmHg. The patient was conscious and alert but less vigorous than usual. Her conjunctivas appeared pale. Brown pigments were visible, particularly on the skin of her hands and bilateral anterior tibia. She had sparse body hair. The nails of both hands were pale and lacked luster, and the fingernail of her ring finger was longitudinally cracked (Figure 1). Small nodules (the size of a red bean) in the right supraclavicular lymph node could be palpated, with clear borders and no adhesions. No edema was noted in either lower limb.

### *Laboratory examinations*

The blood test results were as follows: White blood cell count (11.63 × 10$^9$/L↑), neutrophil count (8.4 × 10$^9$/L↑), hemoglobin 119 g/L (115-150), and platelet count (545 × 10$^9$/L↑). The C-reactive protein level was 1.9 mg/L. The biochemical test results were: Albumin 23.2 g/L (40-55) and blood calcium 1.85 mmol/L (2.11-2.52). The tumor marker test results were as follows: CA19-9 41.1 U/mL (0-37), immunoglobulin E (IgE) 193/mL (0-87), and gastrin 129 ng/L (13-115). Serum *Helicobacter pylori* (*H. pylori*) antibodies were positive. The occult blood test in stool was positive (++), and the fat globule test was positive.

No abnormalities were found in the following test results: Liver and kidney function, coagulation function, troponin level, thyroid function, routine urine, erythrocyte sedimentation rate, immunoglobulin (G, A, M) levels, immunoglobulin G (IgG) 4 level, complement levels, rheumatoid factor level, hepatitis (A, B, C, D, E) antibodies, TORCH (*Toxoplasma gondii*, Rubella virus, Cytomegalovirus, Herpes simplex virus type 1 and 2) antibodies, Epstein-Barr virus antibodies, anemia test (ferritin, folic acid,

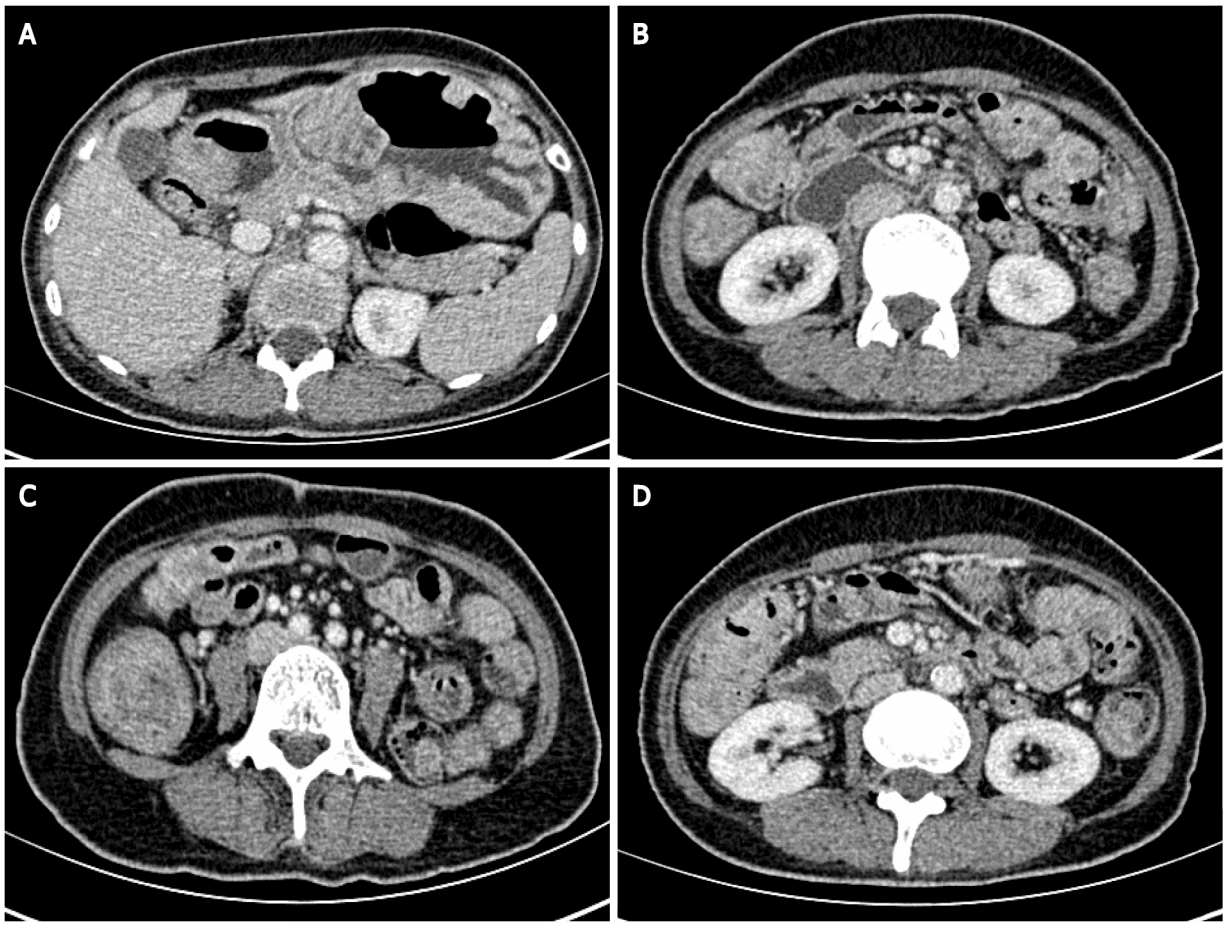



**Figure 2 Abdominal enhanced computed tomography.** Thickening of the gastrointestinal tract with multiple cauliflower-like and nodular protrusions. A: The stomach wall; B: Part of the small intestinal wall; C and D: Part of the colon wall.

vitamin B12), *Mycobacterium tuberculosis* antibodies, tuberculosis infection T cells, anti-neutrophil cytoplasmic antibodies, antinuclear antibodies, and blood lead level.

During the entire treatment, we recommended that the patient undergo further genetic examination, but she refused because of the expense.

### *Imaging examinations*

Contrast-enhanced CT of the abdomen suggested that the gastric wall and part of the small intestine and colon were thickened with multiple cauliflower-like and nodular protrusions and showed obvious heterogeneous enhancement. A diagnosis of multiple polyps (malignant changes were not ruled out) was considered (Figure 2).

Positron-emission tomography (PET)/CT showed multiple nodules with increased $^{18}$F-fluorodeoxyglucose (FDG) intake in the gastric wall (SUVmax 3.4), descending duodenum and bulb, small intestine, and colon (SUVmax 7.3). Multiple areas of nodular thickening with increased FDG intake were noted in the proximal rectum. Based on her medical history, a diagnosis of multiple polyps throughout the gastrointestinal tract (the possibility of malignant changes in individual polyps could not be excluded) was considered (Figure 3).

### *Endoscopic examinations*

Gastroscopy showed extensive diffuse polypoid lumps of 0.5-3.0 cm in the gastric body, gastric fundus and antrum (Figure 4).

Colonoscopy showed multiple polypoid mucosal bulges in the terminal ileum and multiple polyps (0.3-5 cm) throughout the colon. Some were villus-like changes. Severe hyperemia was found on the surface. Larger polyps appeared in the ascending colon and the hepatic flexure (Figure 5).

Gastroscopic pathology showed juvenile polyps in the gastric antrum (*H. pylori*$^{+}$) (Figure 6). Colonoscopic pathology showed juvenile polyps in the ascending colon (Figure 7).

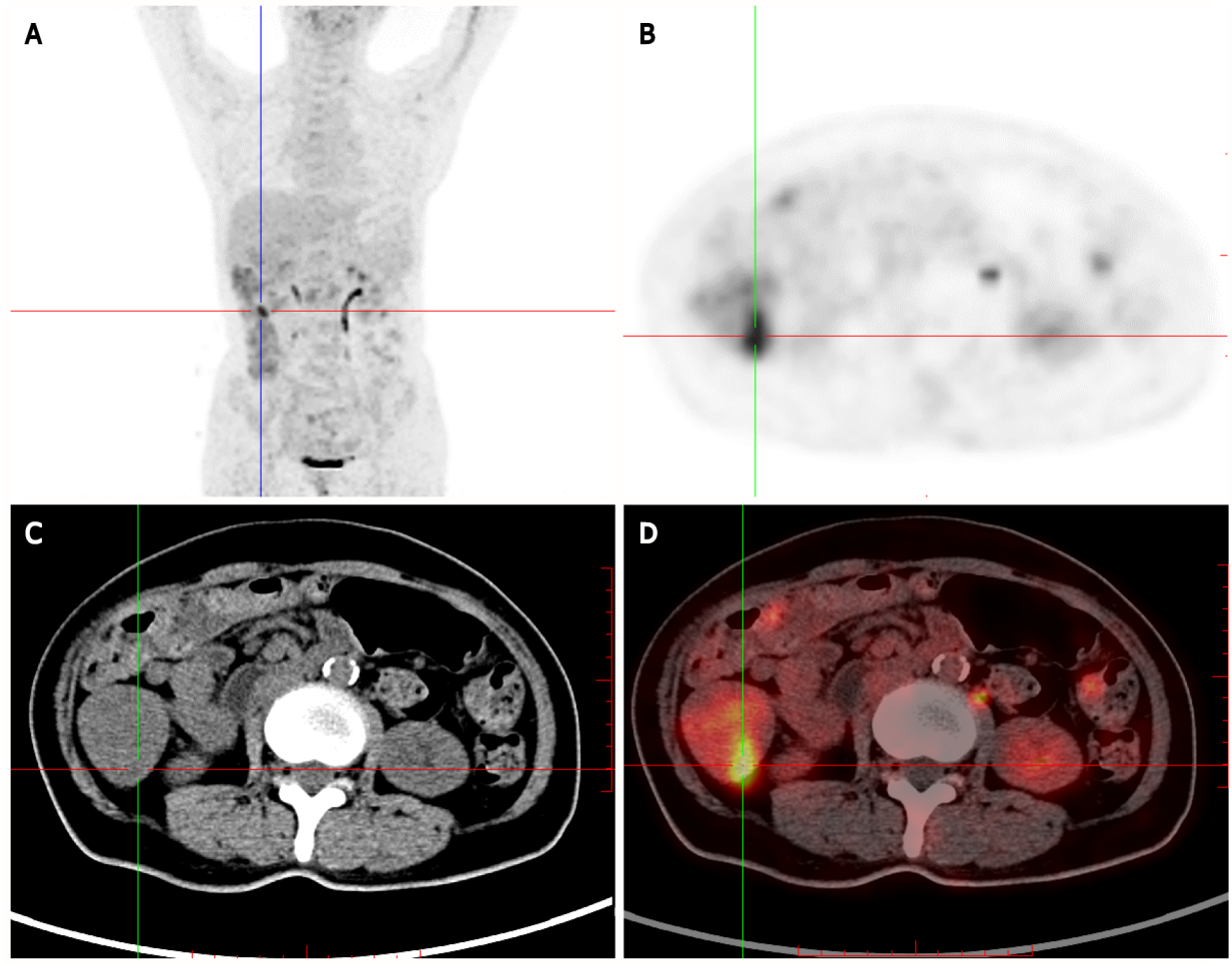



**Figure 3 Positron-emission tomography/computed tomography showing multiple nodules with increased fluorodeoxyglucose uptake in the stomach wall, descending duodenum, and bulb, in the small intestine (obvious increase in the ileum), and the colon (obvious increase in the ascending colon).** Multiple nodular thickening with increased fluorodeoxyglucose (FDG) uptake was observed in the proximal rectum. A: Whole-body maximum intensity projection 18F-FDG and positron-emission tomography (PET) image; B: PET; C: Computed tomography (CT); D: PET/CT.

## FINAL DIAGNOSIS

Cronkhite-Canada syndrome.

## TREATMENT

The patient was admitted to the hospital and treated with nutritional agents, digestive enzymes, a PPI, and anti-*H. pylori* agents (rabeprazole 10 mg bid + bismuth potassium citrate 0.6 g bid + amoxicillin 1 g bid + clarithromycin 0.5 g bid, 14 d). The nail dystrophy and skin pigmentation improved after treatment.

One month after treatment, the patient complained of nausea and vomiting, accompanied by abdominal pain and inability to pass gas or stool. Contrast-enhanced CT of the abdomen showed gastrointestinal polyposis and ileocecal intussusception (Figure 8).

After fasting, gastrointestinal decompression, somatostatin administration, PPI treatment, and total parenteral nutrition, her symptoms were not significantly improved. The patient and family members refused surgical treatment followed by glucocorticoids. Her symptoms worsened 1 mo later, and she underwent right hemicolon + partial transverse colon + partial ilium resection at another hospital. Postoperative pathology showed inflammatory changes.

## OUTCOME AND FOLLOW-UP

After the operation, vomiting and decreased bowel movements recurred. CT showed intestinal

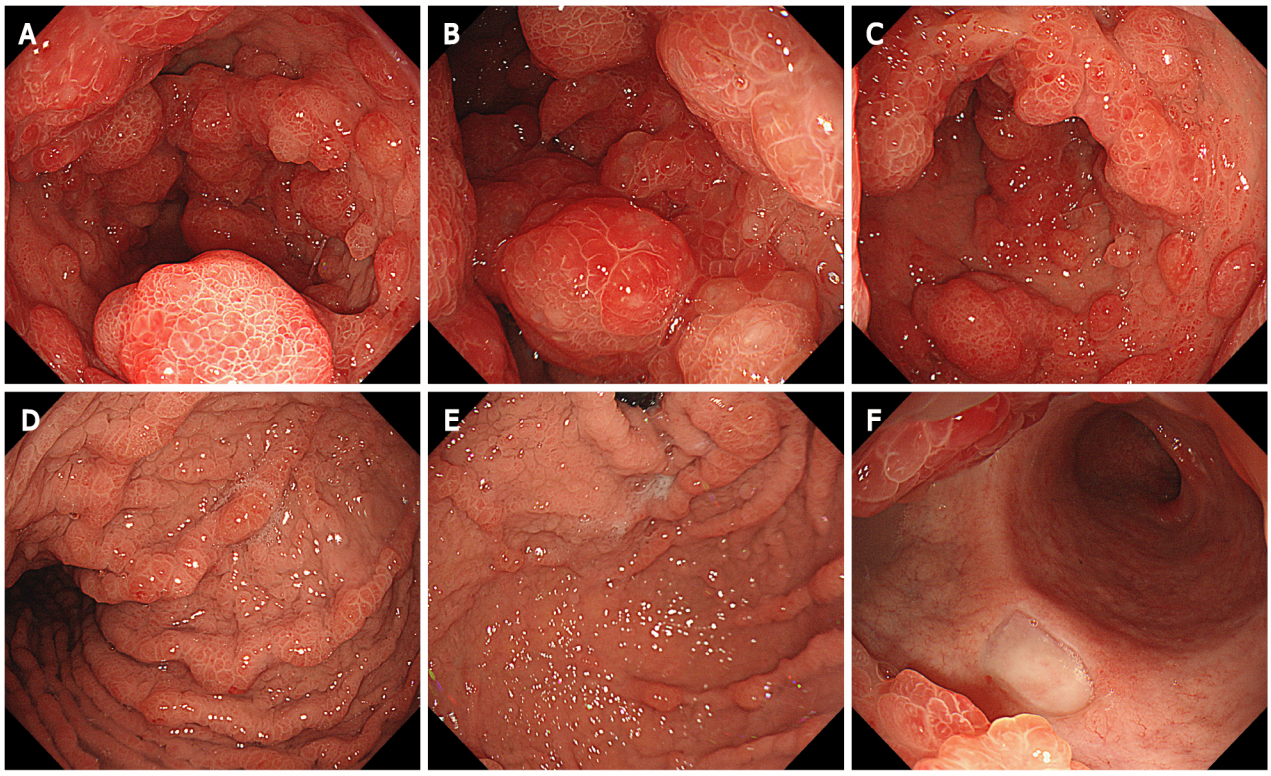



**Figure 4 Endoscopic findings in the stomach.** Extensive and diffuse polypoid eminences in the stomach. A: Antrum; B: Lower part of the gastric body; C: Middle part of the gastric body; D: Upper part of the gastric body; E: Gastric fundus; F: Duodenal bulb.

obstruction. She underwent subtotal gastrectomy 3 mo after the surgery.

## DISCUSSION

Diarrhea and the triad of abnormal ectodermal lesions (hair loss, skin pigmentation, fingernail/toenail atrophy and loss) are the most common clinical manifestations of CCS. Other manifestations include weight loss, hypoalbuminemia, edema of both lower limbs, dysgeusia, abdominal pain, bloating, nausea, vomiting, anorexia, and itching[3]. Some patients also have electrolyte disturbances (most common types: Hypokalemia and hypocalcemia), and fractures have been reported occasionally. Almost all of the clinical features of CCS were present in this patient.

CCS is a rare hereditary or familial disorder with multiple intestinal polyps distributed throughout the digestive tract. Most are in the stomach and colon (90%), followed by 80% in the small intestine and 67% in the rectum. They are rare in the esophagus[6]. Approximately 12.3% (26/211) of CCS patients have esophageal involvement[7]. Endoscopy has demonstrated that most polyps are sessile or broad-based and diffusely distributed, vary in size, and are granular, nodular, or irregular in shape. The polyp mucosa is congested with obvious edema, and intestinal folds are thickened[2,8].

Hyperplastic polyps and hamartoma-like polyps are common in CCS histopathology examinations. In addition, 31%-71% of patients may have digestive tract adenomas or adenomatous changes during the course of this disease[9]. The pathological features of typical CCS polyps include propria edema, mild to moderate inflammatory cell infiltration, eosinophil and lymphocyte infiltration (even IgG4 plasma cell infiltration), tortuous hyperplasia of glands, and some cystic expansion filled with protein-rich liquid or concentrated mucus[2].

The histopathology of non-polyp tissue includes edema, mucus-like expansion of the propria, damage to the crypt structure (dilation or branching)[10], and mixed inflammatory infiltration composed of lymphocytes, plasma cells, and neutrophils[11].

Due to the extremely low incidence of CCS and the small number of studies available, controversies remain regarding the causes, mechanisms, and effective treatments of CCS.

The mainstream view is that the pathogenesis of CCS is related to autoimmune disorders[12,13]. Patients may have abnormal expression of antinuclear antibodies[14], abnormal IgG4 expression[6,12] (elevated serum IgG4 or infiltration of IgG4 plasma cells in the tissue), other autoimmune diseases (such as systemic lupus erythematosus, rheumatoid arthritis and scleroderma)[8,13], and impaired T cell regulatory function[11]. Case studies have shown that steroids and anti-tumor necrosis factor (TNF)-α

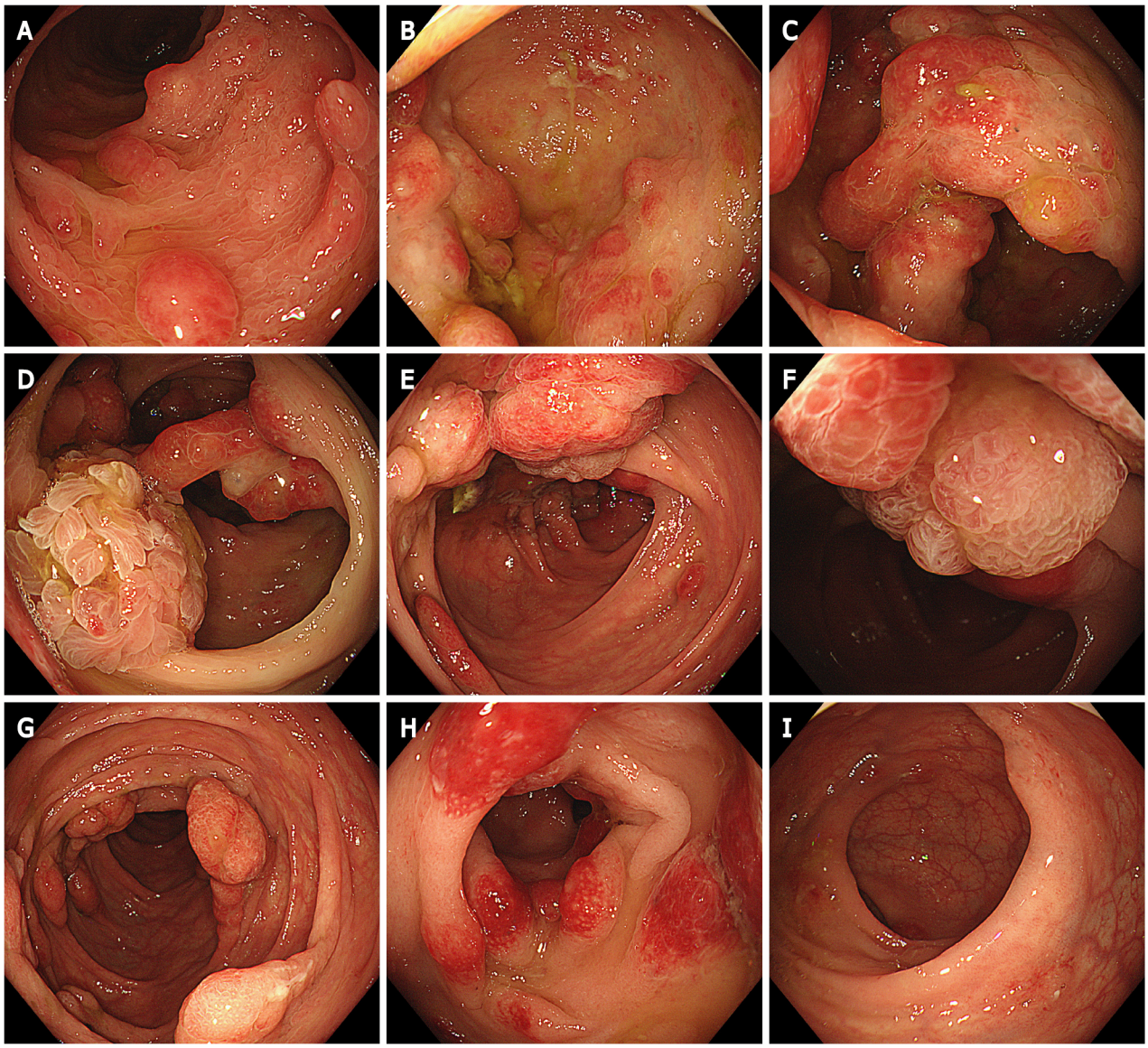



**Figure 5 Endoscopic findings in the colon.** Multiple polypoid mucosal bulges in the distal small intestine and multiple polyps throughout the colon. Some were villus-like changes, and severe hyperemia was observed on the surface. A: Terminal ileum; B: Cecum; C and D: Ascending colon; E and F: Transverse colon; G: Descending colon; H: Sigmoid colon; I: Rectum.

antibody therapy are not effective against CCS in some cases, suggesting that the relationship between CCS and immunity is complicated[15]. The histopathology of the nail matrix of some patients with CCS shows stromal granuloma. Because stromal hypergranulation is common in a variety of inflammatory nail diseases, the inflammatory process may be an important pathogenic factors of CCS[16]. *H. pylori* infection is also believed to play an important role in the pathogenesis of CCS. Watanabe *et al*[7] found that approximately 54% of CCS patients had *H. pylori* infection, and the symptoms of CCS disappeared after anti-*H. pylori* treatment[17,18].

The diagnosis of CCS should be based on comprehensive consideration of the medical history, physical examination, endoscopic examination and histopathological results. CCS needs to be differentiated from juvenile polyposis, Peutz-Jeghers syndrome, Cowden syndrome, Turcot syndrome, and familial adenomatous polyposis[7,19].

The common complications of CCS include gastrointestinal bleeding with anemia, intussusception, gastrointestinal tumors, hypoproteinemia, rectal prolapse, malabsorption, electrolyte imbalance, and vitamin deficiency[20]. Rare complications include recurrent severe acute pancreatitis[21], portal vein thrombosis, membranous glomerulonephritis[14], and recurrent arteriovenous embolism[22]. The probability of a CCS patient with a malignant tumor is 13%[23]. Three histological structures, including polyps[24], adenomas, and adenocarcinomas, may be present concurrently in the gastrointestinal tract in CCS patients. Histological evidence has shown transformation of CCS from polyps to adenomas and then to adenocarcinomas. In 15%-25% of CCS patients, gastric or intestinal carcinoma is diagnosed at the onset of CCS. The total adenoma detection rate over the course of CCS is 31%-71%[7,9]. Therefore, long-

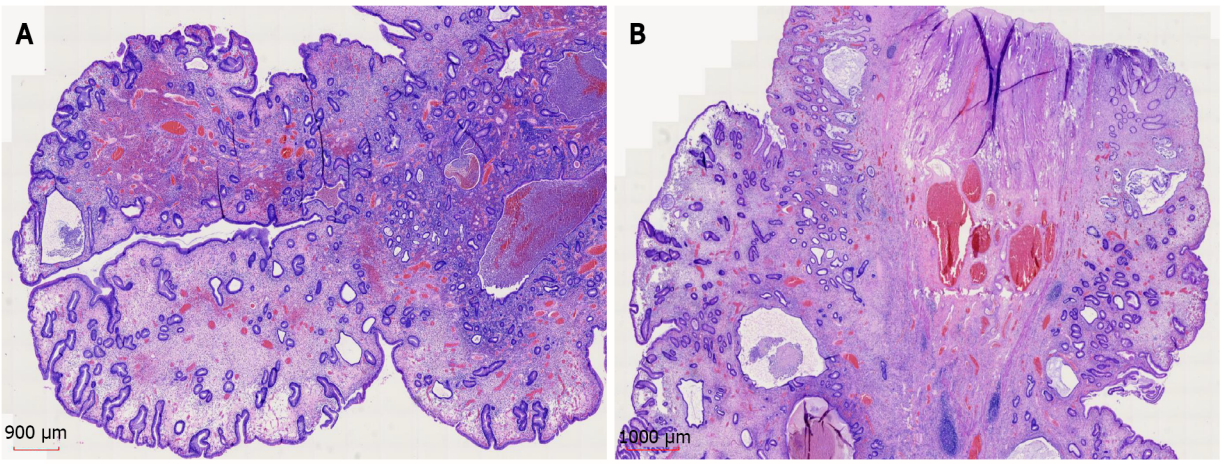



**Figure 6 Histopathology and hematoxylin and eosin staining of gastroscopic pathology samples suggested a diagnosis of juvenile polyps.** A: × 11; B: × 12.5.

term endoscopic monitoring of patients with confirmed or suspected CCS is needed[7].

Due to the low incidence of CCS and the small number of reported cases, no unified or standardized CCS treatment guidelines have been issued in China or abroad. To date, empirical treatment is mainly applied, including steroids, immunosuppressants, biological agents, antibiotics, nonsteroidal anti-inflammatory agents, acid blockers, nutritional support, and endoscopic surgical treatment. Steroids are currently well accepted for the treatment of CCS[12,25]. No consensus has been reached about the steroid dosage or duration. Watanabe *et al*[7] reported that the most significant effective dose of prednisolone for active CCS was 30-49 mg *per* day. Early tapering of steroids may be related to early recurrence, which suggests that the prednisolone dose should be slowly reduced after endoscopic confirmation of polyp regression. Approximately 61.1%[7] to 61.3%[3] of patients achieve clinical relief after steroid treatment. Osteoporosis is a major side effect of steroids. After steroid-induced remission, immunosuppressive maintenance therapy should be continued[26]. If the abovementioned drug treatments are ineffective, biological agents can be an option[27]. However, it has been suggested that steroids and anti-TNF-α antibodies are not effective for some CCS patients. Whether steroids or biological agents have better efficacy in IgG4-positive patients remains to be proven[15]. Early proactive drug treatment may reduce the incidences of intussusception and surgical intervention. Because most adult intussusceptions are accompanied by tumor changes, surgical treatment is the first choice once intussusception is confirmed. Endoscopic reduction is also an option, but with a high risk; in theory, reduction may lead to abdominal perforation and tumor spread[5,28]. Partial endoscopic mucosal resection plus corticosteroids and anti-plasmin treatment can be used to avoid surgery.

The prognosis of CCS is poor. Lesion size, age, and complications are factors for a poor prognosis[3]. Serious complications can be life-threatening. The 5-year survival rate is less than 45%[29]. The main causes of death are gastrointestinal bleeding, infection, malnutrition, electrolyte imbalance, and heart failure[8]. Because CCS is a rare disease, clinicians may misdiagnose it because they are not familiar with it. Meanwhile, CCS has a risk of malignancy[30]. More than 10% of CCS patients relapse after the disease is relieved *via* standardized steroid and endoscopic treatments. Therefore, standardized follow-up and endoscopic monitoring are essential during the whole treatment process to reduce the mortality rate of CCS. Evaluation should be performed at an interval of 6-12 mo after treatment or confirmed diagnosis[7]. During the first year after onset of the illness, the patient and her family members refused glucocorticoids, immunosuppressants, or biological agents for treatment. The disease progressed rapidly even after she received symptomatic treatment, nutritional support, and surgical treatment. An in-depth understanding of CCS and advanced diagnosis and treatment may improve its prognosis; therefore, the prognosis needs to be reassessed after treatment.

## CONCLUSION

In this case, endoscopy did not show large or multiple polyps at the onset of the symptoms one year prior, and no specific treatment was applied during that year. Large polyps appeared quickly in the gastrointestinal tract. After routine nutritional support and anti-*H. pylori* treatment, the polyps did not significantly subside. Because systematic steroids, immunosuppressive agents, and biological agents were not applied, the patient's symptoms quickly progressed, and intussusception occurred. She had to eventually undergo surgery. Thus, CCS, a rare disease with poor prognosis, should be treated aggressively. Learning more about the disease and improved compliance may lead to a better prognosis.

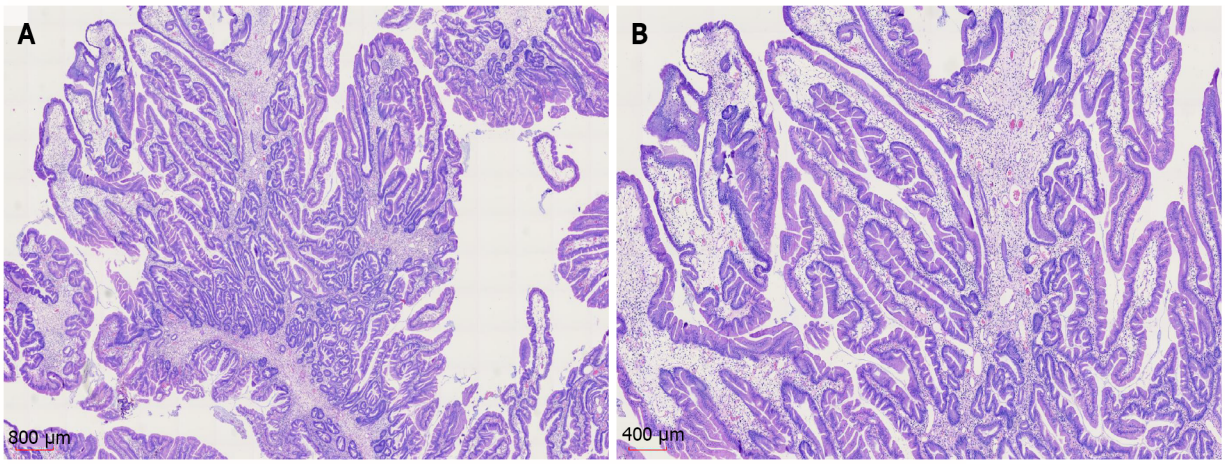



**Figure 7 Histopathology and hematoxylin and eosin staining of colonoscopic pathology samples suggested a diagnosis of juvenile polyps.** A: × 12.5; B: × 25.

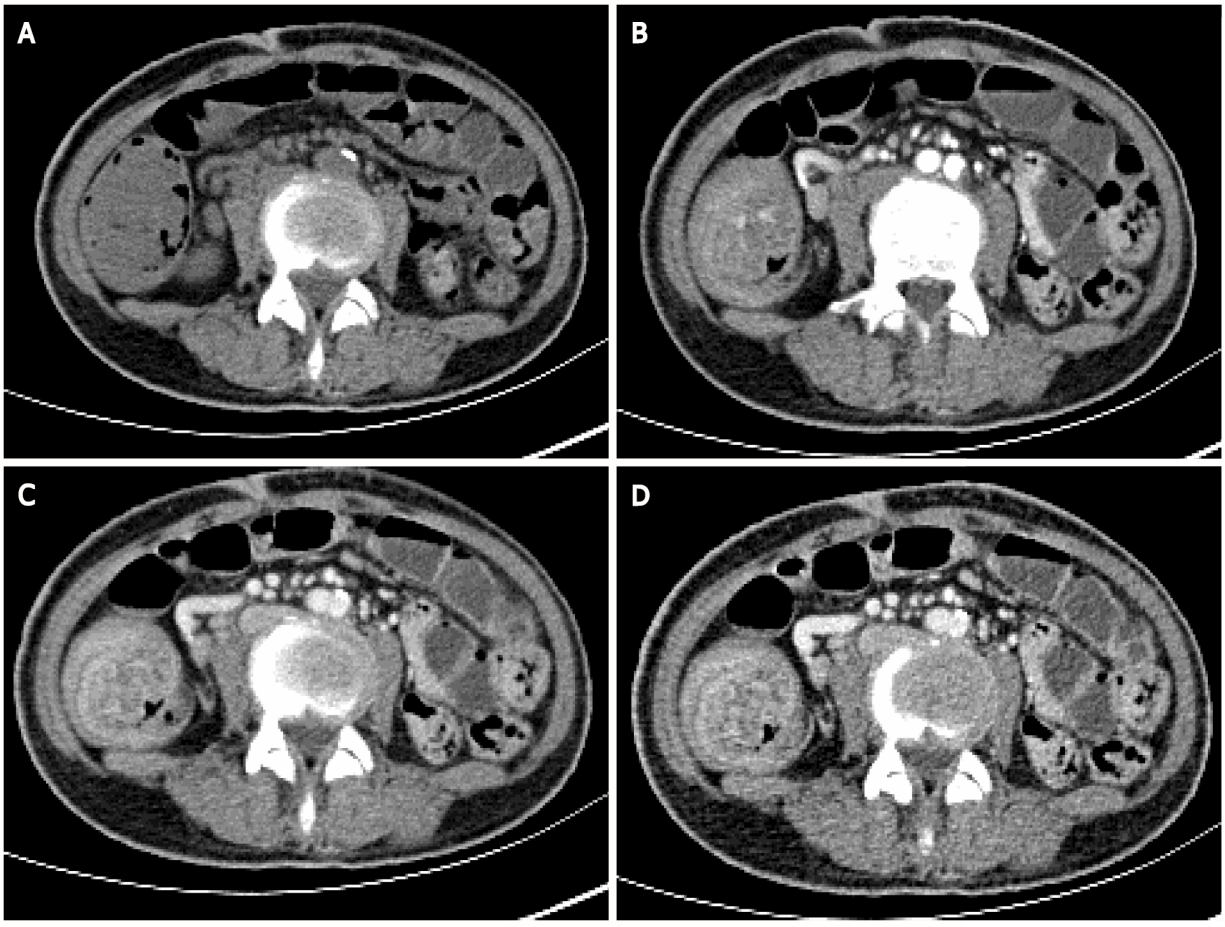



**Figure 8 Abdominal enhanced computed tomography.** Multiple concentric ring signs in the ileocecal area indicating ileocecal intussusception. A: Plain computed tomography scan; B: Arterial phase; C and D: Venous phase.

## ACKNOWLEDGEMENTS

We would like to show our deepest gratitude to our friend, Dr. Yi Chen, a respectable, responsible and resourceful scholar, who has provided us with valuable guidance in every stage of the writing of this manuscript.

## FOOTNOTES

**Author contributions:** Dong J was the patient's doctor in charge, who was responsible for collecting medical history, reviewed the literature and drafting the paper; Tu JF did the literature review; Ma TS was a pathologist who gave the pathological results; Chen YW designed the study with Dong J and made contribution to revise the manuscript; All authors have read and approved the final manuscript.

**Supported by** The Medical Health Science and Technology Project of Zhejiang Provincial Health Commission, No. 2021436506; and General Scientific Research Project of Zhejiang Science and Technology Department, No. Y202044280.

**Informed consent statement:** Informed written consent was obtained from the patient for publication of this report and any accompanying images.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).



**Country/Territory of origin:** China

**ORCID number:** Jie Dong 0000-0002-2338-8955; Tian-Shi Ma 0000-0001-7606-6397; Jiang-Feng Tu 0000-0002-1893-9994; You-Wei Chen 0000-0002-5663-6118.

**S-Editor:** Fan JR
**L-Editor:** A
**P-Editor:** Fan JR

## REFERENCES

1 **Cronkhite LW Jr**, Canada WJ. Generalized gastrointestinal polyposis; an unusual syndrome of polyposis, pigmentation, alopecia and onychotrophia. *N Engl J Med* 1955; **252**: 1011-1015 [PMID: 14383952 DOI: 10.1056/NEJM195506162522401]
2 **Hoekstra E**, van der Laan J, van der Voorn M. Seventy-five-year-old man with unexplained weight loss and alopecia. *Gut* 2020; **69**: 822-900 [PMID: 31248981 DOI: 10.1136/gutjnl-2019-319013]
3 **Liu S**, You Y, Ruan G, Zhou L, Chen D, Wu D, Yan X, Zhang S, Zhou W, Li J, Qian J. The Long-Term Clinical and Endoscopic Outcomes of Cronkhite-Canada Syndrome. *Clin Transl Gastroenterol* 2020; **11**: e00167 [PMID: 32352683 DOI: 10.14309/ctg.0000000000000167]
4 **Oba MS**, Murakami Y, Nishiwaki Y, Asakura K, Ohfuji S, Fukushima W, Nakamura Y, Suzuki Y. Estimated Prevalence of Cronkhite-Canada Syndrome, Chronic Enteropathy Associated With SLCO2A1 Gene, and Intestinal Behçet's Disease in Japan in 2017: A Nationwide Survey. *J Epidemiol* 2021; **31**: 139-144 [PMID: 32092751 DOI: 10.2188/jea.JE20190349]
5 **Brill A**, Lopez RA. Intussusception In Adults. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2020, StatPearls Publishing LLC, 2020
6 **Riegert-Johnson DL**, Osborn N, Smyrk T, Boardman LA. Cronkhite-Canada syndrome hamartomatous polyps are infiltrated with IgG4 plasma cells. *Digestion* 2007; **75**: 96-97 [PMID: 17510553 DOI: 10.1159/000102963]
7 **Watanabe C**, Komoto S, Tomita K, Hokari R, Tanaka M, Hirata I, Hibi T, Kaunitz JD, Miura S. Endoscopic and clinical evaluation of treatment and prognosis of Cronkhite-Canada syndrome: a Japanese nationwide survey. *J Gastroenterol* 2016; **51**: 327-336 [PMID: 26216651 DOI: 10.1007/s00535-015-1107-7]
8 **Slavik T**, Montgomery EA. Cronkhite–Canada syndrome six decades on: the many faces of an enigmatic disease. *J Clin Pathol* 2014; **67**: 891-897 [PMID: 25004941 DOI: 10.1136/jclinpath-2014-202488]
9 **Sweetser S**, Boardman LA. Cronkhite-Canada syndrome: an acquired condition of gastrointestinal polyposis and dermatologic abnormalities. *Gastroenterol Hepatol (N Y)* 2012; **8**: 201-203 [PMID: 22675285]
10 **Ward EM**, Wolfsen HC, Raimondo M. Novel endosonographic findings in Cronkhite-Canada syndrome. *Endoscopy* 2003; **35**: 464 [PMID: 12701028 DOI: 10.1055/s-2003-38761]
11 **Bettington M**, Brown IS, Kumarasinghe MP, de Boer B, Bettington A, Rosty C. The challenging diagnosis of Cronkhite-Canada syndrome in the upper gastrointestinal tract: a series of 7 cases with clinical follow-up. *Am J Surg Pathol* 2014; **38**: 215-223 [PMID: 24418855 DOI: 10.1097/PAS.0000000000000098]
12 **Sweetser S**, Ahlquist DA, Osborn NK, Sanderson SO, Smyrk TC, Chari ST, Boardman LA. Clinicopathologic features and treatment outcomes in Cronkhite-Canada syndrome: support for autoimmunity. *Dig Dis Sci* 2012; **57**: 496-502 [PMID: 21881972 DOI: 10.1007/s10620-011-1874-9]

13 **Kao KT**, Patel JK, Pampati V. Cronkhite-Canada Syndrome: A Case Report and Review of Literature. *J Dig Dis* 2009; **14**: 619378 [DOI: 10.1155/2009/619378]

14 **Takeuchi Y**, Yoshikawa M, Tsukamoto N, Shiroi A, Hoshida Y, Enomoto Y, Kimura T, Yamamoto K, Shiiki H, Kikuchi E, Fukui H. Cronkhite-Canada syndrome with colon cancer, portal thrombosis, high titer of antinuclear antibodies, and membranous glomerulonephritis. *J Gastroenterol* 2003; **38**: 791-795 [PMID: 14505136 DOI: 10.1007/s00535-002-1148-6]

15 **Douglas CP**, Yang PF, Riordan SM, Wong SW. Ileal intussusception and perforation associated with Cronkhite-Canada syndrome. *ANZ J Surg* 2020; **90**: 1194-1195 [PMID: 31628710 DOI: 10.1111/ans.15462]

16 **Chuamanochan M**, Tovanabutra N, Mahanupab P, Kongkarnka S, Chiewchanvit S. Nail Matrix Pathology in Cronkhite-Canada Syndrome: The First Case Report. *Am J Dermatopathol* 2017; **39**: 860-862 [PMID: 29058694 DOI: 10.1097/DAD.0000000000000898]

17 **Okamoto K**, Isomoto H, Shikuwa S, Nishiyama H, Ito M, Kohno S. A case of Cronkhite-Canada syndrome: remission after treatment with anti-Helicobacter pylori regimen. *Digestion* 2008; **78**: 82-87 [PMID: 18948692 DOI: 10.1159/000165354]

18 **Kato K**, Ishii Y, Mazaki T, Uehara T, Nakamura H, Kikuchi H, Yamagami H, Sato H, Mizuno S, Soma M, Henmi A, Masuda H, Moriyama M, Tanaka M. Spontaneous Regression of Polyposis following Abdominal Colectomy and Helicobacter pylori Eradication for Cronkhite-Canada Syndrome. *Case Rep Gastroenterol* 2013; **7**: 140-146 [PMID: 23569441 DOI: 10.1159/000350321]

19 **Liu Y**, Zhang L, Yang Y, Peng T. Cronkhite-Canada syndrome: report of a rare case and review of the literature. *J Int Med Res* 2020; **48**: 300060520922427 [PMID: 32459145 DOI: 10.1177/0300060520922427]

20 **Seshadri D**, Karagiorgos N, Hyser MJ. A case of cronkhite-Canada syndrome and a review of gastrointestinal polyposis syndromes. *Gastroenterol Hepatol (N Y)* 2012; **8**: 197-201 [PMID: 22675284]

21 **Yasuda T**, Ueda T, Matsumoto I, Shirasaka D, Nakajima T, Sawa H, Shinzeki M, Kim Y, Fujino Y, Kuroda Y. Cronkhite-Canada syndrome presenting as recurrent severe acute pancreatitis. *Gastrointest Endosc* 2008; **67**: 570-572 [PMID: 18294523 DOI: 10.1016/j.gie.2007.07.041]

22 **Sampson JE**, Harmon ML, Cushman M, Krawitt EL. Corticosteroid-responsive Cronkhite-Canada syndrome complicated by thrombosis. *Dig Dis Sci* 2007; **52**: 1137-1140 [PMID: 17342394 DOI: 10.1007/s10620-006-9375-y]

23 **Nagata J**, Kijima H, Hasumi K, Suzuki T, Shirai T, Mine T. Adenocarcinoma and multiple adenomas of the large intestine, associated with Cronkhite-Canada syndrome. *Dig Liver Dis* 2003; **35**: 434-438 [PMID: 12868681 DOI: 10.1016/s1590-8658(03)00160-9]

24 **Yashiro M**, Kobayashi H, Kubo N, Nishiguchi Y, Wakasa K, Hirakawa K. Cronkhite-Canada syndrome containing colon cancer and serrated adenoma lesions. *Digestion* 2004; **69**: 57-62 [PMID: 14755154 DOI: 10.1159/000076560]

25 **Chakrabarti S**. Cronkhite-Canada Syndrome (CCS)-A Rare Case Report. *J Clin Diagn Res* 2015; **9**: OD08-OD09 [PMID: 25954656 DOI: 10.7860/JCDR/2015/11919.5700]

26 **Stanich PP**, Lujan G, Hosmer A. Nausea and Diarrhea with Fingernail and Hair Changes. *Gastroenterology* 2021; **161**: e7-e8 [PMID: 33221402 DOI: 10.1053/j.gastro.2020.10.048]

27 **Jiang CD**, Myint H, Tie A, Stace NH. Sustained clinical response to infliximab in refractory Cronkhite-Canada syndrome. *BMJ Case Rep* 2020; **13** [PMID: 33370944 DOI: 10.1136/bcr-2020-236990]

28 **Matsuda S**, Yoshinami N, Motoyoshi T. A Rare Case of Colonic Intussusception in an Adult. *Gastroenterology* 2019; **156**: 26-28 [PMID: 30201350 DOI: 10.1053/j.gastro.2018.07.049]

29 **Poulsen A**, Nielsen MF. [Cronkhite-Canada syndrome is a rare polyposis syndrome]. *Ugeskr Laeger* 2012; **174**: 1612-1613 [PMID: 22673384]

30 **Kobori I**, Katayama Y, Suzuki Y, Yamaguchi M, Funada K, Gyotoku Y, Fujimoto Y, Shirahasi R, Kusano Y, Ban S, Tamano M. A case of Helicobacter pylori-negative gastric cancer associated with Cronkhite-Canada Syndrome. *Clin J Gastroenterol* 2021; **14**: 123-128 [PMID: 33079335 DOI: 10.1007/s12328-020-01268-4]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
**Telephone:** +1-925-3991568
**E-mail:** bpgoffice@wjgnet.com
**Help Desk:** https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 1948-9366 (online)

# World Journal of

# *Gastrointestinal Surgery*

*World J Gastrointest Surg* 2022 March 27; 14(3): 211-270

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 14 Number 3 March 27, 2022

*World Journal of Gastrointestinal Surgery*

**Monthly Volume 14 Number 3 March 27, 2022**

## Contents

## ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Vishal Gupta, FACS, MBBS, MCh, MS, Additional Professor, Surgeon, Department of Surgical Gastroenterology, All India Institute of Medical Sciences, Bhopal 462020, India. vggis@yahoo.co.in

## AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJGS* mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

## INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJGS* as 2.582; IF without journal self cites: 2.564; 5-year IF: 3.378; Journal Citation Indicator: 0.53; Ranking: 97 among 212 journals in surgery; Quartile category: Q2; Ranking: 73 among 92 journals in gastroenterology and hepatology; and Quartile category: Q4.

## RESPONSIBLE EDITORS FOR THIS ISSUE



**NAME OF JOURNAL**
*World Journal of Gastrointestinal Surgery*

**ISSN**
ISSN 1948-9366 (online)

**LAUNCH DATE**
November 30, 2009

**FREQUENCY**
Monthly



**PUBLICATION DATE**
March 27, 2022

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 March 27; 14(3): 211-220

DOI: 10.4240/wjgs.v14.i3.211

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Case Control Study

# Fast-track protocols in laparoscopic liver surgery: Applicability and correlation with difficulty scoring systems

Ruben Ciria, Ana Padial, María Dolores Ayllón, Carmen García-Gaitan, Javier Briceño

**Specialty type:** Surgery

**Provenance and peer review:** Invited article; Externally peer reviewed

**Peer-review report's scientific quality classification**
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Zhou S

**Received:** April 19, 2021
**Peer-review started:** April 19, 2021
**First decision:** June 13, 2021
**Revised:** July 25, 2021
**Accepted:** February 9, 2022
**Article in press:** February 9, 2022
**Published online:** March 27, 2022

**Ruben Ciria, Ana Padial, María Dolores Ayllón, Javier Briceño,** Unit of Hepatobiliary Surgery and Liver Transplantation, University Hospital Reina Sofia, Cordoba 14004, Spain

**Carmen García-Gaitan,** Unit of Anesthesiology, University Hospital Reina Sofia, Cordoba 14004, Spain

**Corresponding author:** Ruben Ciria, FEBS, MD, PhD, Surgeon, Unit of Hepatobiliary Surgery and Liver Transplantation, University Hospital Reina Sofia, Avenida Menéndez Pidal s/n, Cordoba 14004, Spain. rubenciria@gmail.com

## Abstract

***BACKGROUND***

Few series have reported the utility of fast-track protocols (FTP) in minimally invasive liver surgery.

***AIM***

To report the applicability of FTP in minimally invasive liver surgery and to correlate with difficulty scores.

***METHODS***

The series of patients undergoing minimally invasive liver surgery from 2014 was analyzed. Iwate, Southampton and Gayet's scores were compared as predictors of FTP adherence. Accomplishment of FTP was considered within 24-h, 48-h and 72-h. Multivariate models were performed to define discharge < 24 h, < 72 h, complications and readmissions.

***RESULTS***

From 160 cases, 78 were candidates for FTP, of which 22 (28.2%), 19 (24.4%) and 14 (17.9%) were discharged in < 24-h, 48-h and 72-h, respectively (total = 71.5%). Iwate, Southampton and Gayet's scores achieved area under the receiver operating characteristic values for < 24-h stay of 0.780, 0.687 and 0.698, respectively. Sensitivity and specificity values for the best score (Iwate) were 87.7% and 66.7%, respectively (cutoff = 5.5). In multivariate models, < 72 h stay and complications revealed body mass index as a risk factor independent from difficulty scores.

***CONCLUSION***

The development of aggressive FTP is feasible and < 24-h stay can be achieved

even in moderate and advanced complexity cases. Difficulty scores, including body mass index value, may be useful to predict which cases may adhere to these protocols.

**Key Words:** Liver; Fast-track; Enhanced recovery; Laparoscopy



**Core Tip:** The current manuscript shows how fast-track protocols on laparoscopic liver surgery can be accomplished according to difficulty scoring systems.

**Citation:** Ciria R, Padial A, Ayllón MD, García-Gaitan C, Briceño J. Fast-track protocols in laparoscopic liver surgery: Applicability and correlation with difficulty scoring systems. *World J Gastrointest Surg* 2022; 14(3): 211-220
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i3/211.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i3.211

## INTRODUCTION

Minimally invasive liver surgery (MILS) has become wide spread in recent years. Nowadays, the feasibility and advantages of MILS have been widely demonstrated[1,2]. Enhanced recovery after surgery (ERAS) protocols are multimodal pathways developed to overcome the deleterious effect of perioperative stress after major surgery. The last guidelines published in 2016 from the ERAS Society performed a systematic review over more than 30 articles in which the classical 23 ERAS items validated for colorectal surgery were analyzed for liver surgery[3,4]. The conclusion was that the application of ERAS protocols in liver surgery could be beneficial although the available evidence was poor and prospective studies were encouraged.

Several difficulty scores have been reported to date in laparoscopic liver surgery (LLS). The primary endpoints of all of them are intraoperative complications, conversions and degree of difficulty. The most widely used is the Iwate score[5]. There are others like the Southampton score[6] and the Gayet's score [7]. However, none of them have been tested to predict early recovery and/or completion of a fast-track protocol (FTP).

Our liver unit adopted MILS in 2014, and since the very beginning has implemented a very aggressive FTP leading to an innovative 1-d stay protocol. The main aim of our manuscript is to report a prospective validation of our FTP in MILS. As secondary aims, we analyzed our experience with 1-d stay surgery in LLS and the results of FTP grouped by the 3 scores of difficulty in LLS currently reported in literature in order to compare the capability of each score to predict FTP accomplishment.

## MATERIALS AND METHODS

### *Inclusion period and population*

All patients who underwent MILS since the adoption of the laparoscopic approach (October 2014) at the University Hospital Reina Sofía in Córdoba-Spain were included in the study. All patients signed informed consent for the approval of their personal data for research. All cases were included in a prospectively maintained database. Approval number of the institutional review board of the University Hospital Reina Sofia was 4380 (Code 0000-0002).

### *Inclusion criteria*

The inclusion criteria were unrestricted. We started our FTP at case 40 (to avoid learning curve). Regarding comorbidities, no significant heart disease, body mass index (BMI) < 35 and American Society of Anesthesiologists score < 4 were required. Regarding complexity, Iwate and Southampton scores ≥ 10, living donation and synchronic colorectal and liver resections were excluded. Conversions were also excluded from the analysis, being considered an "a posteriori" variable.

### *Calculation of difficulty scores*

According to their original publications, we considered Iwate, Southampton and Gayet's scores for the calculations and the testing. Iwate score was calculated according to its last update in which an "Expert" category was added and up to 12 points could be reached. Southampton and Gayet's scores were calculated according to their original reports as no further modifications have been reported.

### *Perioperative FTP*

Since the decision of developing an FTP for LLS, two different protocols were considered for both minor and major resections, including a 24-h and a 48-h discharge protocol, respectively. The protocols are depicted in Figure 1A and B. Considering that the main aim is maintaining a low central venous pressure during the surgical procedure, most of the interventions in our protocol are focused on an aggressive preoperative emptying of the intravascular compartment, a fluid restriction during the operation and a rapid postoperative recovery with early intake.

### *Surgical procedures and recovery area*

Our laparoscopic liver resection is based on general principles of open and MILS. Our standard position of the patient is supine with tilt left 30º-45º in case of right posterior resections. Our main transection device is ultrasonic surgical aspiration irrigation device with bipolar sealing forceps for vascular structures. Main vessels are transected using endo-staplers. Following the surgery, the patients are admitted to a postoperative recovery area in which patients are monitored continuously by anesthesiologists. Immediately after arrival, blood tests are obtained, and unless abnormal the patient is discharged to our surgical ward in a 2-4 h period.

### *Statistical analysis and main endpoints*

A prospectively maintained database was screened to obtain complexity scores and to identify potential variables not included in the previously reported scores that would increase their prediction capabilities. Comparisons were performed after normality tests (Shapiro-Wilk) using parametric or non-parametric tests, accordingly. Multivariate models were performed by logistic binary regression tests including variables within 0.1 significance in the major models. The final models included variables below 0.05 significance. Receiver operating curves were performed defining the best cutoff point of the complexity scores. The main endpoints of our study were: (1) Global results and discharge 24h/48h/72 h or FTP not accomplished; (2) Prediction capability of early discharge from difficulty scores; (3) Receiver operating curves for "early discharge" accomplishment of scores; and (4) Multivariate models: discharge-24 h/discharge-72 h/general complications/readmissions.

## RESULTS

### *Overall results and completion of FTP*

From a total of 160 LLS, the final dataset for the analysis was 78 cases. Exclusions were defined as depicted in Figure 2. Mean comprehensive complication index was 5.18 ± 11.52 for the group of patients within the FTP. A total of 23% had any kind of complication, from which only 5 cases (6.4%) were major complications (Dindo-Clavien III-IV). Comparisons with the group of patients that were not candidates to enter into a FTP showed that the selection procedure was adequate (Table 1). From the 78 cases of candidates for FTP, 22 (28.2%), 19 (24.4%) and 14 (17.9%) were discharged in less than 24-h, 48-h and 72-h, respectively (total = 71.5%). The rest (29.5%) did not accomplish any kind of FTP because of the following reasons: complication (26.1%), long distance from home > 200 km (17.3%), delay in the discharge from the recovery area > 12 h (34.8%) and weekender/no acceptance from the patients (21.7%). Readmission rate in the whole series was 7.5%. It was lower but did not reach statistical significance in the FTP group compared to the non-FTP group (7.7% *vs* 11.9%; *P* = not significant). In the FTP group, readmissions were related to the surgical procedure but could not be considered a direct consequence of the application of an FTP. One of the cases was a late evisceration that happened 8 d after the discharge.

### *Accomplishment of the FTP according to difficulty scores*

As observed in Figure 3, the accomplishment of an FTP is directly related to the difficulty of the LLS. It should be noted that a low punctuation in the scores predicted a low postoperative stay and that a high difficulty score predicted a non-accomplished FTP. We also analyzed the combination of 2 or 3 scores with equal punctuation in order to find out whether they would benefit and complement each other by adding homogeneity. However, the combination of the scores was lower in the prediction of accomplishment of an FTP. After these findings, a correlation test was performed in order to find out if Iwate and Southampton scores correlated linearly. An $R^2 = 0.2594$ score was obtained. As observed in Figure 4, several cases were not concordant in their punctuation. Several high Iwate score cases were downgraded by the Southampton scoring system.

### *Predicting early discharge with less than 24-h postoperative hospital stay*

By performing receiver operating curves, it could be demonstrated that the difficulty scores could predict early discharge < 24 h. In this sense, it should be noted that the best cutoff points were equivalent for both Iwate and Southampton scores (score = 5.5). The best sensitivity was observed for the Iwate score (S = 85.7%), with a specificity of 66.7% (Figure 5).

**Table 1 Baseline data and complications in the groups of candidates and non-candidates for a fast-track protocol**

| | Whole series (160 cases) | Excluded learning curve (first 40 cases) | Non-candidate for FTP (42 cases) | Candidate for FTP (78 cases) | *P* (FTP *vs* no FTP) |
|---|---|---|---|---|---|
| **Baseline data** | | | | | |
| Age | 59 ± 13 | 59 ± 14 | 58 ±15 | 59 ± 14 | NS |
| Sex (M/F ratio) | 83/77 | 66/54 | 29/13 | 37/41 | 0.023 |
| BMI | 27.56 ± 4.88 | 27.51 ± 5.03 | 27.69 ± 6.21 | 27.43 ± 4.44 | NS |
| Malignancy, *n* (%) | 122 (76.25) | 93 (77.50) | 32 (76.19) | 61 (78.20) | NS |
| Postoperative stay | 4.41 ± 4.68 | 4.50 ± 5.12 | 7.40 ± 7.17 | 2.94 ± 2.46 | 0.001 |
| Operative time | 253.81 ± 91.91 | 258.41 ± 89.81 | 294.19 ± 84.82 | 239.14 ± 86.95 | 0.001 |
| Tradit minor/major | 82/77 | 58/61 | 16/25 | 42/36 | NS |
| Iwate | | | | | 0.02 |
| Low | 26 | 19 | 5 | 14 | |
| Intermediate | 60 | 43 | 9 | 34 | |
| Advanced | 54 | 43 | 13 | 30 | |
| Expert | 19 | 14 | 14 | 0 | |
| Iwate | | | | | 0.009 |
| I | 68 | 48 | 13 | 35 | |
| II | 24 | 18 | 3 | 15 | |
| III | 67 | 53 | 25 | 28 | |
| Iwate | | | | | NS |
| Low | 21 | 13 | 3 | 10 | |
| Moderate | 81 | 58 | 18 | 40 | |
| High | 52 | 43 | 15 | 28 | |
| Extremely high | 4 | 4 | 4 | 0 | |
| Complications | | | | | |
| CCI | 8.10 ± 17.53 | 4.91 ± 12.51 | 16.57 ± 26.34 | 5.18 ± 11.52 | 0.01 |
| No complications, *n* (%) | 117 (73.1) | 33 (82.5) | 24 (57.1) | 60 (76.9) | 0.024 |
| Redo surgery, *n* (%) | 8 (5.0) | 1 (2.5) | 6 (14.3) | 1 (1.3) | 0.04 |
| Readmission, *n* (%) | 12 (7.5) | 1 (2.5) | 5 (11.9) | 6 (7.7) | NS |
| Minor complications (I-II), *n* (%) | 30 (18.8) | 4 (10.0) | 13 (31.0) | 13 (16.7) | 0.024 |
| Major complications (IIIa, IIIb, IV) | 13 (8.1) | 3 (7.5) | 5 (11.9) | 5 (6.4) | NS |
| | 6 IIIa | 1 IIIa | | 4 IIIa | |
| | 2 IIIb | 1 IIIb | | 1 IIIb | |
| | 2 Iva | | 2 Iva | | |
| | 1 IVb | | 1 IVb | | |
| | 2 V | | 2 V | | |

BMI: Body mass index; CCI: Comprehensive complication index; F: Female; FTP: Fast-track protocols; M: Male; NS: Not significant.

### *Multivariate analysis*

Multivariate models were obtained to find out if complexity scores were independent predictors of early discharge, complications and/or readmissions. A model was performed for each of the complexity scores in order to avoid interactions. Age, BMI, sex, American Society of Anesthesiologists score, previous surgery, malignancy, bilobar spread and liver disease were added as variables. All patients in

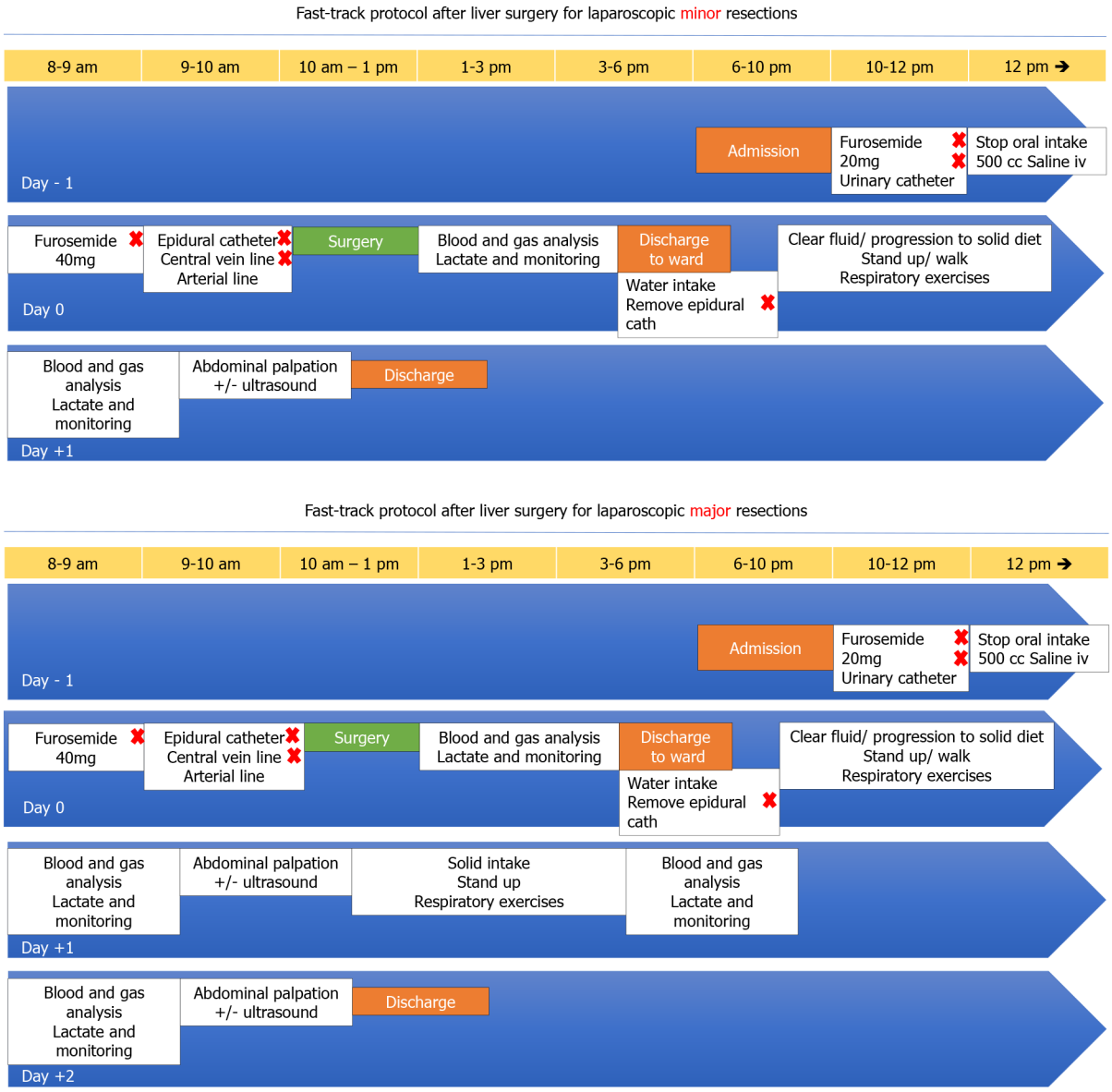



**Figure 1 Perioperative protocols of fast-track in laparoscopic minor (A) and major (B) liver resections.** The minor (A) and the major (B) laparoscopic liver resections are protocols of 24-h and 48-h postoperative hospital stay. Actions with a red cross are under consideration for removal of this protocol after 5 yr of experience.

the series were included (160 cases). As observed in Table 2, in each model the complexity scores were independent risk scores. Interestingly, BMI was a persistent risk factor added to these scores in both the complications and discharge < 72 h models.

## DISCUSSION

Patients undergoing a standard laparoscopic liver resection may be considered as optimal candidates to be included into early recovery protocols, as the surgical procedure needs no anastomosis nor vascular reconstruction. The adoption of LLS by liver teams seems to be clearly exponential, and thus the recovery and postoperative comfort are improving. According to our results, adequate selection may lead to high rates of effectiveness in terms of early discharge, low readmission rates and reduced incidence of complications. Complexity scores may be helpful in the selection process.

Several complexity scores have been reported to date[5-14]. From a technical point of view, most of them have assessed the effect of variables such as tumor location or extent of liver resection. However, liver and patient status have not been considered as important in the scores, and only impaired liver function and previous liver surgery or preoperative chemotherapy have been marginally evaluated. Only Hasegawa *et al*[13] considered BMI score as valuable in a difficulty score. According to our results, BMI score may be considered as important because it may add relevant information about the prognosis

**Table 2 Multivariate models**

| Model | | | | | |
|---|---|---|---|---|---|
| Iwate | | | | | |
| Discharge 24 h | Sig | OR | Discharge 72 h | Sig | OR |
| Iwate | 0.001 | 1.626 (1.2-2.18) | Iwate | 0.01 | 1.46 (1.09-1.95) |
| | | | BMI 25-30 | 0.033 | 6.39 (1.16-35.30) |
| | | | BMI 30-35 | 0.013 | 8.51 (1.57-46.14) |
| Complications | Sig | OR | Readmissions | Sig | OR |
| Iwate | 0.02 | 1.2 (1.03-1.41) | Iwate | 0.007 | 1.58 (1.13-2.22) |
| BMI > 35 | 0.008 | 8.75 (1.76-43.44) | | | |
| Southampton | | | | | |
| Southampton | 0.015 | 1.43 (1.07-1.92) | | | |
| | | | BMI 25-30 | 0.032 | 6.08 (1.16-31.87) |
| | | | BMI 30-35 | 0.006 | 9.85 (1.91-50.70) |
| Complications | Sig | OR | Readmissions | Sig | OR |
| | | | Southampton | 0.036 | 1.3 (1.01-1.68) |
| BMI > 35 | 0.013 | 7.09 (1.52-33.04) | | | |
| Gayet | | | | | |
| Discharge 24 h | Sig | OR | Discharge 72 h | Sig | OR |
| Gayet | 0.004 | 1.85 (1.21-2.81) | Gayet | 0.043 | 1.53 (1.01-2.31) |
| | | | BMI 25-30 | 0.042 | 5.72 (1.06-30.86) |
| | | | BMI 30-35 | 0.014 | 8.08 (1.52-42.99) |
| Complications | Sig | OR | Readmissions | Sig | OR |
| Gayet | 0.008 | 1.48 (1.11-1.98) | Gayet | 0.027 | 2.08 (1.08-4.01) |
| BMI > 35 | 0.009 | 8.56 (1.71-42.85) | | | |

Considering the end-point of discharge in < 24 h and < 72 h, complication rate and readmissions, complexity scores were included and analyzed independently. Age, body mass index, sex, American Society of Anesthesiologists score, previous surgery, malignancy, bilobar spread and liver disease were added as variables. BMI was an independent risk factor added to complexity scores in most of the models analyzed. BMI: Body mass index; OR: Odds ratio; Sig: Significance.

of the patients and the potential adherence to an FTP. In our opinion, liver and patient status have not been adequately considered and should be re-evaluated into difficulty scores. Liver function parameters are only considered by traditional markers (such as Child, platelets or bilirubin). Western and eastern populations are different from a demographical and epidemiological point of view. The main disease, underlying liver impairment and a potential fatty liver or neoadjuvant chemotherapy may surely complement current scores.

A recent meta-analysis performed on 580 laparoscopic liver patients (292 early recovery *vs* 288 traditional) performed on 8 studies highlighted the potential benefit of these protocols in this type of surgery[15]. However, the risk of bias was too high as the authors did not report detailed randomization methods, allocation concealment or blind methods. Moreover, the included studies did not adopt a standard and unified clinical treatment of ERAS programs, and complexity of the resection was not included or controlled as a bias factor. A more recent meta-analysis on ERAS clinical pathways included 4 randomized trials showing several advantages like length of stay and lower complication rates[16]. However, according to the recent recommendations from the ERAS group, liver teams were encouraged to report other components or modifications that could improve results or help spread this clinical pathway.

Our protocol is probably the most aggressive perioperative protocol reported to date in LLS. Our main aim was to reach < 24 h stay in minor hepatectomies and < 48 h in major hepatectomies without any detrimental effect on postoperative outcome. As stated before, about 30% of the cases, if adequately selected, can be discharged in less than 24 h and up to 50% in less than 2 d. It should be noted that 74% of the cases that did not adhere to our FTP were due to non-medical issues or complications. The area to

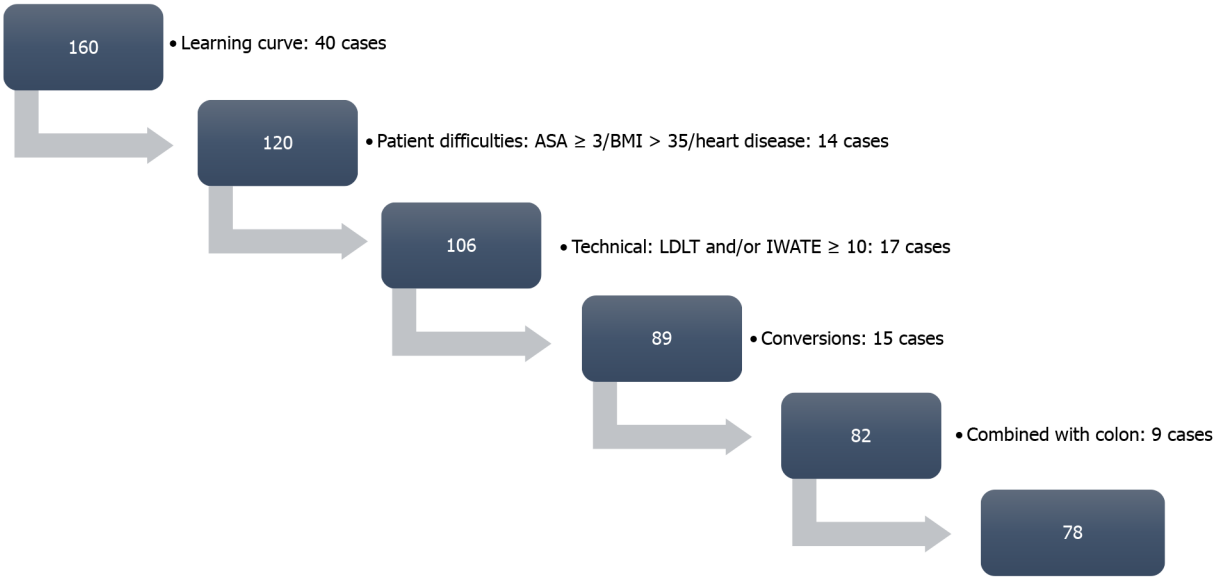



**Figure 2 Flowchart of the patients included in the study.** After removal of excluded cases, a total of 78 cases was the final dataset of patients amenable for inclusion in a fast-track protocol. ASA: American Society of Anesthesiologists; BMI: Body mass index; LDLT: Living donor liver transplantation.

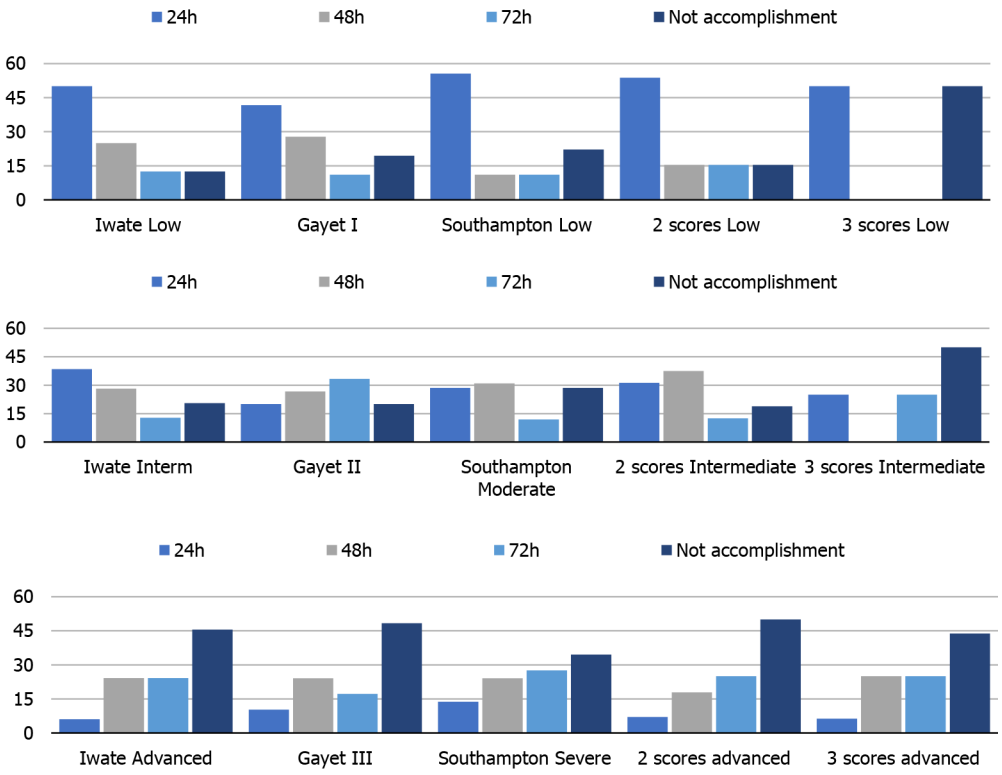



**Figure 3 Accomplishment of fast-track protocols according to difficulty scores.** The accomplishment of a 24-h, 48-h and 72-h fast-track protocol (blue, green and yellow bars, respectively) was analyzed according to the difficulty scores of Iwate, Gayet and Southampton in their subcategories low (above), intermediate (middle) and severe (below). Interm: Intermediate.

which our hospital gives assistance includes regions more than 200 km away from our city. We detected that people from there were reluctant to early discharge after a major abdominal operation as they felt "unsafe."

The perioperative protocol has experienced some changes mainly due to increased experience. Our most recent cases have been performed without epidural catheter and some of them without central line. Similarly, we have stopped urinary catheterization the night before and discontinued furosemide 12 h before the surgery. These improvements are parallel to the better knowledge from our anesthesiologist, which have perfectly adapted the balance between central venous pressure, pneumoperitoneum

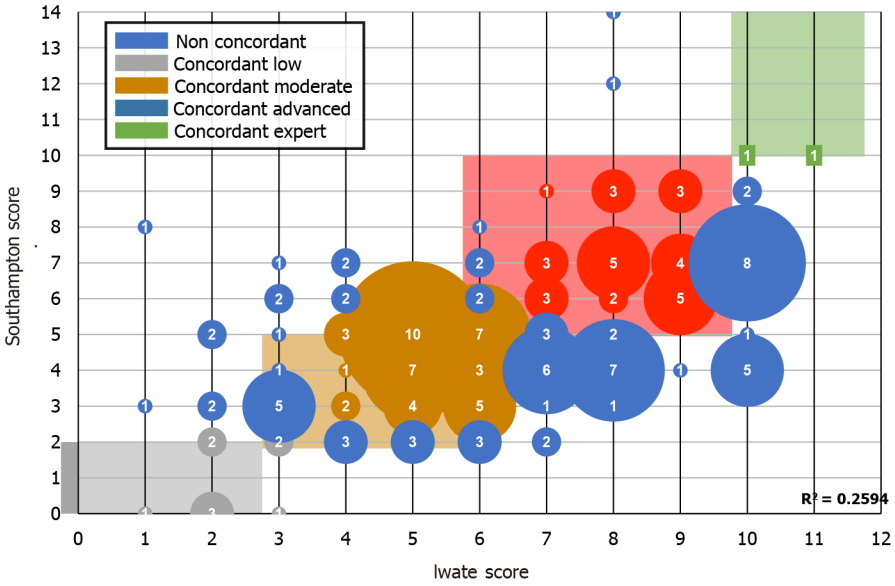



**Figure 4 Correlation of difficulty scores.** A comparison of Iwate (X-axis) and Southampton (Y-axis) scores was performed. As observed, several cases were upgraded or downgraded (blue circles), meaning a non-concordant classification between both scores.

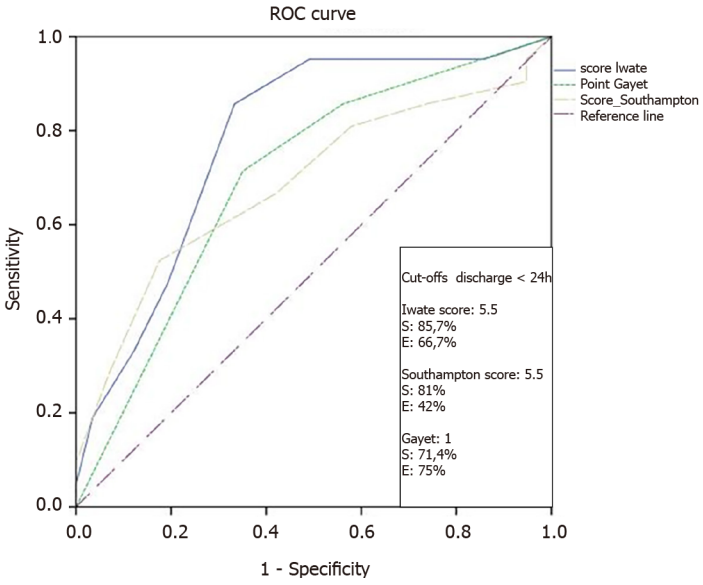



**Figure 5 Receiver operating curves for the prediction of 24-h postoperative hospital stay.** Iwate score was the best score with a cutoff point scoring of 5.5 with a sensitivity and specificity of 85.7% and 66.7%, respectively.

pressure and airway pressure, making surgery a bloodless field[17]. It should be remarked that anesthesiologists are the cornerstone in our LLS. The intraoperative management based on boluses of inotropes rather than fluid administration is a difficult management that needs expertise and experience.

Some limitations of our research should be highlighted. First, the final population in the study was not extremely large; second, the results may have obviously changed according to our improved experience; and third, complexity has too changed, and thus applicability may be limited. However, we offer a homogeneous population in a brief period of time in a recently developed LLS team. This main advantage may be transferable to several liver teams worldwide and may help them face the same difficulties that we have had in a different way. Alternatively, our protocol is the first incorporating a full perioperative pathway within complexity scoring systems, making a 24 h early discharge possible in the setting of LLS.

## CONCLUSION

In conclusion, it is feasible to develop aggressive FTP in LLS, even in high-complexity cases. In fact, our protocols are the first-reported to adequately predict and accomplish a postoperative hospital stay shorter than 24 h. Currently available difficulty scores are useful to define candidates for FTP and may predict a full completion even in aggressive postoperative stay formats. However, we consider that BMI has not been adequately considered and may be added to the scores in order to improve their prediction capabilities.

## ARTICLE HIGHLIGHTS

### *Research background*

There is a lack of evidence regarding the correlation between laparoscopic liver surgery (LLS) difficulty scoring systems and accomplishment of fast-track protocols (FTP).

### *Research motivation*

The main motivation is to identify if current difficulty scoring systems may be used to predict early discharging policies and development of complications after LLS within an FTP.

### *Research objectives*

The main objectives are to define if difficulty scoring systems may predict accomplishment of FTPs in LLS and to determine variables that may complement these scoring systems to increase their prediction capabilities.

### *Research methods*

We analyzed out patients included in an FTP and compared Iwate, Southampton and Gayet's scoring systems. Comparisons were also made in some sets of patients who were included in 24-h and 48-h early discharge protocols for both minor and major resections, respectively.

### *Research results*

Our selection criteria was successful with more than 70% of our patients being discharged in less than 72 h. Iwate scoring system was the most accurate to predict 24-h discharge with an area under the receiver operating characteristic = 0.78 and 87.7% and 66.7% for sensitivity and specificity values, respectively, and a cutoff of 5.5 points.

### *Research conclusions*

Iwate difficulty score is the most accurate to predict adhesion to an FTP after LLS. Body mass index was considered as an independent risk factor that should be added to current scoring systems.

### *Research perspectives*

Incoming difficulty scoring systems may be further evaluated to include variables not considered to date.

## FOOTNOTES

**Author contributions:** Ciria R and Ayllón MD designed the research study; Ciria R, Ayllón MD, Padial A and García-Gaitan C performed the research; all authors analyzed the data and wrote the manuscript; All authors have read and approved the final manuscript; Ciria R and Padial A have equally contributed to the development of this manuscript and research.

**Institutional review board statement:** Approval number of the institutional review board of the University Hospital Reina Sofia was 4380 (Code 0000-0002).

**Conflict-of-interest statement:** The authors declare no conflict of interest in none of the contents within the development of the manuscript.

**Data sharing statement:** Technical appendix, statistical code and dataset available from the corresponding author at rubenciria@gmail.com. Participants gave informed consent for data sharing.

**STROBE statement:** The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

**Country/Territory of origin:** Spain

**ORCID number:** Ruben Ciria 0000-0002-7839-2329; Ana Padial 0000-0002-0608-4175; María Dolores Ayllón 0000-0003-2493-3756; Carmen García-Gaitan 0000-0001-5087-5057; Javier Briceño 0000-0001-7027-7898.

**S-Editor:** Gong ZM
**L-Editor:** Filipodia
**P-Editor:** Wu RR

## REFERENCES

1 **Ciria R**, Gomez-Luque I, Ocaña S, Cipriani F, Halls M, Briceño J, Okuda Y, Troisi R, Rotellar F, Soubrane O, Abu Hilal M. A Systematic Review and Meta-Analysis Comparing the Short- and Long-Term Outcomes for Laparoscopic and Open Liver Resections for Hepatocellular Carcinoma: Updated Results from the European Guidelines Meeting on Laparoscopic Liver Surgery, Southampton, UK, 2017. *Ann Surg Oncol* 2019; **26**: 252-263 [PMID: 30390167 DOI: 10.1245/s10434-018-6926-3]

2 **Ciria R**, Ocaña S, Gomez-Luque I, Cipriani F, Halls M, Fretland ÅA, Okuda Y, Aroori S, Briceño J, Aldrighetti L, Edwin B, Hilal MA. A systematic review and meta-analysis comparing the short- and long-term outcomes for laparoscopic and open liver resections for liver metastases from colorectal cancer. *Surg Endosc* 2020; **34**: 349-360 [PMID: 30989374 DOI: 10.1007/s00464-019-06774-2]

3 **Melloul E**, Hübner M, Scott M, Snowden C, Prentis J, Dejong CH, Garden OJ, Farges O, Kokudo N, Vauthey JN, Clavien PA, Demartines N. Guidelines for Perioperative Care for Liver Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. *World J Surg* 2016; **40**: 2425-2440 [PMID: 27549599 DOI: 10.1007/s00268-016-3700-1]

4 **Dejong CH**, van Dam RM. Enhanced recovery programs in liver surgery. *World J Surg* 2014; **38**: 2683-2684 [PMID: 25123180 DOI: 10.1007/s00268-014-2727-4]

5 **Wakabayashi G**. What has changed after the Morioka consensus conference 2014 on laparoscopic liver resection? *Hepatobiliary Surg Nutr* 2016; **5**: 281-289 [PMID: 27500140 DOI: 10.21037/hbsn.2016.03.03]

6 **Halls MC**, Berardi G, Cipriani F, Barkhatov L, Lainas P, Harris S, D'Hondt M, Rotellar F, Dagher I, Aldrighetti L, Troisi RI, Edwin B, Abu Hilal M. Development and validation of a difficulty score to predict intraoperative complications during laparoscopic liver resection. *Br J Surg* 2018; **105**: 1182-1191 [PMID: 29737513 DOI: 10.1002/bjs.10821]

7 **Kawaguchi Y**, Fuks D, Kokudo N, Gayet B. Difficulty of Laparoscopic Liver Resection: Proposal for a New Classification. *Ann Surg* 2018; **267**: 13-17 [PMID: 28187043 DOI: 10.1097/SLA.0000000000002176]

8 **Ciria R**, Ayllon MD, Briceño J. Difficulty scores in laparoscopic liver surgery-getting closer to a powerful and necessary tool. *Hepatobiliary Surg Nutr* 2019; **8**: 428-430 [PMID: 31489323 DOI: 10.21037/hbsn.2019.02.11]

9 **Troisi RI**, Montalti R, Van Limmen JG, Cavaniglia D, Reyntjens K, Rogiers X, De Hemptinne B. Risk factors and management of conversions to an open approach in laparoscopic liver resection: analysis of 265 consecutive cases. *HPB (Oxford)* 2014; **16**: 75-82 [PMID: 23490275 DOI: 10.1111/hpb.12077]

10 **Ban D**, Tanabe M, Ito H, Otsuka Y, Nitta H, Abe Y, Hasegawa Y, Katagiri T, Takagi C, Itano O, Kaneko H, Wakabayashi G. A novel difficulty scoring system for laparoscopic liver resection. *J Hepatobiliary Pancreat Sci* 2014; **21**: 745-753 [PMID: 25242563 DOI: 10.1002/jhbp.166]

11 **Cauchy F**, Fuks D, Nomi T, Schwarz L, Barbier L, Dokmak S, Scatton O, Belghiti J, Soubrane O, Gayet B. Risk factors and consequences of conversion in laparoscopic major liver resection. *Br J Surg* 2015; **102**: 785-795 [PMID: 25846843 DOI: 10.1002/bjs.9806]

12 **Lee MK 4th**, Gao F, Strasberg SM. Perceived complexity of various liver resections: results of a survey of experts with development of a complexity score and classification. *J Am Coll Surg* 2015; **220**: 64-69 [PMID: 25451665 DOI: 10.1016/j.jamcollsurg.2014.09.017]

13 **Hasegawa Y**, Wakabayashi G, Nitta H, Takahara T, Katagiri H, Umemura A, Makabe K, Sasaki A. A novel model for prediction of pure laparoscopic liver resection surgical difficulty. *Surg Endosc* 2017; **31**: 5356-5363 [PMID: 28593408 DOI: 10.1007/s00464-017-5616-8]

14 **Tong Y**, Li Z, Ji L, Wang Y, Wang W, Ying J, Cai X. A novel scoring system for conversion and complication in laparoscopic liver resection. *Hepatobiliary Surg Nutr* 2018; **7**: 454-465 [PMID: 30652090 DOI: 10.21037/hbsn.2018.10.09]

15 **Yang R**, Tao W, Chen YY, Zhang BH, Tang JM, Zhong S, Chen XX. Enhanced recovery after surgery programs versus traditional perioperative care in laparoscopic hepatectomy: A meta-analysis. *Int J Surg* 2016; **36**: 274-282 [PMID: 27840308 DOI: 10.1016/j.ijsu.2016.11.017]

16 **Rouxel P**, Beloeil H. Enhanced recovery after hepatectomy: A systematic review. *Anaesth Crit Care Pain Med* 2019; **38**: 29-34 [PMID: 29807132 DOI: 10.1016/j.accpm.2018.05.003]

17 **Kobayashi S**, Honda G, Kurata M, Tadano S, Sakamoto K, Okuda Y, Abe K. An Experimental Study on the Relationship Among Airway Pressure, Pneumoperitoneum Pressure, and Central Venous Pressure in Pure Laparoscopic Hepatectomy. *Ann Surg* 2016; **263**: 1159-1163 [PMID: 26595124 DOI: 10.1097/SLA.0000000000001482]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 March 27; 14(3): 221-235

DOI: 10.4240/wjgs.v14.i3.221

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Case Control Study

# Does cranial-medial mixed dominant approach have a unique advantage for laparoscopic right hemicolectomy with complete mesocolic excision?

Li Lin, Si-Bo Yuan, Huan Guo

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** El-Nakeep S, Egypt; Hegazy AA, Egypt

**Received:** September 1, 2021
**Peer-review started:** September 1, 2021
**First decision:** November 7, 2021
**Revised:** November 14, 2021
**Accepted:** March 5, 2022
**Article in press:** March 5, 2022
**Published online:** March 27, 2022

**Li Lin, Si-Bo Yuan, Huan Guo,** Department of Gastrointestinal Surgery and Xiamen City Key Laboratory of Gastrointestinal Cancer, Zhongshan Hospital, Xiamen University, Xiamen 361000, Fujian Province, China

**Corresponding author:** Si-Bo Yuan, MM, Chief Doctor, Department of Gastrointestinal Surgery and Xiamen City Key Laboratory of Gastrointestinal Cancer, Zhongshan Hospital, Xiamen University, No. 201 Hubin South Road, Xiamen 361000, Fujian Province, China.
yuansb8627860592@sina.cn

## Abstract

***BACKGROUND***

Complete mesocolic excision (CME) with central vascular ligation (CVL) was proposed by Hohenberger in 2009. The CME principle has gradually become the technical standard for colon cancer surgery. How to achieve CME with CVL in laparoscopic right hemicolectomy (LRH) is controversial, and a unified standard approach is not yet available. In recent years, the authors' team has integrated the theory of membrane anatomy, tried to combine the cephalic approach with the classic medial approach (MA) for technical optimization, and proposed a cranial-medial mixed dominant approach (CMA).

***AIM***

To explore the feasibility of operational approaches for LRH with CME.

***METHODS***

In this retrospective cohort study, the clinical data of 57 patients with right-sided colon cancer (TNM stage I, II, or III) who underwent LRH with CME from January 2016 to June 2020 were collected and summarized. There were 31 patients in the traditional MA group and 26 in the CMA group.

***RESULTS***

There were no significant differences in baseline data between the two groups. The operation was shorter and the number of lymph nodes dissected was higher in the CMA group than in the MA group, but there was no significant difference in the number of positive lymph nodes, intraoperative blood loss, postoperative exhaust time, feeding time, postoperative hospital stay or postoperative complication incidence.

*CONCLUSION*
Our study shows that the CMA is a safe and feasible procedure for LRH with CME and has a unique advantage.

**Key Words:** Right hemicolectomy; Laparoscopic surgery; Complete mesocolic excision; Mesocolon; Embryology; Colon cancer



**Core Tip:** This work presents the combination of the cranial approach and the classic medial approach and optimization of the combined approach to propose a cranial-medial mixed dominant approach (CMA) based on embryonic development and membrane anatomy. Our study shows that the CMA is a safe and feasible procedure for laparoscopic right hemicolectomy with complete mesocolic excision and has a unique advantage.

**Citation:** Lin L, Yuan SB, Guo H. Does cranial-medial mixed dominant approach have a unique advantage for laparoscopic right hemicolectomy with complete mesocolic excision? *World J Gastrointest Surg* 2022; 14(3): 221-235
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i3/221.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i3.221

## INTRODUCTION

Since Heald[1] proposed the total mesorectal excision (TME) principle in 1982, TME has become the international gold standard for rectal cancer[2]. In 1991, Jacobs *et al*[3] first reported laparoscopic colorectal cancer resection. A similar concept of complete mesocolic excision (CME) with central vascular ligation (CVL) was proposed by Hohenberger *et al*[4] in 2009 based on the concepts of TME. The CME principle has gradually become the technical standard for colon cancer surgery[5,6]. The National Comprehensive Cancer Network (NCCN) guidelines for colon cancer recommended laparoscopic surgery for patients with curable colon cancer[7] for years, but it is generally considered that laparoscopic right hemicolectomy (LRH) is relatively complex and difficult[8]. How to achieve CME with CVL in LRH has been controversial, and a unified standard approach is not yet available. Before this procedure can be generally recommended, a consensus is needed on how the operation can be carried out optimally. However, quite a few approaches have been proposed[9-11]. In recent years, the authors' team has integrated the theory of embryonic development and membrane anatomy, combined the cranial approach with the classic medial approach (MA) and optimized the combined approach to propose a cranial-medial mixed dominant approach (CMA). This approach allows better control of surgical risks, is more compliant with CME requirements, and is more standardized and reproducible.

## MATERIALS AND METHODS

### *Materials*

All the patients, both those in the CMA group and those in the MA group, were admitted to the Department of Gastrointestinal Surgery of Zhongshan Hospital of Xiamen University and underwent LRH with CME and CVL, which was performed by Professor Sibo Yuan. Between January 2016 and December 2020, adult patients who had a confirmed diagnosis of renal cell carcinoma (RCC), who underwent contrast-enhanced CT of the chest, abdomen, and pelvis for clinical staging (cTNM), and who underwent radical colectomy were selected from the database. The selection criteria were as follows: (1) Patients were 15 years of age or older, with no limitation on sex; (2) Patients had a confirmed diagnosis of clinical stage I, II, or III adenocarcinoma through biopsy of the right colon on colonoscopy, including the caecum, ascending colon, hepatic flexure, and proximal transverse colon; and (3) Patients underwent laparoscopic surgery at a scheduled time rather than emergency surgery due to severe obstruction or perforation. During 2016–2018, 36 patients underwent LRH with the traditional MA. From 2018 to 2020, 33 patients underwent treatment with the CMA. Twelve of the 69 patients were excluded from this study due to resection of local metastases of the organ (stomach, uterus, annex, *etc.*) and simultaneous resection of liver metastases and intestinal polyps, for which we could not assess the operative duration, postoperative recovery or other factors. Professor Yuan primarily used the MA before 2018 and proposed and primarily used the CMA after 2018 to complete LRH. Twenty-six patients

were included in the CMA group, and 31 patients were included in the MA group after exclusion (Figure 1). Postoperative clinical tumour staging was based on the Union for International Cancer Control (UICC) cancer staging manual (version 6). Preoperative blood and albumin (ALB) transfusions were performed in cases of anaemia and hypoproteinaemia, respectively. The basic condition of the patients and the outcome data are shown in Table 1.

### *Surgical approaches*

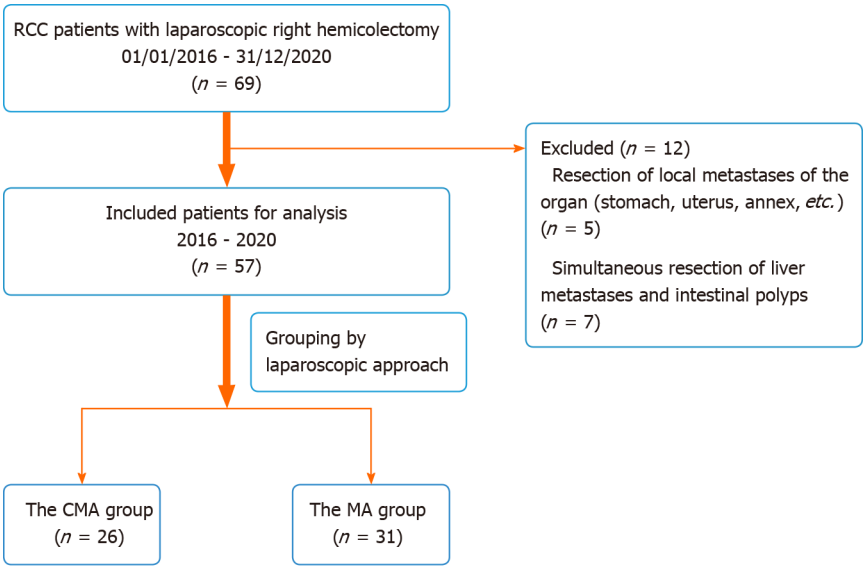
Dissociation of the right colon under laparoscopy was completed in both groups of patients (CMA and MA). Then, the surgeon made a small incision of approximately 4 cm on the right side of the abdomen to complete the anastomosis (routine end-side anastomosis), finally rearranging the bowel.

**CMA:** (1) Establishment of a laparoscopic system and intraperitoneal exploration: All patients were placed in the lithotomy position after the administration of general anaesthesia, with the left leg lowered as much as possible to avoid affecting the operation of the surgeon. Throughout the procedure, the surgeon stood on the left side of the patient, whereas the first assistant stood on the right side, and the second assistant held a mirror and stood between the legs of the patient. Five trocars were used (three 5 mm, one 12 mm, one 10 mm), with one observation and four operation ports. Among these, one observation port with a 10-mm trocar was located 2 cm lower than the umbilicus. One operation port with a 5-mm trocar was placed at Maxwell's point. The second operation port with a 12-mm trocar was placed near the anti-Maxwell point. The third and fourth operation ports with 5-mm trocars were located approximately 2 cm lower than the edge of the rib arch across the left and right clavicular midline intersections (Figure 2). Laparoscopic exploration of the liver lobe, peritoneum, omentum, spleen, stomach, colon, pelvis, and small intestine was performed; the tumour location and size were evaluated to assess the extent of tumour invasion into the surrounding tissue and determine the scope of surgical resection. Then, the projection of the surgical trunk, the superior mesenteric artery (SMA) on the mesocolon and the root of the middle colic vessels were explored; (2) The greater omentum was split with an ultrasonic knife to the left of the superior edge of the transverse colon, the omental bursa was entered, and the greater omentum outside the gastric omental vascular arch (tumour of the ascending colon or ileocaecum) or inside the vascular arch (tumour of the hepatic curvature or right half of the transverse colon) was longitudinally cut off, revealing the right mesenteric fusion region of the transverse mesocolon, the mesogastrium and the underlying visceral duodenal-pancreatic peritoneum (also called the fusion fascia of Fredet)[12,13]; (3) Cephalic-approach procedure (CAP): The first assistant lifted the gastric body and pulled the mesogastrium upwards laterally, and the surgeon used the right hand to pull the transverse mesocolon downwards, which formed an antagonistic force and satisfactorily exposed the right fusion fascia area of the transverse mesocolon and the mesogastrium. The surgeon first dissected the fusion fascia in the innermost area adjacent to the gastric antrum (Figure 3A), entered the dorsal side of the fusion fascia of Fredet (Figure 3B), and then gently expanded the surgical plane between the fusion fascia of Fredet and the visceral duodenal-pancreatic peritoneum in a medial-to-lateral direction. After cleavage of the lateral "white line of Toldt" around the hepatic flexure, the fusion fascia was incised between the hepatic curvature of the colon and the second part of the duodenum and expanded downwards and slightly laterally, and the plane between the fusion fascia of Toldt and the subperitoneal deep fascia (Gerota fascia) near the lateral side of the second part of the duodenum was entered. Using the projection of the superior right colic vein (SRCV) on the fusion fascia of Fredet as a landmark, the surgical plane was expanded medially to expose the gastrocolic trunk of Henle (GCTH), and the nonvascularized mesocolic area was expanded on the left side of the root of the middle colonic vessels, completing the dissection of the surgical area of the GCTH[14,15] (SAGCTH), defined as the area of the superior mesenteric vein (SMV) located at the head of the pancreas and including the venous confluence of the right gastroepiploic vein (RGEV), anterosuperior pancreatic-duodenal vein (ASPV), and SRCV. Then, exposure was continue downwards to the second part of the duodenum, the head of the pancreas and the cranial root of the middle colic vessel; a piece of gauze was placed transversely at the lower edge as a landmark. In this procedure, the most important thing was to maintain the surgical plane between the fusion fascia of Fredet and the visceral duodenal-pancreatic peritoneum and to completely resect the fusion fascia of Fredet (Figure 3C); (4) Medial-approach procedure (MAP): The first assistant pulled up the mesocolon of the middle colic vascular area with the left hand, pulled the mesocolon of the ileocolic vascular area with the right hand, and exposed the projection of the surgical trunk[14,17] on the mesocolon. The surgeon incised the mesentery junction (the fusion point of the mesocolon, the visceral peritoneum, and the intestinal mesentery, approximately 3 cm below the projection of the ileocolic vessels to the confluence of the SMV) with an ultrasonic scalpel (Figure 3D and E), utilized the vapourization effect of the ultrasonic scalpel, sought the fusion fascia of Toldt and then entered the surgical plane between the fusion fascia of Toldt and subperitoneal deep fascia (Figure 3F); then, the surgeon slightly expanded the plane laterally to the white line of Toldt, down to the peritoneal reflexion area of the ileocaecum, and up to the lower margin of duodenum and cut off the right fusion fascia of Toldt at the third portion of the duodenum, where the fusion fascia of Toldt divided into the posterior pancreatic fascia of Treitz and the fusion fascia of Fredet. The dorsal side of the fusion fascia of Fredet was entered to reach a rendezvous of the surgical plane with that of the CAP (Figure 3G and H). The ileocolic artery (ICA) was used as a landmark, revealing the surgical

**Table 1 Basic patient preoperative characteristics**

| Item | CMA group (*n* = 26) | MA group (*n* = 31) | *P* value |
|---|---|---|---|
| Age (yr) | 63.12 ± 13.65 | 61.35 ± 12.27 | 0.61 |
| Sex | | | 0.794 |
| Male | 14 | 18 | |
| Female | 12 | 13 | |
| BMI (kg/m$^2$) | 21.42 ± 3.15 | 22.54 ± 3.43 | 0.209 |
| Tumour size (cm) | 5.18 ± 1.80 | 4.84 ± 2.06 | 0.52 |
| Previous abdominal surgery | | | 0.488 |
| Yes | 3 | 6 | |
| No | 23 | 25 | |
| Tumour location | | | 0.644 |
| Ileocecal junction | 7 | 6 | |
| Ascending colon | 11 | 12 | |
| Flexura hepatica coli | 8 | 13 | |
| Histological grade | | | 0.185 |
| Well | 0 | 1 | |
| Moderate | 18 | 26 | |
| Poor | 8 | 4 | |

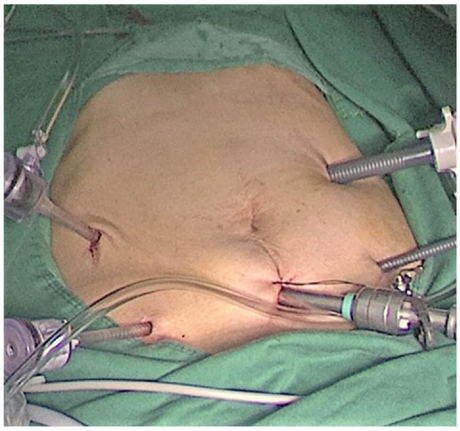
CMA: Cranial-medial mixed dominant approach; MA: Medial approach.




**DOI:** 10.4240/wjgs.v14.i3.221 

**Figure 1 Flow chart of clinical data selection.**

trunk; the mesenteric radix was sharply dissected from the caudal side (small intestinal venous branch of the SMV) to the cranial side (the left root of the middle colic artery (MCA), with the projection of the gauze used as a landmark), and the roots of the vessels (ileocolic vessels, right colic artery, *etc.*) were ligated simultaneously; (5) Rendezvous of the surgical plane after the CAP and MAP. The rendezvous zone: (a) The nonvascularized mesocolic area on the left side of the root of the MCA was dissected to enter the ventral plane of the pancreas; and (b) The connecting line from the right side of the middle colic vessel to the GCTH was opened up, which connected the dorsal side of the fusion fascias of Fredet



**DOI:** 10.4240/wjgs.v14.i3.221 

**Figure 2 The position of the five trocars.**

and Toldt. The root of the right branch of the MCA was ligated simultaneously; and (6) Cleavage of the lateral white line of Toldt was performed around the caecum (Figure 3L), along the ascending colon and around the hepatic flexure, connecting the posterior plane of the expanded fusion fascia of Toldt to complete the overall mobilization of the right colon (Figure 3M). The specimen from the operation was in Figure 4.

**MA:** First, we found the anatomic projection of the ileocolic vessel pedicle. We anatomized the SMV from the caudal side to the cranial side and ligated the roots of the vessels [ileocolic vein (ICV), ileocolic artery (ICA), RCV, right colic artery (RCA), *etc.*]. Then, we followed the fusion space of the hepatic flexure of the colon and completely dissected the colonic hepatic flexure (as mentioned above). Finally, we mobilized the right colon along with the expanded fusion fascia of Toldt.

### Observational indexes

Intraoperative data were obtained regarding the operative duration (duration of the total operation and the laparoscopic procedure), blood loss, specimen length, and number of resected and positive lymph nodes. Postoperative data, including exhaust time, liquid intake time, postoperative hospitalization (days), and postoperative complications, were recorded. Complications were graded according to the Clavien–Dindo classification[18]. Mortality and short-term postoperative complications within the first 30 postoperative days (or during the entire hospital stay if longer than 30 d) were recorded. Postoperative ileus was defined as no tolerance for solid food and no defecation by postoperative day 6 [19]. Postoperative bleeding was defined as bleeding requiring at least one transfusion of packed red cells during surgery or in the subsequent 48 h.

### Statistical analysis

All calculations and analyses were performed by SPSS software, version 22.0 (SPSS, Chicago, IL). Quantitative data are expressed as the mean ± SD. Student's *t* test was used to compare the differences between the two groups; $P < 0.05$ was considered statistically significant.

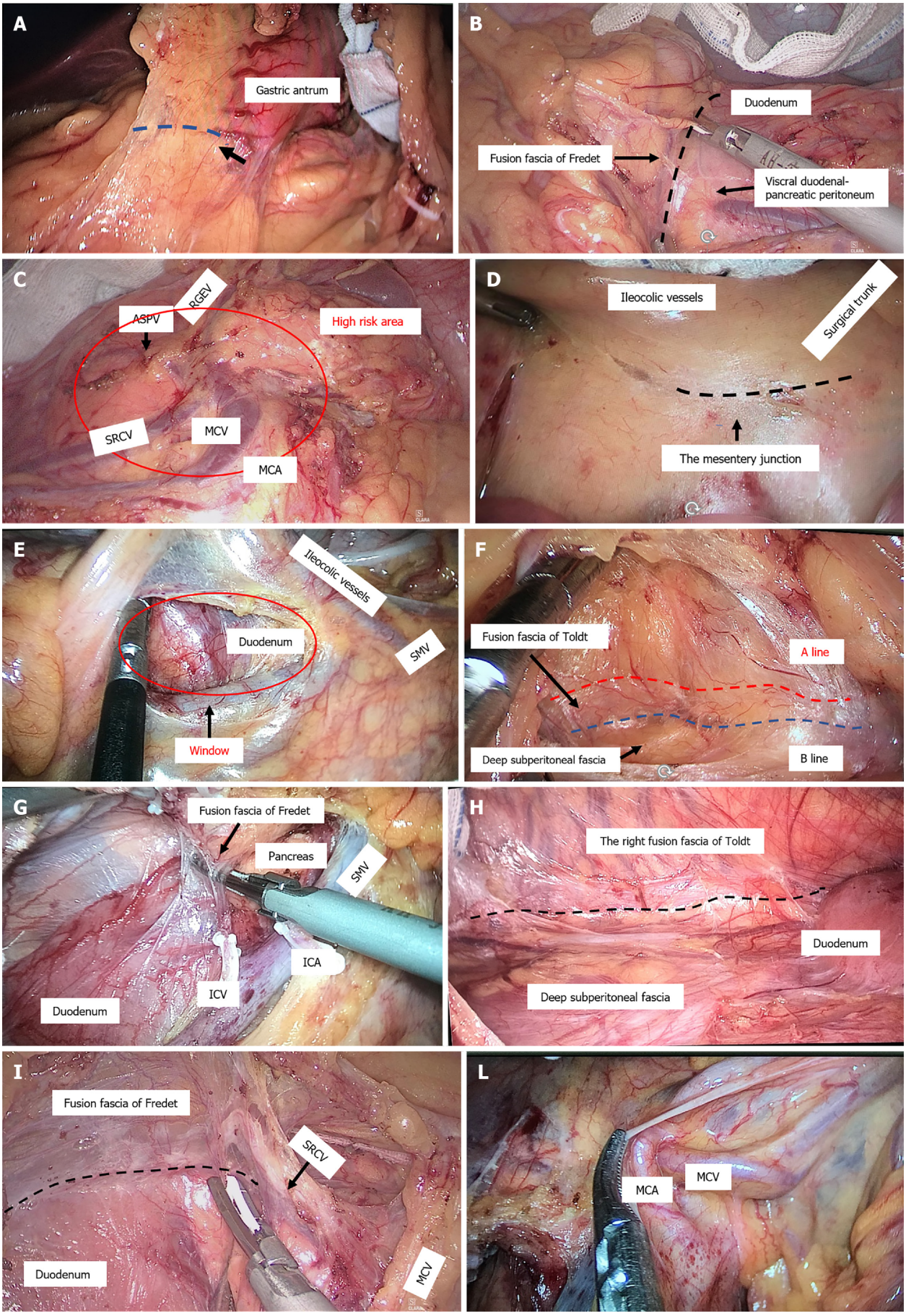
## RESULTS

### General information

Twenty-six and 31 patients were assigned to the MA and CMA groups, respectively (Table 1). There was no significant difference between the groups in sex, tumour location, tumour classification, laboratory results [carcinoembryonic antigen (CEA) level, haemoglobin (HB) level, white blood cell (WBC) count, ALB level, *etc.*] or body mass index.

### Comparison of intraoperative and postoperative conditions

The mean resection sample length in the MA group was 26.95 ± 6.18 cm, which was not different from that in the CMA group (27.926 ± 7.52 cm) ($P = 0.598$). The number of lymph nodes collected in the CMA group was 30.50 ± 15.31, which was significantly greater than that in the MA group (23.81 ± 9.06). The number of positive lymph nodes was similar in both groups. In the CMA group, the operative duration was 135.12 ± 17.47 min, and the laparoscopic procedure time was 69.73 ± 15.13 min, which were significantly lower ($P < 0.05$) than those in the MA group (150.61 ± 26.01 min and 84.81 ± 21.48 min,


A
Gastric antrum
B
Duodenum
Fusion fascia of Fredet
Viscral duodenal-pancreatic peritoneum
C
RGEV
ASPV
High risk area
SRCV
MCV
MCA
D
Ileocolic vessels
Surgical trunk
The mesentery junction
E
Ileocolic vessels
Duodenum
SMV
Window
F
Fusion fascia of Toldt
A line
Deep subperitoneal fascia
B line
G
Fusion fascia of Fredet
Pancreas
SMV
ICA
ICV
Duodenum
H
The right fusion fascia of Toldt
Duodenum
Deep subperitoneal fascia
I
Fusion fascia of Fredet
SRCV
Duodenum
MCV
L
MCA
MCV

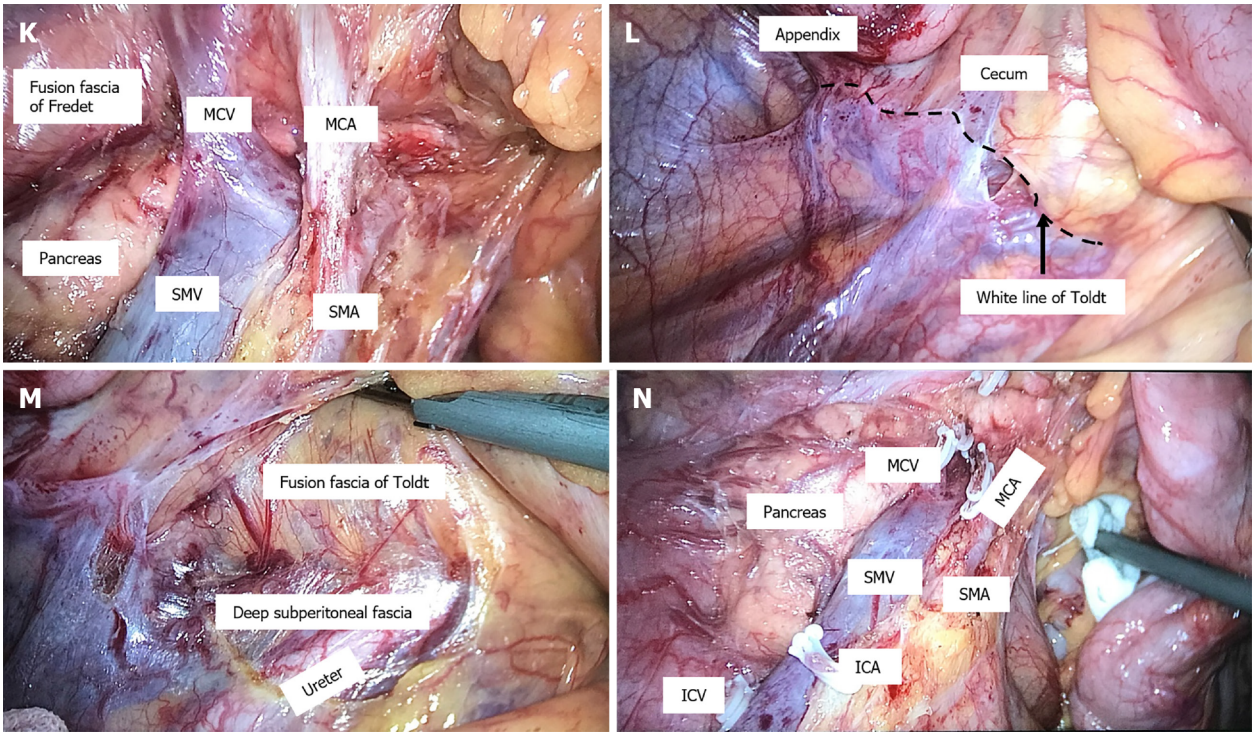



**Figure 3 The cranial-medial mixed dominant approach.** A: The right fusion fascia area of the transverse mesocolon and the mesogastrium. The black arrow indicates the position of the first cut with dissection along the dotted line; B: Expanded surgical plane between the fusion fascia of Fredet and the visceral duodenal-pancreatic peritoneum; C: High-risk area using the superior right colic vein as a landmark included the gastrocolic trunk of Henle, middle colic vein (MCV), and middle colic artery (MCA); D: The mesentery junction fusion point of the mesocolon and the intestinal mesentery, approximately 3 cm below the projection of ileocolic vessels to the confluence of the superior mesenteric vein (SMV); E: The mesocolic window was opened to enter the right retrocolic space; F: Expanded surgical plane of the right retrocolic space between the ventral side of the fusion fascia of Toldt and deep subperitoneal fascia. A line: Red dotted line, B line: Blue dotted line, as indicated by Shinohara[15]; G: Fusion fascia of Fredet; H: Right retrocolic space after resection between the fusion fascia of Toldt and deep subperitoneal fascia; I: Rendezvous view of the surgical plane after the cephalic-approach procedure and medial-approach procedure, cut along the black dotted line on the fusion fascia of Fredet; J: Complex three-dimensional anatomical structure of the root of medial colic vessels; K: Three-dimensional dissection of the mesocolon around the root of the MCVs; L: Lateral white line of Toldt around the ileocaecum; M: Cleavage of the lateral white line of Toldt around the caecum connected to the posterior plane of the expanded fusion fascia of Toldt; N: SMV after lymph node dissection. RGEV: Right gastroepiploic vein; ASPV: Anterosuperior pancreatic-duodenal vein; SRCV: Superior right colic vein; ICA: Ileocolic artery; ICV: Ileocolic vein; SMA: Superior mesenteric artery.

respectively). There was no significant difference in the intraoperative blood loss, feeding fluid time, exhaust time, length of hospital stay or postoperative laboratory results (seven days after the operation) between the two groups ($P > 0.05$) (Table 2).

### *Operational complications*

The incidence of complications in the CMA group was 23%, while that in the CA group was 13%, but the difference was not significant ($P = 0.486$). The 30 d mortality rate was 0 in both groups. However, there were 3 cases of lymphatic fistula in the CMA group, all of which were cured by conservative treatment (Table 3).

## DISCUSSION

Multiple cohort studies have confirmed the oncological effectiveness and surgical safety of CME with CVL[20-22], in which the embryologic tissue planes are resected along the entire enveloped mesocolon. There is a multicentre, prospective, randomized trial comparing conventional (laparoscopic) right hemicolectomy with robotic CME for patients with right-sided colon cancer at 4 centres in the UK currently underway, and we are very much looking forwards to its results[23]. Although there are still some doubts[8], laparoscopic CME has gradually become the technical standard for colon cancer[5]. However, there is no consensus on which standard surgical approach should be used to perform LRH with CME.

The representative approaches of LRH with CME include the MA, cephalic approach, caudal approach and other mixed approaches. European randomized controlled trials (RCTs) have suggested that[24] the MA has advantages in LRH and is both widely used in clinical practice and representative. However, Liang *et al*[9] suggested that the MA is difficult and commonly leads to bleeding due to

**Table 2 Comparison of intraoperative and postoperative conditions between the two groups**

| Item | CMA group (*n* = 26) | MA group (*n* = 31) | *P* value |
|---|---|---|---|
| Sample length (cm) | 26.95 ± 6.18 | 27.926 ± 7.52 | 0.598 |
| No. of lymph nodes collected | 30.50 ± 15.31 | 23.81 ± 9.06 | 0.046 |
| No. of positive lymph nodes | 2.15 ± 2.99 | 1.45 ± 2.32 | 0.323 |
| Nerve invasion | | | 0.524 |
| Yes | 20 | 26 | |
| No | 6 | 5 | |
| Vessel carcinoma embolus | | | 0.432 |
| Yes | 14 | 20 | |
| No | 12 | 11 | |
| Invasive depth | | | 0.021 |
| T1 | 2 | 1 | |
| T2 | 0 | 1 | |
| T3 | 8 | 1 | |
| T4 | 16 | 28 | |
| Lymph node metastasis | | | 0.658 |
| N0 | 13 | 19 | |
| N1 | 9 | 9 | |
| N2 | 4 | 3 | |
| pTNM | | | |
| 0 | 0 | 1 | 0.339 |
| I | 1 | 0 | |
| II | 12 | 16 | |
| III | 11 | 14 | |
| IV | 2 | 0 | |
| Total operation time (min) | 135.12 ± 17.47 | 150.61 ± 26.01 | 0.01 |
| Laparoscopic procedure time (min) | 69.73 ± 15.13 | 84.81 ± 21.48 | 0.003 |
| Intraoperative blood loss (mL) | 48.46 ± 30.07 | 67.10 ± 87.88 | 0.309 |
| Exhaust time (d) | 3.81 ± 1.92 | 4.45 ± 1.15 | 0.123 |
| Liquid intake time (d) | 5.27 ± 1.87 | 4.81 ± 1.22 | 0.266 |
| Postoperative hospitalization (d) | 12.23 ± 2.23 | 11.29 ± 2.02 | 0.101 |

CMA: Cranial-medial mixed dominant approach; MA: Medial approach.

variation in the surgical trunk and its branches. Matsuda *et al*[4] proposed a cranial-to-caudal approach in 2015 and considered that it is easy to expose the pancreas and the root of the middle colic vessels and facilitate lymph node dissection along the surgical trunk for advanced right-sided colon cancer. Zou *et al*[11] proposed a caudal-to-cranial approach and showed that it was easier to enter the dorsal side of the fusion fascia of Toldt. These approaches all have some limitations. In clinical practice, based on the universal principle of embryonic development and fusion fascia theory, is there a more optimized surgical approach?

In recent years, the authors' team has proposed and practised the CMA to perform LRH with CME, with satisfactory results. Compared with the MA group, the CMA group had obvious advantages in the total operative duration, laparoscopic procedure duration and the number of lymph nodes dissected, while the intraoperative blood loss and the incidence of postoperative complications were basically the same between the two groups.

**Table 3 Comparison of complication rates between the two groups, *n* (%)**

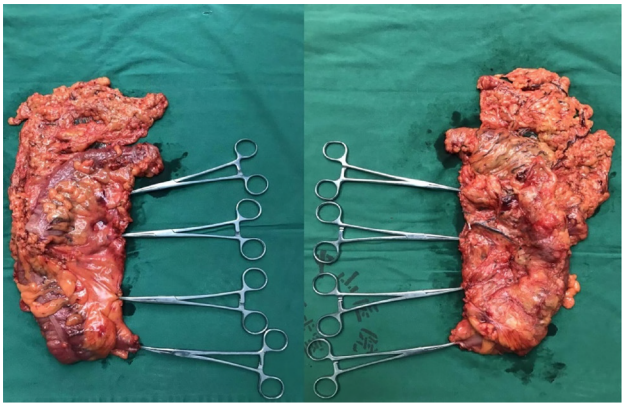
| Item | CMA group (*n* = 26) | MA group (*n* = 31) | *P* value |
|---|---|---|---|
| Complications | 6(23) | 4(13) | 0.486 |
| Anastomotic fistula | 0 | 0 | |
| Anastomotic stenosis | 0 | 0 | |
| Bleeding | 0 | 1 | |
| Lymphatic fistula | 3 | 1 | |
| Ileus | 2 | 0 | |
| Incisional hernia | 0 | 1 | |
| Acute urine retention | 0 | 0 | |
| Incision infection prevention | 1 | 1 | |
| Intra-abdominal infection | 0 | 0 | |
| Pulmonary infection | 0 | 0 | |

CMA: Cranial-medial mixed dominant approach; MA: Medial approach.

The theoretical framework of the CMA is derived from four aspects. First, the fascia of the primitive gut (which develops into the mesogastrium, mesocolon, mesostenium, *etc.*) is continuous during embryonic development[25,26]. Second, during embryological development, the midgut loop rotates 270 counterclockwise around the primary SMA, and the greater omentum and transverse mesocolon overlay the frontal surface of the mesoduodenum[27-29]. The peritoneal membrane at the attachment site fuses and degenerates to form membranous connective tissue called the fusion fascia[29]. Third, the right fusion fascia of Toldt is divided into the posterior pancreatic fascia of Treitz dorsally and the anterior pancreatic fascia of Fredet ventrally at the second portion of the duodenum[13,17]. These fusion fascias are delineated by the posterior layer of the ascending mesocolon ventrally (the mesofascial interface) and by the prerenal fascia, representing the posterior parietal peritoneum covering the retroperitoneum (the retrofascial interface) dorsolaterally[28]. Finally, CME with CVL was defined as follows[4,13]: (1) Dissection between the right mesocolon and the retroperitoneum, following the embryological plane, the dorsal side of the fusion fascia of Toldt and the fusion fascia of Fredet (the retrofascial interface); (2) High ligation of ileocolic vessels, right colic vessels, and the right branches of middle colic vessels; and (3) Removal of a sufficient length of the colon.

In the CAP, after entering the omental bursa, we emphasized the anatomical function of the first cut of the ultrasonic knife and produced the bubble effect when dissecting the fusion fascia in the innermost area adjacent to the gastric antrum (Figure 2A). The bubble effect allows the "angel fair" to form and the surgical space to be confirmed; then, the fusion fascia of the dorsal leaf of the transverse mesocolon and the dorsal mesogastrium can be separated, easily exposing the surgical plane between the fusion fascia of Fredet and the visceral duodenal-pancreatic peritoneum and allowing entry. Garcia-Granero *et al*[14] indicated that the fusion fascia of Fredet should be removed completely. Mike and Kano[17,30] proposed that there are three fusion modes between the transverse mesocolon and mesoduodenum. That is, fusion between the ventral leaf of the transverse mesocolon and mesoduodenum, between the dorsal leaf of the transverse colon and mesoduodenum, and almost no fusion. We found that regardless of which mode was found, through the CAP, we could obtain a clear surgical plane and achieve a bloodless field.

The GCTH enters the SMV, dividing it into the distal "surgical trunk" and proximal "Henle's trunk area" (SAGCTH). The difficulty of LRH lies in the SAGCTH. Due to the anatomy of this region, the risk of injury to the SMV and perioperative bleeding is considered to be high. Causes of bleeding or injury include vascular variations in the GCTH[31-33], improper traction during the operation, and an uneven pancreatic surface. In most cases, the GCTH is close to the lower edge of the pancreas, joining the SMV at the uncinate process of the pancreas. The right gastroepiploic vein is near the upper edge of the pancreatic head, sometimes closely associated with the pancreas, and the signs are difficult to identify. The course of the SRCV is special in that it bridges the gap between the transverse mesocolon and the mesogastrium before it merges into the GCTH[34], and inappropriate tension needs to be avoided in dissection of the SRCV. How can this anatomical region be dissected under laparoscopy? We suggest that the SRCV can be used as a landmark, as its inflow mode is relatively constant[35]. By tracking the direction of SRCV inflow into the GCTH from the outermost side of the pancreatic head and performing ligation at its root, the risk of bleeding caused by anatomical relationships and improper techniques can be avoided. In addition, the dorsal side of the transverse mesocolon can be fully exposed at the lower edge of the uncinate process to overcome the obstacle of the visual field under the traditional MA.



**DOI:** 10.4240/wjgs.v14.i3.221 

**Figure 4 The specimen from the operation.**

In the MAP, we first incised the mesocolon in the ileocolic area approximately 3 cm below the projection of ileocolic vessels to the confluence of the SMV, where a natural depression with colour distinction (yellow–white junction), which is the boundary between the intestinal mesentery and the right mesocolon, can be seen under high-definition laparoscopy. Some experts[36] have called this site the "trijunction", *i.e.*, the fusion point of the mesocolon, the visceral peritoneum, and the intestinal mesentery. Through the incision of this trijunction, we can enter the posterior space of the colon (the dorsal side of the fusion fascia of Toldt) behind the whole ascending colon and ileocecal part and can gently anatomize the whole plane of the posterior space of the colon. There is some controversy about the ideal surgical plane for colon separation. Zhang *et al*[37] considered the right retrocolic space to be ideal but did not define the level of the surgical plane. The separation plane should be behind the fusion fascia of Toldt, that is, between the fusion fascia of Toldt and the deep layer of the posterior subperitoneal fascia, as suggested by Mike M[17,30]. Based on autopsy experience, Culligan *et al*[38] proposed the view that the retrocolic space can be divided into two planes, the mesofascial plane and the retrofascial plane. Shinohara[16] pointed out the A line and the B line. The A line runs along the plane of the ventral side of the fusion fascia of Toldt without cutting it open. It does not affect the degree of lymph node dissection, but in most cases, the fusion fascia of Toldt is cut open, and it is easier to enter and expand the plane along the B line (dorsal side of the fusion fascia of Toldt). Therefore, he recommended dissociating along the B line. Our understanding is that we entered the mesofascial plane following the A line and the retrofascial plane following the B line. Coffey *et al*[39] suggested that the origin and termination of fascial lymphatics should be determined to partly address this question. A previous study[40] found that the fusion fascia of Toldt may serve a barrier function, as rarely in colorectal cancer does one observe the spread of colon cancer through the fascia into the retroperitoneum. Even where the mesocolon has been directly involved, spread through the fascia is unusual. Therefore, we agree with Mike M that complete removal of the fusion fascia of Toldt is necessary.

Coffey *et al*[41] proposed that attention should be given to maintenance of the surgical plane during LRH to meet the requirements of CME. How should the right plane be maintained? Our clinical viewpoint and theoretical basis are as follows: (1) In the process of embryonic development, the peritoneum and mesentery at the attachment site fuse and degenerate to form a single sheet of connective tissue called the fusion fascia at the end of intestinal rotation (the fusion fascias of Toldt and Fredet)[42,43], and the inside of the fusion fascia cannot be dissected by definition. It is easy to enter and expand the surgical plane behind the ascending colon from the dorsal side of the fusion fascia of Toldt; (2) The medial border of the fusion fascia of Fredet is the SMV and GCTH[13]. A safe surgical plane with better exposure can be obtained by entering from the dorsal side of the fusion fascia of Fredet, which can reduce the risk of injury to this area and especially prevent tearing and thus bleeding of the SMV, which can lead to life-threatening complications[43]; and (3) Although Shinohara[16] suggested that separation from the ventral side of the fusion fascia does not affect lymph node dissection, there is no evidence-based medical evidence that this procedure can ensure the integrity of lymphatic dissection. More importantly, this method can easily lead to fascia fragmentation and residue. Our conclusion is that to achieve CME in right-sided colon surgery, complete resection of the fusion fascias of Toldt and Fredet is necessary. How do we judge whether we entered the ventral side of the fusion fascia of Toldt under laparoscopy? First, the plane covered by the smooth, deep subperitoneal fascia (Gerota fascia) can be seen in the operation field, the reproductive vessels and peristaltic ureter can be seen behind this fascia, and the white line of Toldt can be seen faintly laterally. Second, a thin layer of relatively dense connective tissue membrane can be seen below the duodenum when the plane is expanded cephalad, and the duodenal wall can be seen vaguely behind this membrane. Third, the whole dissection process is bloodless. Bleeding indicates entry of the incorrect plane.

Where is the core anatomical area in the rendezvous process of the surgical plane of the CAP and MAP? Matsuda *et al*[10,44] noted that lymph node dissection around the middle colic vessels is technically demanding. The difficulty comes from the fusion of the transverse mesocolon in the middle colic vessel region with the greater omentum, pancreas and duodenum during embryonic development, forming a complex three-dimensional anatomical structure (Figure 2J). A substantial mesenteric tissue mass occurs at the root of the middle colic vessel region formed by midgut rotation during embryonic development. Although the fascia is contiguous, it is interrupted at points where vessels enter or leave the mesentery[39]. The position of the points is the edge of the envelope structure of the mesocolon. There is concentrated lymphatic flow and complex vascular variation at the lower edge of the uncinate process of the pancreas and the root of middle colic vessels[15,45-47]. Therefore, in LRH with CME, the dissection of the mesenteric area at the root of the middle colic vessels is the core anatomical area of the whole operation, and a simple approach such as the MA is difficult to complete. Under the CMA, we treated the cephalic part of the mesocolon of the middle colic vessel region first in the CAP, fully exposed the surgical plane behind the anterior pancreatic fascia to avoid pancreatic injury and safely exposed the GCTH and its branches; we exposed the mesenteric inner and lower boundaries of the SAGCTH and middle colic vessel region; and then we treated the caudal part of the middle colic vessel region to reach the rendezvous region of the surgical plane. Therefore, the mesentery in this area can be dissected in three dimensions to avoid residual mesenteric tissue, pancreatic injury, and injury to vessels such as the GCTH, which may lead to serious intraoperative bleeding.

Different researchers have different understandings of membrane anatomy but achieve the same result by different methods. Mike and Kano[17] have suggested that the membrane is continuous and that the membrane plane is continuous. Zhao *et al*[48] proposed the concept of a "mesenteric window". After incising the inferior edge of the ileocolic vascular pedicle, we could easily enter the natural right retrocolic space and extend the space laterally and cranially. Shinohara[16] affirmed that the SRCV and its confluence with the GCTH constituted the rotation centre of the mesocolon during embryonic development. Coffey *et al*[39] considered that the central mechanism of fixation of the mesocolon and posterior abdominal wall, that is, the connection point of the mesentery and blood vessels, constitutes the "hilum" of the mesentery, which determines the medial boundary of dissection, just as right peritoneal reflection (the white line of Toldt) determines the lateral boundary. Garcia-Granero *et al*[14] found that the medial limit of the fascia of Fredet is represented by the SMV and GCTH, which is also the hilum of the mesocolon. The above research results strongly promote the accuracy of surgery in LRH. According to our understanding, the right mesocolon is fan-shaped, and the SMV axis is the core anatomical marker of the right mesocolon, which connects the mesenteric window and hilum. These two landmarks are the result of fusion of the gastrointestinal mesentery after rotation during embryonic development and are also the important theoretical basis of membrane anatomy for the CMA.

Although this study discusses the surgical approach, the ultimate pursuit of the surgeon is oncological benefits for the patient. An early study by West *et al*[49] suggested that attention should be given to the quality classification of surgical specimens in the surgical treatment of colon cancer, as colon cancer patients who undergo resection with an intact mesocolon achieve 15% better 5-year overall survival than those with defects in the mesocolic specimens. Xie *et al*[50] recommended that in gastrointestinal surgery, the mesentery should be removed completely to prevent cancer leakage. Benz *et al*[51] proposed a new classification system for CME in right-sided colon cancer, with the following distribution: type 0 (best), type I, type II, and type III (poorest). In type 0, the true CME specimen, the stalks of the ileocolic vessels and middle colic vessels are connected by tissue of the surgical trunk (lymphatic tissue package covering the SMV), and the mesocolic window has a complete medial frame of mesocolic tissue. Bertelsen *et al*[52] recently reported five-year outcomes for right-sided colon cancer across the capital region, demonstrating a significant reduction in recurrence in the CME group (9.7% *vs* 17.9%) and the potential for improved long-term outcomes after the resection of all UICC stage I-III right-sided colon adenocarcinomas. The original intention of presenting the CMA was to standardize the surgical procedure and to obtain better specimen quality.

## CONCLUSION

The CMA is based on the theory of embryonic development and membrane anatomy, and the technical route itself weakens the vascular and lymphoid anatomy. The unique advantages of LRH with the CMA are as follows: (1) The team learning curve can be significantly shortened; (2) The operation can be performed with little to no bleeding, with a reduced probability of conversion to laparotomy and improved safety and efficiency; and (3) Higher-quality specimens can be obtained. Therefore, we believe that the CMA is the dominant approach for laparoscopic radical resection of the right colon. However, the CMA currently lacks RCT-based evidence and needs to be validated in further multicentre prospective studies.

## ARTICLE HIGHLIGHTS

### *Research background*

Complete mesocolic excision (CME) with central vascular ligation (CVL) is the technical standard for colon cancer surgery. How to achieve CME with CVL in laparoscopic right hemicolectomy (LRH) is controversial. Several approaches have been proposed, but a unified standard approach is not yet available.

### *Research motivation*

The authors' team has proposed and practised the cranial-medial mixed dominant approach (CMA) to perform LRH with CME for years. We would like to confirm that the CMA does have unique technical advantages through data rather than subjective opinionssby comparing it with the classic medial approach (MA).

### *Research objectives*

To compare the CMA with the classic MA to prove that the CMA has unique advantages in performing LRH.

### *Research methods*

We compared the two groups (CMA and MA) by intraoperative data (operative duration, blood loss, specimen length, number of resected and positive lymph nodes, and postoperative data (exhaust time, liquid intake time, postoperative hospitalization, postoperative complications). Additionally, we described the procedure and technical points of the CMA in detail to facilitate the reader's understanding.

### *Research results*

There were no significant differences in baseline data or the number of positive lymph nodes, intraoperative blood loss, postoperative exhaust time, feeding time, postoperative hospital stay or postoperative complication incidence between the two groups. The operation was shorter and the number of lymph nodes dissected was higher in the CMA group.

### *Research conclusions*

The CMA weakens the vascular and lymphoid anatomy and has unique advantages for LRH with CME and CVL.

### *Research perspectives*

More RCT-based evidence and further multicentre prospective studies are needed to validate the CMA.

## FOOTNOTES

**Author contributions:** Lin L and Yuan SB designed, performed the research study, contributed new reagents and analytic tools and wrote the manuscript; Lin L and Guo H analyzed the data; all authors have read and approve the final manuscript.

**Institutional review board statement:** The study was reviewed and approved by the scientific research sub-committee of the medical ethics committee Institutional Review Board of Zhongshan Hospital Affiliatedto Xiamen University (Approval No. xmzsyyky-2021-159).

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** There are no conflict of interest.

**Data sharing statement:** The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

**STROBE statement:** The authors have read the STROBE Statement checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

**Country/Territory of origin:** China

**ORCID number:** Li Lin 0000-0002-8961-2462; Si-Bo Yuan 0000-0003-0276-1463; Huan Guo 0000-0002-6766-0690.

**S-Editor:** Wang LL
**L-Editor:** A
**P-Editor:** Li X

## REFERENCES

1 **Heald RJ**. The 'Holy Plane' of rectal surgery. *J R Soc Med* 1988; **81**: 503-508 [PMID: 3184105]
2 **Morino M**, Parini U, Giraudo G, Salval M, Brachet Contul R, Garrone C. Laparoscopic total mesorectal excision: a consecutive series of 100 patients. *Ann Surg* 2003; **237**: 335-342 [PMID: 12616116 DOI: 10.1097/01.Sla.0000055270.48242.D2]
3 **Jacobs M**, Verdeja JC, Goldstein HS. Minimally invasive colon resection (laparoscopic colectomy). *Surg Laparosc Endosc* 1991; **1**: 144-150 [PMID: 1688289]
4 **Hohenberger W**, Weber K, Matzel K, Papadopoulos T, Merkel S. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation--technical notes and outcome. *Colorectal Dis* 2009; **11**: 354-64; discussion 364 [PMID: 19016817 DOI: 10.1111/j.1463-1318.2008.01735.x]
5 **Gouvas N**, Agalianos C, Papaparaskeva K, Perrakis A, Hohenberger W, Xynos E. Surgery along the embryological planes for colon cancer: a systematic review of complete mesocolic excision. *Int J Colorectal Dis* 2016; **31**: 1577-1594 [PMID: 27469525 DOI: 10.1007/s00384-016-2626-2]
6 **West NP**, Hohenberger W, Weber K, Perrakis A, Finan PJ, Quirke P. Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. *J Clin Oncol* 2010; **28**: 272-278 [PMID: 19949013 DOI: 10.1200/jco.2009.24.1448]
7 **Benson AB 3rd**, Venook AP, Cederquist L, Chan E, Chen YJ, Cooper HS, Deming D, Engstrom PF, Enzinger PC, Fichera A, Grem JL, Grothey A, Hochster HS, Hoffe S, Hunt S, Kamel A, Kirilcuk N, Krishnamurthi S, Messersmith WA, Mulcahy MF, Murphy JD, Nurkin S, Saltz L, Sharma S, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Wu CS, Gregory KM, Freedman-Cass D. Colon Cancer, Version 1.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2017; **15**: 370-398 [PMID: 28275037 DOI: 10.6004/jnccn.2017.0036]
8 **Bertelsen CA**, Neuenschwander AU, Jansen JE, Kirkegaard-Klitbo A, Tenma JR, Wilhelmsen M, Rasmussen LA, Jepsen LV, Kristensen B, Gögenur I; Copenhagen Complete Mesocolic Excision Study (COMES); Danish Colorectal Cancer Group (DCCG). Short-term outcomes after complete mesocolic excision compared with 'conventional' colonic cancer surgery. *Br J Surg* 2016; **103**: 581-589 [PMID: 26780563 DOI: 10.1002/bjs.10083]
9 **Liang JT**, Lai HS, Lee PH. Laparoscopic medial-to-lateral approach for the curative resection of right-sided colon cancer. *Ann Surg Oncol* 2007; **14**: 1878-1879 [PMID: 17377832 DOI: 10.1245/s10434-006-9153-2]
10 **Matsuda T**, Iwasaki T, Mitsutsuji M, Hirata K, Maekawa Y, Tanaka T, Shimada E, Kakeji Y. Cranial-to-caudal approach for radical lymph node dissection along the surgical trunk in laparoscopic right hemicolectomy. *Surg Endosc* 2015; **29**: 1001 [PMID: 25135445 DOI: 10.1007/s00464-014-3761-x]
11 **Zou LN**, Lu XQ, Wan J. Techniques and Feasibility of the Caudal-to-Cranial Approach for Laparoscopic Right Colectomy With Complete Mesenteric Excision. *Dis Colon Rectum* 2017; **60**: e23-e24 [PMID: 28267015 DOI: 10.1097/dcr.0000000000000799]
12 **Topographique DE**. Anatomie humaine, descriptive et topographique. *Journal of the American Medical Association* 1925; **84**: 464-464 [DOI: 10.1001/jama.1925.02660320056035]
13 **Rouvière H**. Anatomie humaine, descriptive et topographique. Paris: Masson et cie, 1924
14 **Garcia-Granero A**, Pellino G, Frasson M, Fletcher-Sanfeliu D, Bonilla F, Sánchez-Guillén L, Domenech Dolz A, Primo Romaguera V, Sabater Ortí L, Martinez-Soriano F, Garcia-Granero E, Valverde-Navarro AA. The fusion fascia of Fredet: an important embryological landmark for complete mesocolic excision and D3-lymphadenectomy in right colon cancer. *Surg Endosc* 2019; **33**: 3842-3850 [PMID: 31140004 DOI: 10.1007/s00464-019-06869-w]
15 **García-Granero Á**, Sánchez-Guillén L, Fletcher-Sanfeliu D, Sancho-Muriel J, Alvarez-Sarrado E, Pellino G, Delgado-Moraleda JJ, Sabater Ortí L, Valverde-Navarro AA, Frasson M. Surgical anatomy of D3 lymphadenectomy in right colon cancer, gastrocolic trunk of Henle and surgical trunk of Gillot - a video vignette. *Colorectal Dis* 2018; **20**: 935-936 [PMID: 30059191 DOI: 10.1111/codi.14358]
16 **Ignjatovic D**, Spasojevic M, Stimec B. Can the gastrocolic trunk of Henle serve as an anatomical landmark in laparoscopic right colectomy? *Am J Surg* 2010; **199**: 249-254 [PMID: 19892315 DOI: 10.1016/j.amjsurg.2009.03.010]
17 **Mike M**, Kano N. Laparoscopic surgery for colon cancer: a review of the fascial composition of the abdominal cavity. *Surg Today* 2015; **45**: 129-139 [PMID: 24515451 DOI: 10.1007/s00595-014-0857-9]
18 **Slankamenac K**, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. *Ann Surg* 2013; **258**: 1-7 [PMID: 23728278 DOI: 10.1097/SLA.0b013e318296c732]
19 **van Bree SH**, Bemelman WA, Hollmann MW, Zwinderman AH, Matteoli G, El Temna S, The FO, Vlug MS, Bennink RJ, Boeckxstaens GE. Identification of clinical outcome measures for recovery of gastrointestinal motility in postoperative ileus. *Ann Surg* 2014; **259**: 708-714 [PMID: 23657087 DOI: 10.1097/SLA.0b013e318293ee55]
20 **Bertelsen CA**, Neuenschwander AU, Jansen JE, Wilhelmsen M, Kirkegaard-Klitbo A, Tenma JR, Bols B, Ingeholm P, Rasmussen LA, Jepsen LV, Iversen ER, Kristensen B, Gögenur I; Danish Colorectal Cancer Group. Disease-free survival

after complete mesocolic excision compared with conventional colon cancer surgery: a retrospective, population-based study. *Lancet Oncol* 2015; **16**: 161-168 [PMID: 25555421 DOI: 10.1016/s1470-2045(14)71168-4]

21 **Zurleni T**, Cassiano A, Gjoni E, Ballabio A, Serio G, Marzoli L, Zurleni F. Surgical and oncological outcomes after complete mesocolic excision in right-sided colon cancer compared with conventional surgery: a retrospective, single-institution study. *Int J Colorectal Dis* 2018; **33**: 1-8 [PMID: 29038964 DOI: 10.1007/s00384-017-2917-2]

22 **Wang C**, Gao Z, Shen K, Shen Z, Jiang K, Liang B, Yin M, Yang X, Wang S, Ye Y. Safety, quality and effect of complete mesocolic excision *vs* non-complete mesocolic excision in patients with colon cancer: a systemic review and meta-analysis. *Colorectal Dis* 2017; **19**: 962-972 [PMID: 28949060 DOI: 10.1111/codi.13900]

23 **Rutgers M**, Kahn J. Comparing standard laparoscopic hemicolectomy to CME radical right colectomy for patients with right sided colon cancer: a randomized controlled feasibility trial. *Eur J Surg Oncol* 2020; **46**: e15 [DOI: 10.1016/j.ejso.2019.11.460]

24 **Rotholtz NA**, Bun ME, Tessio M, Lencinas SM, Laporte M, Aued ML, Peczan CE, Mezzadri NA. Laparoscopic colectomy: medial *vs* lateral approach. *Surg Laparosc Endosc Percutan Tech* 2009; **19**: 43-47 [PMID: 19238066 DOI: 10.1097/SLE.0b013e31818e91f3]

25 **Coffey JC**, Dillon M, Sehgal R, Dockery P, Quondamatteo F, Walsh D, Walsh L. Mesenteric-Based Surgery Exploits Gastrointestinal, Peritoneal, Mesenteric and Fascial Continuity from Duodenojejunal Flexure to the Anorectal Junction--A Review. *Dig Surg* 2015; **32**: 291-300 [PMID: 26138509 DOI: 10.1159/000431365]

26 **Coffey JC**, O'Leary DP. The mesentery: structure, function, and role in disease. *Lancet Gastroenterol Hepatol* 2016; **1**: 238-247 [PMID: 28404096 DOI: 10.1016/s2468-1253(16)30026-7]

27 **Langman J**, Sadler TW. Langman's medical embryology. Philadelphia, PA: Lippincott Williams & Wilkins, 2004 [DOI: 10.1097/00006534-198801000-00024]

28 **Jeong YJ**, Cho BH, Kinugasa Y, Song CH, Hirai I, Kimura W, Fujimiya M, Murakami G. Fetal topohistology of the mesocolon transversum with special reference to fusion with other mesenteries and fasciae. *Clin Anat* 2009; **22**: 716-729 [PMID: 19644969 DOI: 10.1002/ca.20846]

29 **Shinohara H**, Kurahashi Y, Haruta S, Ishida Y, Sasako M. Universalization of the operative strategy by systematic mesogastric excision for stomach cancer with that for total mesorectal excision and complete mesocolic excision colorectal counterparts. *Ann Gastroenterol Surg* 2018; **2**: 28-36 [PMID: 29863126 DOI: 10.1002/ags3.12048]

30 **Mike M**. Laparoscopic right colectomy. Operative maneuvers based on the fascial composition in the embryological standpoint. In: Kano N. Laparoscopic colorectal cancer surgery operative maneuvers based on the fascial composition in the embryological standpoint. Tokyo: Lgaku-Shoin, 2012: 116-133

31 **Kuzu MA**, İsmail E, Çelik S, Şahin MF, Güner MA, Hohenberger W, Açar Hİ. Variations in the Vascular Anatomy of the Right Colon and Implications for Right-Sided Colon Surgery. *Dis Colon Rectum* 2017; **60**: 290-298 [PMID: 28177991 DOI: 10.1097/dcr.0000000000000777]

32 **Adamina M**, Manwaring ML, Park KJ, Delaney CP. Laparoscopic complete mesocolic excision for right colon cancer. *Surg Endosc* 2012; **26**: 2976-2980 [PMID: 22549374 DOI: 10.1007/s00464-012-2294-4]

33 **Voiglio EJ**, Boutillier du Retail C, Neidhardt JP, Caillot JL, Barale F, Mertens P. Gastrocolic vein. Definition and report of two cases of avulsion. *Surg Radiol Anat* 1998; **20**: 197-201 [PMID: 9706679 DOI: 10.1007/s00276-998-0197-9]

34 **Strey CW**, Wullstein C, Adamina M, Agha A, Aselmann H, Becker T, Grützmann R, Kneist W, Maak M, Mann B, Moesta KT, Runkel N, Schafmayer C, Türler A, Wedel T, Benz S. Laparoscopic right hemicolectomy with CME: standardization using the "critical view" concept. *Surg Endosc* 2018; **32**: 5021-5030 [PMID: 30324463 DOI: 10.1007/s00464-018-6267-0]

35 **Garcia-Granero A**, Sánchez-Guillén L, Frasson M, Sancho Muriel J, Alvarez Sarrado E, Fletcher-Sanfeliu D, Flor Lorente B, Pamies J, Corral Rubio J, Valverde Navarro AA, Martinez Soriano F, Garcia-Granero E. How to reduce the superior mesenteric vein bleeding risk during laparoscopic right hemicolectomy. *Int J Colorectal Dis* 2018; **33**: 235-239 [PMID: 29204697 DOI: 10.1007/s00384-017-2940-3]

36 **Xie D**, Yu C, Gao C, Osaiweran H, Hu J, Gong J. An Optimal Approach for Laparoscopic D3 lymphadenectomy Plus Complete Mesocolic Excision (D3+CME) for Right-Sided Colon Cancer. *Ann Surg Oncol* 2017; **24**: 1312-1313 [PMID: 27995452 DOI: 10.1245/s10434-016-5722-1]

37 **Zhang C**, Ding ZH, Yu HT, Yu J, Wang YN, Hu YF, Li GX. Retrocolic spaces: anatomy of the surgical planes in laparoscopic right hemicolectomy for cancer. *Am Surg* 2011; **77**: 1546-1552 [PMID: 22196672]

38 **Culligan K**, Walsh S, Dunne C, Walsh M, Ryan S, Quondamatteo F, Dockery P, Coffey JC. The mesocolon: a histological and electron microscopic characterization of the mesenteric attachment of the colon prior to and after surgical mobilization. *Ann Surg* 2014; **260**: 1048-1056 [PMID: 24441808 DOI: 10.1097/sla.0000000000000323]

39 **Coffey JC**, Lavery I, Sehgal R, Walsh D. Mesenteric principles of gastrointestinal surgery; basic and applied science. New York, NY: CRC Press, 2017

40 **Gao Z**, Ye Y, Zhang W, Shen D, Zhong Y, Jiang K, Yang X, Yin M, Liang B, Tian L, Wang S. An anatomical, histopathological, and molecular biological function study of the fascias posterior to the interperitoneal colon and its associated mesocolon: their relevance to colonic surgery. *J Anat* 2013; **223**: 123-132 [PMID: 23721400 DOI: 10.1111/joa.12066]

41 **Coffey JC**, Sehgal R, Culligan K, Dunne C, McGrath D, Lawes N, Walsh D. Terminology and nomenclature in colonic surgery: universal application of a rule-based approach derived from updates on mesenteric anatomy. *Tech Coloproctol* 2014; **18**: 789-794 [PMID: 24968936 DOI: 10.1007/s10151-014-1184-2]

42 Tobin CE. The renal fascia and its relation to the transversalis fascia. *Anatomical Record* 1944; **89**: 295-311 [DOI: 10.1002/ar.1090890304]

43 **Woodburne R**, Burkel W. The peritoneum. In: Woodburne R and Burkel W Essentials of human anatomy. New York: Oxford University Press, 1991: 436-446

44 **Matsuda T**, Sumi Y, Yamashita K, Hasegawa H, Yamamoto M, Matsuda Y, Kanaji S, Oshikiri T, Nakamura T, Suzuki S, Kakeji Y. Anatomy of the Transverse Mesocolon Based on Embryology for Laparoscopic Complete Mesocolic Excision of Right-Sided Colon Cancer. *Ann Surg Oncol* 2017; **24**: 3673 [PMID: 28871557 DOI: 10.1245/s10434-017-6070-5]

45 **Jin G**, Tuo H, Sugiyama M, Oki A, Abe N, Mori T, Masaki T, Atomi Y. Anatomic study of the superior right colic vein: its

relevance to pancreatic and colonic surgery. *Am J Surg* 2006; **191**: 100-103 [PMID: 16399115 DOI: 10.1016/j.amjsurg.2005.10.009]

46 **Yada H**, Sawai K, Taniguchi H, Hoshima M, Katoh M, Takahashi T. Analysis of vascular anatomy and lymph node metastases warrants radical segmental bowel resection for colon cancer. *World J Surg* 1997; **21**: 109-115 [PMID: 8943187 DOI: 10.1007/s002689900202]

47 **Yamaguchi S**, Kuroyanagi H, Milsom JW, Sim R, Shimada H. Venous anatomy of the right colon: precise structure of the major veins and gastrocolic trunk in 58 cadavers. *Dis Colon Rectum* 2002; **45**: 1337-1340 [PMID: 12394432 DOI: 10.1097/01.Dcr.0000027284.76452.84]

48 **Zhao LY**, Liu H, Wang YN, Deng HJ, Xue Q, Li GX. Techniques and feasibility of laparoscopic extended right hemicolectomy with D3 lymphadenectomy. *World J Gastroenterol* 2014; **20**: 10531-10536 [PMID: 25132772 DOI: 10.3748/wjg.v20.i30.10531]

49 **West NP**, Morris EJ, Rotimi O, Cairns A, Finan PJ, Quirke P. Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study. *Lancet Oncol* 2008; **9**: 857-865 [PMID: 18667357 DOI: 10.1016/s1470-2045(08)70181-5]

50 **Xie D**, Liu L, Osaiweran H, Yu C, Sheng F, Gao C, Hu J, Gong J. Detection and Characterization of Metastatic Cancer Cells in the Mesogastrium of Gastric Cancer Patients. *PLoS One* 2015; **10**: e0142970 [PMID: 26566136 DOI: 10.1371/journal.pone.0142970]

51 **Benz S**, Tannapfel A, Tam Y, Grünenwald A, Vollmer S, Stricker I. Proposal of a new classification system for complete mesocolic excison in right-sided colon cancer. *Tech Coloproctol* 2019; **23**: 251-257 [PMID: 30838463 DOI: 10.1007/s10151-019-01949-4]

52 **Bertelsen CA**, Neuenschwander AU, Jansen JE, Tenma JR, Wilhelmsen M, Kirkegaard-Klitbo A, Iversen ER, Bols B, Ingeholm P, Rasmussen LA, Jepsen LV, Born PW, Kristensen B, Kleif J. 5-year outcome after complete mesocolic excision for right-sided colon cancer: a population-based cohort study. *Lancet Oncol* 2019; **20**: 1556-1565 [PMID: 31526695 DOI: 10.1016/s1470-2045(19)30485-1]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 March 27; 14(3): 236-246

DOI: 10.4240/wjgs.v14.i3.236

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

# New common bile duct morphological subtypes: Risk predictors of common bile duct stone recurrence

Xu Ji, Zhuo Yang, Shu-Ren Ma, Wen Jia, Qian Zhao, Lu Xu, Ying Kan, Yang Cao, Yao Wang, Bao-Jun Fan

**Specialty type:** Gastroenterology and Hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Awai K, Japan; Thacoor A, United Kingdom

**Received:** November 1, 2021
**Peer-review started:** November 1, 2021
**First decision:** December 4, 2021
**Revised:** December 12, 2021
**Accepted:** March 6, 2022
**Article in press:** March 6, 2022
**Published online:** March 27, 2022

**Xu Ji, Zhuo Yang, Shu-Ren Ma, Wen Jia, Qian Zhao, Lu Xu, Ying Kan, Yang Cao, Yao Wang, Bao-Jun Fan,** Department of Digestive Endoscopy, General Hospital of Northern Theater Command, Shenyang 110840, Liaoning Province, China

**Xu Ji,** Postgraduate College, Dalian Medical University, Dalian 116044, Liaoning Province, China

**Corresponding author:** Zhuo Yang, MD, Chief Doctor, Department of Digestive Endoscopy, General Hospital of Northern Theater Command, No. 83 Wenhua Road, Shenyang 110840, Liaoning Province, China. yangzhuocy@163.com

## Abstract

***BACKGROUND***

Endoscopic retrograde cholangiopancreatography (ERCP) is the primary treatment for removing common bile duct (CBD) stones. The risk factors for CBD stone recurrence after ERCP have been discussed for many years. However, the influence of CBD morphology has never been noticed.

***AIM***

To evaluate CBD morphology and other predictors affecting CBD stone recurrence in average patients.

***METHODS***

A retrospective analysis of 502 CBD stone patients who underwent successful therapeutic ERCP for stone extraction at our centre from February 2020 to January 2021 was conducted. CBD morphology and other predictors affecting CBD stone recurrence were examined by univariate analysis and multivariate logistic regression analysis.

***RESULTS***

CBD morphology ($P < 0.01$), CBD diameter ≥ 1.5 cm [odds ratio (OR) = 2.20, 95%CI: 1.08-4.46, $P = 0.03$], and endoscopic biliary sphincterotomy with balloon dilation (ESBD) (OR = 0.35, 95%CI: 0.17-0.75, $P < 0.01$) are three independent risk factors for CBD stone recurrence. Furthermore, the recurrence rate of patients with the S type was 6.61-fold that of patients with the straight type (OR = 6.61, 95%CI: 2.61-16.77, $P < 0.01$). The recurrence rate of patients with the polyline type was 2.45-fold that of patients with the straight type (OR = 2.45, 95%CI: 1.14-5.26, $P = 0.02$). The recurrence rate of S type patients was 2.70-fold that of patients with

the polyline type (OR = 2.70, 95%CI: 1.08-6.73, $P$ = 0.03). Compared with no-ESBD, ESBD could decrease the risk of recurrence.

*CONCLUSION*

CBD diameter ≥ 1.5 cm and CBD morphology, especially S type and polyline type, were associated with increased recurrence of CBD stones. In addition, ESBD was related to decreased recurrence. Patients with these risk factors should undergo periodic surveillance and standard prophylactic therapy.

**Key Words:** Endoscopic retrograde cholangiopancreatography; Common bile duct stones; Recurrence; Common bile duct morphology; Risk factors



**Core Tip:** Endoscopic retrograde cholangiopancreatography (ERCP) is the primary treatment for removing common bile duct (CBD) stones. The risk factors for CBD stone recurrence after ERCP have been discussed for many years. However, the influence of CBD morphology has never been reported. We demonstrate that CBD morphology was an independent risk factor for CBD stone recurrence in patients. Furthermore, the S type and polyline type were associated with an increased risk of recurrent CBD stones. This information represents a new perspective by defining the shape of the common bile duct on cholangiograms, which could redefine the risk factors and models of recurrence and predict periodic follow-up.

**Citation:** Ji X, Yang Z, Ma SR, Jia W, Zhao Q, Xu L, Kan Y, Cao Y, Wang Y, Fan BJ. New common bile duct morphological subtypes: Risk predictors of common bile duct stone recurrence. *World J Gastrointest Surg* 2022; 14(3): 236-246

**URL:** https://www.wjgnet.com/1948-9366/full/v14/i3/236.htm

**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i3.236

## INTRODUCTION

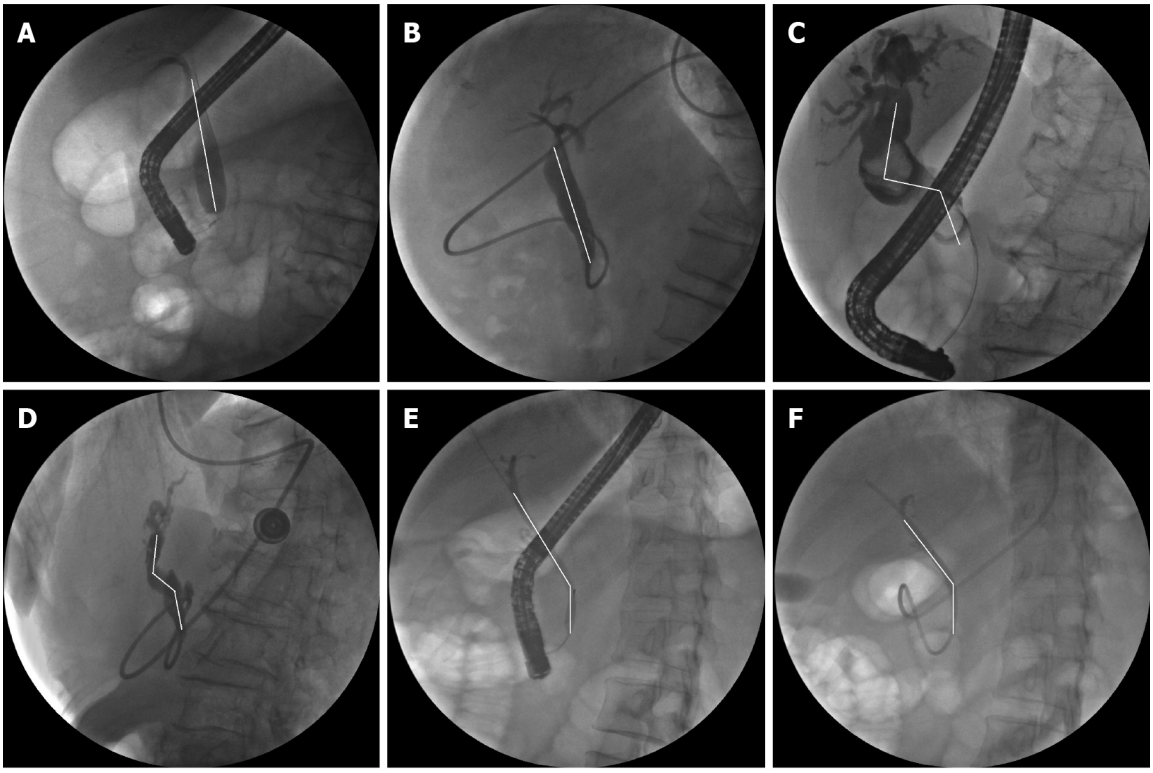
As a minimally invasive endoscopic procedure, endoscopic retrograde cholangiopancreatography (ERCP) is widely performed to treat common bile duct (CBD) stones. However, challenging problems, such as patients with gastrectomy who require multiple procedures and post ERCP complications, are typically encountered[1]. Choledocholithiasis recurrence is a long-term complication[2-5], and the recurrence rate after therapeutic ERCP was 2%-22% in the literature[6-9]. My previous studies reported that CBD morphology in Billroth II anatomy patients is an independent risk factor for CBD stone recurrence[10]. Therefore, we also aim to investigate CBD morphology in average patients with or without gastrectomy and clarify the association between CBD morphology and stone recurrence.

To date, there are a wide range of risk factors for recurrent CBD stones, and the most common predictors are operative related factors, such as age[11], periampullary diverticulum (PAD)[12,13], CBD diameter[14,15], CBD stone diameter[11,16], multiple CBD stones[12,17], endoscopic biliary sphincterotomy (EST)[11,16,18], endoscopic papillary balloon dilation (EPBD)[11], endoscopic papillary large balloon dilation (EPLBD)[19,20], EST with balloon dilation (ESBD)[15,21,22], cholecystectomy[23], gastrectomy[24,25], and CBD angulation[26-28]. However, there have been no reports concerning CBD morphology before my previous study. This is also the first study to report the best evidence regarding CBD morphology in average patients. In the present study, CBD morphology was defined as cholangiogram morphology from the confluence of the left and right hepatic ducts to the distal CBD entering the duodenum, including straight type, S type, and polyline type (Figure 1)[10].

## MATERIALS AND METHODS

### *Patients*

From February 2020 to January 2021, 790 patients underwent ERCP at the General Hospital of Northern Theater Command, and 502 patients were included in this study. The exclusion criteria were as follows: (1) patients with tumours of the duodenal papilla, CBD, liver, or gallbladder; (2) patients without specific stones during ERCP; (3) patients who had not removed their stones completely after the first ERCP; and (4) patients with incomplete data. Stone recurrence was defined as the presence of CBD stones at least 6 mo after previous CBD stones were completely removed by ERCP. At least two stone




**DOI:** 10.4240/wjgs.v14.i3.236 

**Figure 1 Common bile duct morphology on cholangiograms.** A, B: Straight type; C, D: S type; E, F: Polyline type.

recurrences were defined as multiple recurrences after the first ERCP[27]. Patients with CBD stones who visited our hospital were confirmed by abdominal computed tomography and ERCP.

### *ERCP procedure*

All endoscopists performed the ERCP procedures with at least 500 cases of experience. In our institution, prophylactic antibiotics are used in patients without evidence of cholangitis before ERCP. Firstly, the patient was sedated in the left lateral decubitus position. Endoscopists used a side-viewing duodenoscope or a forward-viewing gastroscope (Olympus Medical, Tokyo, Japan) entering the stomach. The first step was to perform the wire-guided biliary cannulation. Precut sphincterotomy or the double-wire technique can be prepared after biliary cannulation failed. As selective biliary cannulation was achieved, depending on CBD stones, the operator executed the therapeutic intervention, which included EST, ESBD, EPBD, and EPLBD. After the therapeutic intervention, the operator chose to remove stones with a retrieval balloon and/or a retrieval basket with or without mechanical lithotripsy. After CBD stone removal, an endoscopic nasobiliary drainage (ENBD) tube was placed in all patients to determine the complete clearance of CBD stones. After 3-5 d of observation, endoscopists confirmed that no residual stones were present and identified the CBD morphology again by cholangiography.

### *Parameter measurements on cholangiograms*

Assessed factors, such as the CBD morphology, the largest stone, and the diameter of the CBD, were measured with the patient placed in the left lateral decubitus position during the operation. Furthermore, cholangiography was performed to determine the CBD morphology and the clearance of CBD stones through an ENBD tube before the tube was removed. CBD morphology was identified by at least two experienced endoscopists with operative and postoperative cholangiograms. The definition of CBD morphology was cholangiogram morphology from the confluence of the left and right hepatic ducts to the distal CBD entering the duodenum. We classified the CBD morphology as follows: straight type, the CBD was straight without bending; S type, the CBD was S-shaped with two bends; and polyline type, the CBD had one bend.

### *Statistical analysis*

Statistical analyses were performed with SPSS 26.0. Univariate analysis was performed using Student's $t$ test, Fisher's exact test and $\chi^2$ test. Independent risk factors were analyzed by multivariate logistic regression analysis with a backwards likelihood ratio. A value of $P < 0.05$ was considered statistically significant.

## RESULTS

### Patient characteristics

A total of 502 patients with CBD stones were retrospectively identified from the collected database. The average follow-up was 19 mo. Among the 502 patients, recurrence was detected in 43 patients, and multiple recurrences were detected in 9 patients. The rates of recurrence and multiple recurrences were 8.6% (43/502) and 1.8% (9/502), respectively. No statistically significant differences in patient characteristics, such as sex, PAD, CBD diameter, largest CBD stone diameter ≥ 1.5 cm, CBD stone number ≥ 2, muddy stones, initial ampullary intervention (EST), cholecystectomy, and procedure time, were observed between the recurrence group and nonrecurrence groups (Table 1 and Table 2).

### Patient characteristics according to CBD morphology

As shown in Table 3, the presence of a CBD diameter ≥ 1.5 cm ($P$ = 0.01) differed significantly among different CBD morphologies and was detected in 96 (33.2%), 22 (48.9%), and 42 (25.0%) patients with straight type, S type, and polyline type, respectively. The proportion of patients with a CBD diameter ≥ 1.5 cm in the straight type group was the highest of all the groups. Other factors showed no significant difference.

### Patient characteristics according to multiple recurrences

Characteristics of patients with single recurrence and multiple recurrences are shown in Table 4. All factors were not related to multiple recurrences given that significant differences were noted ($P$ > 0.05). The results regarding PAD ($P$ = 0.06) and ESBD ($P$ = 0.07) were probably limited by the small sample size.

### Risk factors for CBD stone recurrence

In univariate analysis, age ≥ 70 years ($P$ = 0.01), CBD diameter ≥ 1.5 cm ($P$ < 0.01), EPBD/EPLBD ($P$ < 0.01), ESBD ($P$ < 0.01), gastrectomy ($P$ = 0.03), and CBD morphology ($P$ < 0.01) were significant factors for CBD stone recurrence.

Multicollinearity analysis showed all the results were VIF < 5, which represented no relationship among age ≥ 70 years, CBD diameter ≥ 1.5 cm, EPBD/EPLBD, ESBD, gastrectomy, and CBD morphology.

In multivariate analysis, CBD morphology ($P$ < 0.01), CBD diameter ≥ 1.5 cm [odds ratio (OR) = 2.20, 95%CI: 1.08-4.46, $P$ = 0.03], and ESBD (OR = 0.35, 95%CI: 0.17-0.75, $P$ < 0.01) were identified as independent risk factors. Moreover, the recurrence rate of patients with the S type was 6.61-fold that of patients with the straight type (OR = 6.61, 95%CI: 2.61-16.77, $P$ < 0.01). The recurrence rate of patients with the polyline type was 2.45-fold that of patients with the straight type (OR = 2.45, 95%CI: 1.14-5.26, $P$ = 0.02), and the recurrence rate of S type patients was 2.70-fold that of patients with the polyline type (OR = 2.70, 95%CI: 1.08-6.73, $P$ = 0.03) (Table 5).

## DISCUSSION

ERCP remains the primary choice to extract CBD stones given its minimally invasive nature. However, risk factors for recurrent CBD stones have not been thoroughly defined. In our previous study, we hypothesized that the altered anatomy that resulted from gastrectomy could affect the shape of the CBD. Therefore, we classified the CBD morphology into straight type, S type, and polyline type. The results showed that CBD morphology was related to CBD stone recurrence in gastrectomy patients[10]. As the present study shows, CBD morphology was also related to recurrence in patients without gastrectomy. This clinical observation assumed that the biliary system could undergo anatomic variations as it developed from the primitive midgut and was further changed by surgery, such as gastrectomy. The complexity of CBD development potentially influences its normal function[29,30].

The incidence of CBD stone recurrence in this study was 8.6% with a median 19-month follow-up, which is compatible with previous studies. In multivariate analysis, CBD morphology, CBD diameter ≥ 1.5 cm, and ESBD represent three independent risk factors. More specifically, the recurrence rate of patients with the S type was greater than that of patients with other types. As reported, bile stasis, duodenal-biliary reflux, and bacterial infection are essential factors in the pathogenesis of CBD stone recurrence[31,32]. Given the pathophysiology and the clinical significance of CBD morphology, we can assume the mechanism of recurrence caused by the S type and polyline type. First, a curved CBD is prone to bile stasis, which also predisposes patients to bacterial infection. Second, different shapes of the CBD enter the duodenum at different angles. S-type and polyline-type CBDs enter the duodenum at angles close to a right angle and are prone to intestinal fluid reflux. Duodenal-biliary reflux may cause changes in the bile duct loop and bacterial infection[33].

Our study demonstrated that a CBD diameter ≥ 1.5 cm was an independent risk factor for recurrence. However, the mechanism of CBD dilation is unclear. Some studies assumed that CBD dilation could

**Table 1 Patient characteristics**

| Characteristics | *n* (%) |
|---|---|
| Patients | 502 |
| Recurrence | 43 (8.6) |
| Multiple recurrences | 9 (1.8) |
| Male | 287 (57.2) |
| Age (mean ± SD, yr) | 65.2 ± 15.6 |
| Age  70 yr | 201 (40.0) |
| PAD | 243 (48.4) |
| CBD diameter (mean ± SD, cm) | 1.3 ± 0.7 |
| CBD diameter  1.5 cm | 160 (31.9) |
| Largest CBD stone diameter  1.5 cm | 83 (16.3) |
| CBD stone number  2 | 189 (37.6) |
| Muddy stones | 131 (26.1) |
| Initial ampullary intervention | |
| EST | 141 (28.1) |
| EPBD/EPLBD | 31 (6.2) |
| ESBD | 315 (62.7) |
| CBD morphology | |
| Straight type | 289 (57.6) |
| S type | 45 (9.0) |
| Polyline type | 168 (33.5) |
| Cholecystectomy | 26 (5.2) |
| Gastrectomy | 9 (1.8) |
| Procedure time (mean ± SD, min) | 20.0 ± 13.7 |

PAD: Periampullary diverticulum; CBD: Common bile duct; EST: Endoscopic biliary sphincterotomy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; ESBD: Endoscopic biliary sphincterotomy with balloon dilation.

lead to CBD stone formation[34-36]. The decreased hydrostatic force of bile and loss of normal CBD functional movement may predispose patients to stone reformation[37].

Some studies have shown that age ≥ 70 years is clinically significant for CBD stone recurrence[30,38]. However, this facto was significant in univariate analysis and insignificant in multivariate analysis in our study. Park *et al*[39] reported that cholecystectomy could be routinely recommended to prevent newly developed gallstones, but it should be considered carefully in patients ≥ 70 of age due to high surgical comorbidity. However, the differences in cholecystectomy were not statistically significant in our study, which was probably limited by the small sample size. Patients aged ≥ 70 years and without cholecystectomy were suggested to undergo careful follow-up for CBD stone recurrence.

Several studies have proposed that gastrectomy patients have an increased risk of cholelithiasis, and the incidence of CBD stones is 10%-25%[24,40-42]. However, gastrectomy did not reach a significant difference due to the small sample size in multivariate analysis. Sugiyama *et al*[43]. reported that patients with CBD stone recurrence were prone to subsequent recurrence. Our study showed that the subsequent recurrence rate in patients with recurrent CBD stones was greater than the CBD stone recurrence rate (20.9% *vs* 8.6%). However, significant differences between single recurrence and multiple recurrences were not observed in our study.

EST, EPLBD, EPBD, and ESBD are important ERCP techniques for stone removal. Dong *et al*[44] conducted a meta-analysis to demonstrate that ESBD exhibited better efficacy and fewer early complications than EST. Another network meta-analysis showed that pancreatitis among ESBD, EPBD and EST did not reach a statistically significant difference. The risk of bleeding in ESBD and EST was higher than that in EPBD[45]. However, neither of them investigated the influence of initial ampullary interventions on recurrent CBD stones. Furthermore, several studies reported that different interventions were unrelated to CBD stone recurrence[30,46,47]. However, our study presented the result that ESBD was an

**Table 2 Patient characteristics of patients with and without common bile duct stone recurrence, *n* (%)**

| Characteristics | Recurrence (*n* = 43) | Nonrecurrence (*n* = 459) | *P* value |
|---|---|---|---|
| Sex (male/female) | 23/20 | 264/195 | 0.61 |
| Age ≥ 70 yr | 25 (58.1) | 176 (38.3) | 0.01 |
| PAD | 23 (53.5) | 220 (47.9) | 0.49 |
| CBD diameter (mean ± SD, cm) | 1.5 ± 0.5 | 1.3 ± 0.7 | 0.06 |
| CBD diameter ≥ 1.5 cm | 23 (53.5) | 137 (29.8) | < 0.01 |
| Largest CBD stone diameter ≥ 1.5 cm | 11 (25.6) | 71 (15.5) | 0.09 |
| CBD stone number ≥ 2 | 15 (34.9) | 174 (37.9) | 0.70 |
| Muddy stones | 12 (27.9) | 119 (25.9) | 0.78 |
| Initial ampullary intervention | | | |
| EST | 13 (30.2) | 128 (27.9) | 0.74 |
| EPBD/EPLBD | 9 (20.9) | 22 (4.8) | < 0.01 |
| ESBD | 17 (39.5) | 298 (64.9) | < 0.01 |
| CBD morphology | | | < 0.01 |
| Straight type | 14 (32.6) | 275 (59.9) | |
| S type | 11 (25.6) | 34 (7.4) | |
| Polyline type | 18 (41.9) | 150 (32.7) | |
| Cholecystectomy | 5 (11.6) | 21 (4.6) | 0.06 |
| Procedure time (mean ± SD, min) | 19.3 ± 14.2 | 20.1 ± 13.6 | 0.71 |
| Gastrectomy | 3 (7.0) | 6 (1.3) | 0.03 |

PAD: Periampullary diverticulum; CBD: Common bile duct; EST: Endoscopic biliary sphincterotomy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; ESBD: Endoscopic biliary sphincterotomy with balloon dilation.

independent risk factor for stone recurrence. Compared with no-ESBD, ESBD decreased the risk of recurrence.

In some studies, the potential contributors influencing ERCP technical difficulty have included the size and number of CBD stones, tapering distal CBD, and the distal CBD arm and angulation[48-50]. However, CBD morphology has never been defined as an independent risk factor for technical difficulty. Prospective and multicentric clinical trials should be conducted to explore the influence of CBD morphology on the ERCP process. Information on CBD morphology should be reported by endoscopists to predict the efficacy of certain devices and therapeutic interventions for CBD stone removal by ERCP and to achieve complete stone clearance.

Ando *et al*[6] and Cheon *et al*[51] recommended specific periodic follow-up after therapeutic ERCP, but these authors were not focused on CBD morphology. The exploration of CBD morphology leads to an accurate understanding of potential contributors to recurrent CBD stones. Comprehensive risk factors and a model could provide specific guidance for endoscopists and patients.

To date, our research is the first to evaluate CBD morphology as a risk factor for CBD stone recurrence in average patients. By comparing operative cholangiograms and postoperative ENBD cholangiograms, our study implied that pulling the duodenoscope during the operation could affect CBD angulation and CBD morphology. Therefore, we identified CBD morphology using postoperative ENBD cholangiograms to eliminate bias. During cholangiography, patients were all placed in the left lateral decubitus position. Postoperative cholangiography with ENBD could improve the accuracy of CBD morphology assessment and determine the clearance of CBD stones.

There are several limitations to this study. First, this study was retrospective. Second, we did not evaluate stone components, and this information might have clinical significance for stone recurrence. Third, the follow-up period was short, and a prospective study with a long follow-up could be performed to explore CBD stone recurrence in the future.

**Table 3 Patient characteristics of patients with different common bile duct morphologies, *n* (%)**

| Characteristics | Straight type (*n* = 289) | S type (*n* = 45) | Polyline type (*n* = 168) | *P* value |
|---|---|---|---|---|
| Sex (male/female) | 166/123 | 30/15 | 91/77 | 0.32 |
| Age ≥ 70 yr | 104 (36.0) | 20 (44.4) | 77 (45.8) | 0.10 |
| PAD | 136 (47.1) | 20 (44.4) | 87 (51.8) | 0.53 |
| CBD diameter (mean ± SD, cm) | 1.3 ± 0.4 | 1.5 ± 0.5 | 1.4 ± 0.9 | 0.14 |
| CBD diameter ≥ 1.5 cm | 96 (33.2) | 22 (48.9) | 42 (25.0) | 0.01 |
| Largest CBD stone diameter ≥ 1.5 cm | 42 (14.5) | 8 (17.8) | 32 (19.0) | 0.44 |
| CBD stone number ≥ 2 | 105 (36.3) | 17 (37.8) | 67 (39.9) | 0.75 |
| Muddy stones | 78 (27.0) | 11 (24.4) | 42 (25.0) | 0.87 |
| Initial ampullary intervention | | | | |
| EST | 84 (29.1) | 11 (24.4) | 46 (27.4) | 0.79 |
| EPBD/EPLBD | 18 (6.2) | 3 (6.7) | 10 (6.0) | 0.98 |
| ESBD | 180 (62.3) | 30 (66.7) | 105 (62.5) | 0.85 |
| Cholecystectomy | 19 (6.6) | 2 (4.4) | 5 (3.0) | 0.24 |
| Procedure time (mean ± SD, min) | 19.8 ± 11.7 | 19.7 ± 13.1 | 20.6 ± 16.7 | 0.81 |
| Gastrectomy | 5 (1.7) | 0 (0.0) | 4 (2.4) | 0.38 |

PAD: Periampullary diverticulum; CBD: Common bile duct; EST: Endoscopic biliary sphincterotomy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; ESBD: Endoscopic biliary sphincterotomy with balloon dilation.

**Table 4 Characteristics of patients with single recurrence and multiple recurrences, *n* (%)**

| Characteristics | Single recurrence (*n* = 34) | Multiple recurrences (*n* = 9) | *P* value |
|---|---|---|---|
| Sex (male/female) | 19/15 | 4/5 | 0.71 |
| Age (mean ± SD, yr) | 71.3 ± 13.7 | 68.6 ± 12.2 | 0.59 |
| Age ≥ 70 yr | 21 (61.8) | 4 (44.4) | 0.46 |
| PAD | 21 (61.8) | 2 (22.2) | 0.06 |
| CBD diameter (mean ± SD, cm) | 1.5 ± 0.5 | 1.6 ± 0.6 | 0.43 |
| CBD diameter ≥ 1.5 cm | 18 (52.9) | 5 (55.6) | 1.00 |
| Largest CBD stone diameter ≥ 1.5 cm | 10 (29.4) | 1 (11.1) | 0.41 |
| CBD stone number ≥ 2 | 12 (35.3) | 3 (33.3) | 1.00 |
| Muddy stones | 10 (29.4) | 2 (22.2) | 1.00 |
| Initial ampullary intervention | | | |
| EST | 10 (29.4) | 3 (33.3) | 1.00 |
| EPBD/EPLBD | 6 (17.6) | 3 (33.3) | 0.37 |
| ESBD | 16 (47.1) | 1 (11.1) | 0.07 |
| CBD morphology | | | 0.22 |
| straight type | 12 (35.3) | 2 (22.2) | |
| S type | 10 (29.4) | 1 (11.1) | |
| polyline type | 12 (35.3) | 6 (66.7) | |
| Cholecystectomy | 5 (14.7) | 0 (0.0) | 0.57 |
| Gastrectomy | 3 (8.8) | 0 (0.0) | 1.00 |
| Procedure time (mean ± SD, min) | 19.9 ± 15.7 | 17.0 ± 6.3 | 0.60 |

PAD: Periampullary diverticulum; CBD: Common bile duct; EST: Endoscopic biliary sphincterotomy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; ESBD: Endoscopic biliary sphincterotomy with balloon dilation.

**Table 5 Risk factors for common bile duct stone recurrence**

| Factor | B | OR (95%CI) | *P* value | B | OR (95%CI) | *P* value |
|---|---|---|---|---|---|---|
| Age ≥ 70yr | 0.69 | 1.99 (0.99-4.00) | 0.06 | | | |
| CBD diameter ≥ 1.5 cm | 0.79 | 2.20 (1.08-4.46) | 0.03 | | | |
| EPBD/EPLBD | 0.92 | 2.51 (0.89-7.06) | 0.08 | | | |
| ESBD | -1.04 | 0.35 (0.17-0.75) | < 0.01 | | | |
| Gastrectomy | 1.46 | 4.29 (0.84-21.83) | 0.08 | | | |
| CBD morphology | | | < 0.01 | | | < 0.01 |
| Straight type | | Reference | | -0.90 | 0.41 (0.19-0.88) | 0.02 |
| S type | 1.89 | 6.61 (2.61-16.77) | < 0.01 | 0.99 | 2.70 (1.08-6.73) | 0.03 |
| Polyline type | 0.90 | 2.45 (1.14-5.26) | 0.02 | | Reference | |

CBD: Common bile duct; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; ESBD: Endoscopic biliary sphincterotomy with balloon dilation; OR: Odds ratio.

## CONCLUSION

In conclusion, CBD morphology was a unique risk factor, and CBD morphology, CBD diameter ≥ 1.5 cm, and ESBD represent three independent risk factors. Further study is needed to reveal the mechanism, predict the procedure difficulty, and instruct the postoperative follow-up.

## ARTICLE HIGHLIGHTS

### *Research background*

Preventing recurrent common bile duct (CBD) stones is an indispensable study. However, the risk factors for CBD stone recurrence after Endoscopic retrograde cholangiopancreatography (ERCP) are unclear.

### *Research motivation*

The CBD on the cholangiogram is common in every ERCP operations. But CBD morphology has never been classified and discussed.

### *Research objectives*

The aim was to investigate the relationship between CBD morphology and recurrent CBD stones in patients after ERCP.

### *Research methods*

From February 2020 to January 2021, 502 patients after ERCP at our center were included in the retrospective case-control study. Univariate analysis and multivariate logistic regression analysis were performed to identify risk factors for CBD stone recurrence.

### *Research results*

CBD morphology, CBD diameter ≥ 1.5 cm, and endoscopic biliary sphincterotomy with balloon dilation (ESBD) are three independent risk factors for CBD stone recurrence. Furthermore, CBD diameter ≥ 1.5 cm could increase the risk of recurrence and ESBD could decrease the risk of recurrence.

### *Research conclusions*

Of the three CBD morphology, patients with the S type had the highest risk of recurrent CBD stones, followed by those with the polyline type and the lowest were the straight type.

### *Research perspectives*

A large-scale prospective study should be performed to verified patients with above risk factors could prevent recurrence with medical treatment, such as Ursodeoxycholic acid. And the surveillance period needs further research.

## ACKNOWLEDGEMENTS

The study was supported by the Digestive Endoscopy Centre at General Hospital of Northern Theater Command.

## FOOTNOTES

**Author contributions:** Ji X and Yang Z contributed to drafting the final manuscript; Ji X, Ma SR, Jia W, Zhao Q, Xu L, Ka Y, Cao Y, Wang Y, Fan BJ, Yang Z contributed to study design, data collection, statistical analysis, and reading and approving the final manuscript.

**Supported by** Key Research and Development Program of Liaoning Province, China, No. 2019JH2/10300026.

**Institutional review board statement:** The study was reviewed and approved by the General Hospital of Northern Theater Command Institutional Review Board [No. Y(2021)067].

**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

**Conflict-of-interest statement:** The authors disclose no conflicts.

**Data sharing statement:** No additional data are available.



**Country/Territory of origin:** China

**ORCID number:** Xu Ji 0000-0003-3174-3918; Zhuo Yang 0000-0001-8337-8380; Shu-Ren Ma 0000-0003-4966-2622; Wen Jia 0000-0002-5969-3695; Qian Zhao 0000-0002-5031-9656; Lu Xu 0000-0001-6179-9758; Ying Kan 0000-0001-6662-8798; Yang Cao 0000-0001-9963-326X; Yao Wang 0000-0002-1448-6254; Bao-Jun Fan 0000-0002-7065-0530.

**S-Editor:** Wang JL
**L-Editor:** A
**P-Editor:** Wang JL

## REFERENCES

1 **Fujita Y**, Iwasaki A, Sato T, Fujisawa T, Sekino Y, Hosono K, Matsuhashi N, Sakamaki K, Nakajima A, Kubota K. Feasibility of Endoscopic Papillary Large Balloon Dilation in Patients with Difficult Bile Duct Stones without Dilatation of the Lower Part of the Extrahepatic Bile Duct. *Gut Liver* 2017; **11**: 149-155 [PMID: 27538442 DOI: 10.5009/gnl15634]
2 **Faylona JM**, Qadir A, Chan AC, Lau JY, Chung SC. Small-bowel perforations related to endoscopic retrograde cholangiopancreatography (ERCP) in patients with Billroth II gastrectomy. *Endoscopy* 1999; **31**: 546-549 [PMID: 10533739 DOI: 10.1055/s-1999-61]
3 **Osnes M**, Rosseland AR, Aabakken L. Endoscopic retrograde cholangiography and endoscopic papillotomy in patients with a previous Billroth-II resection. *Gut* 1986; **27**: 1193-1198 [PMID: 3781333 DOI: 10.1136/gut.27.10.1193]
4 **Freeman ML**, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, Fennerty MB, Ryan ME, Shaw MJ, Lande JD, Pheley AM. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996; **335**: 909-918 [PMID: 8782497 DOI: 10.1056/nejm199609263351301]
5 **Shimatani M**, Matsushita M, Takaoka M, Koyabu M, Ikeura T, Kato K, Fukui T, Uchida K, Okazaki K. Effective "short" double-balloon enteroscope for diagnostic and therapeutic ERCP in patients with altered gastrointestinal anatomy: a large case series. *Endoscopy* 2009; **41**: 849-854 [PMID: 19750447 DOI: 10.1055/s-0029-1215108]
6 **Ando T**, Tsuyuguchi T, Okugawa T, Saito M, Ishihara T, Yamaguchi T, Saisho H. Risk factors for recurrent bile duct stones after endoscopic papillotomy. *Gut* 2003; **52**: 116-121 [PMID: 12477771 DOI: 10.1136/gut.52.1.116]

7 **Keizman D**, Ish Shalom M, Konikoff FM. Recurrent symptomatic common bile duct stones after endoscopic stone extraction in elderly patients. *Gastrointest Endosc* 2006; **64**: 60-65 [PMID: 16813804 DOI: 10.1016/j.gie.2006.01.022]

8 **Kim DI**, Kim MH, Lee SK, Seo DW, Choi WB, Lee SS, Park HJ, Joo YH, Yoo KS, Kim HJ, Min YI. Risk factors for recurrence of primary bile duct stones after endoscopic biliary sphincterotomy. *Gastrointest Endosc* 2001; **54**: 42-48 [PMID: 11427840 DOI: 10.1067/mge.2001.115335]

9 **Sugiyama M**, Atomi Y. Risk factors predictive of late complications after endoscopic sphincterotomy for bile duct stones: long-term (more than 10 years) follow-up study. *Am J Gastroenterol* 2002; **97**: 2763-2767 [PMID: 12425545 DOI: 10.1111/j.1572-0241.2002.07019.x]

10 **Ji X**, Jia W, Zhao Q, Wang Y, Ma SR, Xu L, Kan Y, Cao Y, Fan BJ, Yang Z. Common bile duct morphology is associated with recurrence of common bile duct stones in Billroth II anatomy patients. *World J Clin Cases* 2021; **9**: 7671-7681 [PMID: 34621818 DOI: 10.12998/wjcc.v9.i26.7671]

11 **Deng F**, Zhou M, Liu PP, Hong JB, Li GH, Zhou XJ, Chen YX. Causes associated with recurrent choledocholithiasis following therapeutic endoscopic retrograde cholangiopancreatography: A large sample sized retrospective study. *World J Clin Cases* 2019; **7**: 1028-1037 [PMID: 31123675 DOI: 10.12998/wjcc.v7.i9.1028]

12 **Oak JH**, Paik CN, Chung WC, Lee KM, Yang JM. Risk factors for recurrence of symptomatic common bile duct stones after cholecystectomy. *Gastroenterol Res Pract* 2012; **2012**: 417821 [PMID: 22991508 DOI: 10.1155/2012/417821]

13 **Kim MH**, Myung SJ, Seo DW, Lee SK, Kim YS, Lee MH, Yoo BM, Min MI. Association of periampullary diverticula with primary choledocholithiasis but not with secondary choledocholithiasis. *Endoscopy* 1998; **30**: 601-604 [PMID: 9826137 DOI: 10.1055/s-2007-1001363]

14 **Konstantakis C**, Triantos C, Theopistos V, Theocharis G, Maroulis I, Diamantopoulou G, Thomopoulos K. Recurrence of choledocholithiasis following endoscopic bile duct clearance: Long term results and factors associated with recurrent bile duct stones. *World J Gastrointest Endosc* 2017; **9**: 26-33 [PMID: 28101305 DOI: 10.4253/wjge.v9.i1.26]

15 **Paspatis GA**, Paraskeva K, Vardas E, Papastergiou V, Tavernaraki A, Fragaki M, Theodoropoulou A, Chlouverakis G. Long-term recurrence of bile duct stones after endoscopic papillary large balloon dilation with sphincterotomy: 4-year extended follow-up of a randomized trial. *Surg Endosc* 2017; **31**: 650-655 [PMID: 27317037 DOI: 10.1007/s00464-016-5012-9]

16 **Mu H**, Gao J, Kong Q, Jiang K, Wang C, Wang A, Zeng X, Li Y. Prognostic Factors and Postoperative Recurrence of Calculus Following Small-Incision Sphincterotomy with Papillary Balloon Dilation for the Treatment of Intractable Choledocholithiasis: A 72-Month Follow-Up Study. *Dig Dis Sci* 2015; **60**: 2144-2149 [PMID: 25875753 DOI: 10.1007/s10620-015-3559-2]

17 **Kato S**, Chinen K, Shinoura S, Kikuchi K. Predictors for bile duct stone recurrence after endoscopic extraction for naïve major duodenal papilla: A cohort study. *PLoS One* 2017; **12**: e0180536 [PMID: 28692706 DOI: 10.1371/journal.pone.0180536]

18 **Nzenza TC**, Al-Habbal Y, Guerra GR, Manolas S, Yong T, McQuillan T. Recurrent common bile duct stones as a late complication of endoscopic sphincterotomy. *BMC Gastroenterol* 2018; **18**: 39 [PMID: 29544453 DOI: 10.1186/s12876-018-0765-3]

19 **Zhao HC**, He L, Zhou DC, Geng XP, Pan FM. Meta-analysis comparison of endoscopic papillary balloon dilatation and endoscopic sphincteropapillotomy. *World J Gastroenterol* 2013; **19**: 3883-3891 [PMID: 23840129 DOI: 10.3748/wjg.v19.i24.3883]

20 **Kang DU**, Choi Y, Lee HS, Lee HJ, Park SH, Yang DH, Yoon SM, Kim KJ, Ye BD, Myung SJ, Yang SK, Kim JH, Byeon JS. Endoscopic and Clinical Factors Affecting the Prognosis of Colorectal Endoscopic Submucosal Dissection-Related Perforation. *Gut Liver* 2016; **10**: 420-428 [PMID: 26780090 DOI: 10.5009/gnl15252]

21 **Xu XD**, Chen B, Dai JJ, Qian JQ, Xu CF. Minor endoscopic sphincterotomy followed by large balloon dilation for large choledocholith treatment. *World J Gastroenterol* 2017; **23**: 5739-5745 [PMID: 28883699 DOI: 10.3748/wjg.v23.i31.5739]

22 **Guo SB**, Meng H, Duan ZJ, Li CY. Small sphincterotomy combined with endoscopic papillary large balloon dilation *vs* sphincterotomy alone for removal of common bile duct stones. *World J Gastroenterol* 2014; **20**: 17962-17969 [PMID: 25548495 DOI: 10.3748/wjg.v20.i47.17962]

23 **Manes G**, Paspatis G, Aabakken L, Anderloni A, Arvanitakis M, Ah-Soune P, Barthet M, Domagk D, Dumonceau JM, Gigot JF, Hritz I, Karamanolis G, Laghi A, Mariani A, Paraskeva K, Pohl J, Ponchon T, Swahn F, Ter Steege RWF, Tringali A, Vezakis A, Williams EJ, van Hooft JE. Endoscopic management of common bile duct stones: European Society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy* 2019; **51**: 472-491 [PMID: 30943551 DOI: 10.1055/a-0862-0346]

24 **Bove V**, Tringali A, Familiari P, Gigante G, Boškoski I, Perri V, Mutignani M, Costamagna G. ERCP in patients with prior Billroth II gastrectomy: report of 30 years' experience. *Endoscopy* 2015; **47**: 611-616 [PMID: 25730282 DOI: 10.1055/s-0034-1391567]

25 **Hashimoto M**, Imamura T, Tamura T, Koyama R, Koizumi Y, Makuuchi M, Matsuda M, Watanabe G. Treatment of biliary tract stones after gastrectomy in the era of laparoscopic cholecystectomy. *J Hepatobiliary Pancreat Sci* 2016; **23**: 703-707 [PMID: 27526946 DOI: 10.1002/jhbp.393]

26 **Strnad P**, von Figura G, Gruss R, Jareis KM, Stiehl A, Kulaksiz H. Oblique bile duct predisposes to the recurrence of bile duct stones. *PLoS One* 2013; **8**: e54601 [PMID: 23365676 DOI: 10.1371/journal.pone.0054601]

27 **Zhang R**, Luo H, Pan Y, Zhao L, Dong J, Liu Z, Wang X, Tao Q, Lu G, Guo X. Rate of duodenal-biliary reflux increases in patients with recurrent common bile duct stones: evidence from barium meal examination. *Gastrointest Endosc* 2015; **82**: 660-665 [PMID: 25952091 DOI: 10.1016/j.gie.2015.03.1908]

28 **Seo DB**, Bang BW, Jeong S, Lee DH, Park SG, Jeon YS, Lee JI, Lee JW. Does the bile duct angulation affect recurrence of choledocholithiasis? *World J Gastroenterol* 2011; **17**: 4118-4123 [PMID: 22039327 DOI: 10.3748/wjg.v17.i36.4118]

29 **Ando H**. Embryology of the biliary tract. *Dig Surg* 2010; **27**: 87-89 [PMID: 20551648 DOI: 10.1159/000286463]

30 **Choi SJ**, Yoon JH, Koh DH, Lee HL, Jun DW, Choi HS. Low insertion of cystic duct increases risk for common bile duct stone recurrence. *Surg Endosc* 2021 [PMID: 34031744 DOI: 10.1007/s00464-021-08563-2]

31 **Kullman E**, Borch K, Lindström E, Anséhn S, Ihse I, Anderberg B. Bacteremia following diagnostic and therapeutic

ERCP. *Gastrointest Endosc* 1992; **38**: 444-449 [PMID: 1511819 DOI: 10.1016/s0016-5107(92)70474-x]
32 **Leung JW**, Liu YL, Leung PS, Chan RC, Inciardi JF, Cheng AF. Expression of bacterial beta-glucuronidase in human bile: an *in vitro* study. *Gastrointest Endosc* 2001; **54**: 346-350 [PMID: 11522976 DOI: 10.1067/mge.2001.117546]
33 **Zhang Q**, Ye M, Su W, Chen Y, Lou Y, Yang J, Ma T, Chen W, Gao S, Que R, Zhang B, Li H, Bai X, Liang T. Sphincter of Oddi laxity alters bile duct microbiota and contributes to the recurrence of choledocholithiasis. *Ann Transl Med* 2020; **8**: 1383 [PMID: 33313128 DOI: 10.21037/atm-20-3295]
34 **Kim KH**, Rhu JH, Kim TN. Recurrence of bile duct stones after endoscopic papillary large balloon dilation combined with limited sphincterotomy: long-term follow-up study. *Gut Liver* 2012; **6**: 107-112 [PMID: 22375179 DOI: 10.5009/gnl.2012.6.1.107]
35 **Costamagna G**, Tringali A, Shah SK, Mutignani M, Zuccalà G, Perri V. Long-term follow-up of patients after endoscopic sphincterotomy for choledocholithiasis, and risk factors for recurrence. *Endoscopy* 2002; **34**: 273-279 [PMID: 11932781 DOI: 10.1055/s-2002-23632]
36 **Ohashi A**, Tamada K, Wada S, Hatanaka H, Tomiyama T, Tano S, Nakazawa K, Sugano K. Risk factors for recurrent bile duct stones after endoscopic papillary balloon dilation: long-term follow-up study. *Dig Endosc* 2009; **21**: 73-77 [PMID: 19691777 DOI: 10.1111/j.1443-1661.2009.00835.x]
37 **Zhou XD**, Chen QF, Zhang YY, Yu MJ, Zhong C, Liu ZJ, Li GH, Zhou XJ, Hong JB, Chen YX. Outcomes of endoscopic sphincterotomy *vs* open choledochotomy for common bile duct stones. *World J Gastroenterol* 2019; **25**: 485-497 [PMID: 30700944 DOI: 10.3748/wjg.v25.i4.485]
38 **Kim KY**, Han J, Kim HG, Kim BS, Jung JT, Kwon JG, Kim EY, Lee CH. Late Complications and Stone Recurrence Rates after Bile Duct Stone Removal by Endoscopic Sphincterotomy and Large Balloon Dilation are Similar to Those after Endoscopic Sphincterotomy Alone. *Clin Endosc* 2013; **46**: 637-642 [PMID: 24340257 DOI: 10.5946/ce.2013.46.6.637]
39 **Park BK**, Seo JH, Jeon HH, Choi JW, Won SY, Cho YS, Lee CK, Park H, Kim DW. A nationwide population-based study of common bile duct stone recurrence after endoscopic stone removal in Korea. *J Gastroenterol* 2018; **53**: 670-678 [PMID: 29192348 DOI: 10.1007/s00535-017-1419-x]
40 **Paik KH**, Lee JC, Kim HW, Kang J, Lee YS, Hwang JH, Ahn SH, Park DJ, Kim HH, Kim J. Risk Factors for Gallstone Formation in Resected Gastric Cancer Patients. *Medicine (Baltimore)* 2016; **95**: e3157 [PMID: 27082555 DOI: 10.1097/MD.0000000000003157]
41 **Hosouchi Y**, Nagamachi Y, Hara T. Evaluation of transverse colon interposition following total gastrectomy in patients with gastric carcinoma. *Oncol Rep* 1998; **5**: 87-98 [PMID: 9458300 DOI: 10.3892/or.5.1.87]
42 **Hauters P**, de Neve de Roden A, Pourbaix A, Aupaix F, Coumans P, Therasse G. Cholelithiasis: a serious complication after total gastrectomy. *Br J Surg* 1988; **75**: 899-900 [PMID: 3179669 DOI: 10.1002/bjs.1800750923]
43 **Sugiyama M**, Suzuki Y, Abe N, Masaki T, Mori T, Atomi Y. Endoscopic retreatment of recurrent choledocholithiasis after sphincterotomy. *Gut* 2004; **53**: 1856-1859 [PMID: 15542528 DOI: 10.1136/gut.2004.041020]
44 **Dong SQ**, Singh TP, Zhao Q, Li JJ, Wang HL. Sphincterotomy plus balloon dilation *vs* sphincterotomy alone for choledocholithiasis: a meta-analysis. *Endoscopy* 2019; **51**: 763-771 [PMID: 30786316 DOI: 10.1055/a-0848-8271]
45 **Park CH**, Jung JH, Nam E, Kim EH, Kim MG, Kim JH, Park SW. Comparative efficacy of various endoscopic techniques for the treatment of common bile duct stones: a network meta-analysis. *Gastrointest Endosc* 2018; **87**: 43-57.e10 [PMID: 28756105 DOI: 10.1016/j.gie.2017.07.038]
46 **Choe JW**, Kim SY, Lee DW, Hyun JJ, Ahn KR, Yoon I, Jung SW, Jung YK, Koo JS, Yim HJ, Lee SW. Incidence and risk factors for postoperative common bile duct stones in patients undergoing endoscopic extraction and subsequent cholecystectomy. *Gastrointest Endosc* 2021; **93**: 608-615 [PMID: 32598960 DOI: 10.1016/j.gie.2020.06.060]
47 **Chae MK**, Lee SH, Joo KR. Assessment of the possible risk factors for primary common bile duct stone recurrence after cholecystectomy. *Surg Endosc* 2021; **35**: 6497-6504 [PMID: 33201313 DOI: 10.1007/s00464-020-08143-w]
48 **Kim HJ**, Choi HS, Park JH, Park DI, Cho YK, Sohn CI, Jeon WK, Kim BI, Choi SH. Factors influencing the technical difficulty of endoscopic clearance of bile duct stones. *Gastrointest Endosc* 2007; **66**: 1154-1160 [PMID: 17945223 DOI: 10.1016/j.gie.2007.04.033]
49 **Huang L**, Lu X, Huang X, Zou X, Wu L, Zhou Z, Wu D, Tang D, Chen D, Wan X, Zhu Z, Deng T, Shen L, Liu J, Zhu Y, Gong D, Zhong Y, Liu F, Yu H. Intelligent difficulty scoring and assistance system for endoscopic extraction of common bile duct stones based on deep learning: multicenter study. *Endoscopy* 2021; **53**: 491-498 [PMID: 32838430 DOI: 10.1055/a-1244-5698]
50 **Park SJ**, Kim JH, Hwang JC, Kim HG, Lee DH, Jeong S, Cha SW, Cho YD, Kim HJ, Moon JH, Park SH, Itoi T, Isayama H, Kogure H, Lee SJ, Jung KT, Lee HS, Baron TH, Lee DK. Factors predictive of adverse events following endoscopic papillary large balloon dilation: results from a multicenter series. *Dig Dis Sci* 2013; **58**: 1100-1109 [PMID: 23225136 DOI: 10.1007/s10620-012-2494-8]
51 **Cheon YK**, Lehman GA. Identification of risk factors for stone recurrence after endoscopic treatment of bile duct stones. *Eur J Gastroenterol Hepatol* 2006; **18**: 461-464 [PMID: 16607138 DOI: 10.1097/00042737-200605000-00001]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 March 27; 14(3): 247-259

DOI: 10.4240/wjgs.v14.i3.247

ISSN 1948-9366 (online)

META-ANALYSIS

# Peroral endoscopic longer *vs* shorter esophageal myotomy for achalasia treatment: A systematic review and meta-analysis

Chun-Yan Weng, Cheng-Hai He, Ming-Yang Zhuang, Jing-Li Xu, Bin Lyu

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

**P-Reviewer:** Beraldo RF, Cabezuelo AS, Oda M

**Received:** September 27, 2021
**Peer-review started:** September 27, 2021
**First decision:** December 4, 2021
**Revised:** December 9, 2021
**Accepted:** February 16, 2022
**Article in press:** February 16, 2022
**Published online:** March 27, 2022

**Chun-Yan Weng,** Department of Gastroenterology, The First Clinical Medical College of Zhejiang Chinese Medical University, Hangzhou 310053, Zhejiang Province, China

**Cheng-Hai He,** Department of Gastroenterology, The Affiliated Hospital of Hangzhou Normal University, Hangzhou 310006, Zhejiang Province, China

**Ming-Yang Zhuang,** Internal Medicine of Chinese Medicine, The First Clinical Medical College of Zhejiang Chinese Medical University, Hangzhou 310053, Zhejiang Province, China

**Jing-Li Xu,** Department of Surgery, The First Clinical Medical College of Zhejiang Chinese Medical University, Hangzhou 310053, Zhejiang Province, China

**Bin Lyu,** Department of Gastroenterology, The First Affiliated Hospital of Zhejiang Chinese Medicine University, Hangzhou 310006, Zhejiang Province, China

**Corresponding author:** Bin Lyu, PhD, Professor, Department of Gastroenterology, The First Affiliated Hospital of Zhejiang Chinese Medicine University, No. 54 Youdian Road, Hangzhou 310006, Zhejiang Province, China. lvbin@medmail.com.cn

## Abstract

### *BACKGROUND*

Peroral endoscopic myotomy (POEM) has been demonstrated to be safe and effective in the treatment of achalasia. Longer myotomy is the standard POEM procedure for achalasia but when compared with shorter myotomy, its effectiveness is not as well known.

### *AIM*

To compare the clinical effectiveness of longer and shorter myotomy.

### *METHODS*

PubMed, EmBase, Cochrane Library, web of science and clinicaltrials.gov were queried for studies comparing shorter and longer POEM for achalasia treatment. The primary outcome was clinical success rate. Secondary outcomes comprised of operative time, adverse events (AEs) rate, gastroesophageal reflux disease (GERD) and procedure-related parameters. The Mantel-Haenszel fixed-effects model was primarily used for the analysis. Publication bias was assessed.

### *RESULTS*

Six studies were included in this analysis with a total of 514 participants. During the follow-up period of 1-28.7 mo, longer and shorter myotomy in treating

achalasia showed similar excellent effectiveness [overall clinical success (OR = 1, 95%CI: 0.46-2.17, $P$ = 1, $I^2$: 0%; subgroup of abstract (OR = 1.19, 95%CI: 0.38 to 3.73; $P$ = 0.76; $I^2$: 0%); subgroup of full text (OR = 0.86 95%CI: 0.30 to 2.49; $P$ = 0.78; $I^2$: 0%)]. Shorter myotomy had significantly reduced mean operative time compared with the longer procedure. There were no statistically significant differences in AEs rates, including GERD (overall OR = 1.21, 95%CI: 0.76-1.91; $P$ = 0.42; $I^2$: 9%; subgroup of abstract OR = 0.77, 95%CI: 0.40-1.47; $P$ = 0.43; $I^2$: 0%; subgroup of full text OR = 1.91, 95%CI: 0.98-3.75; $P$ = 0.06; $I^2$: 0%), hospital stay (overall MD = -0.07, 95%CI: -0.30 to 0.16; $P$ = 0.55; $I^2$: 24%; subgroup of abstract MD = 0.20, 95%CI: -0.25 to 0.65; $P$ = 0.39; $I^2$: 0; subgroup of full text MD = -0.16, 95%CI: -0.42 to 0.10; $P$ = 0.23; $I^2$: 42%), and major bleeding (overall OR = 1.25, 95%CI: 0.58-2.71; $P$ = 0.56; $I^2$: 0%) between the two procedures. These differences remained statistically non-significant in all sensitivity analyses.

***CONCLUSION***

POEM was effective in treating achalasia. Shorter and longer myotomy procedures provided similar therapeutic effects in terms of long-term effectiveness. In addition, shorter myotomy reduced the operative time.

**Key Words:** Endoscopy; Meta-analysis; Myotomy; Peroral endoscopic myotomy; Gastroesophageal reflux disease



**Core Tip:** We evaluated the peroral endoscopic longer *vs* shorter myotomy for achalasia treatment in our study. To our knowledge, this is the first meta-analysis aiming to compare longer and shorter myotomy during peroral endoscopic myotomy for the treatment of achalasia regarding clinical success, safety and procedure-related outcomes. Shorter and longer myotomy procedures showed similar therapeutic effects in terms of long-term effectiveness. In addition, shorter myotomy reduced the operative time.

**Citation:** Weng CY, He CH, Zhuang MY, Xu JL, Lyu B. Peroral endoscopic longer *vs* shorter esophageal myotomy for achalasia treatment: A systematic review and meta-analysis. *World J Gastrointest Surg* 2022; 14(3): 247-259
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i3/247.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i3.247

## INTRODUCTION

Achalasia is a rare esophageal motor disease with a prevalence of approximately 1 case/100000 adults. The pathophysiology of achalasia disorder involves incomplete relaxation of the lower esophageal sphincter (LES) and impaired esophageal peristalsis[1]. Its clinical manifestations comprise dysphagia, regurgitation, chest pain and weight loss. Currently, endoscopic botulinum toxin injection or pneumatic dilation and laparoscopic Heller myotomy (LHM) are used to treat achalasia[2]. Inoue and colleagues[3] carried out the first peroral endoscopic myotomy (POEM) surgery to treat 17 achalasia patients in 2010 with 100% technical success. POEM is a novel, minimally invasive therapeutic modality for achalasia and related disorders, which was first reported by Inoue *et al*[3] in 2010. Since then, POEM has been widely used in the treatment of achalasia in many studies and achieves excellent efficacy[4-7].

However, the technique of POEM has changed very little since its introduction[3]. During POEM, the variable extent of gastric myotomy and esophageal myotomy range from 2 cm to 3 cm and 6 cm to 10 cm, respectively. Meanwhile, previous studies have demonstrated the significance of the extent of the myotomy on the gastric side[8,9]. However, the clinical relevance of myotomy length on the esophagus remains unknown. Some researchers have also adopted shorter myotomy in POEM and achieved similar efficacy in recent years[10].

The existing literature lacks high-quality evidence to compare the clinical outcomes of short-length and long-length POEM for achalasia treatment. Furthermore, for shorter or longer myotomy in POEM, which is more effective remains unknown. In this study, we compared the two myotomy modalities based on clinical outcomes and the incidence of postoperative adverse events.

## MATERIALS AND METHODS

### Data source and search strategy

The present systematic review and meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed, EmBase, Web of Science, Cochrane Library and clinicaltrials.gov databases were searched for relevant studies published from January 2010 to October 2020, because POEM was first reported in humans in 2010[3]. The searching language of publications was restricted to English. The Medical Subject Headings (MESH) terms employed included Achalasia's, Esophageal OR Esophageal Achalasia's OR Cardiospasm OR Cardiospasms OR Achalasia OR Achalasia's OR Achalasia, Esophageal OR Megaesophagus OR Esophageal Achalasia AND POEM OR Peroral endoscopic myotomy OR esophageal myotomy OR Peroral endoscopic myotomy AND shorter OR longer OR modified. The reference lists of eligible articles were further assessed for additional studies of interest. Two investigators independently performed the search and data extraction, assessed the quality of the articles and the discrepancies were resolved by consensual discussion. The third investigator reviewed the extracted data. Discussion with senior authors solved any arising issues. Randomized clinical trials (RCTs) and retrospective studies were qualified for the search.

### Study selection

Article title and abstract eligibility screening was performed in an independent way by two investigators. Open-label double-blinded RCTs, as well as retrospective trials evaluating patients and comparing peroral endoscopic shorter and longer myotomy for the treatment of achalasia were included. Exclusion criteria were: (1) Experimental studies; (2) Publication language other than English; and (3) An editorial, a case report, a review or case series.

The data parameters obtained from each study were: (1) Trial features such as study design, sample size, follow-up duration and publication year; (2) Primary outcome, *i.e.* clinical success; and (3) Secondary outcomes, including (i) operative time, (ii) GERD (the main indicator was endoscopic reflux esophagitis), (iii) total number of adverse events (AEs) such as major bleeding, and (iv) procedure-related parameters.

### Quality assessment

The Cochrane "risk of bias" tool and the Newcastle-Ottawa Scale (NOS) were employed for assessing methodological quality of included studies[11]. Discrepancies between the two investigators were resolved by consensual discussion.

### Statistical analysis

Review Manager 5.3 (RevMan) was utilized to analyze the extracted data and determine odds ratios (ORs) and 95% confidence intervals (CIs). Heterogeneity was determined by inspection of forest plots, the Cochrane Q test, and the $I^2$ statistic. A Q test with $P<0.10$ was considered significant. According to the Cochrane Handbook for Systematic Reviews of Interventions (https://training.cochrane.org/handbook), $I^2$ values were categorized as: < 30%, low heterogeneity; 30%-50%, moderate heterogeneity; > 50%, substantial heterogeneity; > 75%, high heterogeneity.

## RESULTS

### Patient baseline features

Details of the selection process were outlined in Figure 1. Overall, 711 articles were initially selected. After ruling out duplicates, reviews, case series, irrelevant and nonstandard records, 6 studies were included which involved 3RCTs and 3 retrospective trials[12-17] and covered 545 patients. Their features are summarized in Table 1. The quality assessment of the studies was depicted in Figure 2. No significant differences were found in age, sex, American Society of Anesthesiologists (ASA) classification and previous interventions[18]. The detailed study quality evaluation items were presented in Table 2. Compared with the long myotomy (LM) group, the length of esophageal myotomy in the short myotomy (SM) group was significantly reduced. The total incision range of the LM group was 8-25 cm, including 6-20 cm on the esophagus and 2-5 cm on the stomach. For the SM group, the cut range was 3-7cm, including 2-6 cm on the esophagus and 1-3 cm on the stomach.

### Clinical success

All patients were followed up for clinical success rate and Eckardt score. Data on clinical success after POEM were available in six studies (Figure 3) [overall clinical success (OR = 1, 95%CI: 0.46-2.17, $P$ = 1, $I^2$: 0%; subgroup of abstract (OR = 1.19, 95%CI: 0.38 to 3.73; $P$ = 0.76; $I^2$: 0%); subgroup of full text (OR = 0.86 95%CI: 0.30 to 2.49; $P$ = 0.78; $I^2$: 0%)]. Therefore, clinical success of POEM showed no statistically significant difference between the two groups.

**Table 1 Articles' features**

| Ref. | Total sample | Sex, male/female, *n* | Age, yr | Symptoms duration, yr or mo | MBI | Classification, *n* (%) | Pre-ECK scores | LESP, mmHg | IRP, mmHg |
|---|---|---|---|---|---|---|---|---|---|
| Familiari *et al*[15], 2016 | LM: 38<br>SM: 35 | NA | NA | NA | NA | NA | NA | NA | NA |
| Gao *et al* [16], 2017 | LM: 53 | LM: 29/24; SM: 25/22 | LM: 37.83 ± 14.36 | LM: 5.23 ± 5.87 | LM: 19.76 ± 3.07 | NA | LM: 6.75 ± 1.86 | LM: 43.03 ± 13.73 | NA |
| | SM: 47 | | SM: 43.96 ± 11.69 | SM: 5.30 ± 4.87 | SM: 20.25 ± 2.97 | | SM: 6.34 ± 1.74 | SM: 41.93 ± 14.93 | |
| Gong *et al* [17], 2016 | LM: 59; SM: 38 | Female; LM: 29; SM: 19 | LM: 39.8 ± 12.4; SM: 41.5 ± 7.2 | LM: 6.5 ± 5.5; SM: 7.9 ± 4.3 | LM: 20.7 ± 2.6; SM: 20.1 ± 3.2 | ASAC I: LM: 47; SM: 29; II: LM: 11; SM: 7; III: LM: 1; SM: 2; CC I: LM: 21; SM: 12 II: LM: 38; SM: 26 | LM: 7.2 ± 2.4; SM: 6.8 ± 1.7 | LM: 42.1 ± 12.9; SM: 44.6 ± 13.2 | NA |
| Gu *et al* [14], 2020 | LM: 48; SM: 46 | LM: 23/25; SM: 21/25 | LM: 42.8 ± 10.2; SM: 43.6 ± 11.4 | LM: 4.1(0.3~31.0); SM: 5.0(0.3~34.0□ | NA | CC II: LM: 48; SM: 46 | LM: 7.1 ± 1.6; SM: 7.5 ± 1.5 | LM: 32.4 ± 5.3; SM: 33.5 ± 5.0 | LM: 21.5 ± 4.6; SM: 23.2 ± 4.8 |
| Huang *et al* [13], 2020 | LM: 74; SM: 36 | Female; LM: 34; SM: 17 | LM: 37.7 ± 13.0; SM: 40.8 ± 11.1 | LM: 8.9 ± 5.8; SM: 8.8 ± 5.5 | LM: 19.4 ± 3.1; SM: 20.3 ± 2.6 | ASAC I: LM: 58; SM: 33; II: LM: 15; SM: 2; III: LM: 1; SM: 1; CC I: LM: 26; SM: 12; II: LM: 48; SM: 24 | LM: 7.5 ± 1.9; SM: 7.1 ± 1.6 | LM: 39.8 ± 13.7; SM: 41.8 ± 14.3 | NA |
| Nabi *et al* [12],2020 | LM: 37; SM: 34 | LM: 24/13; SM: 18/16 | LM: 41.3 ± 14.4; SM: 40.1 ± 16.8 | LM: 3;SM: 3 | NA | ASAC I: LM: 13; SM: 12; II: LM: 24; SM: 22 | LM: 6.75 ± 1.32; SM: 6.02 ± 1.33 | NA | LM: 28.50 ± 11.01; SM: 26.40 ± 13.9 |

Data are presented as mean ± standard deviation or *n* (%). ASAC: American Society of Anesthesiologists classification; BMI: Body mass index; CC: Chicago classification; IRP: Integrated relaxation pressure; LESP: Lower esophagus sphincter pressure; LM: Long myotomy; NA: Not Applied; Pre-ECK scores: Preoperative- peroral endoscopic myotomy Eckardt scores; SM: Short myotomy.

Five studies presented pre-POEM Eckardt score as a quantitative variable. The score was 6.75 ± 1.86, 7.2 ± 2.4, 7.1 ± 1.6, 7.5 ± 1.9, 6.75 ± 1.32 in the LM group, respectively. In the SM group, the score was 6.34 ± 1.74, 6.8 ± 1.7, 7.5 ± 1.5, 7.1 ± 1.6 and 6.02 ± 1.33, respectively. Six studies provided postoperative Eckardt scores, which were also comparable between the LM and SM group. The postoperative Eckardt score in the LM group was 0.5 ± 0.8; 0.98 ± 1.14; 1.2 ± 1.2; 0.72 ± 0.42; 1.6 ± 1.3; 0.818 ± 0.983, respectively. Similarly, the score in the SM group was 0.5 ± 0.8; 1.06 ± 1.42; 1.0 ± 0.9; 0.76 ± 0.51; 1.3 ± 1.2 and 0.935 ± 0.929, respectively.

### *Procedure-related outcomes*

**Operative time:** Total procedure duration was available in all six articles including a total of 521 patients. The operative time in the LM group was 59.2 ± 16.7, 63.13 ± 26.50, 68.5 ± 23.2, 45.6 ± 16.2, 62.1 ± 25.2 and 72.43 ± 27.28, respectively. For the SM group, the time was 47.7 ± 13.2, 50.62 ± 20.02, 44.2 ± 16.3, 31.2 ± 15.3, 46.6 ± 18.5 and 44.03 ± 13.78, respectively. Obviously, the operative times in the SM group were shorter than that in the LM group (Figure 4).

**Length of myotomy:** A total of 3 RCTs and 2 retrospective studies involving 421 cases were meta-analyzed, with 180 cases in the SM group and 241 cases in the LM group. Myotomy length in POEM included the span of esophageal and gastric myotomy. The total length of myotomy in the LM group was 11.10 ± 2.0, 11.5 ± 3.1 and 11.7 ± 2.4 cm, respectively. Among them, the esophageal myotomy length was 8.42 ± 2.13, 8.2 ± 2.7, 10.14 ± 0.54, 7.97 ± 2.40 and 8.5 ± 2.6 cm, respectively, and the gastromyotomy length was 2.49 ± 0.70, 3.2 ± 1.4, 3.2 ± 1.2 and 2.84 ± 0.63 cm, respectively. The following myotomy values were obtained in the SM group of six studies: total length in three studies, 6.04 ± 0.69, 6.1 ± 0.5 and 6.0 ± 0.6 cm, respectively; esophageal length in five studies, 3.87 ± 0.61, 4.0 ± 0.9, 5.66 ± 0.14, 4.0 ± 0.7 and 2.76 ± 0.41 cm, respectively; and gastric length in four studies, 2.21 ± 0.41, 2.1 ± 0.3, 3.2 ± 1.2 and 2.70 ± 0.73 cm, respectively.

**Manometry outcomes:** Preoperative LES pressure in POEM was available in four articles with a total of 401 patients, and five articles including 450 individuals assessed postoperative LES pressure. The level of preoperative LES pressure in the LM group was 43.03 ± 13.73, 42.1 ± 12.9, 32.4 ± 5.3 and 39.8 ± 13.7 mmHg respectively, and the value was 41.93 ± 14.93, 44.6 ± 13.2, 33.5 ± 5.0 and 41.8 ± 14.3 mmHg,

**Table 2 The detailed study quality evaluation items**

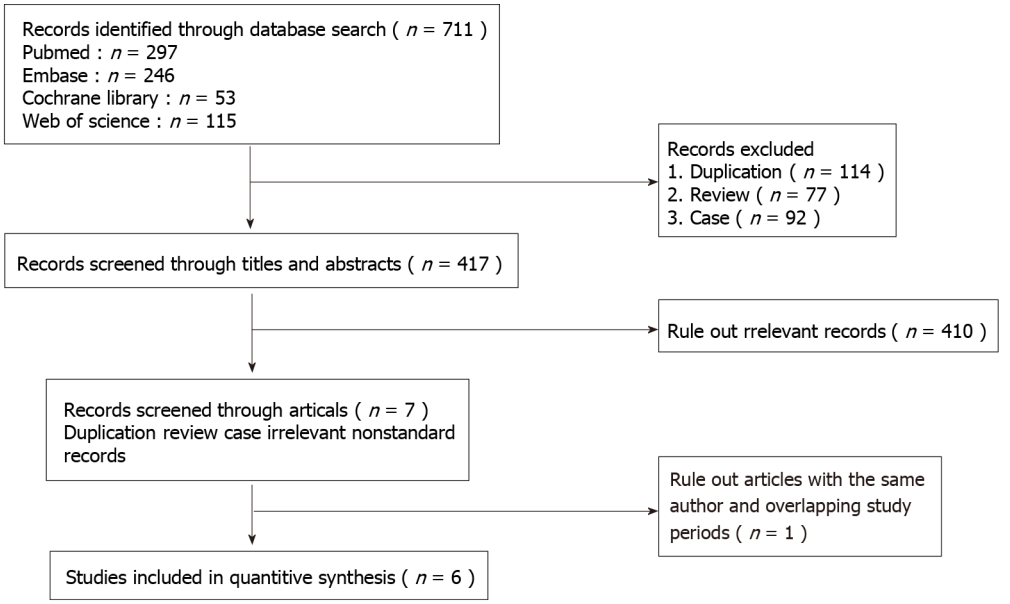
| Ref. | Follow-up sample | Length of the myotomy, cm | Operative time, min | Myotomy length, cm | Follow-up time, mo | Clinical success | GERD, % | LESP, mmHg | HRM, mmHg | Post-ECK scores | Adverse events |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Familiari *et al*[15], 2016 | LM: 23 SM: 26 | LM: 13 SM: 8 | LM: 59.2 ± 16.7 SM: 47.7 ± 13.2 | ES: LM: 8.42 ± 2.13 SM: 3.87 ± 0.61 ST: LM: 2.49 ± 0.70 SM: 2.21 ± 0.41 TO: LM: 10.94 ± 2.11 SM: 6.04 ± 0.69 | 8 | LM: 100% SM: 100% | LM: 42.9% SM: 65% | LM: 17 ± 9.7 SM: 11.4 ± 6.5 | LM: 8.6 ± 4.9 SM: 5.9 ± 5.0 | LM: 0.5 ± 0.8 SM: 0.5 ± 0.8 | No |
| Gao *et al*[16], 2017 | LM: 53 SM: 47 | LM: > 7 SM: ≤7 | LM: 63.13 ± 26.5 SM: 50.62 ± 20.02 | NA | 3,6,12 | LM: 96.2% SM: 93.6% | LM: 11.3% SM: 12.8% | LM: 16.51 ± 5.01 SM: 17.41 ± 3.69 | NA | LM: 0.98 ± 1.14 SM: 1.06 ± 1.42 | MB: LM: 0, SM: 0 MP: LM: 1; SM: 0 HS: LM: 10.19 ± 4.03 SM: 10.21 ± 3.78 |
| Gong *et al* [17], 2016 | LM: 59 SM: 38 | LM: > 7 SM: ≤7 | LM: 68.5 ± 23.2 SM: 44.2 ± 16.3 | ES: LM: 8.5 ± 2.6 SM: 4.0 ± 0.9 ST: LM: 3.2 ± 1.4 SM: 2.1+0.3 TO: LM: 11.7 ± 2.4 SM: 6.1 ± 0.5 | NA | LM: 91.5% SM: 92.1% | LM: 18.6% SM: 15.8% | LM: 19.3 ± 8.5 SM: 16.7 ± 4.3 | NA | LM: 1.2 ± 1.2 SM: 1.0 ± 0.9 | MB: LM: 3; SM: 2 MP: LM: 1; SM: 0 HS: LM: 6.6 ± 1.1 SM: 6.4 ± 1.2 |
| Gu *et al*[14], 2020 | LM: 48 SM: 46 | LM: 7-8 SM: 3-4 | LM: 45.6 ± 16.2 SM: 31.2 ± 15.3 | ES: LM: 10.14 ± 0.54 SM: 5.66 ± 0.14 | 1,3,6,12 | LM: 93.8% SM: 95.7% | LM: 22.9% SM: 15.2% | LM: 12.1 ± 3.9 SM: 11.8 ± 4.4 | LM: 9.7 ± 2.6 SM: 10.1 ± 2.4 | LM: 0.72 ± 0.42 SM: 0.76 ± 0.51 | HS: LM: 6: 5 ± 1.6 SM: 7.0 ± 0.9 |
| Huang *et al* [13], 2020 | LM: 74 SM: 36 | LM > 7 SM≤ 7 | LM: 62.1 ± 25.2 SM: 46.6 ± 18.5 | ES: LM: 8.2 ± 2.7 SM: 4.0 ± 0.7 ST: LM: 3.2 ± 1.2 SM: 3.2 ± 1.2 TO: LM: 11.5 ± 3.1 SM: 6.0 ± 0.6 | 28.7 | LM: 91.9% SM: 94.4% | LM: 14.9% SM: 8.3% | LM: 13.3 ± 5.7 SM: 15.9 ± 3.2 | NA | LM: 1.6 ± 1.3 SM: 1.3 ± 1.2 | MB: LM: 3; SM: 2 MP: LM: 1; SM: 0 HS: LM: 9.3 ± 2.9 SM: 9.9 ± 2.4 |
| Nabi *et al* [12], 2020 | LM: 37 SM: 34 | LM: ≥ 6 SM: ≤ 3 | LM: 72.43 ± 27.28 SM: 44.03 ± 13.78 | ES: LM: 7.97 ± 2.40 SM: 2.76 ± 0.41 ST: LM: 2.84 ± 0.63 SM: 2.70 ± 0.73 | 12 | LM: 96.97% SM: 93.55% | LM: 56.67%SM: 44.4% | NA | LM: 7.44 ± 4.30 SM: 8.60 ± 1.30 | LM: 0.818 ± 0.983 SM: 0.935 ± 0.929 | MB: LM: 17; SM: 12 HS: LM: 2.81 ± 0.70 SM: 2.82 ± 0.67 |

Data are presented as mean ± standard deviation or *n* (%). Eck: Eckardt score; ES: Esophageal; HS: Hospitalization, mean days; MB: Major bleeding; MP: Mucosal perforation; Post-ECK scores: Postoperative- peroral endoscopic myotomy Eckardt scores; POEM: Peroral endoscopic myotomy; GERD: Gastroesophageal reflux disease; LM: Long myotomy; NA: Not Applied; SM: Short myotomy; ST: Stomach; TO: Total.

respectively, in the SM group. Postoperative LES pressure level in the LM group was 17 ± 9.7, 16.51 ± 5.01, 19.3 ± 8.5, 12.1 ± 3.9 and 13.3 ± 5.7 mmHg, respectively, and the pressure level was 11.4 ± 6.5, 17.41 ± 3.69, 16.7 ± 4.3, 11.8 ± 4.4 and 15.9 ± 3.2 mmHg, respectively, in the SM group.

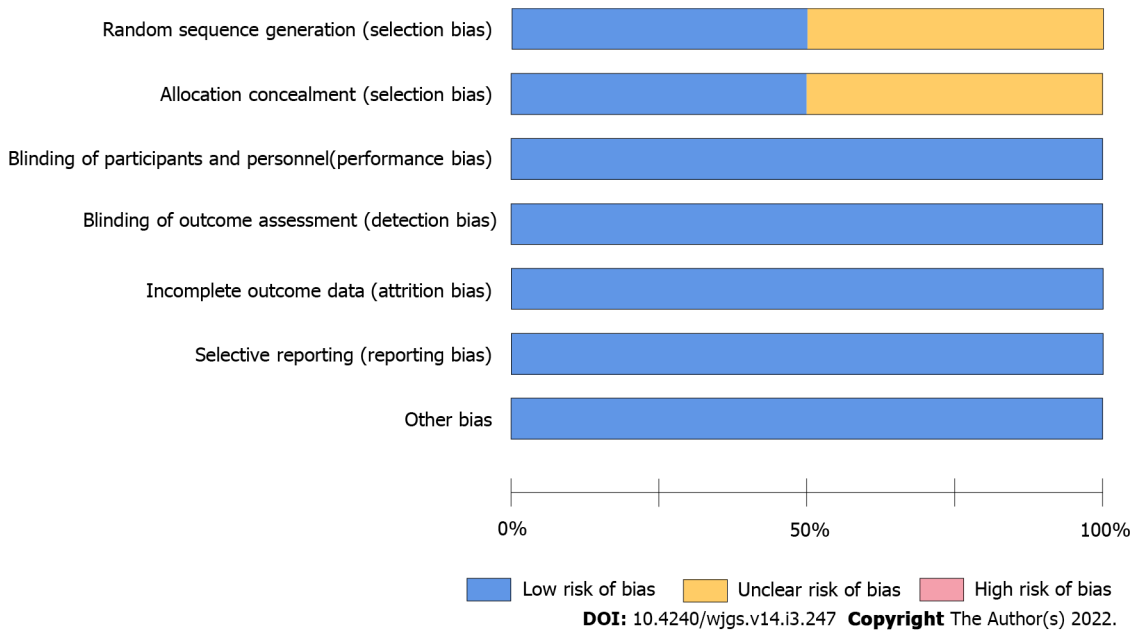
**Integrated relaxation pressure:** Preoperative integrated relaxation pressure (IRP) in POEM was available in two articles with a total of 165 patients, and three articles including 214 individuals assessed postoperative IRP pressure. The levels of preoperative IRP in the LM group were 21.5 ± 4.6 mmHg and 28.50 ± 11.01 mmHg, and in the SM group, the values were 23.2 ± 4.8 mmHg and 26.40 ± 13.9 mmHg. Postoperative IRP level in the LM group was 8.6 ± 4.9, 9.7 ± 2.6, and 7.44 ± 4.30 mmHg, respectively, and this pressure level was 5.9 ± 5.0, 10.1 ± 2.4 and 8.60 ± 1.30 mmHg, respectively, in the SM group.

**Endoscopic reflux esophagitis:** This meta-analysis found no difference in endoscopic reflux esophagitis between the two procedures (total OR = 1.21, 95%CI: 0.76-1.91; $P$ = 0.42; $I^2$: 9%; subgroup of abstract OR = 0.77, 95%CI: 0.40-1.47; $P$ = 0.43; $I^2$: 0%; subgroup of full text OR = 1.91, 95%CI: 0.98-3.75; $P$ = 0.06; $I^2$: 0%), with low heterogeneity found. Hence, random- and fixed-effects models yielded identical results (Figure 5A).




**DOI:** 10.4240/wjgs.v14.i3.247 

**Figure 1 Flow diagram of the study selection process.**




**DOI:** 10.4240/wjgs.v14.i3.247 

**Figure 2 Risk of bias of the enrolled studies.** The methodological quality of the included studies was similar. No study had a high risk for confounding variables.

**AEs:** The incidence rates of AEs in different studies are detailed in Table 2. No procedure-related deaths were recorded. The rate of hospitalization showed no difference between the two procedures (total MD = -0.07, 95%CI: -0.30 to 0.16; $P$ = 0.55; $I^2$: 24%; subgroup of abstract MD = 0.20, 95%CI: -0.25 to 0.65; $P$ = 0.39; $I^2$: 0; subgroup of full text MD = -0.16, 95%CI: -0.42 to 0.10; $P$ = 0.23; $I^2$: 42%), with no heterogeneity detected (Figure 5B). The incidence rate of major bleeding was similar comparing the two groups (total OR = 1.25, 95%CI: 0.58-2.71; $P$ = 0.56; $I^2$: 0%) (Figure 5C). These differences remained statistically significant in all sensitivity analyses.

## DISCUSSION

In this meta-analysis, we critically assessed the available RCTs and retrospective studies comparing SM and LM during POEM for the treatment of achalasia. Our main findings were that both approaches

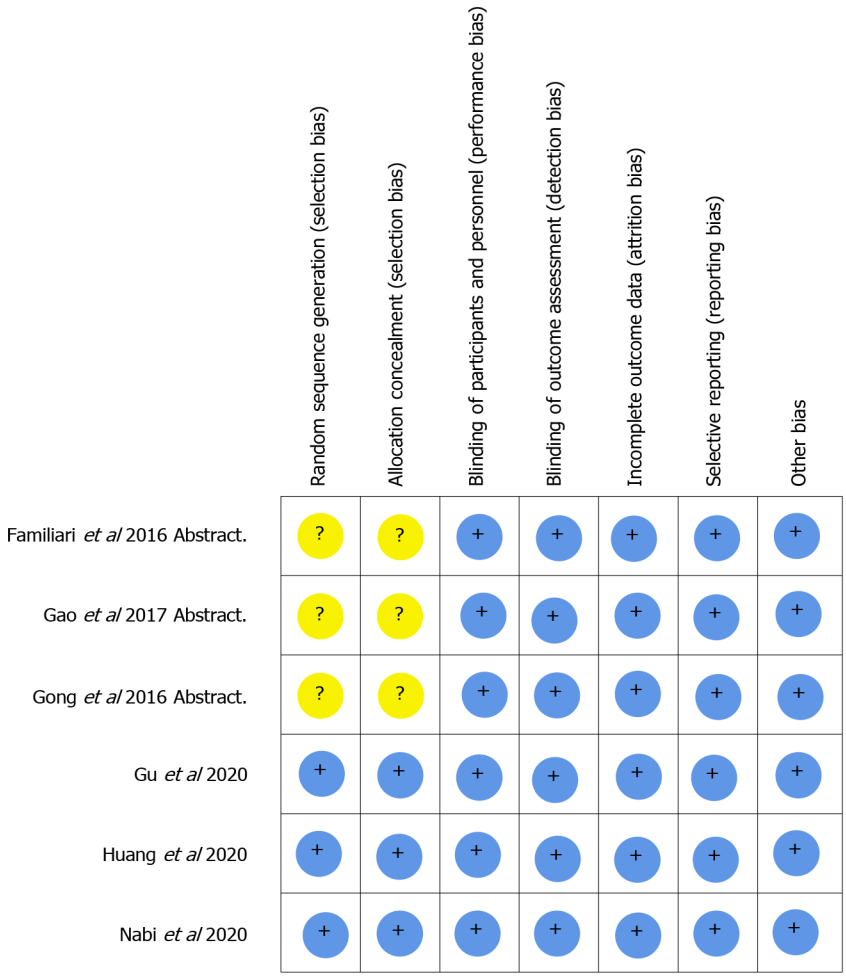
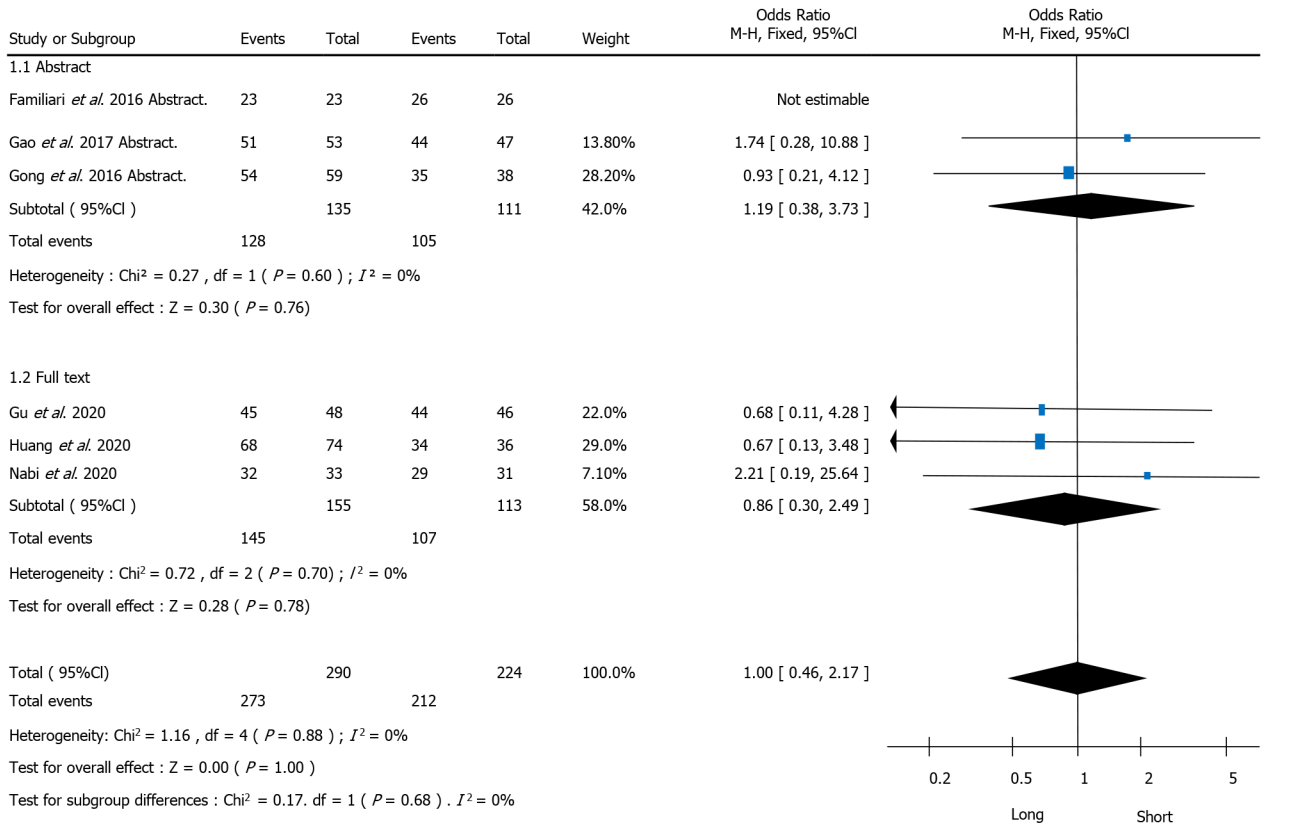


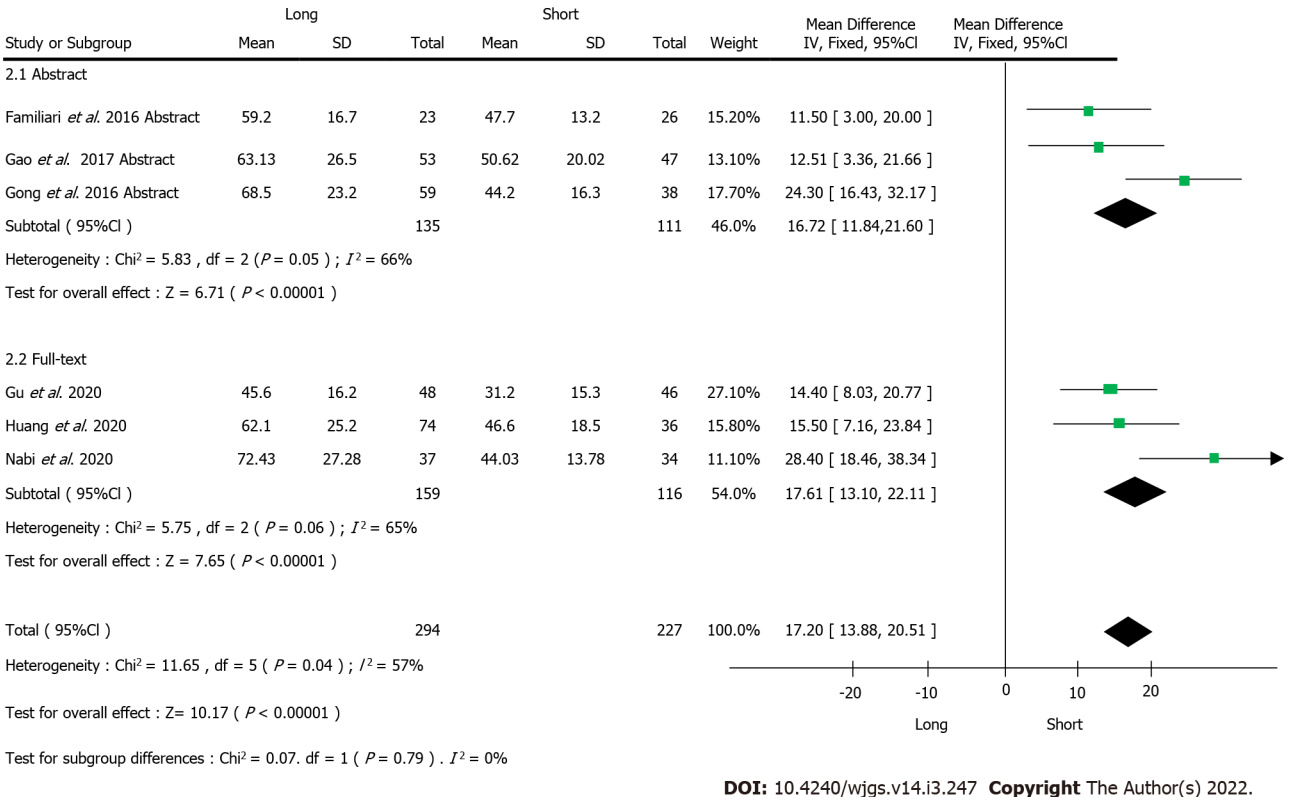

**Figure 3 Long *vs* short myotomy.** Meta-analysis of primary outcomes (clinical success rate).

were equally effective yet the shorter procedure required reduced operation time. Heterogeneity across the studies was low and a comprehensive sensitivity analysis was consistent with our primary findings. No publication bias was detected.

The notion of endoscopic myotomy was first put forward by Ortega and collaborators[19], with an electrosurgical knife utilized for dissecting the lower esophageal rosette without manipulating the distal anti-reflux zone. Nevertheless, direct endoscopic myotomy has serious complications, and it has been abandoned. POEM was first reported by Pasricha and collaborators[20] in 2007 with pigs and utilized a submucosal tunnel for LES myotomy. In 2010, Inoue and collaborators[3] first applied POEM clinically using seven individuals who received a relatively shorter myotomy (mean length of 4.9 cm and 1.0 cm on the gastric side) but had worse clinical outcomes compared with the 10 cases undergoing a longer myotomy (mean length of 10.4 cm). With regard to myotomy length in POEM, Inoue and colleagues recommended to use a length of > 10 cm (average 13 cm) as the standard[21]. Since then, POEM has been considered as an emerging treatment modality and is the preferred therapeutic option for achalasia and has shown success in all age groups and different types and stages of achalasia[22]. In addition, POEM is promising in the treatment for spastic esophageal motility ailments. Avoiding abdominal incisions could reduce surgical invasiveness, improve cosmetic effects and shorten convalescence time [23]. Moreover, POEM has been widely used clinically due to its advantages over LHM[24] including no abdominal cut, faster recovery and the possibility of avoiding general anesthesia. In addition, unlike LHM, POEM does not involve GEJ dissection[25].

The major differences in the implementation of POEM worldwide include myotomy orientation (anterior or posterior), thickness (full or partial) and length (shorter and longer). With regard to myotomy length in POEM surgery, Von Renteln and colleagues (Germany), Costamagna and collaborators (Italy), Chiu and co-workers (Hong Kong, China) and Minami and colleagues (Japan), all performed LM to treat achalasia with a mean incision length of 12, 10, 10.8 or 14.4 cm, and promising efficacy and safety have been achieved[26-29]. However, these trials adopted the original LM POEM technique by Inoue *et al*[21], with a myotomy length of about 10 cm. Meanwhile, the average LES length was only 3.2 cm, ranging from 2.4 to 4.0 cm in healthy and achalasia individuals[30]. According to the



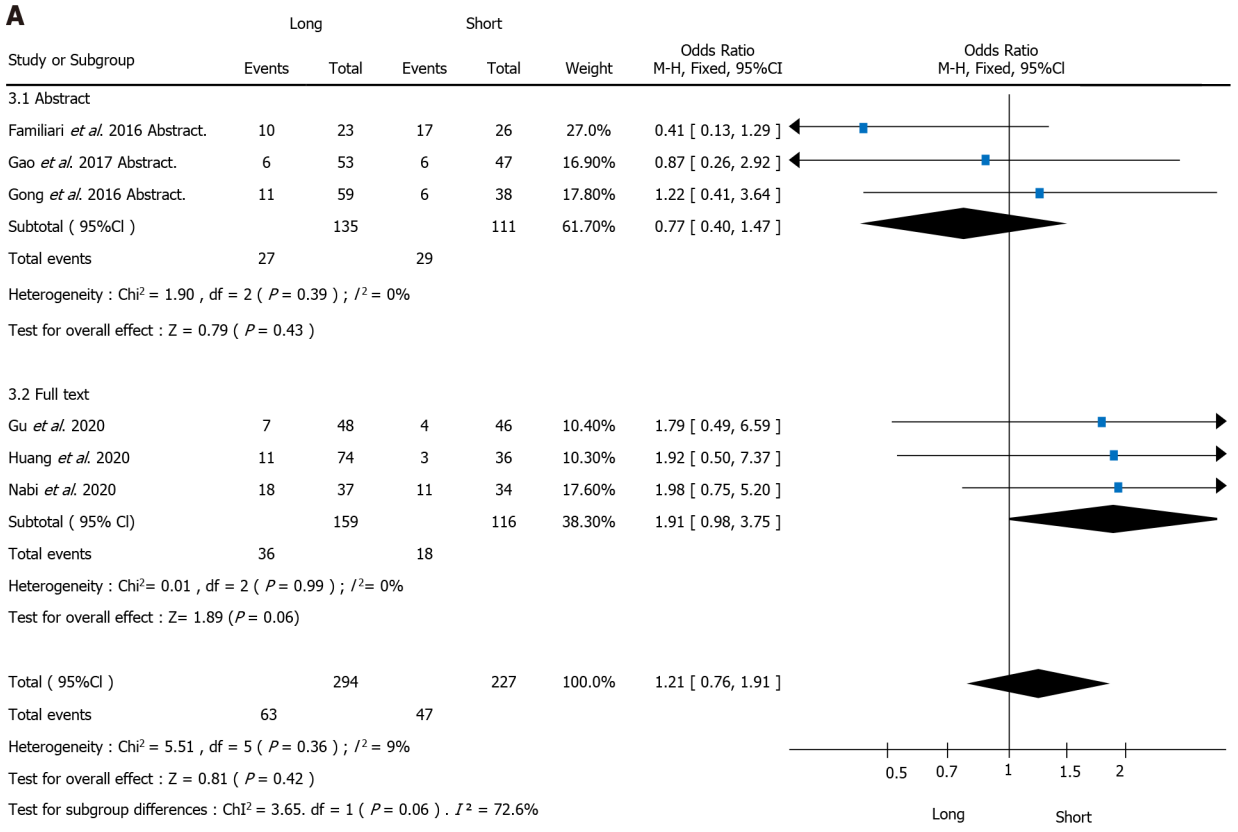




**DOI:** 10.4240/wjgs.v14.i3.247 

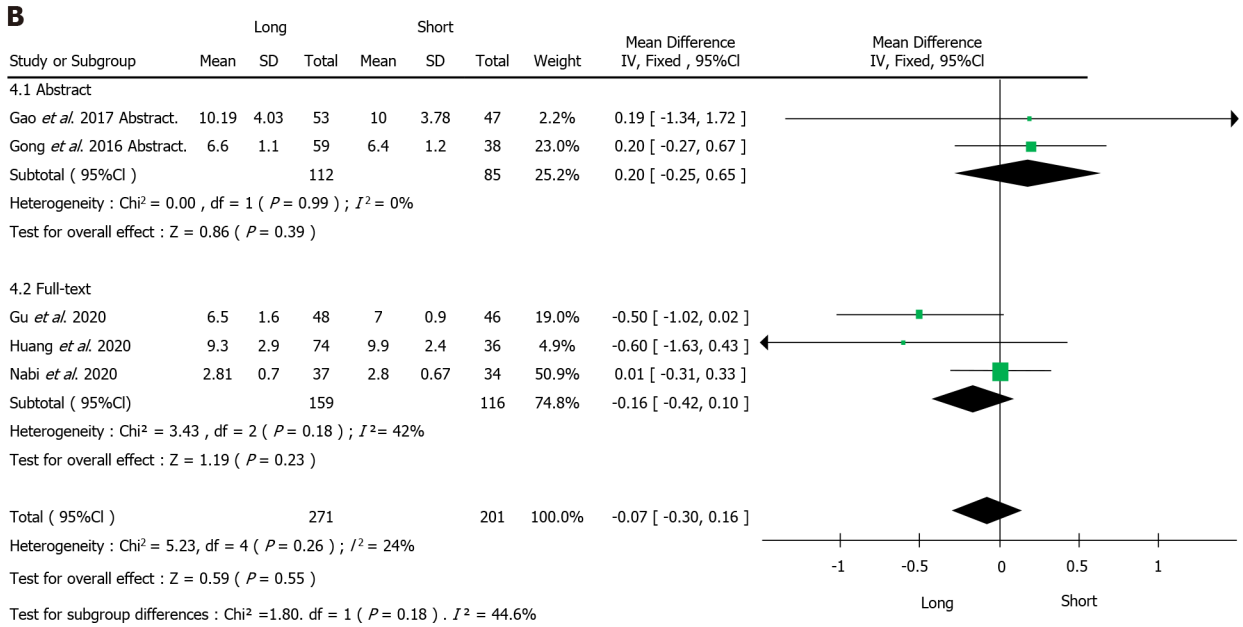
**Figure 4 Operative time of long *vs* short myotomy.**

guidelines of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), for cases of achalasia, esophageal myotomy length should be ≥ 4 cm and the gastromyotomy length should be 1-2 cm[31]. Therefore, it was hypothesized that a modified POEM procedure with a LM might be as effective as the LM procedure in achalasia treatment as it ensured sufficient LES cutting while ameliorating complications and decreasing operation time. To test this hypothesis, Wang *et al*[10] enrolled 46 patients who underwent modified POEM with shorter submucosal tunnel (average length

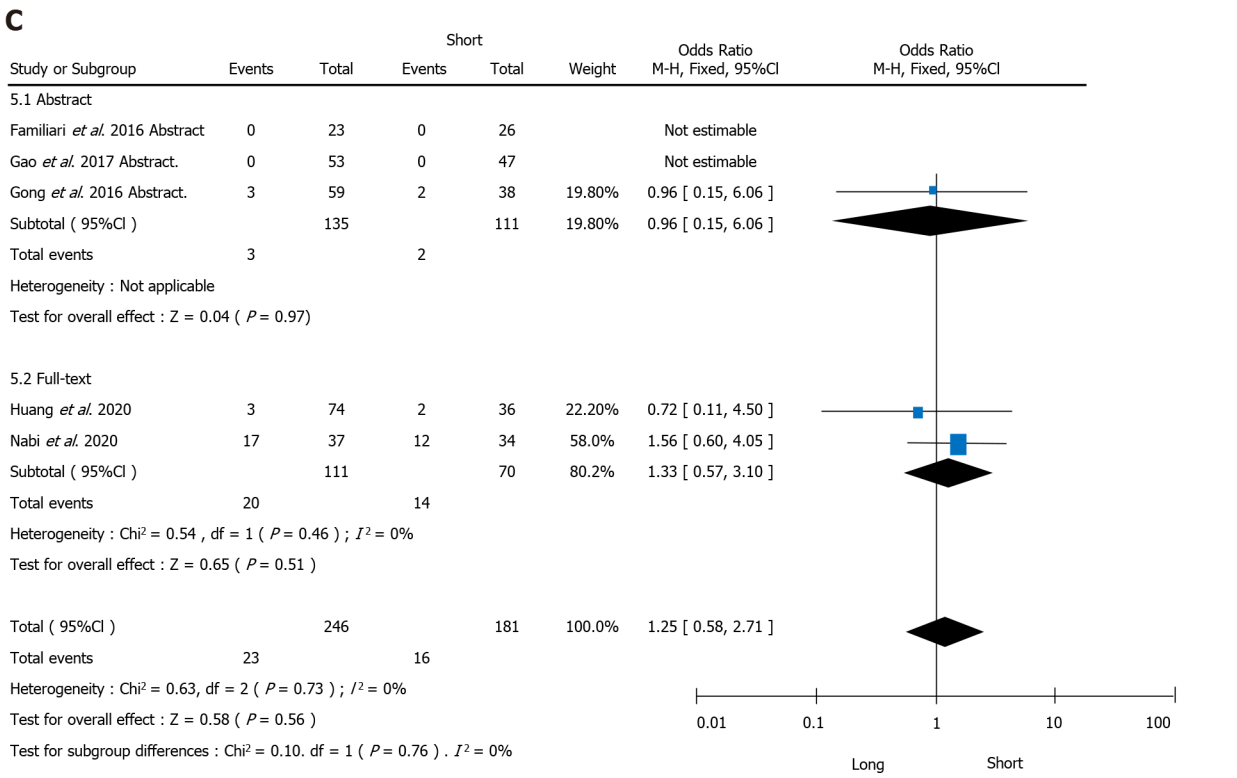
**A**




**B**




**DOI:** 10.4240/wjgs.v14.i3.247 




**DOI:** 10.4240/wjgs.v14.i3.247 

**Figure 5 Long *vs* short myotomy.** Meta-analysis of secondary outcomes. A: Endoscopic reflux esophagitis; B: Hospitalization; C: Major bleeding.

6.8 cm) and endoscopic myotomy of muscle bundles (total average length 5.4 cm). They reported that modified POEM with LM showed great safety and commendable short-term efficacy in treating achalasia. However, for patients with type I and II achalasia, a short esophageal myotomy may be sufficient[10].

The present analysis, which was based on RCTs and a retrospective study, confirmed that POEM offered excellent efficacy with a high clinical success rate. The treatment efficacy was similar between the SM and LM procedures, regardless of the definition used, length of myotomy, publication type and the statistical method employed to pool the data. The meta-analysis of manometric outcomes, where no significant disparities were detected, further endorsed the lack of clinical differences between LM and SM.

Another matter of debate is GERD after POEM[32]. Several technical refinements have been attempted to decrease the odds of post-POEM GERD, including a selective myotomy of the inner circular muscle[33], endoscopic fundoplication[34], or limiting the length of gastromyotomy[35]. The proper location of the gastroesophageal junction (GEJ) is critical in ensuring the procedure's effectiveness and may have an impact on GERD[36,37]. Many reports showed a lower GERD incidence after POEM due to the preservation of the pharyngoesophageal ligament[38,39]. In the present meta-analysis, the incidence rate of GERD was similar between the SM and LM procedures.

Regarding POEM-related AEs, multicenter studies showed that the technique was associated with a low incidence of severe AEs (< 1%)[40,41]. Interestingly, we found that the total incidence rate of AEs, including hospitalization and major bleeding, were comparable between the two groups. Procedure-related outcomes were also evaluated. As expected from our clinical experience, the SM took much less time compared with the LM but the treatment effects were similar.

This meta-analysis had some limitations. First, the number of studies was very small and three RCTs were only retrieved as abstracts. Although we conducted subgroup analysis based on abstract and full-text, more studies were still needed to analyze the results. Second, only three articles evaluated IRP after POEM treatment. Third, a longer myotomy is thought to be more effective on controlling symptoms caused by the esophageal spasm of type III achalasia. However, in this meta-analysis, due to the small number of patients with type III achalasia and recent literature[18], our conclusions might not apply to type III achalasia treatment and a short myotomy could not be recommended. We expected more RCTs to examine the effect of shorter or longer in the treatment of type III achalasia. Due to the lack of relevant research articles, we did not evaluate the postoperative efficacy of POEM for achalasia subtypes. Fourth, the follow-up duration was relatively short so this study was unable to compare the long-term efficacy and AES between LM and SM procedures.

## CONCLUSION

In conclusion, short myotomy has the advantage of reduced procedure time in the treatment of achalasia compared to long myotomy, but the clinical success rate, AEs, and reflux rate were comparable. Thus, peroral endoscopic shorter myotomy could have a great clinical application prospect. Our results are restricted by the small number of patients, short follow-up duration, and a lack of specific definition of short myotomy. Future studies with a larger sample size and longer follow-up duration are warranted to evaluate the long-term efficacy and safety of these two procedures in POEM.

## ARTICLE HIGHLIGHTS

### *Research background*

For a long time, peroral endoscopic myotomy (POEM) has been demonstrated to be safe and effective in the treatment of achalasia.

### *Research motivation*

Longer myotomy is the standard POEM procedure for achalasia, but its effectiveness compared with shorter myotomy is not well known. Thus, we want to provide an analysis to assess the clinical outcomes of shorter and longer myotomy.

### *Research objectives*

To conduct a meta-analysis to compare the clinical effectiveness of the two procedures.

### *Research methods*

The PubMed, Web of Science, Cochrane Library, clinicaltrials.gov, and EMBASE databases were used to search for relevant studies to compare shorter and longer myotomy in POEM for achalasia treatment.

### *Research results*

Longer and shorter myotomy groups in treating achalasia had similar excellent effectiveness. Shorter myotomy had significantly reduced mean operative time compared with the longer procedure. There were no statistically significant differences in AE's rates, including gastroesophageal reflux diseases, hospital stay and major bleeding between the two procedures.

### *Research conclusions*

Short myotomy has the advantage of shorter procedure time in the treatment of achalasia compared to long myotomy, but the clinical success rate, adverse events , and reflux rate were comparable.

### *Research perspectives*

Future randomized clinical trials should determine whether the benefits remain comparable after years of follow-up.

## FOOTNOTES

**Author contributions:** Weng CY and He CH collected data; Zhuang MY analyzed the data and wrote the first draft of the manuscript; Xu JL and Lyu B were major contributors in editing the manuscript; All authors read and approved the final manuscript.

**Supported by** the National Natural Science Foundation of China, No. 8177030774.

**Conflict-of-interest statement:** The authors declare they have no competing financial and non-financial interests.

**PRISMA 2009 Checklist statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).



**Country/Territory of origin:** China

**ORCID number:** Chun-Yan Weng 0000-0003-3618-9629; Cheng-Hai He 0000-0001-8322-2669; Ming-Yang Zhuang 0000-0001-6392-716X; Jing-Li Xu 0000-0002-2264-8591; Bin Lyu 0000-0002-6247-571X.

**S-Editor:** Wang LL
**L-Editor:** Filipodia
**P-Editor:** Wu RR

## REFERENCES

1 **Boeckxstaens GE**, Zaninotto G, Richter JE. Achalasia. *Lancet* 2014; **383**: 83-93 [PMID: 23871090 DOI: 10.1016/s0140-6736(13)60651-0]
2 **Vaezi MF**, Pandolfino JE, Yadlapati RH, Greer KB, Kavitt RT. ACG Clinical Guidelines: Diagnosis and Management of Achalasia. *Am J Gastroenterol* 2020; **115**: 1393-1411 [PMID: 32773454 DOI: 10.14309/ajg.0000000000000731]
3 **Inoue H**, Minami H, Kobayashi Y, Sato Y, Kaga M, Suzuki M, Satodate H, Odaka N, Itoh H, Kudo S. Peroral endoscopic myotomy (POEM) for esophageal achalasia. *Endoscopy* 2010; **42**: 265-271 [PMID: 20354937 DOI: 10.1055/s-0029-1244080]
4 **Inoue H**, Sato H, Ikeda H, Onimaru M, Sato C, Minami H, Yokomichi H, Kobayashi Y, Grimes KL, Kudo SE. Per-Oral Endoscopic Myotomy: A Series of 500 Patients. *J Am Coll Surg* 2015; **221**: 256-264 [PMID: 26206634 DOI: 10.1016/j.jamcollsurg.2015.03.057]
5 **Nabi Z**, Ramchandani M, Chavan R, Kalapala R, Darisetty S, Rao GV, Reddy N. Per-oral endoscopic myotomy for achalasia cardia: outcomes in over 400 consecutive patients. *Endosc Int Open* 2017; **5**: E331-E339 [PMID: 28484733 DOI: 10.1055/s-0043-105517]
6 **Youn YH**, Minami H, Chiu PW, Park H. Peroral Endoscopic Myotomy for Treating Achalasia and Esophageal Motility Disorders. *J Neurogastroenterol Motil* 2016; **22**: 14-24 [PMID: 26717928 DOI: 10.5056/jnm15191]
7 **He C**, Li M, Lu B, Ying X, Gao C, Wang S, Ma C, Jin C. Long-Term Efficacy of Peroral Endoscopic Myotomy for Patients with Achalasia: Outcomes with a Median Follow-Up of 36 mo. *Dig Dis Sci* 2019; **64**: 803-810 [PMID: 30478767 DOI: 10.1007/s10620-018-5373-0]
8 **Inoue H**, Shiwaku H, Kobayashi Y, Chiu PWY, Hawes RH, Neuhaus H, Costamagna G, Stavropoulos SN, Fukami N, Seewald S, Onimaru M, Minami H, Tanaka S, Shimamura Y, Santi EG, Grimes K, Tajiri H. Statement for gastroesophageal reflux disease after peroral endoscopic myotomy from an international multicenter experience. *Esophagus* 2020; **17**: 3-10 [PMID: 31559513 DOI: 10.1007/s10388-019-00689-6]
9 **Grimes KL**, Bechara R, Shimamura Y, Ikeda H, Inoue H. Gastric myotomy length affects severity but not rate of post-procedure reflux: 3-year follow-up of a prospective randomized controlled trial of double-scope per-oral endoscopic myotomy (POEM) for esophageal achalasia. *Surg Endosc* 2020; **34**: 2963-2968 [PMID: 31463720 DOI: 10.1007/s00464-019-07079-0]
10 **Wang J**, Tan N, Xiao Y, Chen J, Chen B, Ma Z, Zhang D, Chen M, Cui Y. Safety and efficacy of the modified peroral endoscopic myotomy with shorter myotomy for achalasia patients: a prospective study. *Dis Esophagus* 2015; **28**: 720-727 [PMID: 25214469 DOI: 10.1111/dote.12280]
11 **Cochrane Handbook for Systematic Reviews of Interventions [Internet]**. [cited 20 July 2021]. Available from: https://training.cochrane.org/handbook
12 **Nabi Z**, Ramchandani M, Sayyed M, Chavan R, Darisetty S, Goud R, Murthy HVV, Reddy DN. Comparison of Short Versus Long Esophageal Myotomy in Cases With Idiopathic Achalasia: A Randomized Controlled Trial. *J Neurogastroenterol Motil* 2021; **27**: 63-70 [PMID: 32675389 DOI: 10.5056/jnm20022]
13 **Huang S**, Ren Y, Peng W, Gao Q, Peng Y, Gong W, Tang X. Peroral endoscopic shorter versus longer myotomy for the treatment of achalasia: a comparative retrospective study. *Esophagus* 2020; **17**: 477-483 [PMID: 32361976 DOI: 10.1007/s10388-020-00739-4]
14 **Gu L**, Ouyang Z, Lv L, Liang C, Zhu H, Liu D. Safety and efficacy of peroral endoscopic myotomy with standard myotomy versus short myotomy for treatment-naïve patients with type II achalasia: a prospective randomized trial. *Gastrointest Endosc* 2021; **93**: 1304-1312 [PMID: 33058884 DOI: 10.1016/j.gie.2020.10.006]
15 **Familiari Pietro**, Anna Calì, Rosario Landi, Giovanni Gigante, Ivo Boskoski, Federico Barbaro, Andrea Tringali, Santiago Andrade Zurita, Vincenzo Perri, Guido Costamagna. Long vs Short POEM for the Treatment of Achalasia. Interim Analysis of a Randomized Controlled Trial. *Gastrointestinal Endoscopy* 2016; **83**
16 **Gao QP**, Tu SF, Tang XW, Huang SL, Gong W. Mid-term Outcomes of a Single Center Randomized Controlled Trial Comparing Peroral Endoscopic Short versus Long Myotomy for Achalasia in China. *The American Journal of Gastroenterology*
17 **Gong W**, Tang XW, Huang SL, Ren YT, Gao QP, Zhou JQ, Zhang XF, Bo Jiang. Peroral Endoscopic Shorter versus Longer Myotomy for the Treatment of Achalasia: A Comparative Study. *The American Journal of Gastroenterology*
18 **Kumbhari V**, Tieu AH, Onimaru M, El Zein MH, Teitelbaum EN, Ujiki MB, Gitelis ME, Modayil RJ, Hungness ES, Stavropoulos SN, Shiwaku H, Kunda R, Chiu P, Saxena P, Messallam AA, Inoue H, Khashab MA. Peroral endoscopic myotomy (POEM) vs laparoscopic Heller myotomy (LHM) for the treatment of Type III achalasia in 75 patients: a multicenter comparative study. *Endosc Int Open* 2015; **3**: E195-E201 [PMID: 26171430 DOI: 10.1055/s-0034-1391668]
19 **Ortega JA**, Madureri V, Perez L. Endoscopic myotomy in the treatment of achalasia. *Gastrointest Endosc* 1980; **26**: 8-10 [PMID: 7358270 DOI: 10.1016/s0016-5107(80)73249-2]
20 **Pasricha PJ**, Hawari R, Ahmed I, Chen J, Cotton PB, Hawes RH, Kalloo AN, Kantsevoy SV, Gostout CJ. Submucosal endoscopic esophageal myotomy: a novel experimental approach for the treatment of achalasia. *Endoscopy* 2007; **39**: 761-764 [PMID: 17703382 DOI: 10.1055/s-2007-966764]

21 **Inoue H**, Santi EG, Onimaru M, Kudo SE. Submucosal endoscopy: from ESD to POEM and beyond. *Gastrointest Endosc Clin N Am* 2014; **24**: 257-264 [PMID: 24679236 DOI: 10.1016/j.giec.2013.12.003]

22 **NOSCAR POEM White Paper Committee**. , Stavropoulos SN, Desilets DJ, Fuchs KH, Gostout CJ, Haber G, Inoue H, Kochman ML, Modayil R, Savides T, Scott DJ, Swanstrom LL, Vassiliou MC. Per-oral endoscopic myotomy white paper summary. *Gastrointest Endosc* 2014; **80**: 1-15 [PMID: 24950639 DOI: 10.1016/j.gie.2014.04.014]

23 **Cho YK**, Kim SH. Current Status of Peroral Endoscopic Myotomy. *Clin Endosc* 2018; **51**: 13-18 [PMID: 29397656 DOI: 10.5946/ce.2017.165]

24 **Ponds FA**, Fockens P, Lei A, Neuhaus H, Beyna T, Kandler J, Frieling T, Chiu PWY, Wu JCY, Wong VWY, Costamagna G, Familiari P, Kahrilas PJ, Pandolfino JE, Smout AJPM, Bredenoord AJ. Effect of Peroral Endoscopic Myotomy vs Pneumatic Dilation on Symptom Severity and Treatment Outcomes Among Treatment-Naive Patients With Achalasia: A Randomized Clinical Trial. *JAMA* 2019; **322**: 134-144 [PMID: 31287522 DOI: 10.1001/jama.2019.8859]

25 **Kahrilas PJ**, Katzka D, Richter JE. Clinical Practice Update: The Use of Per-Oral Endoscopic Myotomy in Achalasia: Expert Review and Best Practice Advice From the AGA Institute. *Gastroenterology* 2017; **153**: 1205-1211 [PMID: 28989059 DOI: 10.1053/j.gastro.2017.10.001]

26 **von Renteln D**, Inoue H, Minami H, Werner YB, Pace A, Kersten JF, Much CC, Schachschal G, Mann O, Keller J, Fuchs KH, Rösch T. Peroral endoscopic myotomy for the treatment of achalasia: a prospective single center study. *Am J Gastroenterol* 2012; **107**: 411-417 [PMID: 22068665 DOI: 10.1038/ajg.2011.388]

27 **Costamagna G**, Marchese M, Familiari P, Tringali A, Inoue H, Perri V. Peroral endoscopic myotomy (POEM) for oesophageal achalasia: preliminary results in humans. *Dig Liver Dis* 2012; **44**: 827-832 [PMID: 22609465 DOI: 10.1016/j.dld.2012.04.003]

28 **Chiu PW**, Wu JC, Teoh AY, Chan Y, Wong SK, Liu SY, Yung MY, Lam CC, Sung JJ, Chan FK, Lau JY, Ng EK. Peroral endoscopic myotomy for treatment of achalasia: from bench to bedside (with video). *Gastrointest Endosc* 2013; **77**: 29-38 [PMID: 23043852 DOI: 10.1016/j.gie.2012.08.018]

29 **Minami H**, Isomoto H, Yamaguchi N, Matsushima K, Akazawa Y, Ohnita K, Takeshima F, Inoue H, Nakao K. Peroral endoscopic myotomy for esophageal achalasia: clinical impact of 28 cases. *Dig Endosc* 2014; **26**: 43-51 [PMID: 23581563 DOI: 10.1111/den.12086]

30 **Shi Y**, Xiao Y, Peng S, Lin J, Xiong L, Chen M. Normative data of high-resolution impedance manometry in the Chinese population. *J Gastroenterol Hepatol* 2013; **28**: 1611-1615 [PMID: 23730912 DOI: 10.1111/jgh.12285]

31 **Stefanidis D**, Richardson W, Farrell TM, Kohn GP, Augenstein V, Fanelli RD; Society of American Gastrointestinal and Endoscopic Surgeons. SAGES guidelines for the surgical treatment of esophageal achalasia. *Surg Endosc* 2012; **26**: 296-311 [PMID: 22044977 DOI: 10.1007/s00464-011-2017-2]

32 **Rösch T**, Repici A, Boeckxstaens G. Will Reflux Kill POEM? *Endoscopy* 2017; **49**: 625-628 [PMID: 28658688 DOI: 10.1055/s-0043-112490]

33 **Wang XH**, Tan YY, Zhu HY, Li CJ, Liu DL. Full-thickness myotomy is associated with higher rate of postoperative gastroesophageal reflux disease. *World J Gastroenterol* 2016; **22**: 9419-9426 [PMID: 27895430 DOI: 10.3748/wjg.v22.i42.9419]

34 **Tyberg A**, Choi A, Gaidhane M, Kahaleh M. Transoral incisional fundoplication for reflux after peroral endoscopic myotomy: a crucial addition to our arsenal. *Endosc Int Open* 2018; **6**: E549-E552 [PMID: 29756011 DOI: 10.1055/a-0584-6802]

35 **Inoue H**, Shiwaku H, Iwakiri K, Onimaru M, Kobayashi Y, Minami H, Sato H, Kitano S, Iwakiri R, Omura N, Murakami K, Fukami N, Fujimoto K, Tajiri H. Clinical practice guidelines for peroral endoscopic myotomy. *Dig Endosc* 2018; **30**: 563-579 [PMID: 30022514 DOI: 10.1111/den.13239]

36 **Teitelbaum EN**, Sternbach JM, El Khoury R, Soper NJ, Pandolfino JE, Kahrilas PJ, Lin Z, Hungness ES. The effect of incremental distal gastric myotomy lengths on EGJ distensibility during POEM for achalasia. *Surg Endosc* 2016; **30**: 745-750 [PMID: 26092005 DOI: 10.1007/s00464-015-4269-8]

37 **Teitelbaum EN**, Soper NJ, Pandolfino JE, Kahrilas PJ, Hirano I, Boris L, Nicodème F, Lin Z, Hungness ES. Esophagogastric junction distensibility measurements during Heller myotomy and POEM for achalasia predict postoperative symptomatic outcomes. *Surg Endosc* 2015; **29**: 522-528 [PMID: 25055891 DOI: 10.1007/s00464-014-3733-1]

38 **Awaiz A**, Yunus RM, Khan S, Memon B, Memon MA. Systematic Review and Meta-Analysis of Perioperative Outcomes of Peroral Endoscopic Myotomy (POEM) and Laparoscopic Heller Myotomy (LHM) for Achalasia. *Surg Laparosc Endosc Percutan Tech* 2017; **27**: 123-131 [PMID: 28472017 DOI: 10.1097/sle.0000000000000402]

39 **Schneider AM**, Louie BE, Warren HF, Farivar AS, Schembre DB, Aye RW. A Matched Comparison of Per Oral Endoscopic Myotomy to Laparoscopic Heller Myotomy in the Treatment of Achalasia. *J Gastrointest Surg* 2016; **20**: 1789-1796 [PMID: 27514392 DOI: 10.1007/s11605-016-3232-x]

40 **Haito-Chavez Y**, Inoue H, Beard KW, Draganov PV, Ujiki M, Rahden BHA, Desai PN, Pioche M, Hayee B, Haji A, Saxena P, Reavis K, Onimaru M, Balassone V, Nakamura J, Hata Y, Yang D, Pannu D, Abbas A, Perbtani YB, Patel LY, Filser J, Roman S, Rivory J, Mion F, Ponchon T, Perretta S, Wong V, Maselli R, Ngamruengphong S, Chen YI, Bukhari M, Hajiyeva G, Ismail A, Pieratti R, Kumbhari V, Galdos-Cardenas G, Repici A, Khashab MA. Comprehensive Analysis of Adverse Events Associated With Per Oral Endoscopic Myotomy in 1826 Patients: An International Multicenter Study. *Am J Gastroenterol* 2017; **112**: 1267-1276 [PMID: 28534521 DOI: 10.1038/ajg.2017.139]

41 **Werner YB**, von Renteln D, Noder T, Schachschal G, Denzer UW, Groth S, Nast JF, Kersten JF, Petzoldt M, Adam G, Mann O, Repici A, Hassan C, Rösch T. Early adverse events of per-oral endoscopic myotomy. *Gastrointest Endosc* 2017; **85**: 708-718.e2 [PMID: 27609778 DOI: 10.1016/j.gie.2016.08.033]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 March 27; 14(3): 260-267

DOI: 10.4240/wjgs.v14.i3.260

ISSN 1948-9366 (online)

*CASE REPORT*

# Successful treatment with laparoscopic surgery and sequential multikinase inhibitor therapy for hepatocellular carcinoma: A case report

Yutaka Endo, Motohide Shimazu, Tadayuki Sakuragawa, Yusuke Uchi, Motonori Edanami, Ken Sunamura, Soji Ozawa, Naokazu Chiba, Shigeyuki Kawachi

**Specialty type:** Surgery

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Luo XZ, China; Mukthinuthalapati VVPK, United States; Nenu I, Romania

**Received:** November 30, 2021
**Peer-review started:** November 30, 2021
**First decision:** December 26, 2021
**Revised:** January 8, 2022
**Accepted:** March 16, 2022
**Article in press:** March 16, 2022
**Published online:** March 27, 2022

**Yutaka Endo, Motohide Shimazu, Tadayuki Sakuragawa, Yusuke Uchi, Motonori Edanami, Ken Sunamura, Soji Ozawa,** Department of Surgery, Tama Kyuryo Hospital, Tokyo 1940297, Japan

**Naokazu Chiba, Shigeyuki Kawachi,** Department of Digestive and Transplantation Surgery, Tokyo Medical University Hachioji Medical Center, Tokyo 1930998, Japan

**Corresponding author:** Motohide Shimazu, MD, PhD, Chief Doctor, Department of Surgery, Tama Kyuryo Hospital, 1491 Shimo-oyamadacho, Machida, Tokyo 1940297, Japan. shimazu@tokyo-med.ac.jp

## Abstract

### *BACKGROUND*

Hepatocellular carcinoma (HCC) with massive portal vein tumor thrombosis (PVTT) and distant metastasis is considered unresectable. However, due to recent developments in systemic chemotherapy, successful cases of conversion therapy for unresectable diseases have been reported. Herein, we report a successful multidisciplinary approach for treatment of multi-visceral recurrence with sequential multikinase inhibitor and laparoscopic surgery.

### *CASE SUMMARY*

A 63-year-old woman with chronic hepatitis B virus infection was diagnosed with HCC. Subsequently, she underwent two rounds of laparoscopic partial hepatectomy, laparoscopic left adrenalectomy, and transcatheter arterial chemoembolization plus sorafenib for recurrence. Four years after initial hepatectomy, she presented with a 43-mm mass in the spleen and tumor thrombus involving the main portal vein trunk with ascites. Her liver function was Child-Pugh B (8), and protein induced by vitamin K absence or antagonist II (PIVKA II) levels were elevated up to 46.291 mAU/mL. Since initial treatment with regorafenib for three months was unsuccessful, the patient was administered lenvatinib. Ten months post-treatment, there was no contrast enhancement of PVTT or splenic metastasis. Chemotherapy was discontinued due to severe diarrhea. Afterward, splenic metastasis became viable, and PIVKA II increased. Therefore, hand-assisted laparoscopic splenectomy was performed. She experienced no clinical recurrence 14 mo after resection.

*CONCLUSION*
Conversion surgery after successful multikinase inhibitor treatment might be considered an effective treatment option for advanced HCC.

**Key Words:** Hepatocellular carcinoma; Lenvatinib; Portal vein; Venous thrombosis; Splenic neoplasms; Case report



**Core Tip:** A 63-year-old woman had chronic hepatitis B virus infection and previous treatment history of hepatocellular carcinoma. She developed a 43-mm splenic mass and tumor thrombus involving the right portal branch and an umbilical portion extending down to the main trunk with severe ascites. She was initially treated with regorafenib and then lenvatinib. Ten months post-treatment, there was no contrast enhancement of portal vein tumor thrombosis or splenic metastases. However, after lenvatinib discontinuation due to severe diarrhea, splenic metastases showed partial contrast enhancement. Subsequently, hand-assisted laparoscopic splenectomy was performed with no remarkable postoperative complications. She experienced no recurrence for 14 mo.

**Citation:** Endo Y, Shimazu M, Sakuragawa T, Uchi Y, Edanami M, Sunamura K, Ozawa S, Chiba N, Kawachi S. Successful treatment with laparoscopic surgery and sequential multikinase inhibitor therapy for hepatocellular carcinoma: A case report. *World J Gastrointest Surg* 2022; 14(3): 260-267
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i3/260.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i3.260

## INTRODUCTION

Treatment strategy recommendations for hepatocellular carcinoma (HCC) have been introduced in various guidelines. These guidelines include the Clinical Practice Guidelines for Hepatocellular Carcinoma in Japan[1], Barcelona Clinic Liver Cancer (BCLC) Guidelines[2], and American Association for the Study of the Liver Diseases Guidelines[3]. According to these guidelines, indications for liver resection are limited by tumor progression. Moreover, many cases with distant metastasis or local major vessel invasion are not eligible for resection. Recently, development of effective molecular-targeted agents, including sorafenib[4], regorafenib[5], ramucirumab[6], and lenvatinib (LEN)[7] has prolonged patient survival and occasionally enabled multidisciplinary treatments combined with chemotherapy and liver resection for HCC. Among these agents, LEN, which is an oral multikinase inhibitor targeting kinases, is known to achieve a higher rate of objective response rate (ORR)[7]. These kinases include vascular endothelial growth factor receptor 1-3, fibroblast growth factor receptor (FGFR) 1-4, platelet-derived growth factor receptor-α (PDGFR), RET, and KIT. Therefore, there have been a limited number of reports on conversion surgery after LEN treatment[8-17]. However, to the best of our knowledge, there are only a few reports on long-term remission with portal vein tumor thrombus[8,16].

Herein, we report a successful multidisciplinary approach for treatment of unresectable HCC recurrence with sequential multikinase inhibitor therapy and laparoscopic surgery.

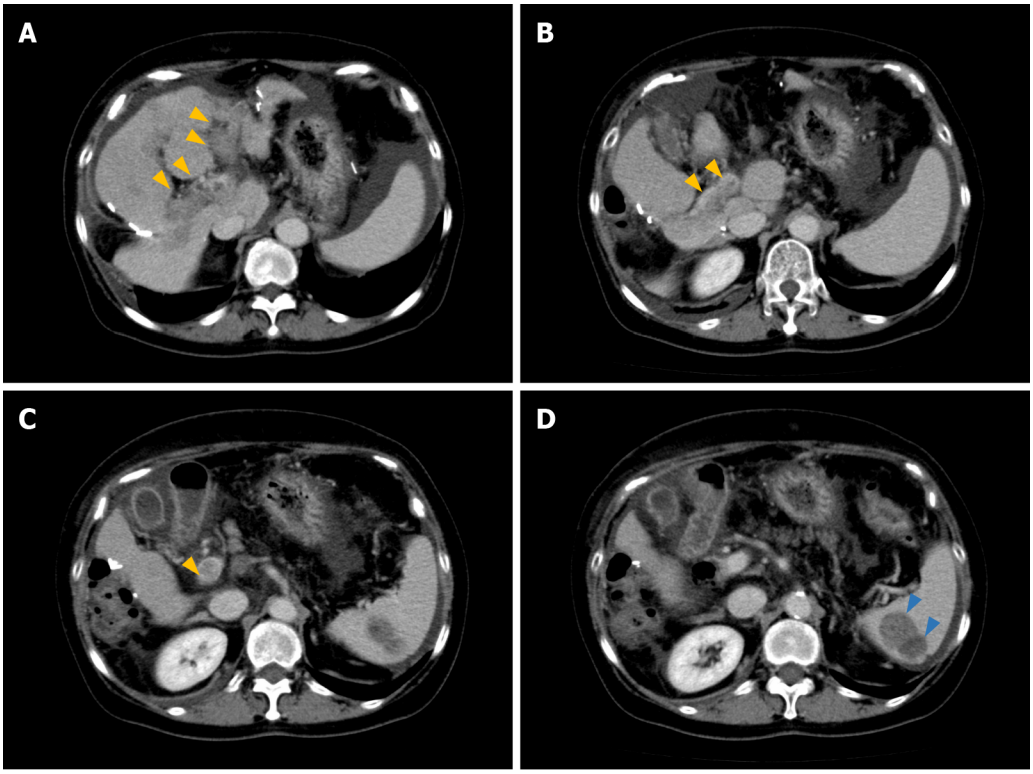
## CASE PRESENTATION

### *Chief complaints*

A 63-year-old woman with chronic hepatitis B virus infection was referred to our clinic due to incidental detection of a hepatic mass. Alpha-fetoprotein and protein induced by vitamin K absence or antagonist II (PIVKA II) levels were 25.24 ng/mL and 3021 mAU/mL, respectively. The patient was diagnosed with HCC in December 2014. Thereafter, she underwent hand-assisted laparoscopic partial hepatectomy for a solitary tumor with 5 cm in diameter in the right posterior sector. Pathological findings showed that the lesion was 40 mm in size, moderately differentiated, solitary HCC without any macroscopic vascular invasion (T1bN0M0 and stage IB, based on the 8$^{th}$ Union for International Cancer Control staging of HCC). Liver fibrosis was evident during initial surgery (METVIR F2-3).

### *History of present illness*

Six months after initial surgery, multiple recurrent lesions in the liver were observed. Consequently, the




**DOI:** 10.4240/wjgs.v14.i3.260 

**Figure 1 Radiological findings of hepatocellular carcinoma with portal vein tumor thrombosis and splenic metastasis.** A: Hypervascular lesion in the left and right anterior portal branches (yellow arrows) suggesting portal vein tumor thrombosis. Ascites are located around the spleen. Dynamic computed tomography (CT), portal phase; B and C: Hypervascular lesions in the main portal branch (yellow arrows). Dynamic CT, portal phase; D: Heterogenic, largely a hypodense lesion with high contrast enhancement in the lower pole of the spleen (blue arrows). Dynamic CT, portal phase.

patient was treated with lipiodol-transcatheter arterial chemoembolization (TACE). After this successful TACE, sorafenib (400 mg per day) was administered. Six months later, she underwent laparoscopic left adrenalectomy for adrenal metastasis (pathology revealed metastatic, moderately differentiated HCC). Eight months after the adrenalectomy, the patient underwent laparoscopic partial hepatectomy for a solitary recurrence in the lateral sector (pathology revealed moderately differentiated HCC, background liver condition; METAVIR F3). Eight months after the second hepatectomy, the patient was treated with sorafenib (400 mg per day, followed by 600 mg per day) for increased PIVKA II levels. Despite 9-mo treatment with sorafenib, she was found to have a 43-mm mass in the spleen and portal vein tumor thrombosis (PVTT) that involved both the right and left portal branches down to the main trunk (Vp4) on computed tomography (CT) (Figure 1).

### *History of past illness*
Hepatitis B infection.

### *Personal and family history*
Her personal and family history was unremarkable.

### *Physical examination*
Her vital signs were normal. There were no remarkable findings other than abdominal distention.

### *Laboratory examinations*
PIVKA II levels increased tremendously up to 46.291 mAU/mL. The BCLC staging system classified the patient into stage C. Aspartate aminotransferase, alanine aminotransferase, and platelet count were 49 IU/L, 40 IU/L, and 14.7 × $10^4$/μL, respectively. The FIB-4 index was calculated as 3.71, suggesting that she was likely to be cirrhotic. Her cirrhosis was classified into Child-Pugh B (8) and modified albumin-bilirubin grade 1.

### *Imaging examinations*
CT findings revealed moderate ascites, which indicated portal hypertension due to tumor thrombosis. This also demonstrated irregularity of the external contour of the left lobe of the liver, suggesting cirrhosis.

## MULTIDISCIPLINARY EXPERT CONSULTATION

***Seishi Nakatsuka, MD, PhD, Assistant Professor, Department of Radiology, Keio University***

On contrast enhanced CT scan, a hypodense mass with a size of 43 mm in the spleen and PVTT that involved the right anterior, posterior, and left portal branches down to main trunk (Vp4) were seen. Moreover, moderate ascites was observed. No obvious liver masses were recognized.

## FINAL DIAGNOSIS

HCC with PVTT and splenic metastases, which led to massive ascites, possibly due to portal hypertension, was observed.

## TREATMENT

Initially, she was treated with regorafenib (400 mg/d) and tolvaptan for ascites.

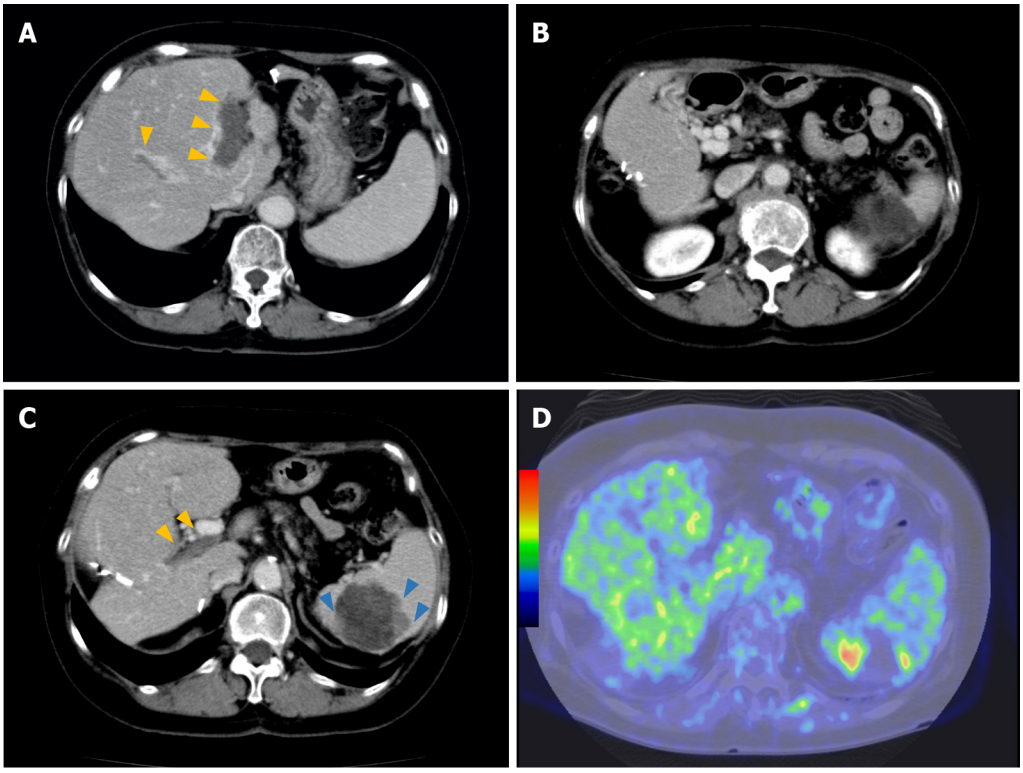
## OUTCOME AND FOLLOW-UP

Three months after initiation of regorafenib treatment, the tumor thrombus and spleen metastasis continued to increase in size with elevated PIVKA II levels (129.815 mAU/mL). However, improvement of liver function by resolution of portal hypertension due to cavernous transformation occurred. Her ascites and liver function improved [Child-Pugh A (5)]. Therefore, LEN was orally administered at a dose of 8 mg/d. No severe side effects were observed, except for grade 2 hypertension and anorexia. Ten months after initiation of LEN therapy, the patient had a clinically complete response, according to radiological findings (Figure 2A and B). Additionally, PIVKA II level markedly decreased from 1.637 to 4 mAU/mL and was sustained within the normal range with continued therapy. After 18 mo, LEN treatment was ceased because the patient developed severe diarrhea. At that time, a follow-up CT examination revealed that the tumor burden had significantly decreased. However, after 7 mo, PIVKA II levels increased again, with contrast-enhancement of the splenic lesion on CT and positron emission tomography (PET) findings (Figure 2C and D). Splenectomy was required to control the disease. Therefore, a hand-assisted laparoscopic splenectomy was performed for solitary spleen metastasis. The patient's postoperative course was uneventful. Macroscopic and microscopic histopathological examinations showed necrosis of HCC with slightly viable tumor cells. Surgical margins were negative (Figure 3). There was no clinical evidence of recurrence 14 mo after splenectomy and 81 mo after initial hepatectomy. Levels of PIVKA II remained within the normal range.

## DISCUSSION

Based on our experience, LEN therapy could successfully lead to a hypovascular status of PVTT 10 mo after its initiation. In addition, conversion surgery was performed effectively for progression of solitary splenic metastasis after LEN discontinuation. To the best of our knowledge, there have been few reports regarding successful conversion surgery after multikinase inhibitor treatment for HCC with massive tumor thrombus[8,16].

We experienced good control of PVTT with LEN administration. In our case, PVTT became hypovascular 10 mo after LEN administration, along with a necrosis of the splenic lesion. After LEN discontinuation, PVTT continued to be hypovascular, whereas the splenic lesion progressed. There have been two case reports showing disappearance of PVTT[8,16]. Takeda *et al*[8] reported a female patient with advanced HCC and PVTT who was treated with LEN monotherapy and experienced a long-term antitumor effect. Rapidly, LEN caused hypovascularity in the main hypervascular target lesion, and PVTT became undetectable 11 mo after LEN initiation. Takahashi *et al*[16] also reported a 59-year-old male patient with a recurrent liver mass diffusely located at the lateral segment with a massive Vp4 PVTT extending from the umbilical portion to the main and contralateral third-order portal branches. Three months after starting LEN, PVTT critically regressed and retreated to the contralateral first-order portal branch. After LEN cessation for 7 d, radical left lobectomy and PVTT thrombectomy were performed. The majority of PVTT cases showed necrosis. They argued that LEN may have a relatively strong antitumor effect not only on main tumor, but also on PVTT, which is attributed to an antiangiogenic effect. According to two previous reports, LEN exerts both immediate antiangiogenic and long-term antitumor effects on PVTT. According to previous basic studies[18-20], FGFR plays an important role in this antitumor effect *via* inhibition of FGF19-FGFR autocrine loop and antiangiogenic effects




**DOI:** 10.4240/wjgs.v14.i3.260 

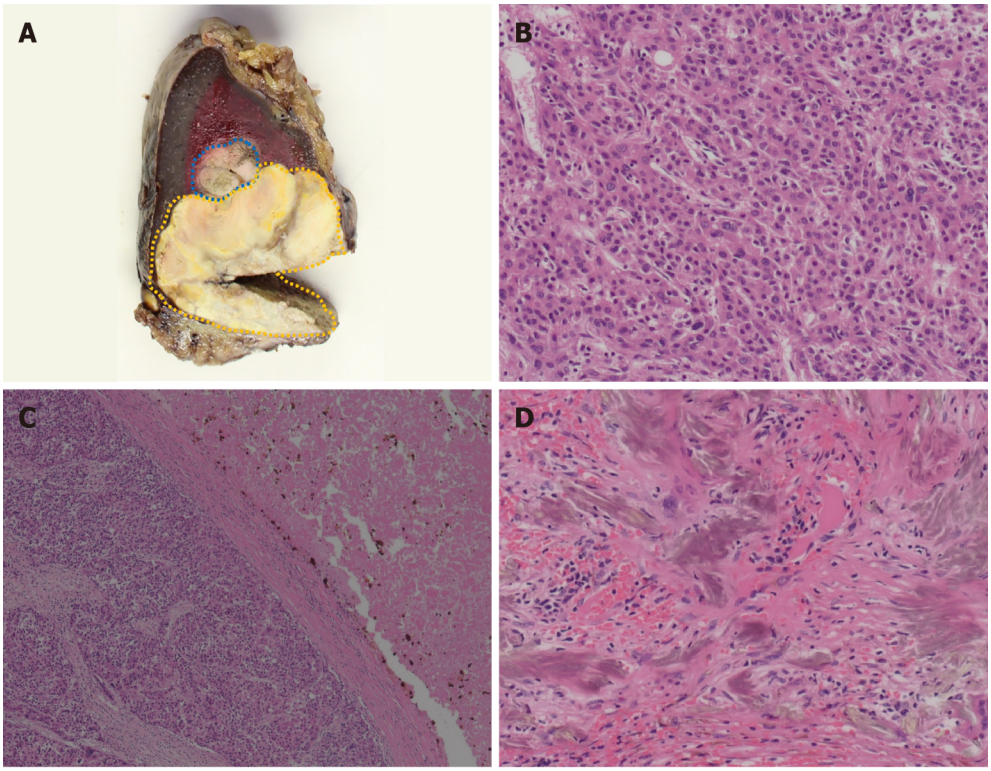
**Figure 2 Radiological findings after the lenvatinib treatment.** A: Portal vein tumor thrombus (PVTT) becomes hypovascular (yellow arrows) 10 mo after the administration of lenvatinib. Dynamic computed tomography (CT), portal phase; B: The main portal vein is hypovascular, suggesting the organization of PVTT 10 mo after the administration of lenvatinib. Numerous collateral veins are seen around the portal vein. Dynamic CT, portal phase; C: PVTT remains hypovascular (yellow arrows), whereas hypervascular lesions increase the peripheral lesions of the spleen metastases (blue arrows) 8 mo after the cessation of lenvatinib. Dynamic CT, portal phase; D: Fluorodeoxyglucose (FDG) uptakes in the lower pole of the spleen (blue arrows) corresponding to hypervascular lesions on CT. FDG-positron emission tomography.

through inhibition of FGFR/PDGFR. This explains why PVTT and hepatic lesions became hypovascular in 10 mo and continued to be in a hypovascular status approximately 2 years after LEN cessation in our patient.

Importantly, the safety of LEN administration for main PVTT (Vp4) has not been established. Kuzuya *et al*[21] compared the outcomes of advanced HCC with Vp3/4 between sorafenib and LEN as the first-line systemic therapy. The ORR was significantly higher in the LEN group than in the sorafenib group (53.8% *vs* 14.3%, $P$ = 0.0193), and the median overall survival (OS) and time to progression were significantly longer in the LEN group than in the sorafenib group. None of these patients discontinued LEN treatment due to treatment-related adverse events in their series. Chuma *et al*[22] recently have reported the safety and efficacy of LEN treatment in highly advanced HCC. In this report, 20 patients with Vp4 HCC were included, and 12 patients (60%) experienced grade ≥ 3 adverse effects. The ORRs were 26.7% in patients with Child-Pugh A and 0% in those with Child-Pugh B. These findings suggest that LEN administration with close monitoring of patients' live conditions would be acceptable.

It was notable that regorafenib, which has also anti-angiogenic properties did not have any impact on cavernous transformation of the portal vein and portal vein thrombosis. Although they have not been fully elucidated, the various reactions of regorafenib and LEN may originate from the different mechanisms of action between the two agents. The genes downregulated by regorafenib might be different from those manipulated by LEN. That would lead to their different effects. There have been few cases regarding regorafenib and conversion therapy for HCC with PVTT, despite REFLECT trial included patients with macrovascular invasion[5].

Since metastatic splenic lesions became viable after LEN cessation, splenectomy was necessary to control the disease. There have been a few cases of spleen metastases resection[23-26]. The spleen is an important organ in the immune system, and metastases to this organ usually involve multiple lesions, and solitary splenic metastasis seems rare. According to previous reports[23-25], splenectomy for spleen metastases led to favorable outcomes, despite some patients having dismal outcomes (OS, 2-84 mo). Kim *et al*[26] have reported lesions detected by fluorodeoxyglucose-PET, which was similar to those in our patient. It has been assumed that splenic metastasis could be transformed into poor differentiation through multiple treatments.




**DOI:** 10.4240/wjgs.v14.i3.260 

**Figure 3 Pathological findings of metastatic splenic lesions.** A: Macroscopic finding shows that splenic lesions surrounded by fibrous capsule, and a border part (blue area) is distinguished from other parts (yellow area) with its color, suggesting viable lesions; B: Microscopic finding of viable tumor lesion shows moderately to poorly differentiated hepatocellular carcinoma. Hematoxylin-eosin stain, high-power field (× 200); C: Microscopic findings of mixed component of viable cells and necrotic tissue demonstrated that coagulative and partially liquefactive necrosis (right-side) is surrounded by fibrous capsule, and viable cells (left-side). Hematoxylin-eosin stain, low-power field (× 50); D: Gamma-Gandy bodies shown in the splenic lesions, suggesting previous history of portal hypertension due to portal vein tumor thrombosis. Hematoxylin-eosin stain, high-power field (× 200).

## CONCLUSION

We report the rare case of a patient with advanced HCC in whom LEN monotherapy showed long-term antitumor activity. Clinicians should be aware of radiological changes suggestive of intratumoral vascularity during treatment with the novel antiangiogenic agent LEN in patients with advanced HCC. Further studies are needed to elucidate the background of patients' favorable outcomes.

## ACKNOWLEDGEMENTS

We would like to thank Dr. Hiromi Serizawa from the Department of Pathology, Hachioji Medical Center Tokyo Medical University for their insightful comment on pathological findings; Dr. Seishi Nakatsuka from the Department of Radiology, Keio University for his precise comment on radiological findings.

## FOOTNOTES

**Author contributions:** Endo Y participated in the patient care, conceptualization, data curation, visualization and wrote the original article; Shimazu M participated in the patient care, reviewed the article, and supervised this report; Ozawa S, Kawachi S, Chiba N, Sakuragawa T, Uchi Y, Sunamura K reviewed the article; Edanami M participated in the patient care.

**Informed consent statement:** Written informed consent was obtained from this patient.

**Conflict-of-interest statement:** The authors have no conflict of interest to disclose.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

**Country/Territory of origin:** Japan

**ORCID number:** Yutaka Endo 0000-0001-7187-0124; Motohide Shimazu 0000-0001-5369-2256; Tadayuki Sakuragawa 0000-0002-4410-4923; Yusuke Uchi 0000-0002-0373-2659; Motonori Edanami 0000-0002-7169-1860; Ken Sunamura 0000-0001-7014-4550; Soji Ozawa 0000-0001-6130-1753; Naokazu Chiba 0000-0002-1846-5987; Shigeyuki Kawachi 0000-0001-7870-9149.

**S-Editor:** Yan JP
**L-Editor:** A
**P-Editor:** Yan JP

## REFERENCES

1 **Kokudo N**, Takemura N, Hasegawa K, Takayama T, Kubo S, Shimada M, Nagano H, Hatano E, Izumi N, Kaneko S, Kudo M, Iijima H, Genda T, Tateishi R, Torimura T, Igaki H, Kobayashi S, Sakurai H, Murakami T, Watadani T, Matsuyama Y. Clinical practice guidelines for hepatocellular carcinoma: The Japan Society of Hepatology 2017 (4th JSH-HCC guidelines) 2019 update. *Hepatol Res* 2019; **49**: 1109-1113 [PMID: 31336394 DOI: 10.1111/hepr.13411]

2 **Llovet JM**, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999; **19**: 329-338 [PMID: 10518312 DOI: 10.1055/s-2007-1007122]

3 **Heimbach JK**, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, Zhu AX, Murad MH, Marrero JA. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018; **67**: 358-380 [PMID: 28130846 DOI: 10.1002/hep.29086]

4 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]

5 **Bruix J**, Qin S, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, Yokosuka O, Rosmorduc O, Breder V, Gerolami R, Masi G, Ross PJ, Song T, Bronowicki JP, Ollivier-Hourmand I, Kudo M, Cheng AL, Llovet JM, Finn RS, LeBerre MA, Baumhauer A, Meinhardt G, Han G; RESORCE Investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017; **389**: 56-66 [PMID: 27932229 DOI: 10.1016/S0140-6736(16)32453-9]

6 **Zhu AX**, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, Assenat E, Brandi G, Pracht M, Lim HY, Rau KM, Motomura K, Ohno I, Merle P, Daniele B, Shin DB, Gerken G, Borg C, Hiriart JB, Okusaka T, Morimoto M, Hsu Y, Abada PB, Kudo M; REACH-2 study investigators. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2019; **20**: 282-296 [PMID: 30665869 DOI: 10.1016/S1470-2045(18)30937-9]

7 **Kudo M**, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018; **391**: 1163-1173 [PMID: 29433850 DOI: 10.1016/S0140-6736(18)30207-1]

8 **Takeda H**, Nishijima N, Nasu A, Komekado H, Kita R, Kimura T, Kudo M, Osaki Y. Long-term antitumor effect of lenvatinib on unresectable hepatocellular carcinoma with portal vein invasion. *Hepatol Res* 2019; **49**: 594-599 [PMID: 30499247 DOI: 10.1111/hepr.13294]

9 **Sato N**, Beppu T, Kinoshita K, Yuki H, Suyama K, Chiyonaga S, Motohara T, Komohara Y, Hara A, Akahoshi S. Conversion Hepatectomy for Huge Hepatocellular Carcinoma With Arterioportal Shunt After Chemoembolization and Lenvatinib Therapy. *Anticancer Res* 2019; **39**: 5695-5701 [PMID: 31570469 DOI: 10.21873/anticanres.13768]

10 **Liu Z**, Fu Z, Li G, Lin D. Downstaging of Recurrent Advanced Hepatocellular Carcinoma After Lenvatinib Treatment: Opportunities or Pitfalls? *Onco Targets Ther* 2020; **13**: 10267-10273 [PMID: 33116607 DOI: 10.2147/OTT.S261521]

11 **Matsuki R**, Kawai K, Suzuki Y, Kogure M, Nakazato T, Naruge D, Okano N, Seki S, Ohmori Y, Kawamura N, Kamma H, Hisamatsu T, Shibahara J, Mori T, Furuse J, Sakamoto Y. Pathological Complete Response in Conversion Hepatectomy Induced by Lenvatinib for Advanced Hepatocellular Carcinoma. *Liver Cancer* 2020; **9**: 358-360 [PMID: 32647636 DOI: 10.1159/000506202]

12 **Ohya Y**, Hayashida S, Tsuji A, Kuramoto K, Shibata H, Setoyama H, Hayashi H, Kuriwaki K, Sasaki M, Iizaka M, Nakahara O, Inomata Y. Conversion hepatectomy for advanced hepatocellular carcinoma after right portal vein transection and lenvatinib therapy. *Surg Case Rep* 2020; **6**: 318 [PMID: 33301055 DOI: 10.1186/s40792-020-01078-3]

13 **Tomonari T**, Sato Y, Tanaka H, Tanaka T, Taniguchi T, Sogabe M, Okamoto K, Miyamoto H, Muguruma N, Saito Y, Imura S, Bando Y, Shimada M, Takayama T. Conversion therapy for unresectable hepatocellular carcinoma after lenvatinib: Three case reports. *Medicine (Baltimore)* 2020; **99**: e22782 [PMID: 33080748 DOI: 10.1097/MD.0000000000022782]

14 **Yokoo H**, Takahashi H, Hagiwara M, Iwata H, Imai K, Saito Y, Matsuno N, Furukawa H. Successful hepatic resection for

recurrent hepatocellular carcinoma after lenvatinib treatment: A case report. *World J Hepatol* 2020; **12**: 1349-1357 [PMID: 33442460 DOI: 10.4254/wjh.v12.i12.1349]

15 **Chen S**, Wu Z, Shi F, Mai Q, Wang L, Wang F, Zhuang W, Chen X, Chen H, Xu B, Lai J, Guo W. Lenvatinib plus TACE with or without pembrolizumab for the treatment of initially unresectable hepatocellular carcinoma harbouring PD-L1 expression: a retrospective study. *J Cancer Res Clin Oncol* 2021 [PMID: 34453221 DOI: 10.1007/s00432-021-03767-4]

16 **Takahashi K**, Kim J, Takahashi A, Hashimoto S, Doi M, Furuya K, Hashimoto R, Owada Y, Ogawa K, Ohara Y, Akashi Y, Hisakura K, Enomoto T, Shimomura O, Noguchi M, Oda T. Conversion hepatectomy for hepatocellular carcinoma with main portal vein tumour thrombus after lenvatinib treatment: A case report. *World J Hepatol* 2021; **13**: 384-392 [PMID: 33815680 DOI: 10.4254/wjh.v13.i3.384]

17 **Yang X**, Xu H, Zuo B, Yang X, Bian J, Long J, Wang D, Zhang J, Ning C, Wang Y, Xun Z, Lu X, Mao Y, Sang X, Zhao H. Downstaging and resection of hepatocellular carcinoma in patients with extrahepatic metastases after stereotactic therapy. *Hepatobiliary Surg Nutr* 2021; **10**: 434-442 [PMID: 34430522 DOI: 10.21037/hbsn-21-188]

18 **Okamoto K**, Ikemori-Kawada M, Jestel A, von König K, Funahashi Y, Matsushima T, Tsuruoka A, Inoue A, Matsui J. Distinct binding mode of multikinase inhibitor lenvatinib revealed by biochemical characterization. *ACS Med Chem Lett* 2015; **6**: 89-94 [PMID: 25589937 DOI: 10.1021/ml500394m]

19 **Matsuki M**, Hoshi T, Yamamoto Y, Ikemori-Kawada M, Minoshima Y, Funahashi Y, Matsui J. Lenvatinib inhibits angiogenesis and tumor fibroblast growth factor signaling pathways in human hepatocellular carcinoma models. *Cancer Med* 2018; **7**: 2641-2653 [PMID: 29733511 DOI: 10.1002/cam4.1517]

20 **Kanzaki H**, Chiba T, Ao J, Koroki K, Kanayama K, Maruta S, Maeda T, Kusakabe Y, Kobayashi K, Kanogawa N, Kiyono S, Nakamura M, Kondo T, Saito T, Nakagawa R, Ogasawara S, Suzuki E, Ooka Y, Muroyama R, Nakamoto S, Yasui S, Tawada A, Arai M, Kanda T, Maruyama H, Mimura N, Kato J, Zen Y, Ohtsuka M, Iwama A, Kato N. The impact of FGF19/FGFR4 signaling inhibition in antitumor activity of multi-kinase inhibitors in hepatocellular carcinoma. *Sci Rep* 2021; **11**: 5303 [PMID: 33674622 DOI: 10.1038/s41598-021-84117-9]

21 **Kuzuya T**, Ishigami M, Ito T, Ishizu Y, Honda T, Ishikawa T, Fujishiro M. Sorafenib *vs*. Lenvatinib as First-line Therapy for Advanced Hepatocellular Carcinoma With Portal Vein Tumor Thrombosis. *Anticancer Res* 2020; **40**: 2283-2290 [PMID: 32234927 DOI: 10.21873/anticanres.14193]

22 **Chuma M**, Uojima H, Hiraoka A, Kobayashi S, Toyoda H, Tada T, Hidaka H, Iwabuchi S, Numata K, Itobayashi E, Itokawa N, Kariyama K, Ohama H, Hattori N, Hirose S, Shibata H, Tani J, Imai M, Tajiri K, Moriya S, Wada N, Iwasaki S, Fukushima T, Ueno M, Yasuda S, Atsukawa M, Nouso K, Fukunishi S, Watanabe T, Ishikawa T, Nakamura S, Morimoto M, Kagawa T, Sakamoto M, Kumada T, Maeda S. Analysis of efficacy of lenvatinib treatment in highly advanced hepatocellular carcinoma with tumor thrombus in the main trunk of the portal vein or tumor with more than 50% liver occupation: A multicenter analysis. *Hepatol Res* 2021; **51**: 201-215 [PMID: 33270323 DOI: 10.1111/hepr.13592]

23 **Hanada K**, Saito A, Nozawa H, Haruyama K, Hayashi N, Yamada M, Katagiri S, Katsuragawa H, Otsubo T, Takasaki K. Histopathologically-diagnosed splenic metastasis in a hepatocellular carcinoma case with adrenal metastasis. *Intern Med* 2004; **43**: 484-489 [PMID: 15283184 DOI: 10.2169/internalmedicine.43.484]

24 **Iwaki K**, Ohta M, Ishio T, Kai S, Iwashita Y, Shibata K, Himeno K, Seike M, Fujioka T, Kitano S. Metastasis of hepatocellular carcinoma to spleen and small intestine. *J Hepatobiliary Pancreat Surg* 2008; **15**: 213-219 [PMID: 18392718 DOI: 10.1007/s00534-007-1230-9]

25 **Sanefuji K**, Fukuzawa K, Okamoto M, Kai S, Takaki H, Hirotoshi Y, Motohiro A, Wakasugi K. Long-term surviving patient with inferior vena cava tumor thrombus and extrahepatic metastasis after spontaneous ruptured hepatocellular carcinoma. *Clin J Gastroenterol* 2011; **4**: 123-128 [PMID: 26190719 DOI: 10.1007/s12328-011-0205-1]

26 **Kim DH**, Jeong SY, Lee SW, Lee J, Ahn BC. Solitary splenic metastasis from hepatocellular carcinoma detected on (18)F-FDG PET/CT. *Clin Nucl Med* 2015; **40**: e325-e327 [PMID: 25546205 DOI: 10.1097/RLU.0000000000000659]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 March 27; 14(3): 268-270

DOI: 10.4240/wjgs.v14.i3.268

ISSN 1948-9366 (online)

LETTER TO THE EDITOR

# Is it sufficient to evaluate only preoperative systemic inflammatory biomarkers to predict postoperative complications after pancreaticoduodenectomy?

Semra Demirli Atici, Erdinc Kamer

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Shah OJ, India; Xu X, China

**Received:** November 21, 2021
**Peer-review started:** November 21, 2021
**First decision:** December 27, 2021
**Revised:** January 7, 2022
**Accepted:** March 6, 2022
**Article in press:** March 6, 2022
**Published online:** March 27, 2022

**Semra Demirli Atici, Erdinc Kamer,** Department of General Surgery, University of Health Sciences Tepecik Training and Research Hospital, İzmir 35180, Turkey

**Corresponding author:** Semra Demirli Atici, MD, Surgeon, Department of General Surgery, University of Health Sciences Tepecik Training and Research Hospital, Güney Mahallesi, 1140/1 Sokak No. 1 Yenişehir/Konak, İzmir 35180, Turkey. smrdemirli@hotmail.com

## Abstract

Postoperative morbidity and mortality rates are still very high among patients undergoing pancreaticoduodenectomy (PD). However, mortality rates secondary to morbidities that are detected early and well-managed postoperatively are lower among patients undergoing PD. Since early detection of complications plays a very important role in the management of these patients, many ongoing studies are being conducted on this subject. Recent endoscopic retrograde cholangiopancreatography and biliary drainage history of the patient study group is important for comparison of C-reactive protein (CRP), an inflammatory parameter evaluated in the retrospective study by Coppola *et al* published in the *World Journal of Gastrointestinal Surgery* and titled "Utility of preoperative systemic inflammatory biomarkers in predicting postoperative complications after pancreaticoduodenectomy: Literature review and single center experience". Therefore, it may be more appropriate to compare CRP values in randomized patients.

**Key Words:** Pancreaticoduodenectomy; Biliary drainage; Complications; C-reactive protein; CRP; Postoperative pancreatic fistula; Preoperative inflammatory markers

**Core Tip:** Predicting the complications that may develop after pancreaticoduodenectomy is very important in the management of patients. Preoperative and intraoperative scoring of patients with the combination of many parameters, such as pancreatic structure, pancreatic duct diameter, preoperative biliary drainage history and laboratory parameters, can guide the estimation of postoperative morbidity and management. Inflammatory biomarkers are easily affected by preoperative treatment. In order to discuss such situations, we think that it would be more appropriate to prospectively randomize patients in whom dynamic changes of inflammatory parameters can be observed with reported risk factors, including not only C-reactive protein value but also other inflammatory parameters, rather than these preoperative values.

**Citation:** Demirli Atici S, Kamer E. Is it sufficient to evaluate only preoperative systemic inflammatory biomarkers to predict postoperative complications after pancreaticoduodenectomy? *World J Gastrointest Surg* 2022; 14(3): 268-270
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i3/268.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i3.268

## TO THE EDITOR

Coppola *et al*[1] recently published a retrospective study on the role of preoperative inflammatory markers to detect the predictive efficiency of postoperative morbidity and mortality in pancreaticoduodenectomy (PD) patients.

Most patients diagnosed with pancreatic cancer undergo preoperative endoscopic retrograde cholangiopancreatography (ERCP) for diagnostic purposes. Preoperative biliary drainage (PBD) can be performed in addition to ERCP in these patients, who may also present with the complaint of obstructive jaundice[2].

PBD itself, duration of the PBD and the ERCP procedure can each increase the inflammatory response [3,4]. Coppola *et al*[1] found that preoperative C-reactive protein (CRP) level of > 8.81 mg/dL was a high-risk factor for general complications and abdominal collection, which was associated with the inflammatory parameters examined prior to PD operations. Unfortunately, the authors did not report the number of PBD procedures performed on the individual patients included in their study, nor did they provide information on the duration of time before the ERCP procedure was performed for any. This missing information may preclude our ability to make conclusions on the effectiveness of the baseline CRP value, since the recent history of ERCP and the history of PBD are unknown for the study's patients. A history of PBD will cause an increased inflammatory response. In addition, increased postoperative complication rates have been demonstrated in relation to a history of PBD and duration of biliary drainage. Prospective randomized controlled trials would be more instructive in determining the efficacy of preoperative inflammatory markers and their importance in the rates of postoperative complications due to PD.

## FOOTNOTES

**Author contributions:** Demirli Atici S and Kamer E wrote the manuscript; Kamer E reviewed and supervised the manuscript preparation; Both authors read and agreed to the published version of the manuscript.

**Conflict-of-interest statement:** The authors declare having no potential conflicts of interest with respect to the research, authorship and/or publication of this article.



**Country/Territory of origin:** Turkey

**ORCID number:** Semra Demirli Atici 0000-0002-8287-067X; Erdinc Kamer 0000-0002-5084-5867.

**Corresponding Author's Membership in Professional Societies:** Association of Surgeons of Great Britain & Ireland (ASGBI); Association of Coloproctology of Great Britain and Ireland (ACPGBI).

**S-Editor:** Wu YXJ

**L-Editor:** A
**P-Editor:** Wu YXJ

## REFERENCES

1 **Coppola A**, La Vaccara V, Caggiati L, Carbone L, Spoto S, Ciccozzi M, Angeletti S, Coppola R, Caputo D. Utility of preoperative systemic inflammatory biomarkers in predicting postoperative complications after pancreaticoduodenectomy: Literature review and single center experience. *World J Gastrointest Surg* 2021; **13**: 1216-1225 [PMID: 34754389 DOI: 10.4240/wjgs.v13.i10.1216]
2 **Sato N**, Kimura T, Kenjo A, Kofunato Y, Okada R, Ishigame T, Watanabe J, Marubashi S. Early intra-abdominal infection following pancreaticoduodenectomy:associated factors and clinical impact on surgical outcome. *Fukushima J Med Sci* 2020; **66**: 124-132 [PMID: 32963204 DOI: 10.5387/fms.2020-11]
3 **Adas G**, Kemik A, Adas M, Koc B, Gurbuz E, Akcakaya A, Karahan S. Metabolic and inflammatory responses after ERCP. *Int J Biomed Sci* 2013; **9**: 237-242 [PMID: 24711760]
4 **Matsumoto M**, Nakabayashi Y, Fujiwara Y, Funamizu N, Noaki R, Eto S, Sugano H, Otsuka M, Yanaga K. Duration of Preoperative Biliary Drainage as a Prognostic Factor After Pancreaticoduodenectomy for Pancreatic Head Cancer. *Anticancer Res* 2017; **37**: 3215-3219 [PMID: 28551667 DOI: 10.21873/anticanres.11683]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
**Telephone:** +1-925-3991568
**E-mail:** bpgoffice@wjgnet.com
**Help Desk:** https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 1948-9366 (online)

# World Journal of *Gastrointestinal Surgery*

*World J Gastrointest Surg* 2022 April 27; 14(4): 271-373

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 14 Number 4 April 27, 2022

*World Journal of Gastrointestinal Surgery*

**Monthly Volume 14 Number 4 April 27, 2022**

## Contents

### LETTER TO THE EDITOR

*World Journal of Gastrointestinal Surgery*

**Monthly Volume 14 Number 4 April 27, 2022**

## Contents

## ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Tatsuya Kin, MD, PhD, Adjunct Professor, Senior Scientist, Surgeon, Department of Clinical Islet Laboratory, University of Alberta, Edmonton T6G2C8, Alberta, Canada. tkin@ualberta.ca

## AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJGS* mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

## INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJGS* as 2.582; IF without journal self cites: 2.564; 5-year IF: 3.378; Journal Citation Indicator: 0.53; Ranking: 97 among 212 journals in surgery; Quartile category: Q2; Ranking: 73 among 92 journals in gastroenterology and hepatology; and Quartile category: Q4.

## RESPONSIBLE EDITORS FOR THIS ISSUE



**NAME OF JOURNAL**
*World Journal of Gastrointestinal Surgery*

**ISSN**
ISSN 1948-9366 (online)

**LAUNCH DATE**
November 30, 2009

**FREQUENCY**
Monthly



**PUBLICATION DATE**
April 27, 2022

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 April 27; 14(4): 271-275

DOI: 10.4240/wjgs.v14.i4.271

ISSN 1948-9366 (online)

DIAGNOSTIC AND THERAPEUTIC NORMS

# Including video and novel parameter-height of penetration of external anal sphincter-in magnetic resonance imaging reporting of anal fistula

Pankaj Garg, Baljit Kaur, Vipul D Yagnik, Sushil Dawka

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Ankrah AO, Netherlands; Ma C, China

**Received:** November 17, 2021
**Peer-review started:** November 17, 2021
**First decision:** December 27, 2021
**Revised:** December 28, 2021
**Accepted:** April 4, 2022
**Article in press:** April 4, 2022
**Published online:** April 27, 2022

**Pankaj Garg,** Department of Colorectal Surgery, Garg Fistula Research Institute, Panchkula 134113, Haryana, India

**Pankaj Garg,** Department of Colorectal Surgery, Indus International Hospital, Mohali 140507, Punjab, India

**Baljit Kaur,** Department of Radiology, SSRD Magnetic Resonance Imaging Institute, Chandigarh 160011, Chandigarh, India

**Vipul D Yagnik,** Department of Surgical Gastroenterology, Nishtha Surgical Hospital and Research Center, Patan 384265, Gujarat, India

**Sushil Dawka,** Department of Surgery, SSR Medical College, Belle Rive 744101, Belle Rive, Mauritius

**Corresponding author:** Pankaj Garg, MS, Associate Professor, Department of Colorectal Surgery, Garg Fistula Research Institute, 1043/15, Panchkula 134113, Haryana, India.
drgargpankaj@gmail.com

## Abstract

The main purpose of a radiologist's expertise in evaluation of anal fistula magnetic resonance imaging (MRI) is to benefit patients by decreasing the incontinence rate and increasing the healing rate. Any loss of vital information during the transfer of this data from the radiologist to the operating surgeon is unwarranted and is best prevented. In this regard, two methods are suggested. First, a short video to be attached with the standardized written report highlighting the vital parameters of the fistula. This would ensure minimum loss of information when it is conveyed from the radiologist to the operating surgeon. Second, inclusion of a new parameter, the amount of external sphincter involvement by the anal fistula. This parameter is usually not included in the MRI report. This can be evaluated as the height of penetration of the external anal sphincter (HOPE) by the fistula. The external anal sphincter plays a pivotal role in maintaining continence. This parameter (HOPE) is distinct from the 'height of internal opening' and assumes immense importance as its knowledge is paramount to prevent damage to the external anal sphincter by the surgeon during surgery.

**Key Words:** Magnetic resonance imaging; Anal fistula; External anal sphincter; Video reporting; Incontinence



**Core Tip:** There is loss of vital information when a fistula-in-ano magnetic resonance imaging (MRI) report from the radiologist is interpreted by the operating surgeon. To prevent this loss, a novel method is suggested: sending a small video highlighting vital fistula parameters along with the written MRI report. Also, another vital parameter is the amount of external sphincter involvement by the fistula. This parameter is not included in the MRI report and can be evaluated from the height of penetration of the external anal sphincter (HOPE) by the fistula. This parameter (HOPE) is distinct from the 'height of internal opening' and would help prevent damage to the external anal sphincter during surgery.

**Citation:** Garg P, Kaur B, Yagnik VD, Dawka S. Including video and novel parameter-height of penetration of external anal sphincter-in magnetic resonance imaging reporting of anal fistula. *World J Gastrointest Surg* 2022; 14(4): 271-275
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i4/271.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i4.271

## INTRODUCTION

Anal fistulas are associated with a high rate of recurrence and risk to the anal continence mechanism. The operating surgeons need to understand the exact position of the anal fistula and its relation to the anatomical structures in order to achieve high cure rate especially in complex anal fistulas. Magnetic resonance imaging (MRI) is the gold standard investigation used for anal fistulas. Usually, the MRI is interpreted by the radiologists who then send a written report to the operating surgeon and the surgeon performs the surgery after reading the radiologist's report. Formats have been suggested for reporting the MRI in fistulas[1,2]. However, utility of MRI to the operating surgeon can be improved immensely if the two features discussed below (inclusion of an MRI video and addition of HOPE parameter) are added to MRI report (Table 1).

First, when only a written report is sent by the radiologist who has analyzed the MRI scans, then a lot of important information is lost. This happens because the three-dimensional picture created in the radiologist's mind by the detailed visual analysis of the MRI scans cannot be replicated in the surgeon's mind just by reading the text in the radiologist's report. This loss of three-dimensional visual data can be prevented by sending a small video highlighting all relevant parameters along with the written report. Second, as discussed, the two main concerns in anal fistulas are recurrence and incontinence[3]. It is a known fact that the recurrence risk of fistula is directly related to surgeon's knowledge about the precise location of fistula tract's internal opening (where the fistula opens into the anal canal)[4,5]. On the other hand, the accurate assessment of the amount of external anal sphincter (EAS) involvement is key to prevent sphincter damage (incontinence)[6]. The importance of reporting the location of the internal opening has now been established[7], but the other equally important parameter, HOPE (height of penetration of external anal sphincter by the fistula) parameter is not reported by the radiologists (Figure 1). The EAS is mainly responsible for anal continence. HOPE parameter conveys the extent of involvement of the EAS to the operating surgeon and is thus pivotal to avoid damaging the EAS. The studies have demonstrated that when the surgeon performing the surgery is unsure of the accurate extent of EAS involvement, then the fistulotomy procedure is generally avoided and remains largely underutilized, even in simple anal fistulas, due to fear of incontinence in the mind of surgeons[8]. Fistulotomy is the simplest procedure for low anal fistulas and is associated with the maximum cure rate (93%-99%) and no other procedure has been shown to have success rate comparable to fistulotomy [6,8]. Therefore, lack of knowledge of HOPE (EAS involvement) leads to a lower healing rate which can be prevented by proper MRI reporting.

As the origin of most fistulas is at the level of the dentate line, the location of the internal opening in most of them is at that level only. The location of the internal opening does not accurately correspond to the amount of involvement of the EAS as penetration of the EAS by the fistula is often at a different level (Figure 1 and Video 1). Therefore, HOPE is the parameter which should be reported separately for helping the operating surgeon to precisely assess the amount of involvement of the EAS.

The level of understanding of fistula anatomy is greatly enhanced in the surgeon's mind when a small video of MRI scan showing the fistula characteristics is send along with the written report (Video 1). The key points regarding the fistula characteristics can be highlighted by using a pointer in the video

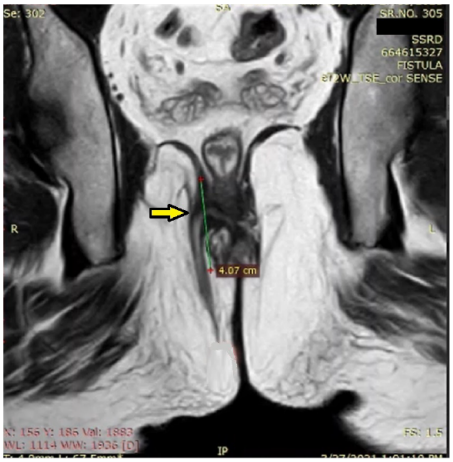
**Table 1 Format for the written magnetic resonance imaging report**

| Parameters | Example |
|---|---|
| **Primary tract** | The primary fistula tract |
| External opening | Is opening in perianal skin at 7 o'clock position |
| Course and location | It extends superiorly in right ischiorectal fossa from 7 to 8 o'clock position |
| Length | For a length of 6.35 cm |
| Location and height of penetration of EAS (HOPE) | and penetrates the EAS at 8 o'clock position involving approximately two-thirds of the EAS. It then bends inferiorly and |
| Intersphincteric tract | follows an intersphincteric route from 8 to 6 o'clock |
| Location and height Internal opening | and opens in the anal canal at the level of dentate line |
| Secondary extension- intersphincteric/ ischiorectal fossa/supralevator | There are no secondary extensions of primary tract |
| **Secondary tract** | There are no secondary tracts, |
| External opening | |
| Course and location | |
| **Associated abscess** | No associated abscess |
| **Supralevator or suprasphincteric tract** | And supralevator tract |
| **Sphincter anatomy** | The sphincters look normally preserved |
| **Classification** | Parks grade -II, SJUH[1] grade III |

[1]SJUH- St James's University Hospital classification.

Report: The primary fistula tract is opening in perianal skin at 7 o'clock position. It extends superiorly in right ischiorectal fossa from 7 to 8 o'clock position for a length of 6.35 cm and penetrates the external anal sphincter (EAS) at 8 o'clock position involving approximately two-thirds of the EAS. It then bends inferiorly and follows an intersphincteric route from 8 to 6 o'clock and opens in the anal canal at the level of dentate line. There are no secondary extensions of primary tract. There are no secondary tracts, no associated abscess, and no supralevator tract. The sphincters look normally preserved.

Impression- A right transsphincteric high fistula involving about two-thirds of the external anal sphincter, intersphincteric tract from 8 to 6 o'clock and internal opening at 6 o'clock at the level of dentate line. No secondary tract, abscess or supralevator extensions. Parks grade -II, SJUH grade III.




**DOI:** 10.4240/wjgs.v14.i4.271 **Copyright** ©The Author(s) 2022.

**Figure 1 Height of penetration of external sphincter parameter.** Demonstration of height of penetration of external anal sphincter by the fistula tract in the patient included in accompanying video (Video 1). Approximately 2/3 of the external sphincter is involved by the fistula tract. The yellow arrow demonstrates the point of penetration of external anal sphincter by the fistula tract.

(Video 1). The fistula parameters which should be mentioned and highlighted in the video have been listed in Table 2. The MRI report should also be standardized as shown in Table 1. An example of a final written report (of the fistula shown in Video 1 has been included at the bottom of Table 1 to clarify the format).

As can be seen, the novel parameter reported in this study, HOPE (height of penetration of external anal sphincter by the fistula tract) has also been incorporated in the video (Video 1) as well as the report

**Table 2 Format for reporting the fistula magnetic resonance imaging in the video**

| Axial Section T2-weighted |
|---|
| 1 External opening- location |
| 2 Define primary tracts |
| Location and course – Ischiorectal fossa/ Intersphincteric and clock-dial position |
| Location and 'height' of penetration of external anal sphincter (HOPE)- Point of penetration of external anal sphincter |
| Intersphincteric course |
| Location and height of internal opening- clock-dial position and whether it is at dentate line or higher |
| 3 Secondary tracts |
| 4 Associated abscesses |
| 5 Supralevator extension |
| 6 Additional internal opening |
| 7 Sphincter anatomy |
| **Axial section-STIR** |
| 1 Confirm findings of Axial-T2 |
| 2 Additional areas with inflammation |
| **Coronal T2-weighted** |
| 1 Confirm findings of Axial-T2 |
| 2 Length of tract |
| 3 Supralevator or suprasphincteric tract |
| 4 Confirm the 'height' of penetration of external anal sphincter (HOPE) by the fistula tract – Indicates the amount of external sphincter involved |
| 5 Confirm the 'height' of the site of internal opening |
| 6 Extent of fistula tract in anterior fistulas- relation with urethra |
| 7 Sphincter anatomy |
| **Coronal section- STIR** |
| 1 Confirm findings of Coronal-T2 |
| 2 Good to detect thin Intersphincteric collections |
| **Biplanar (Axial T-2 weighted + Coronal T-2 weighted)** |
| 1 Confirm the 'height' of the site of penetration of external sphincter by the fistula tract – Indicates the amount of external sphincter involved |
| 2 Confirm the 'height' of the site of internal opening |
| **Sagittal section** |
| 1 Extent of fistula tract in posterior fistulas- Relation with sacrococcygeal spine, presacral space |
| 2 Extent of fistula tract in anterior fistulas- Relation with urethra |

format (Table 1) (Figure 1). This parameter (HOPE) conveys the amount of EAS involved by the fistula tract (Figure 1).

The study concept was reviewed and approved by the Hospital-Institute Ethics Committee.

## CONCLUSION

This paper describes two novel additions to the MRI reporting of anal fistulas. The first is inclusion of a video along with the standardized written report (Tables 1 and 2, Video 1). This would prevent loss of vital three-dimensional data about the disease when the information is being transferred from the radiologist to the operating surgeon and would significantly enhance the surgeon's understanding of the fistula anatomy. Second, when the HOPE parameter (height of penetration of external anal sphincter by the fistula) is incorporated in the video as well as written report, the risk of EAS damage would be drastically reduced and the success rate of the surgical procedure would also be enhanced. Therefore,

HOPE should be reported as a separate parameter apart from the location of the internal opening. This format of MRI reporting (including a video) can also be stored on PACS (picture archiving and communication system)[9,10]. PACS provide storage and convenient access to medical images from where the clinician can see the report, images as well as the video as per their convenience[9,10].

## FOOTNOTES

**Author contributions:** Garg P conceived and designed the study, collected, and analyzed the data, revised the data, finally approved and submitted the manuscript (Guarantor of the review); Kaur B and Yagnik VD collected, and analyzed the data, revised the data, finally approved and submitted the manuscript; Dawka S critically analyzed the data, reviewed and edited the manuscript, finally approved and submitted the manuscript

**Conflict-of-interest statement:** None for all the authors.



**Country/Territory of origin:** India

**ORCID number:** Pankaj Garg 0000-0002-0800-3578; Baljit Kaur 0000-0002-3882-7578; Vipul D Yagnik 0000-0003-4008-6040; Sushil Dawka 0000-0002-9372-3683.

**Corresponding Author's Membership in Professional Societies:** American Society of Colon Rectum Surgeons; American Society of Gastrointestinal Endoscopic Surgeons; Endoscopic and Laparoscopic Surgeons of Asia; Association of Surgeons of India.

**S-Editor:** Wu YXJ
**L-Editor:** A
**P-Editor:** Wu YXJ

## REFERENCES

1 **Tuncyurek O**, Garces-Descovich A, Jaramillo-Cardoso A, Durán EE, Cataldo TE, Poylin VY, Gómez SF, Cabrera AM, Hegazi T, Beker K, Mortele KJ. Structured *vs* narrative reporting of pelvic MRI in perianal fistulizing disease: impact on clarity, completeness, and surgical planning. *Abdom Radiol (NY)* 2019; **44**: 811-820 [PMID: 30519819 DOI: 10.1007/s00261-018-1858-8]

2 **Ho E**, Rickard MJFX, Suen M, Keshava A, Kwik C, Ong YY, Yang J. Perianal sepsis: surgical perspective and practical MRI reporting for radiologists. *Abdom Radiol (NY)* 2019; **44**: 1744-1755 [PMID: 30770939 DOI: 10.1007/s00261-019-01920-9]

3 **Włodarczyk M**, Włodarczyk J, Sobolewska-Włodarczyk A, Trzciński R, Dziki Ł, Fichna J. Current concepts in the pathogenesis of cryptoglandular perianal fistula. *J Int Med Res* 2021; **49**: 300060520986669 [PMID: 33595349 DOI: 10.1177/0300060520986669]

4 **Mei Z**, Wang Q, Zhang Y, Liu P, Ge M, Du P, Yang W, He Y. Risk Factors for Recurrence after anal fistula surgery: A meta-analysis. *Int J Surg* 2019; **69**: 153-164 [PMID: 31400504 DOI: 10.1016/j.ijsu.2019.08.003]

5 **Sygut A**, Mik M, Trzcinski R, Dziki A. How the location of the internal opening of anal fistulas affect the treatment results of primary transsphincteric fistulas. *Langenbecks Arch Surg* 2010; **395**: 1055-1059 [PMID: 19924437 DOI: 10.1007/s00423-009-0562-0]

6 **Garg P**, Kaur B, Goyal A, Yagnik VD, Dawka S, Menon GR. Lessons learned from an audit of 1250 anal fistula patients operated at a single center: A retrospective review. *World J Gastrointest Surg* 2021; **13**: 340-354 [PMID: 33968301 DOI: 10.4240/wjgs.v13.i4.340]

7 **Halligan S**, Tolan D, Amitai MM, Hoeffel C, Kim SH, Maccioni F, Morrin MM, Mortele KJ, Rafaelsen SR, Rimola J, Schmidt S, Stoker J, Yang J. ESGAR consensus statement on the imaging of fistula-in-ano and other causes of anal sepsis. *Eur Radiol* 2020; **30**: 4734-4740 [PMID: 32307564 DOI: 10.1007/s00330-020-06826-5]

8 **Garg P**. Is fistulotomy still the gold standard in present era and is it highly underutilized? *Int J Surg* 2018; **56**: 26-30 [PMID: 29886281 DOI: 10.1016/j.ijsu.2018.06.009]

9 **Glazer DI**, Zhao AH, Lacson R, Burk KS, DiPiro PJ, Kapoor N, Khorasani R. Use of a PACS Embedded System for Communicating Radiologist to Technologist Learning Opportunities and Patient Callbacks. *Curr Probl Diagn Radiol* 2021 [DOI: 10.1067/j.cpradiol.2021.09.007]

10 **Huang HK**. Medical imaging, PACS, and imaging informatics: retrospective. *Radiol Phys Technol* 2014; **7**: 5-24 [PMID: 24311236 DOI: 10.1007/s12194-013-0245-y]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 April 27; 14(4): 276-285

DOI: 10.4240/wjgs.v14.i4.276

ISSN 1948-9366 (online)

*MINIREVIEWS*

# Current status of surgical management of patients with gastroenteropancreatic neuroendocrine neoplasms

Rafał Stankiewicz, Michał Grąt

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): E

**P-Reviewer:** Cigrovski Berkovic M, Croatia; Liu L, China; Wang WQ, China; Yang Z, China

**Received:** October 16, 2021
**Peer-review started:** October 16, 2021
**First decision:** December 3, 2021
**Revised:** December 18, 2021
**Accepted:** April 9, 2022
**Article in press:** April 9, 2022
**Published online:** April 27, 2022

**Rafał Stankiewicz, Michał Grąt,** Department of General, Transplant and Liver Surgery, Medical University of Warsaw, Warsaw 02-097, Poland

**Corresponding author:** Rafał Stankiewicz, MD, PhD, Surgeon, Department of General, Transplant and Liver Surgery, Medical University of Warsaw, 1A Banacha Street, Warsaw 02-097, Poland. rstankiewicz0@gmail.com

## Abstract

Neuroendocrine neoplasms (NENs) of the gastroenteropancreatic system are rare and heterogeneous tumours, yet with increasing prevalence. The most frequent primary sites are the small intestine, rectum, pancreas, and stomach. For a localized disease, surgical resection with local lymph nodes is usually curative with good overall and disease free survival. More complex situation is the treatment of locally advanced lesions, liver metastases, and, surprisingly, small asymptomatic tumours of the rectum and pancreas. In this review, we focus on the current role of surgical management of gastroenteropancreatic NENs. We present surgical approach for the most frequent primary sites. We highlight the role of endoscopic surgery and the watch-and-wait strategy for selected cases. As liver metastases pose an important clinical challenge, we present current indications and contraindications for liver resection and a role of liver transplantation for metastatic NENs.

**Key Words:** Gastroenteropancreatic neuroendocrine neoplasms; Treatment; Management; Liver metastases; Liver transplantation; Surgery



**Core Tip:** Neuroendocrine neoplasms of the gastroenteropancreatic system are a rare and heterogeneous group of tumours. Due to the advancement of the diagnostic methods like new serum biomarkers and more accurate imaging modalities (including positron emission tomography), its incidence is rising. We present a review focused on up-to-date recommended surgical management of these tumours. We discuss key points of treatment for the most frequent primary sites and liver metastases. Finally, we point areas where univocal consensus is still being achieved by presenting recommendations of various Oncological and Surgical Societies.

**Citation:** Stankiewicz R, Grąt M. Current status of surgical management of patients with gastroenteropancreatic neuroendocrine neoplasms. *World J Gastrointest Surg* 2022; 14(4): 276-285
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i4/276.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i4.276

## INTRODUCTION

Neuroendocrine neoplasms (NENs) arise from the diffuse neuroendocrine cell system and may occur at many different sites. NENs constitute a heterogeneous group of malignancies with neural phenotype and capacity to secrete amines and hormones. The gastroenteropancreatic (GEP) system and lungs are the most common primary tumour sites[1]. In this review, we focus on GEP-NENs.

Histological diagnosis is mandatory in all patients and can be carried out on resection specimen or core biopsies in an advanced disease. GEP-NENs should be classified based on morphology and proliferation into well-differentiated neuroendocrine tumours (NETs) (G1 to G3) and poorly-differentiated neuroendocrine cancers (NECs) (always G3) as shown in Table 1[2].

GEP-NENs are rare tumours with an annual incidence of 6.98 *per* 100000 persons in 2012 in the United States. According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, the rise in the annual number of cases can be observed in the last few decades with the most dramatic rise in patients older than 65 years (25.3 *per* 100000 persons). The order of frequency in NENs is the small intestine (1.05 *per* 100000), rectum (1.04 *per* 100000), and pancreas (0.48 *per* 100000)[3]. Hepatic metastases occur in 50%-75% of patients with NENs[4]. The most common primary sites in patients with NEN liver metastasis are the small intestine (56%), pancreas (10%), and colon (10%)[5]. The overall survival (OS) varies depending on primary site and grade. According to the SEER, the median OS for all patients is 9.3 years. NENs in the rectum and appendix had the best median OS, while NENs in the pancreas had the worst median OS. Localized, low grade (G1/G2) NETs have the best prognosis of long OS[3].

In this review, we focus on NENs of the GEP system and their step-by-step surgical management. We discuss tumours of the stomach, small intestine, rectum, and pancreas. Special emphasis is put on the treatment of hepatic metastases with the role of liver transplantation (LT).

## NENs OF THE STOMACH

Gastric NENs are slow growing, indolent tumours but with potential for aggressiveness and metastases. They are very often incidental findings with tendency to being multi-focal. Registries show a rising frequency in diagnosis of gastric NEN[6]. The SEER estimates an incidence of gastric NENs at 0.5 *per* 100000 persons[3].

There are three types of gastric NETs. Type I (70%-80%) is characterized by rare metastases and excellent prognosis and evolves on the background of chronic atrophic gastritis. Type II (5%-10%) is a result of Zollinger-Ellison syndrome and metastases to lymph nodes and the liver can be expected. The prognosis in patients with type II is very good. Type III (15%-20%) is a sporadic tumour with a very high prevalence of metastases either to lymph nodes (50%-100%) or the liver (22%-75%), and the prognosis is similar to that of gastric adenocarcinoma[7].

Endoscopic assessment of the lesions is crucial for further treatment. In addition to taking biopsies, the number and size of tumours should also be noted. Large lesions (> 1-2 cm) should also be assessed by endoscopic ultrasound (EUS) in terms of invasion depth and positive lymph nodes[8].

Surgical management of gastric NETs depends on several factors, such as tumour subtype, degree of differentiation, and presence or absence of invasion.

Treatments for type I and II gastric NETs are: (1) < 1 cm–endoscopic removal or monitoring by close endoscopic surveillance; (2) 1-2 cm and lesions with submucosal invasion (EUS)–snare polypectomy or endoscopic mucosal resection (EMR); and (3) > 2 cm–individualized strategy, either endoscopic resection (if possible) or surgical resection.

Treatments for type III gastric NETs are: Partial gastrectomy and lymph node dissection; in selected cases with lesions < 1-2 cm in size, EMR or endoscopic submucosal dissection (ESD) should be considered[9].

A potential alternative for patients with small type I lesions who cannot be managed endoscopically is treatment with somatostatin analogues (SSA)[10,11]. Also, netazepide (gastrin/cholecystokinin receptor antagonist) seems a promising option for patients with type I gastric NETs[12]. The downside of this agent though, is that if this treatment is stopped, tumours will regrow.

**Table 1 The 2019 World Health Organization classification for gastroenteropancreatic neuroendocrine neoplasms**

| Morphology | Grade | Mitotic count (2 mm²)[1] | Ki-67 index (%)[2] |
|---|---|---|---|
| Well-differentiated NETs | G1 | < 2 | < 3 |
| | G2 | 2-20 | 3-20 |
| | G3 | > 20 | > 20 |
| Poorly-differentiated NECs | | > 20 | > 20 |

[1]Of ten high power fields = 2 mm², at least 40 fields (at × 40 magnification) evaluated in areas of highest mitotic density.
[2]MIB1 antibody; percentage of 500-2000 tumour cells in areas with the highest nuclear labeling.
NET: Neuroendocrine tumour; NEC: Neuroendocrine cancer.

## NENs OF THE SMALL INTESTINE

The small intestine is the most common primary site of NENs. The presence of carcinoid heart disease, mesenteric lymph node metastases, distal abdominal lymph node metastases, liver metastatic burden, extra-abdominal metastases, skeletal involvement, and peritoneal carcinomatosis are independent prognostic factors for OS[13].

Surgical strategy for any locoregional small intestine NENs (SI-NENs) should be *en bloc* resection with its lymphatic drainage field, including the mesentery[14]. The entire small and large intestines should be evaluated (pre- and intra-operatively), as up to 40% of SI-NENs may have more than one site of primary gastrointestinal tract malignancy. Therefore, open resection seems preferred over laparoscopic, unless the latter enables a thorough examination by palpation, *i.e.*, by small incision[15].

SI-NENs have a significant metastatic potential, and even for lesions < 1 cm, nodal and distant metastases can be found in 12% and 5% of cases, respectively[16]. The liver is the most common site of metastases. In the setting of resectable synchronous primary tumour and hepatic metastases, resection of the primary tumour and lymph nodes, with combination with liver metastases is warranted[14]. According to ESMO guidelines, patients qualified for synchronous resection must have a tumour with a Ki-67 index < 10% (or slow growing tumour) and metastases limited to the liver[17]. Those exceeding the above mentioned criteria should be qualified for medical therapy (Figure 1).

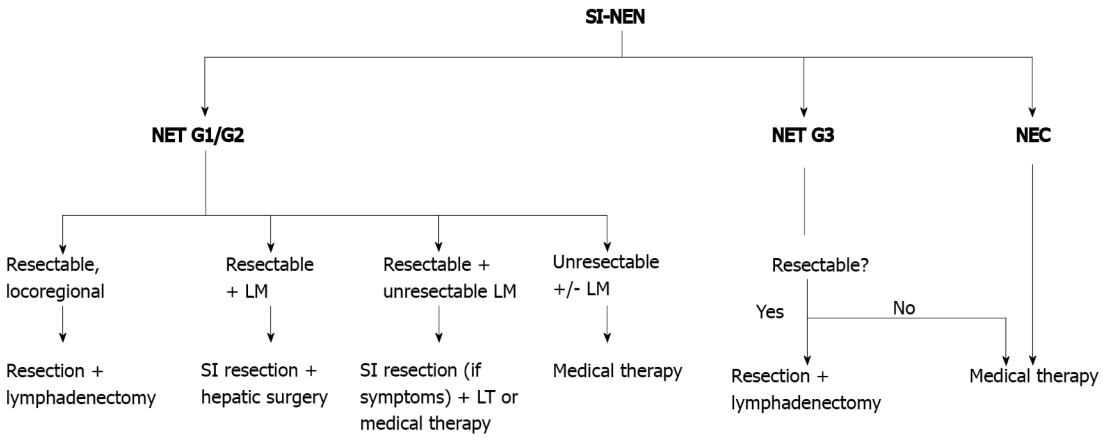
There are controversies over whether to resect or not the primary SI-NEN in the case of unresectable liver metastases. For symptomatic SI-NENs, resection with lymphadenectomy is advised[17]. ENETS guidelines acknowledge that the lack of prospective evidence does not permit a definite conclusion on any potential survival benefit in case of an asymptomatic disease–risk and benefit of the surgical intervention need to be considered individually[18]. In a systematic review, Capurso *et al*[19] presented benefit in survival (75-139 mo *vs* 50-88 mo) for patients who underwent primary site resection. This was based on six retrospective cohort studies which included a total number of 971 patients[19]. These findings were supported by the meta-analysis conducted by Almond *et al*[20]. They found an increase in median survival from 22 to 112 mo across six studies for patients who underwent primary site resection [20]. Conversely, a study by Daskalakis *et al*[21] based on the Swedish prospective database found no difference in terms of OS, morbidity, and 30-d mortality. Both groups of patients (161 underwent up-front locoregional surgery and 202 underwent delayed surgery) received systematic oncologic therapy for NENs (SSAs, interferon-alfa, liver-directed treatment, and peptide receptor radionuclide therapy) [21].

There is also some experience with intestinal transplantation for advanced local SI-NENs with unresectable mesenteric lymph node metastases[22]. This kind of therapy is still anecdotal and not accessible for all patients amenable for this treatment.

## NENs OF THE RECTUM

Rectal NENs are subepithelial lesions that are diagnosed with an increasing frequency. They constitute about 1% of rectal lesions, and are often accidental findings in colonoscopy[23]. Rectal NENs are usually small (< 1 cm in diameter) single lesions located 5-10 cm from the dental line[24]. Due to its typical macroscopic appearance, 95.9% of cases can be diagnosed on endoscopy alone[25]. Therefore, biopsy should only be considered in doubtful cases (atypical features) and in tumours that are more than 2 cm in size. Methods of treatment are either EMR, ESD, transanal endoscopic microsurgery, or surgery, depending on tumour size, grade, and lymph node and distant metastases. EUS is indicated for lesions more than 5 mm in size, to identify muscular layer invasion[23].

There is an accordance across the guidelines that all tumours larger than 2 cm should be removed surgically, either by low anterior resection or abdominoperineal resection. Tumours < 1 cm (G1, G2, and G3) should be removed by TEM or endoscopy. There are differences in the treatment strategy




**DOI:** 10.4240/wjgs.v14.i4.276 

**Figure 1 Therapeutic options for small intestinal neuroendocrine neoplasm.** SI-NEN: Small intestine neuroendocrine neoplasm; NET: Neuroendocrine tumour; G: Grade; NEC: Neuroendocrine cancer; LM: Liver metastases; LT: Liver transplantation.

concerning lesions 1-2 cm in diameter. In general, those lesions with muscularis propria invasion should be resected surgically. Other lesions should be considered individually with tendency to TEM or endoscopy[14,23,26].

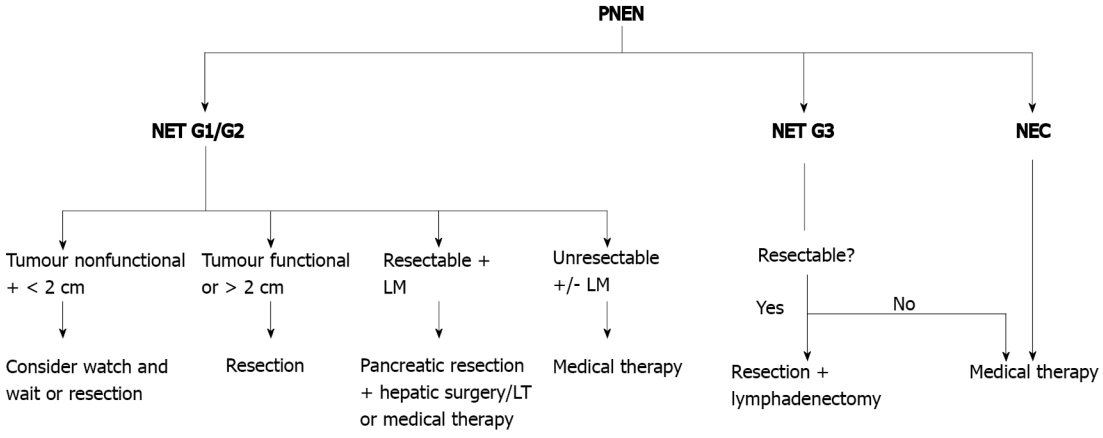
## NENs OF THE PANCREAS

Pancreatic neuroendocrine neoplasms (PNENs) are a subgroup of NENs that have relatively distinct biological behavior and clinical management compared with pancreatic adenocarcinoma. Like other NENs, they have a capacity to produce amines and hormones. PNENs are believed to arise from islet cells precursors[27]. Tumours that overproduce hormones may be associated with various clinical syndromes and are referred to as functional. In contrast, those that do not secrete hormones or secrete peptides which do not result in an obvious syndrome are termed non-functional (70% of PNENs). The most common hormones produced by PNENs are: Insulin (insulinoma; 1-32 million *per* year), gastrin (gastrinoma; 0.5-21.5 million *per* year), vasoactive intestinal peptide (VIPoma; 0.05-.02 million *per* year), and glucagon (glucagonoma; 0.01-0.1 million *per* year)[28]. Most PNENs are malignant, and upwards of 60% of patients will have metastatic disease at the time of diagnosis[27]. Ten to twenty percent are associated with inherited cancer syndromes, such as multiple endocrine neoplasia type 1 (MEN-1), von Hippel-Lindau syndrome, and neurofibromatosis type 1 (NF-1)[29]. Detailed management of these syndromes is beyond the scope of this review.

Disease stage and tumour grade (Table 1) must be assessed along with hormonal activity (if symptoms occur). Computed tomography is the most commonly used modality for staging. It is quick and widely available, and provides excellent anatomic definition of the pancreas, and lymph node or liver metastases. Histological diagnosis is usually based on samples taken by fine-needle aspiration or biopsy under EUS guidance.

Patients with functional PNENs irrespective of their size, should be evaluated for surgery[30]. Typical resections (pancreaticoduodenectomy, distal pancreatectomy, or total pancreatectomy) or tumour enucleation may be used. The latter should be considered primarily for small (< 2 cm), peripheral insulinomas[14]. The advantage of enucleation over standard resection is that the former is associated with a lower rate of postoperative pancreatic insufficiency, shorter operative time, and less operative blood loss[31]. In high-grade PNETs or PNECs, only oncologic resection (pancreaticoduodenectomy or distal pancreatectomy with lymphadenectomy) should be considered[9] (Figure 2).

Non-functional PNETs < 2 cm can be managed either surgically or by the wait-and-watch approach. In the meta-analysis conducted by Sallinen *et al*[32], small, sporadic PNETs in 344 patients were observed with satisfactory results[32]. In only 22% of cases, tumour growth was observed and no metastases were reported. Twelve percent of patients had surgery, and the most common indications were tumour growth (47%) and patients' preferences (31%). The same study showed more aggressive character of the small MEN-1 related PNETs. Over half of these patients had tumour growth during observation and in 9% of cases metastases were reported (distant and nodal). Opposite results come from the meta-analysis by Finkelstein *et al*[31]. Seven hundred and fourteen patients had tumours ≤ 2 cm, of which 587 underwent surgical resection and 127 were managed nonsurgically. Analysis showed an improved OS in the resection group at 1 year ($P = 0.745$), 3 years ($P < 0.001$), and 5 years ($P < 0.001$).




**DOI:** 10.4240/wjgs.v14.i4.276 

**Figure 2 Therapeutic options for pancreatic neuroendocrine neoplasm.** PNEN: Pancreatic neuroendocrine neoplasm; NET: Neuroendocrine tumour; G: Grade; NEC: Neuroendocrine cancer; LM: Liver metastases; LT: Liver transplantation.

In the management of small (< 2 cm in size) PNENs, the malignant potential of the tumour (rather small in most of the cases) and consequences of the aggressive pancreatic surgery (about a 30% complication rate and 1.7% mortality) must be taken under consideration[33]. Each patient should be individually assessed and when conservative approach is decided, close follow-up is recommended[14, 17].

## LIVER METASTASES

GEP-NENs at diagnosis are metastatic in 40%-95% of cases[4]. The most common metastatic sites are the liver, other intraperitoneal sites, bone, and the lung. Of all liver metastases, over half are from the small intestine. In about 10% of patients with liver NEN metastases, the primary site remains unknown[5]. Liver metastases represent the most crucial prognostic factor, irrespective of the primary NEN site. As G3 NETs and NECs present with aggressive behaviour (multifocal or bilobar growth, and anticipated high recurrence rate), systemic therapy is more commonly used than resection of the metastases.

Despite a high recurrence rate after resection (80%-95% within 5 years[34]), surgery remains the most favorable approach for selected (G1 and G2 NET) patients with liver metastases. Surgical treatment comprises resection and cytoreductive surgery for symptom management and improvement of survival. For a few decades, debulking threshold of resection was debated. In the first series presented in 1977, the authors achieved good symptom control with a threshold of 95% for debulking[35]. After being confirmed by other authors, such a threshold of approximately 90% for debulking was a goal to achieve [34,36]. Graff-Baker *et al*[37] found no difference in progression free survival between groups with > 70% debulking and > 90% debulking, and the OS for the study population was 88%[37]. Adoption of this lower debulking threshold of > 70%, along with the use of parenchymal-sparing techniques, allowed for more than 75% of patients to undergo hepatic cytoreduction. Also, when > 70% debulking is achieved, despite less than complete resection (R1/R0), comparable survival outcomes are observed as for R0 resection with > 70% cytoreduction[37]. In patients with carcinoid syndrome, it is important to control the hypersecretion of serotonin with SSA prior to surgery, in order to prevent carcinoid crisis [18].

When evaluating patients with NET liver metastases for surgical treatment, one must remember that current imaging modalities are limited in detecting small lesions. Accuracy of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging is calculated to be only 24%, 38%, and 49%, respectively. Lesions smaller than 2 mm are not visible in the preoperative assessment [38].

In patients who cannot be qualified for partial liver resection, LT is an option for a improved survival for selected patients[39]. LT for metastatic NETs provides a 5-year OS rate between 47% and 71%[40]. Each patient should be considered individually for prognostic factors that would impact post-LT outcomes. These prognostic factors are: (1) Histologic grade. LT is reserved for G1 and G2 NETs[39,41]. Le Treut *et al*[42] found a difference in survival between well and poorly differentiated NENs in the European Liver Transplant Registry (ELTR), reaching almost 30% in 5-year OS[42]. The histologic grade can be different between primary and metastatic tumours in the liver, and treatment is guided by the worst grade in the available specimen; (2) Tumour burden. The cut-off < 50% for this factor was arbitrarily set by Mazzaferro *et al*[39]. Data from the ELTR found that the 5-year OS rate after LT was 42% when the estimated tumoral invasion was over 50%, while it was 61% for tumours under 50%[42].

Some data challenge this threshold of 50% tumour burden, stating underestimation of tumour burden in the pre-LT workup in the early, ELTR-based studies[43]; (3) Primary tumour site. While Mazzaferro *et al* [39] allowed only NET liver metastases originating from portal venous drainage to be suitable for LT, further analysis of ELTR data did not support this idea[39,42]. Among the patients in the ELTR study, the 5-year survival rate of patients with bronchial tree origin NETs was comparable to that of patients with GEP NETs (53% and 40%-62%, respectively); and (4) Surgical control of the primary tumour. It is recommended to resect primary tumour before LT. This is to monitor biologic response of the liver metastases and to avoid surgical complications from simultaneous surgeries. Data from the ELTR showed an inferior 5-year OS rate in cases where primary tumour was resected during LT compared to those cases where tumour was resected before LT (22% and 56%, respectively). The same study found that in 13% to 14% of cases of NETs with liver metastases, the primary tumour is unknown. The 5-year survival of this cohort was 54%[42]. As such, patients without identifiable primary tumour are still good candidates for LT.

There are two major, widely accepted patients selection criteria for LT in NET metastases. The group from Milan proposed their criteria in 2007 and revised them in 2016[39,44]. The Milan-NET selection criteria are: (1) Histologic grade G1 or G2; (2) Portal drainage of the primary tumour; (3) Pre-transplant curative resection of all extrahepatic lesions; (4) Hepatic tumour invasion under 50%; (5) Duration of stable disease over 6 mo; and (6) Age under 60 year (relative).

The Milan group reported 5-year OS and disease-free survival rates of 97% and 89%, respectively. However, only 15% of patients referred to LT underwent LT[44].

In the United States, the current guidelines regarding LT for NET liver metastases are based on the Milan-NET criteria[45] with the following additional criteria: (1) Unresectable liver metastases; (2) Radiographic characteristics of NET of the liver lesions; (3) Negative metastatic workup by positron emission tomography (PET) scan; (4) Lack of extrahepatic tumour recurrence during the past 3 mo; (5) In the presence of positive findings for lymph node metastases by PET scan, the finding should become negative for 6 mo before re-listing; and (6) In the presence of extrahepatic solid organ metastases, the case will be permanently delisted.

There is no uniformly accepted selection criteria for NET-LT. Some of the above mentioned factors are still debated and waiting for validation, *i.e.,* patients age, primary resection before LT, hepatic tumour burden, and wait time for disease stabilization[45].

The high recurrence rate after NET-LT (31%-57%) remains an important clinical problem[40]. Available data on neoadjuvant or adjuvant therapy in NET-LT are scarce. Most of clinical experience comes from the series of patients who underwent liver resection[46-48].

For patients with unresectable primary GEP-NET and liver metastases, multivisceral transplantation (MVT) is also an option. Data on this treatment are limited by small case series and quality of the reported outcome. In the systematic review by Moris *et al*[40], the authors found that only 5.7% of patients from single center studies had MVT with various outcomes.

For patients with NET liver metastases beyond resection or LT, there is a number of liver-directed therapies. Ablative methods include microwave ablation, radiofrequency ablation, cryotherapy, and irreversible electroporation. Ischemia and necrosis of NET liver metastases can be achieved by occlusion of the arterial blood supply. Various methods are being used: Bland embolization, chemoembolization, drug eluting beads, and transarterial radioembolization ($^{90}$Ytrium). Detailed application of these methods is beyond the scope of this review.

## EXTRAHEPATIC METASTASES

The most common metastatic NEN sites are the liver, other intraperitoneal sites, bone, and the lung. Liver metastases occur in 40%-95% of cases[4], but peritoneal metastases can be a part of the metastatic tumour load in approximately 20% of cases[13]. The most common primary site for peritoneal metastases is the small bowel. Presence of peritoneal metastases has an adverse impact on patient survival, irrespective of the hepatic metastases[49,50]. For patients with well-differentiated G1/G2 NETs, complete cytoreductive surgery can prolong overall and disease free survival. In a study from France, patients with peritoneal metastasis were treated by peritonectomy with or without partial hepatectomy[48]. The 5-year and 10-year OS rates were 69% and 52%, respectively, and the 5-year and 10-year disease free survival rates were 17% and 6%, respectively. The benefit from addition of hyperthermic intraperitoneal chemotherapy to complete cytoreductive surgery is questionable, according to the authors of that study. For high-grade NEN peritoneal metastases, only medical treatment is advised[17].

## HIGH-GRADE GEP-NEN

Recent WHO classification of the NEN (Table 1) distinguished two groups of high-grade NENs[2]. Those are well-differentiated NETs G3 with a Ki-67 index > 20% and poorly-differentiated NECs. The

**Table 2 Clinical trials for surgical intervention in neuroendocrine neoplasm with open recruitment**

| Study title | Resection of metastatic PNETs after induction system treatment | Single-cell sequencing and establishment of models in NEN | Endoscopic ultrasound-guided radiofrequency ablation for the treatment | Prophylactic cholecystectomy in midgut NET patients who require primary tumor surgery |
|---|---|---|---|---|
| Primary site | Pancreas | GEP NEN | Pancreas | Jejunum, ileum, proximal colon |
| Study type | Observational | Observational | Interventional | Interventional |
| Multicentric | No | No | Yes | Yes |
| Primary purpose | NA | NA | Treatment | Treatment |
| Allocation | NA | NA | NA | Randomized |
| Estimated enrollment | 180 participants | 200 participants | 70 participants | 100 participants |
| Estimated study completion date | July 25, 2025 | December 2022 | June 1, 2021 | April 2025 |

NEN: Neuroendocrine neoplasm; PNET: Pancreatic neuroendocrine tumour; NET: Neuroendocrine tumour; GEP: Gastroenteropancreatic; NA: Non-announced.

term NENs G3 covers both types of those malignancies. The NEN G3 patients are a heterogeneous group concerning prognosis and treatment benefit. GEP NECs are usually highly aggressive, with a propensity for early metastases and dismal prognosis[51]. In the SEER database, the median survival is 34 mo with localized disease, 14-16 mo with regional disease, and 5 mo with distant disease[52]. Data on the NET G3 subgroup are extremely scarce, and they are mainly located in the pancreas and have a better prognosis than NEC[51].

The treatment recommendations for NEN G3 patients are mostly expert consensus supported by heterogeneous retrospective studies. The opinion is that surgery alone is rarely curative and that patients with limited disease should receive multimodality based treatment. The 5-year survival for localized disease depends on the primary site; the best is for colorectal, stomach, and pancreas primaries (40%-50%)[52]. Metastatic surgery for GEP NEC is not recommended and the treatment is with systemic chemotherapy (etoposide and a platinum agent)[53].

A National Cancer Database Study summarized the treatment and outcome of 1861 patients with high-grade NENs[54]. Over 64% of patients was in stage IV of the disease at the moment of diagnosis. The most common primary site was the large bowel (26.6%). Only about 28% of the study population were amenable for surgery. The median survival was 9.3 mo. That study did not distinguish NETs G3 and NECs due to disparity of study period and the novel WHO classification.

## FUTURE PERSPECTIVES

Most of the ongoing or recently finished clinical trials examined medical therapies in advanced NENs, demonstrating prolongation of the progression free survival[55]. NEN clinical trials pose logistical challenges due to the relative rarity of NENs and the necessity of multi-centric collaboration to ensure adequate recruitment. This is especially relevant to the concept of surgical trials in metastatic NENs, where only a quarter of patients may be amenable for surgery.

There are four ongoing, still recruiting, NEN clinical trials with surgical intervention (diagnostic or curative) (Table 2)[56]. Two are observational. One of those studies gives medical or surgical treatment dependent of patients' decision. Two studies are interventional and multicentric. None of those trials opens new surgical fields. For that to happen, new diagnostic and predictive tools must be developed. Clift *et al*[55] proposed three key areas: (1) The development of increasingly informative functional imaging; (2) The integration with imaging of real-time multianalyte genomic analysis of individual tumour; and (3) The application of system biology strategies to a multidimensional assessment of the relationship of the metabolome, the microbiome, and the proliferome to neuroendocrine neoplasia and the delineation of disease progression[55].

## CONCLUSION

Treatment of solitary NEN is often limited to tumour and local lymph node resection. When metastases appear, a multidisciplinary approach is often mandatory. A great variety of treatment modalities combined with a low incidence rate of NENs and their heterogeneity makes this group of tumours a

clinical challenge. Patients should be treated in experienced centers with access to the above mentioned modalities. Even in advanced metastatic NETs, selected groups of patients can reach a 5-year OS rate over 50%.

## FOOTNOTES

**Author contributions:** Stankiewicz R conceptualized the study, did literature search, wrote the paper, and approved the final version of the article; Grąt M conceptualized the study, did literature search, critically reviewed the paper, and approved the final version of the article.

**Conflict-of-interest statement:** None to declare.



**Country/Territory of origin:** Poland

**ORCID number:** Rafał Stankiewicz 0000-0003-0198-8287; Michał Grąt 0000-0003-3372-3072.

**Corresponding Author's Membership in Professional Societies:** Polish Transplant Society; Polish Society of Surgical Oncology.

**S-Editor:** Fan JR
**L-Editor:** Wang TQ
**P-Editor:** Fan JR

## REFERENCES

1 **Anaizi A**, Rizvi-Toner A, Valestin J, Schey R. Large cell neuroendocrine carcinoma of the lung presenting as pseudoachalasia: a case report. *J Med Case Rep* 2015; **9**: 56 [PMID: 25853982 DOI: 10.1186/s13256-015-0514-y]
2 **Nagtegaal ID**, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, Washington KM, Carneiro F, Cree IA; WHO Classification of Tumours Editorial Board. The 2019 WHO classification of tumours of the digestive system. *Histopathology* 2020; **76**: 182-188 [PMID: 31433515 DOI: 10.1111/his.13975]
3 **Dasari A**, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T, Yao JC. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol* 2017; **3**: 1335-1342 [PMID: 28448665 DOI: 10.1001/jamaoncol.2017.0589]
4 **Modlin IM**, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, Caplin M, Delle Fave G, Kaltsas GA, Krenning EP, Moss SF, Nilsson O, Rindi G, Salazar R, Ruszniewski P, Sundin A. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol* 2008; **9**: 61-72 [PMID: 18177818 DOI: 10.1016/S1470-2045(07)70410-2]
5 **Riihimäki M**, Hemminki A, Sundquist K, Sundquist J, Hemminki K. The epidemiology of metastases in neuroendocrine tumors. *Int J Cancer* 2016; **139**: 2679-2686 [PMID: 27553864 DOI: 10.1002/ijc.30400]
6 **Scherübl H**, Cadiot G, Jensen RT, Rösch T, Stölzel U, Klöppel G. Neuroendocrine tumors of the stomach (gastric carcinoids) are on the rise: small tumors, small problems? *Endoscopy* 2010; **42**: 664-671 [PMID: 20669078 DOI: 10.1055/s-0030-1255564]
7 **Grozinsky-Glasberg S**, Alexandraki KI, Angelousi A, Chatzellis E, Sougioultzis S, Kaltsas G. Gastric Carcinoids. *Endocrinol Metab Clin North Am* 2018; **47**: 645-660 [PMID: 30098721 DOI: 10.1016/j.ecl.2018.04.013]
8 **Metz DC**. Diagnosis of the Zollinger–Ellison syndrome. *Clin Gastroenterol Hepatol* 2012; **10**: 126-130 [PMID: 21806955 DOI: 10.1016/j.cgh.2011.07.012]
9 **Kunz PL**, Reidy-Lagunes D, Anthony LB, Bertino EM, Brendtro K, Chan JA, Chen H, Jensen RT, Kim MK, Klimstra DS, Kulke MH, Liu EH, Metz DC, Phan AT, Sippel RS, Strosberg JR, Yao JC; North American Neuroendocrine Tumor Society. Consensus guidelines for the management and treatment of neuroendocrine tumors. *Pancreas* 2013; **42**: 557-577 [PMID: 23591432 DOI: 10.1097/MPA.0b013e31828e34a4]
10 **Lau SC**, Abdel-Rahman O, Cheung WY. Improved survival with higher doses of octreotide long-acting release in gastroenteropancreatic neuroendocrine tumors. *Med Oncol* 2018; **35**: 123 [PMID: 30078166 DOI: 10.1007/s12032-018-1189-1]
11 **Massironi S**, Zilli A, Fanetti I, Ciafardini C, Conte D, Peracchi M. Intermittent treatment of recurrent type-1 gastric carcinoids with somatostatin analogues in patients with chronic autoimmune atrophic gastritis. *Dig Liver Dis* 2015; **47**: 978-983 [PMID: 26321479 DOI: 10.1016/j.dld.2015.07.155]
12 **Boyce M**, Moore AR, Sagatun L, Parsons BN, Varro A, Campbell F, Fossmark R, Waldum HL, Pritchard DM. Netazepide, a gastrin/cholecystokinin-2 receptor antagonist, can eradicate gastric neuroendocrine tumours in patients with autoimmune chronic atrophic gastritis. *Br J Clin Pharmacol* 2017; **83**: 466-475 [PMID: 27704617 DOI: 10.1111/bcp.13146]
13 **Norlén O**, Stålberg P, Öberg K, Eriksson J, Hedberg J, Hessman O, Janson ET, Hellman P, Åkerström G. Long-term

results of surgery for small intestinal neuroendocrine tumors at a tertiary referral center. *World J Surg* 2012; **36**: 1419-1431 [PMID: 21984144 DOI: 10.1007/s00268-011-1296-z]

14 **Shah MH**, Goldner WS, Benson AB, Bergsland E, Blaszkowsky LS, Brock P, Chan J, Das S, Dickson PV, Fanta P, Giordano T, Halfdanarson TR, Halperin D, He J, Heaney A, Heslin MJ, Kandeel F, Kardan A, Khan SA, Kuvshinoff BW, Lieu C, Miller K, Pillarisetty VG, Reidy D, Salgado SA, Shaheen S, Soares HP, Soulen MC, Strosberg JR, Sussman CR, Trikalinos NA, Uboha NA, Vijayvergia N, Wong T, Lynn B, Hochstetler C. Neuroendocrine and Adrenal Tumors, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2021; **19**: 839-868 [PMID: 34340212 DOI: 10.6004/jnccn.2021.0032]

15 **Pasquer A**, Walter T, Hervieu V, Forestier J, Scoazec JY, Lombard-Bohas C, Poncet G. Surgical Management of Small Bowel Neuroendocrine Tumors: Specific Requirements and Their Impact on Staging and Prognosis. *Ann Surg Oncol* 2015; **22** Suppl 3: S742-S749 [PMID: 26014153 DOI: 10.1245/s10434-015-4620-2]

16 **Rorstad O**. Prognostic indicators for carcinoid neuroendocrine tumors of the gastrointestinal tract. *J Surg Oncol* 2005; **89**: 151-160 [PMID: 15719376 DOI: 10.1002/jso.20179]

17 **Pavel M**, Öberg K, Falconi M, Krenning EP, Sundin A, Perren A, Berruti A; ESMO Guidelines Committee. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2020; **31**: 844-860 [PMID: 32272208 DOI: 10.1016/j.annonc.2020.03.304]

18 **Pavel M**, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, Krenning E, Knigge U, Salazar R, Pape UF, Öberg K; Vienna Consensus Conference participants. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. *Neuroendocrinology* 2016; **103**: 172-185 [PMID: 26731013 DOI: 10.1159/000443167]

19 **Capurso G**, Rinzivillo M, Bettini R, Boninsegna L, Delle Fave G, Falconi M. Systematic review of resection of primary midgut carcinoid tumour in patients with unresectable liver metastases. *Br J Surg* 2012; **99**: 1480-1486 [PMID: 22972490 DOI: 10.1002/bjs.8842]

20 **Almond LM**, Hodson J, Ford SJ, Gourevitch D, Roberts KJ, Shah T, Isaac J, Desai A. Role of palliative resection of the primary tumour in advanced pancreatic and small intestinal neuroendocrine tumours: A systematic review and meta-analysis. *Eur J Surg Oncol* 2017; **43**: 1808-1815 [PMID: 28583792 DOI: 10.1016/j.ejso.2017.05.016]

21 **Daskalakis K**, Karakatsanis A, Hessman O, Stuart HC, Welin S, Tiensuu Janson E, Öberg K, Hellman P, Norlén O, Stålberg P. Association of a Prophylactic Surgical Approach to Stage IV Small Intestinal Neuroendocrine Tumors With Survival. *JAMA Oncol* 2018; **4**: 183-189 [PMID: 29049611 DOI: 10.1001/jamaoncol.2017.3326]

22 **Frilling A**, Giele H, Vrakas G, Reddy S, Macedo R, Al-Nahhas A, Wasan H, Clift AK, Gondolesi GE, Vianna RM, Friend P, Vaidya A. Modified liver-free multivisceral transplantation for a metastatic small bowel neuroendocrine tumor: a case report. *Transplant Proc* 2015; **47**: 858-862 [PMID: 25689880 DOI: 10.1016/j.transproceed.2015.01.007]

23 **Ramage JK**, De Herder WW, Delle Fave G, Ferolla P, Ferone D, Ito T, Ruszniewski P, Sundin A, Weber W, Zheng-Pei Z, Taal B, Pascher A; Vienna Consensus Conference participants. ENETS Consensus Guidelines Update for Colorectal Neuroendocrine Neoplasms. *Neuroendocrinology* 2016; **103**: 139-143 [PMID: 26730835 DOI: 10.1159/000443166]

24 **Chablaney S**, Zator ZA, Kumta NA. Diagnosis and Management of Rectal Neuroendocrine Tumors. *Clin Endosc* 2017; **50**: 530-536 [PMID: 29207857 DOI: 10.5946/ce.2017.134]

25 **Lee SP**, Sung IK, Kim JH, Lee SY, Park HS, Shim CS. The effect of preceding biopsy on complete endoscopic resection in rectal carcinoid tumor. *J Korean Med Sci* 2014; **29**: 512-518 [PMID: 24753698 DOI: 10.3346/jkms.2014.29.4.512]

26 **Anthony LB**, Strosberg JR, Klimstra DS, Maples WJ, O'Dorisio TM, Warner RR, Wiseman GA, Benson AB 3rd, Pommier RF; North American Neuroendocrine Tumor Society (NANETS). The NANETS consensus guidelines for the diagnosis and management of gastrointestinal neuroendocrine tumors (nets): well-differentiated nets of the distal colon and rectum. *Pancreas* 2010; **39**: 767-774 [PMID: 20664474 DOI: 10.1097/MPA.0b013e3181ec1261]

27 **Schimmack S**, Svejda B, Lawrence B, Kidd M, Modlin IM. The diversity and commonalities of gastroenteropancreatic neuroendocrine tumors. *Langenbecks Arch Surg* 2011; **396**: 273-298 [PMID: 21274559 DOI: 10.1007/s00423-011-0739-1]

28 **Ma ZY**, Gong YF, Zhuang HK, Zhou ZX, Huang SZ, Zou YP, Huang BW, Sun ZH, Zhang CZ, Tang YQ, Hou BH. Pancreatic neuroendocrine tumors: A review of serum biomarkers, staging, and management. *World J Gastroenterol* 2020; **26**: 2305-2322 [PMID: 32476795 DOI: 10.3748/wjg.v26.i19.2305]

29 **Scott AT**, Howe JR. Evaluation and Management of Neuroendocrine Tumors of the Pancreas. *Surg Clin North Am* 2019; **99**: 793-814 [PMID: 31255207 DOI: 10.1016/j.suc.2019.04.014]

30 **Maurizi A**, Partelli S, Falconi M. Pancreatic Surgery. *Front Horm Res* 2015; **44**: 139-148 [PMID: 26303709 DOI: 10.1159/000382143]

31 **Finkelstein P**, Sharma R, Picado O, Gadde R, Stuart H, Ripat C, Livingstone AS, Sleeman D, Merchant N, Yakoub D. Pancreatic Neuroendocrine Tumors (panNETs): Analysis of Overall Survival of Nonsurgical Management Versus Surgical Resection. *J Gastrointest Surg* 2017; **21**: 855-866 [PMID: 28255853 DOI: 10.1007/s11605-017-3365-6]

32 **Sallinen V**, Le Large TY, Galeev S, Kovalenko Z, Tieftrunk E, Araujo R, Ceyhan GO, Gaujoux S. Surveillance strategy for small asymptomatic non-functional pancreatic neuroendocrine tumors - a systematic review and meta-analysis. *HPB (Oxford)* 2017; **19**: 310-320 [PMID: 28254159 DOI: 10.1016/j.hpb.2016.12.010]

33 **Jung JG**, Lee KT, Woo YS, Lee JK, Lee KH, Jang KT, Rhee JC. Behavior of Small, Asymptomatic, Nonfunctioning Pancreatic Neuroendocrine Tumors (NF-PNETs). *Medicine (Baltimore)* 2015; **94**: e983 [PMID: 26131843 DOI: 10.1097/MD.0000000000000983]

34 **Sarmiento JM**, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, Que FG. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. *J Am Coll Surg* 2003; **197**: 29-37 [PMID: 12831921 DOI: 10.1016/S1072-7515(03)00230-8]

35 **Foster JH**, Berman MM. Solid liver tumors. *Major Probl Clin Surg* 1977; **22**: 1-342 [PMID: 839860]

36 **Que FG**, Nagorney DM, Batts KP, Linz LJ, Kvols LK. Hepatic resection for metastatic neuroendocrine carcinomas. *Am J Surg* 1995; **169**: 36-42; discussion 42 [PMID: 7817996 DOI: 10.1016/s0002-9610(99)80107-x]

37 **Graff-Baker AN**, Sauer DA, Pommier SJ, Pommier RF. Expanded criteria for carcinoid liver debulking: Maintaining survival and increasing the number of eligible patients. *Surgery* 2014; **156**: 1369-76; discussion 1376 [PMID: 25456912

DOI: 10.1016/j.surg.2014.08.009]
38 **Elias D**, Lefevre JH, Duvillard P, Goéré D, Dromain C, Dumont F, Baudin E. Hepatic metastases from neuroendocrine tumors with a "thin slice" pathological examination: they are many more than you think. *Ann Surg* 2010; **251**: 307-310 [PMID: 20010089 DOI: 10.1097/SLA.0b013e3181bdf8cf]
39 **Mazzaferro V**, Pulvirenti A, Coppa J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? *J Hepatol* 2007; **47**: 460-466 [PMID: 17697723 DOI: 10.1016/j.jhep.2007.07.004]
40 **Moris D**, Tsilimigras DI, Ntanasis-Stathopoulos I, Beal EW, Felekouras E, Vernadakis S, Fung JJ, Pawlik TM. Liver transplantation in patients with liver metastases from neuroendocrine tumors: A systematic review. *Surgery* 2017; **162**: 525-536 [PMID: 28624178 DOI: 10.1016/j.surg.2017.05.006]
41 **Shimata K**, Sugawara Y, Hibi T. Liver transplantation for unresectable pancreatic neuroendocrine tumors with liver metastases in an era of transplant oncology. *Gland Surg* 2018; **7**: 42-46 [PMID: 29629319 DOI: 10.21037/gs.2017.12.11]
42 **Le Treut YP**, Grégoire E, Klempnauer J, Belghiti J, Jouve E, Lerut J, Castaing D, Soubrane O, Boillot O, Mantion G, Homayounfar K, Bustamante M, Azoulay D, Wolf P, Krawczyk M, Pascher A, Suc B, Chiche L, de Urbina JO, Mejzlik V, Pascual M, Lodge JP, Gruttadauria S, Paye F, Pruvot FR, Thorban S, Foss A, Adam R; For ELITA. Liver transplantation for neuroendocrine tumors in Europe-results and trends in patient selection: a 213-case European liver transplant registry study. *Ann Surg* 2013; **257**: 807-815 [PMID: 23532105 DOI: 10.1097/SLA.0b013e31828ee17c]
43 **Olausson M**, Friman S, Herlenius G, Cahlin C, Nilsson O, Jansson S, Wängberg B, Ahlman H. Orthotopic liver or multivisceral transplantation as treatment of metastatic neuroendocrine tumors. *Liver Transpl* 2007; **13**: 327-333 [PMID: 17318853 DOI: 10.1002/Lt.21056]
44 **Mazzaferro V**, Sposito C, Coppa J, Miceli R, Bhoori S, Bongini M, Camerini T, Milione M, Regalia E, Spreafico C, Gangeri L, Buzzoni R, de Braud FG, De Feo T, Mariani L. The Long-Term Benefit of Liver Transplantation for Hepatic Metastases From Neuroendocrine Tumors. *Am J Transplant* 2016; **16**: 2892-2902 [PMID: 27134017 DOI: 10.1111/ajt.13831]
45 **OPTN/UNOS Liver and Intestinal Organ Transplantation Committee**. Briefing Paper: Liver Review Board Guidance Documents. 2017. [cited 14 December 2021]. Available from: https://optn.transplant.hrsa.gov/media/2175/Liver_boardreport_guidance_201706.pdf
46 **Frilling A**, Modlin IM, Kidd M, Russell C, Breitenstein S, Salem R, Kwekkeboom D, Lau WY, Klersy C, Vilgrain V, Davidson B, Siegler M, Caplin M, Solcia E, Schilsky R; Working Group on Neuroendocrine Liver Metastases. Recommendations for management of patients with neuroendocrine liver metastases. *Lancet Oncol* 2014; **15**: e8-21 [PMID: 24384494 DOI: 10.1016/S1470-2045(13)70362-0]
47 **Sowa-Staszczak A**, Pach D, Chrzan R, Trofimiuk M, Stefańska A, Tomaszuk M, Kołodziej M, Mikołajczak R, Pawlak D, Hubalewska-Dydejczyk A. Peptide receptor radionuclide therapy as a potential tool for neoadjuvant therapy in patients with inoperable neuroendocrine tumours (NETs). *Eur J Nucl Med Mol Imaging* 2011; **38**: 1669-1674 [PMID: 21559978 DOI: 10.1007/s00259-011-1835-8]
48 **Maire F**, Hammel P, Kianmanesh R, Hentic O, Couvelard A, Rebours V, Zappa M, Raymond E, Sauvanet A, Louvet C, Lévy P, Belghiti J, Ruszniewski P. Is adjuvant therapy with streptozotocin and 5-fluorouracil useful after resection of liver metastases from digestive endocrine tumors? *Surgery* 2009; **145**: 69-75 [PMID: 19081477 DOI: 10.1016/j.surg.2008.08.007]
49 **Wright MF**, Cates J, Gonzalez RS, Das S, Berlin JD, Shi C. Impact of Peritoneal Metastasis on Survival of Patients With Small Intestinal Neuroendocrine Tumor. *Am J Surg Pathol* 2019; **43**: 559-563 [PMID: 30702499 DOI: 10.1097/PAS.0000000000001225]
50 **Das S**, Shi C, Koyama T, Huang Y, Gonzalez R, Idrees K, Bailey CE, Berlin J. Peritoneal Carcinomatosis in Well-Differentiated Small-Intestinal Neuroendocrine Tumors with Mesenteric Tumor Deposits. *J Med Surg Pathol* 2019; **4**: 1-10 [PMID: 32322781]
51 **Heetfeld M**, Chougnet CN, Olsen IH, Rinke A, Borbath I, Crespo G, Barriuso J, Pavel M, O'Toole D, Walter T; other Knowledge Network members. Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer* 2015; **22**: 657-664 [PMID: 26113608 DOI: 10.1530/ERC-15-0119]
52 **Dasari A**, Mehta K, Byers LA, Sorbye H, Yao JC. Comparative study of lung and extrapulmonary poorly differentiated neuroendocrine carcinomas: A SEER database analysis of 162,983 cases. *Cancer* 2018; **124**: 807-815 [PMID: 29211313 DOI: 10.1002/cncr.31124]
53 **Patta A**, Fakih M. First-line cisplatin plus etoposide in high-grade metastatic neuroendocrine tumors of colon and rectum (MCRC NET): review of 8 cases. *Anticancer Res* 2011; **31**: 975-978 [PMID: 21498724]
54 **Alese OB**, Jiang R, Shaib W, Wu C, Akce M, Behera M, El-Rayes BF. High-Grade Gastrointestinal Neuroendocrine Carcinoma Management and Outcomes: A National Cancer Database Study. *Oncologist* 2019; **24**: 911-920 [PMID: 30482824 DOI: 10.1634/theoncologist.2018-0382]
55 **Clift AK**, Kidd M, Bodei L, Toumpanakis C, Baum RP, Oberg K, Modlin IM, Frilling A. Neuroendocrine Neoplasms of the Small Bowel and Pancreas. *Neuroendocrinology* 2020; **110**: 444-476 [PMID: 31557758 DOI: 10.1159/000503721]
56 **NIH**. ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world. [cited 14 December 2021]. Available from: https://clinicaltrials.gov/

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 April 27; 14(4): 286-303

DOI: 10.4240/wjgs.v14.i4.286

ISSN 1948-9366 (online)

*MINIREVIEWS*

# Gastrostomy tubes: Fundamentals, periprocedural considerations, and best practices

Anand Rajan, Peerapol Wangrattanapranee, Jonathan Kessler, Trilokesh Dey Kidambi, James H Tabibian

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Balakrishnan DS, India; Masaki S, Japan

**Received:** December 18, 2021
**Peer-review started:** December 18, 2021
**First decision:** January 27, 2022
**Revised:** February 9, 2022
**Accepted:** April 3, 2022
**Article in press:** April 3, 2022
**Published online:** April 27, 2022

**Anand Rajan,** Department ofGastroenterology, Olive View-UCLA Medical Center, Sylmar, CA 91342, United States

**Anand Rajan, Trilokesh Dey Kidambi,** Department ofGastroenterology, City of Hope Medical Center, Duarte, CA 91010, United States

**Peerapol Wangrattanapranee,** Department ofMedicine, Keck School of Medicine of USC, Los Angeles, CA 90033, United States

**Jonathan Kessler,** Department ofInterventional Radiology, City of Hope Medical Center, Duarte, CA 91010, United States

**James H Tabibian,** Department ofGastroenterology, UCLA-Olive View Medical Center, Sylmar, CA 91342, United States

**Corresponding author:** James H Tabibian, FACP, MD, PhD, Associate Professor, Department of Gastroenterology, UCLA-Olive View Medical Center, 14445 Olive View Drive, Sylmar, CA 91342, United States. jtabibian@dhs.lacounty.gov

## Abstract

Gastrostomy tube placement is a procedure that achieves enteral access for nutrition, decompression, and medication administration. Preprocedural evaluation and selection of patients is necessary to provide optimal benefit and reduce the risk of adverse events (AEs). Appropriate indications, contraindications, ethical considerations, and comorbidities of patients referred for gastrostomy placement should be weighed and balanced. Additionally, endoscopist should consider either a transoral or transabdominal approach is appropriate, and radiologic or surgical gastrostomy tube placement is needed. However, medical history, physical examination, and imaging prior to the procedure should be considered to tailor the appropriate approach and reduce the risk of AEs.

**Key Words:** Gastrostomy; Gastropexy; Enterostomy; Decompression; Enteral nutrition; Endoscopy

**Core Tip:** We reviewed 179 articles and compiled suggested considerations, especially for endoscopists, in the preprocedural evaluation of gastrostomy candidates. Patients referred to for gastrostomy tube placement should be evaluated for indications, contraindications, ethical considerations, and comorbidities. Additionally, the proceduralist should consider whether radiologic or surgical tube placement may be more appropriate, and whether a transoral or transabdominal approach is appropriate. Prior to the procedure, physical examination, imaging, and other interventions should be performed to reduce adverse events.

**Citation:** Rajan A, Wangrattanapranee P, Kessler J, Kidambi TD, Tabibian JH. Gastrostomy tubes: Fundamentals, periprocedural considerations, and best practices. *World J Gastrointest Surg* 2022; 14(4): 286-303
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i4/286.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i4.286

## INTRODUCTION

Percutaneous gastrostomy is a method of inserting a tube transabdominally into the stomach to provide nutrition, decompress, and/or administer medication. The first of these is the most common indication for gastrostomy tube placement and is critical to preserve nutritional status and improve prognosis for a wide spectrum of conditions and illnesses[1]. Minimally invasive methods of gastrostomy placement have been developed and include, but are not limited to, percutaneous endoscopic gastrostomy (PEG). Since this is an invasive procedure associated with a number of potential adverse events (AEs), appropriate patients and technique selection is essential.

Over the past decade, all-cause mortality from PEG placement has decreased approximately 40% despite AE rates, time to placement, indications, and comorbidities of patients having generally remained the same[2]. This could be attributable to better patient selection and optimization of placement technique. However, there is still a considerable patient cohort that is exposed to PEG and/or other gastrostomy tube placement without adequate preprocedural planning[3].

In this review, we discuss gastrostomy tube indications, contraindications, optimal gastrostomy technique, informed consent, physical exam tenets, and imaging considerations as well as management of anticoagulation and antibiotic prophylaxis. We also provide practical pearls to decrease the risk of various AEs and equip the proceduralist with a comprehensive preprocedural approach, as summarized in Table 1.

## GASTROSTOMY TUBE INDICATIONS

Regardless of clinical context, gastrostomy tube placement is mostly indicated to provide nutrition and bypass obstruction. In certain conditions such as gastric volvulus, gastrostomy tube can be utilized for gastropexy procedure, though these are beyond the scope of the discussion.

It is appropriate to place the gastrostomy tube in patients with underlying conditions that require more than four weeks of artificial enteral nutrition. Such conditions include Guillain-Barre syndrome, acute stroke, intracranial trauma, anorexia nervosa, hyperemesis gravidarum, severe burns, facial trauma, esophageal disease, malnutrition especially in patients prior to transplantation, and head and neck tumors undergoing treatment[4]. Moreover, it may also be appropriate to place gastrostomy tubes permanently in certain conditions with poor prognosis to improve quality of life. Such conditions include neurological diseases like multiple sclerosis and amyotrophic lateral sclerosis, advanced head and neck tumors, oropharyngeal malformations, advanced esophageal or gastric malignancy, rheumatologic disorders associated with esophageal dysfunction such as scleroderma, cystic fibrosis, and amyloidosis[5] (Table 2).

## CONTRAINDICATIONS

Relative contraindications include recent gastrointestinal (GI) bleeding, hemodynamic instability, ascites, respiratory failure, peritoneal carcinomatosis, and anatomical alterations[2]. Absolute contraindications include mechanical obstruction of the GI tract unless procedure is indicated for decompression, active peritonitis, uncorrectable coagulopathy, and bowel ischemia[5] (Table 3).

**Table 1 Periprocedural pearls for gastrostomy tube placement**

| |
|---|
| Recognize indications, relative contraindications, and absolute contraindications for gastrostomy tube placement |
| Ensure appropriate informed consent and discussion of the benefits of gastrostomy tubes |
| Ensure correct selection of gastrostomy technique: |
| Transoral techniques should be first line except in select indications where transabdominal techniques maybe more appropriate |
| Placement by radiology is appropriate when the endoscopist is not trained in the transoral or transabdominal technique necessary or lacks availability of materials |
| Laparoscopic tube placement should be utilized when endoscopic or radiographic gastrostomy fails or is contraindicated |
| Perform certain periprocedural interventions to reduce adverse events: |
| Physical exam for oropharyngeal and abdominal wall abnormalities, ascites, and obesity |
| Hold anticoagulation and antiplatelet therapy appropriately and correct coagulopathy to avoid bleeding |
| Administer antibiotic prophylaxis targeting skin flora thirty minutes prior to procedure to prevent infection |
| Drain ascites beforehand and avoid gastrostomy tube placement if fluid reaccumulation is expected to occur within 7-10 d |
| Obtain cross-sectional imaging (*e.g.*, computed tomography) if colonic interposition and other suspected anatomical abnormalities are suspected |
| Use reverse Trendelenburg patient positioning, proper transillumination and palpation of anterior gastric wall, and use of safe track maneuver during initial needle puncture to prevent inadvertent liver or colonic puncture |
| Minimize external bumper traction and ensure tube is rotatable to prevent buried bumper syndrome and ulceration |
| Consider abdominal binders to restrict access, gastropexy devices, and low-profile gastrostomy button with detachable tubing to prevent patient tube dislodgement |

**Table 2 Select Indications for gastrostomy placement**

| | |
|---|---|
| **Palliative venting for malignant obstruction and peritoneal carcinomatosis**[20,46,120-124] | Can reduce symptoms of nausea and vomiting without a cumbersome NG tube |
| **Head and neck malignancy**[20,125-130] | Reactive rather than prophylactic gastrostomy can reduce treatment related critical weight loss |
| **Esophageal malignancy**[131-136] | Achieves adequate nutritional status better than self-expandable metal stent insertion |
| **Ventilator-dependent respiratory failure including COVID-19**[137-144] | Early enteral nutrition can decrease complication rates and length of stay due to a catabolic state in prolonged ventilation |
| **Stroke with dysphagia**[145-147] | Can be placed after 28 d if prolonged enteral nutrition is needed |
| **Non-stroke neurologic disease**[148-155] | Supported in amyotrophic lateral sclerosis. No guideline specific recommendations in Parkinson's disease, multiple sclerosis complicated by dysphagia, cerebral palsy, or trauma patients with severe cerebral injury but has been effective |
| **Pregnancy complicated by severe hyperemesis gravidarum**[156-159] | Successfully performed in up to a 29 wk gestation with favorable maternal and fetal outcomes |
| **Gastric bypass** | Can be performed in concurrence with surgery to avoid reoperation in patients who are at higher risk for an anastomotic leak or gastro-enteric obstruction[20,160,161] |

## METHODS OF MINIMALLY INVASIVE GASTROSTOMY TUBE PLACEMENT

Percutaneous gastrostomy has supplanted open gastrostomy and can be performed with tube introduction transorally or transabdominally, using endoscopic (Figure 1), imaging (Figure 2), or laparoscopic guidance (Figure 3)[2].

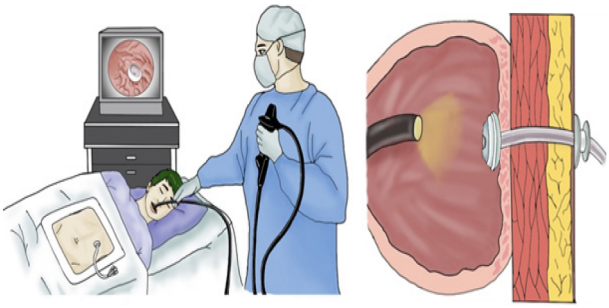
### *Endoscopic placement: Brief overview of technique*

With endoscopic guidance for PEG, the "pull" (Ponsky-Gauderer) technique[6,7], "push-over-wire" (Sacks-Vine) technique[8,9], and "introducer" (Russell)[10,11] technique can be used depending on training or operator preference. The introducer method is the only true transabdominal method that can be used to avoid transoral passage of the PEG tube. For patients with near-obstructing head and neck malignancy, the "SLiC" technique can be performed with a small-bore endoscopy if fluoroscopy cannot be used[12].

Transoral approach is usually performed in both push-over-wire and pull techniques. Upper endoscopy is performed to insufflate and transilluminate the stomach. A site for placement is chosen *via* endoscopic visualization combined with manual palpation of the stomach. After local anesthesia is

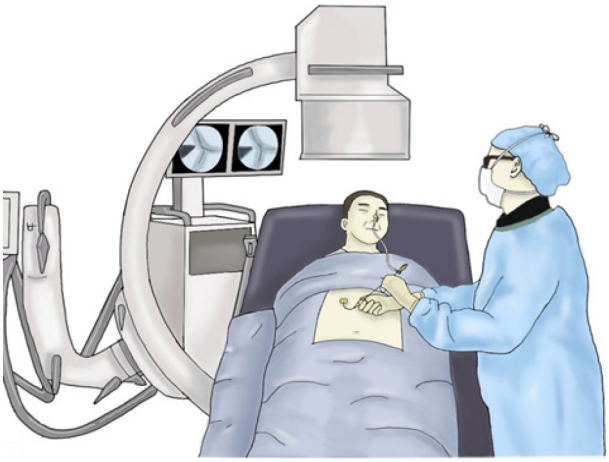
**Table 3 Select relative contraindications to gastrostomy placement**

| | Comments |
|---|---|
| **Certain alterations in abdominal anatomy and motility**[2,5] | Open abdomen, ostomy sites, drain tubes, and surgical scars can alter or preclude location for gastrostomy tube placement |
| **Altered oropharyngeal anatomy**[2] | Vocal cord paralysis, active radiation, head/neck tumors, facial and skull fractures, and high cervical fractures can obstruct the gastrostomy tube and create an airway emergency |
| **Massive refractory ascites**[2,162,163] | Increased risk for bacterial peritonitis, impairment of stoma tract maturation, and tube dislodgement if ascites rapidly reaccumulates over 7-10 d despite paracentesis or PleurX catheter placement; gastropexy devices can increase success |
| **Upper GI bleeding from ulcer or varices**[2] | Bleeding peptic ulcers and esophageal varices can have high rates of recurrent bleeding; bleeding from stress gastropathy, gastritis, or angiodysplasia are less likely to recur, and do not need a delay in enteral access |
| **Obesity**[2] | Shifting of panniculus increases the risk of tube dislodgement from the stomach into the peritoneal space |
| **Early feeding in stroke with dysphagia**[20,29,164-166] | Enteral tubes prior to 28 d rather than temporary NG tubes had greater development of pressure ulcers, sepsis, pneumonia, and GI bleeding over 2 yr |
| **Nutrition in terminal metastatic malignancy**[2,167,168] | Administration of nutrition beyond specific patient request plays a minimal role in comfort and does not improve complication rate, survival, or functionality in terminal malignancy |
| **VP shunts**[20,46,169,170] | May increase risk of ascending meningitis |
| **Irreversible dementias**[171-179] | Does not improve mortality or rehospitalization rate |



**DOI:** 10.4240/wjgs.v14.i4.286 **Copyright** ©The Author(s) 2022.

**Figure 1 Endoscopic gastrostomy tube placement.**

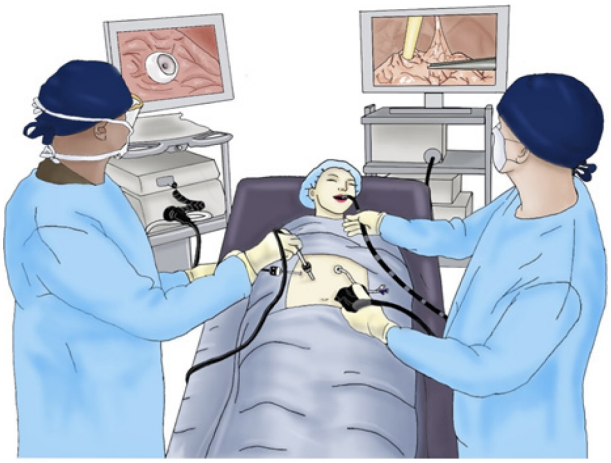


**DOI:** 10.4240/wjgs.v14.i4.286 **Copyright** ©The Author(s) 2022.

**Figure 2 Radiologic gastrostomy tube placement.**

given through the chosen site and a small cutaneous incision is performed to the fascia. A catheter over needle is passed percutaneously into the stomach. A snare is passed through the endoscope.

Subsequently with the pull method, the needle is removed and a silk suture loop ("string") is passed through the remaining catheter into the stomach. The snare that passed through the endoscope grasps the string. The string is pulled out *via* endoscope through the mouth. The wire loop of the string is then



**DOI:** 10.4240/wjgs.v14.i4.286 

**Figure 3 Laparoscopic-assisted endoscopic gastrostomy tube placement.**

tied to the wire loop of the PEG tube. The tube is then "pulled" *via* string back through the mouth to the stomach, and then out the abdominal wall. The endoscope is then reinserted to confirm placement.

With the push-over-wire technique, a guidewire instead is placed into the stomach after needle removal. Similarly, the endoscope pulls the wire through the mouth *via* snare. The PEG tube is placed over guidewire exiting the mouth and pushed out through the stomach and abdominal wall. To accomplish this, a long plastic tapered dilator is fused to the tip of the PEG tube to facilitate passage[13].

Unlike the push-over-wire and pull methods, the introducer method avoids PEG tube contact with the oropharyngeal cavity[13,14]. This technique is more employed in fluoroscopic placement by radiology, though can be performed by the endoscopist as well. The initial steps are similar wherein a trocar is placed into the stomach with endoscopic visualization, and guidewire is passed into the stomach. The wire is held by endoscopic snare to secure it. Two to four T-fasteners are then deployed into the stomach *via* cannula around the trocar for gastropexy. The tract through which the guidewire passes is then dilated serially, and a peel-away sheath is passed over the wire[13]. There are other variations in which other gastropexy methods are used such as a double-lumen gastropexy device[11]. The PEG tube is passed through the sheath over wire and sheath removed, with balloon tip inflation to secure the tube in the stomach[13].

The SLiC technique is similar to the introducer technique but avoids the need for T-fasteners which are not widely available[12]. After a blunt 7-8 mm AutoSuture Mini Step Trocar is placed into the stomach with endoscopic visualization, the blunt needle within is withdrawn leaving the radially expandable sleeve in place. A tapered blunt dilater with cannula is inserted to expand the trocar sleeve radially. The dilator is then removed from the cannula, leaving a self-anchoring 7-8 mm working port through the cannula. A metal stylet is passed through a 20 french Malecot catheter (the PEG tube) and together they are inserted into the port. The port surrounding the PEG tube is then removed while the tube is held in place with endoscopic verification.

### *Radiologic placement: Brief overview*

With fluoroscopy, computed tomography (CT), or ultrasound guidance, percutaneous radiological gastrostomy (PRG) can be performed transabdominally with push type A technique (Seldinger) and push type B technique (Peel-away sheath). If desired, PRG can achieve gastropexy similar to the introducer technique with T-fasteners or other devices[15-17]. Similar to the PEG "push-over-wire" technique, hybrid per-oral image guided gastrostomy technique (PIG) has also been used for transoral placement[18,19]. Alternatively, percutaneous transesophageal gastrotubing (PTEG) with image guidance can be used to place esophagostomy when gastrostomy is contraindicated such as massive refractory ascites, hostile abdomen, or massive peritoneal carcinomatosis[20-25].

### *Laparoscopic placement: Brief overview*

Gastrostomy tube placement can be performed with laparoscopic guidance. Percutaneous laparoscopic assisted gastrostomy (PLAG) requires two midline trocars to perform gastropexy with sutures and place the tube[20,26-29]. A novel hybrid laparoscopic-assisted PEG (LAPEG) is a combination of endoscopy with laparoscopic visualization[30-34], as shown in Figure 3.

### *Comparison of endoscopic gastrostomy methods*

Although the use of each technique depends on institution and clinical scenario, transoral PEG placement is often first-line, though variation exists across institutions. The pull technique may have

lower rates of AEs in non-oropharyngeal cancer patients, especially for palliative decompression[35]. Additionally, a larger and more robust tube can be placed with transoral technique. The smaller diameter of available introducer trocars limits transabdominal technique. This may lead to higher rate of tube blockage and occlusions[36,37]. Transoral technique also allows placement of mushroom type catheters without need for gastropexy. Lastly, transoral technique can present a lower minor bleeding rate (0.6% *vs* 6.6%) likely due to the additional needle punctures needed for gastropexy and use of a larger trocar[38].

Though technically more complicated for the endoscopist, the introducer technique could provide a stronger gastropexy with T-fasteners and avoid tube dislodgement[39], especially in patients with neurologic impairment[40,41]. Furthermore, this method is associated with a lower rate of mild peristomal wound infection[42]. The introducer method is more effective than the transoral method in patients with oropharynx or esophageal stricture from radiation, inflammation, or malignancy. Recent studies showed that the introducer technique is widely used in patients with advanced head and neck malignancy due to lower rates of AEs and PEG site metastases related to possible contact with malignant cells with the pull technique[43-47]. However, some institutions continue to use the transoral technique given the low incidence of abdominal wall metastases and the need for large randomized controlled trials comparing the procedural *vs* metastatic risk[48].

Overall, the pull technique has a higher rate of infection but a lower rate of bleeding compared to the introducer technique[38]. Therefore, the type of technique for gastrostomy tube placement should be chosen based on patient characteristics and operator's skill. The introducer technique should be considered in patients with head and neck malignancy. However, further studies are warranted.

The Russell introducer technique is inferior to the SLiC technique described in the prior section, and may also be technically harder for the endoscopist. First, the size of the PEG tube is limited by the extent of dilation that can be achieved and using larger dilators without T-fasteners increases the likelihood of the stomach being pushed away from the abdominal wall. Second, T-fasteners may not be readily available at all institutions. The Mini Step Trocar used in the SLiC technique dilates axially in one step without the need of T-fasteners[12]. Third, the balloon catheter used in the introducer technique has a greater chance of rupture and dislodgement than mushroom catheters including the Malecot catheter used in the SLiC technique[49]. Thus, in selected patients in whom the conventional push-over-wire or pull techniques cannot be performed, the SLiC technique should be considered over the introducer technique where larger PEG tube are preferred and T-fasteners are not available. Other modified introducer methods involving direct placement of bumper-button-type catheters have been described [50,51] and can also be considered over the Russell technique if preferred.

### *Comparison of endoscopic, radiologic, and laparoscopic gastrostomy tube placement methods*

There is a large confusion of nomenclature in the surgical, radiological, and gastroenterological literatures. For endoscopic placement, the pull and push-over-wire methods are performed transorally. There are no differences in the success and AE rate between both methods. Thus, either method can be used depending on operator's experience, though the pull method is more widely employed[13,52,53]. Several studies comparing the "pull" *vs* "push" method are referring to a comparison between the transoral and transabdominal introducer methods or other "push" trocar methods. Multidisciplinary guidelines describe transoral gastrostomy as the pull PEG technique and transabdominal gastrostomy as type A or B push PRG techniques[2].

If the less common PIG technique is readily available, the choice of transoral PEG *vs* PIG technique depends on institutional preference and operator capability due to similar AE rates[18,19]. PRG *vs* transoral PEG placement parallels the choice of transoral *vs* transabdominal PEG technique in the previous section. Only a large meta-analysis study reported a higher success rate but lower morbidity rate in PRG technique[54], but other previous studies showed lower rates of AEs, mortality, and readmission in PEG technique especially in those with head and neck malignancy[20,55,56]. In contrast, several studies demonstrated a similar AE rate between PRG and PEG technique[42,57-61]. However, the AE profile of each study may be different. Despite lower rates of bleeding and pain, PEG pull technique could cause more superficial wound infection and buried bumpers than PRG technique[60]. PRG may be considered if transabdominal PEG cannot be performed due to lack of endoscopic training or resources.

Endoscopic feeding tube placement has the advantage of placement at bedside as opposed to the radiology suite for PIG/PRG or operating room for PLAG[13]. This may be particularly useful in critically-ill patients. Transabdominal PEG should be favored over transoral PEG in patients with obstruction or stricture due to oropharyngeal mass and those with head and neck malignancy who are at risk of tumor seeding from the PEG site. However, if the endoscopist lacks experience or resources are unavailable, the gastrostomy tube placement by interventional radiology is more appropriate.

PLAG is a safe and preferred method of placement if PEG or PRG cannot be performed due to unsuccessful endoscopic trans-illumination and finger palpation, inadequate imaging window, or inability to insufflate the stomach[28,62]. It does not preclude PEG placement, as it can be used when PEG is contraindicated to ensure that there is no obstruction or blood vessels at the site of tube placement. Such conditions include morbid obesity, need for lysis of adhesions, organ interposition, gastric varices, large hiatal hernia, ileus, intraabdominal mass, gravid uterus, ascites, use of peritoneal

dialysis, or altered anatomy due to gastric bypass[30,63]. Though PEG technique has been utilized in altered Roux-en-Y anatomy with double balloon enteroscopy, it requires fluoroscopy and is not widely used[20]. In pediatric patients, PLAG is more preferred in to avoid serious AEs such as intestinal fistula formation[64-66]. Laparoscopic placement should also be considered when jejunostomy is needed for more durable long-term enteral access compared to jejunal extension tubing[67].

LAPEG is a hybrid approach for gastrostomy tube placement as it allows direct visualization of all cavities. If available, it can be considered over PLAG due to the advantage of luminal visualization. It also allows transoral tube placement, conferring the advantages described in prior sections over transabdominal method. However, this technique requires physicians with advanced expertise in laparoscopy with PLAG, increased peritoneal insufflation, and placement of multiple ports[30-34].

## APPROPRIATE INFORMED CONSENT AND MANAGING EXPECTATIONS

Gastrostomy tube placement should involve the informed and educated consent of the patient in order to respect patient autonomy over perceived beneficence. Informed consent for gastrostomy tube placement is often inadequate[42,68,69]. Legal precedence over the past thirty years has determined that artificial nutrition should not be thought of as different from any other medical therapy, and that there is no obligation to provide it if it is unwanted[2,70]. If the patient cannot provide consent, the consent of the health care proxy from an advanced directive should be obtained. The living will should be followed if the patient is considered terminally ill[2,70].

Appropriate expectations must be set about what benefit the gastrostomy tube can provide for the patient. Clinical indications can start the decision-making process but are rarely adequate alone[20]. Social support should also be evaluated, as it plays a significant role at reducing gastrostomy tube dependence[71]. In conditions such as anorexia from advanced malignancy, it has been suggested that gastrostomy tube not even be offered due to an inability to utilize nutrients from feeding[72]. In conditions such as a permanent vegetative state, gastrostomy tube can be offered but should be recommended against due to inability of the patient to experience any quality of life. In contrast, if the patient has uncomplicated dysphagia with preserved quality of life otherwise, gastrostomy tube should be offered and recommended due to unequivocal nutritional benefit[73]. Furthermore, in malignant gastrointestinal obstruction, gastrostomy tube venting provides clear symptomatic benefit.

Decision-making is most difficult in equivocal indications such as recurrent strokes, and can lead to decision regret among surrogate decisionmakers[74]. Gastrostomy tubes that are frequently placed into elderly or neurological impaired patients have a significant financial burden on the healthcare system associated with dislodgement[75]. Gastrostomy insertion in such patients provides a greater health-related quality of life improvement for caregivers than patients[20,76], purportedly due to greater ease of medication administration and greater sense of accomplishment by the caregiver[70]. The intervention can provide physiologic benefit in prolonged life but may not actually improve quality of life. Given that data on long term functional outcomes are often lacking, decision-makers focus on short-term procedural safety and potential for improved nutrition[77]. A limited feeding trial can be discussed, but strict criteria on what constitutes a successful response to feeding should be defined in discussion with the patient or health care proxy[20].

## PRE-PROCEDURAL PHYSICAL EXAM AND IMAGING CONSIDERATIONS

Physical examination may help identify certain contraindications to gastrostomy tube placement and prevent occurrence of AEs. The oropharynx and head should be inspected for features that preclude endoscopic approach such as facial fractures or complete obstruction. An anesthesia or sedation team should additionally look for features that may impact sedation such as stridor, large neck circumference, or presence of obstructive sleep apnea to reduce procedure-related cardiopulmonary AEs[78].

The abdomen should be examined for ascites and obesity, which can increase the risk of tube dislodgement, failed transillumination, or failed gastropexy. To avoid puncture of liver, the caudal and lower edge of the liver should be identified with percussion before gastrostomy placement[78]. Any devices such as VP shunts should be noted as well so that the endoscopist can be aware of any infection risk. The patient's mental status should be examined to determine ability to consent.

Abdominal imaging with CT or radiography can be obtained prior to the procedure if abnormal anatomy is suspected or known due to prior surgery. Certain patients requiring gastrostomy tubes may have structural deformities of the spine, previous abdominal surgery, or chronic constipation, which predispose transposition of the transverse colon in front of the anterior gastric wall. Preprocedural abdominal radiographs can be obtained and subsequent enema administration can be performed to decompress the colon if interposed on imaging[79,80]. Furthermore, use of abdominal x-ray after insufflation of 500 cc of air may help identify an optimal gastric puncture point[81]. Concordance between pre-procedural CT scan and abdominal radiography was reported to be approximately 73% [82]. CT scan increased the success rate of gastrostomy tube placement from 77% to 98% due to high

sensitivity of adequate window identification[82].

## ANTIBIOTIC PROPHYLAXIS

Patients undergoing PEG tube placement are more prone to infection due to poor nutrition, advanced age, immunocompromise, age, and comorbidities (diabetes, obesity, malnutrition). Infection may occur more frequently with transoral technique due to exposure to oral flora and is one of the most common AEs of external bolster traction[48,71-80]. Major peristomal infection is rare, seen in less than 1.6% of cases. The incidence of minor infection ranges from 5.4%-30%[20,83,84].

Pre-procedural antibiotic prophylaxis is recommended to reduce infectious AEs. Pooled analysis of thirteen randomized control trials evaluating use of prophylactic antibiotics during PEG tube placement showed a significant reduction in incidence of peristomal infection[85]. The introducer technique can be used to avoid oral flora contamination with the pull method to confer lower infection risk[64,86] especially in head and neck cancer patients with overgrowth of oral flora related to tumor[44]. However, there are some reports of increased intraperitoneal abscess and leakage with the introducer method[87]. Prophylactic antibiotics may still be needed regardless of technique[88].

The choice of antibiotic does not necessarily seem to matter if appropriate cutaneous flora is covered. According to the ASGE guideline, antibiotic prophylaxis with IV cefazolin 1 g or equivalent antibiotic thirty minutes before gastrostomy tube placement is recommended to cover cutaneous organisms if patient has not already received appropriate antibiotics[89]. One clinical trial found that administering a single dose of oral Bactrim through PEG tube after insertion is not inferior to a single dose of intravenous 1.5 g cefuroxime before insertion[90]. Another study showed that three doses of IV cefuroxime prior to the procedure with post-procedural betadine spray modestly decreased the rate of stomal infection during the first week[20]. In contrast, a clinical trial found no significant differences between 2 g of cefotaxime and 0.5-4 g of piperacillin-tazobactam prior to the procedure as normal skin flora was mostly considered as a cause of topical wound infection[84].

## MANAGEMENT OF ANTIPLATELET AND ANTICOAGULANT AGENTS AND COAGULOPATHY

Gastrostomy placement is a high-risk procedure according to consensus GI society guidelines and moderate risk procedure according to SIR guidelines in patients receiving anticoagulant or antiplatelet therapy[20,83,91-94]. The risk of bleeding should be weighed against thromboembolic event risk after stopping medication. Additionally, resumption of medication is dependent on achieving proper hemostasis[2].

Patients on antiplatelet agents do not necessarily need to have low-dose aspirin withheld. Thienopyridines such as clopidogrel, prasugrel, ticagrelor, and ticlopidine should be withheld 5-7 d before gastrostomy placement. They can be resumed one day after the procedure with the exception of the non-loading dose of clopidogrel, which can be resumed as early as six hours after. Aspirin should additionally be started in the interim if the patient is not already taking it when temporarily discontinuing these antiplatelet agents. There have been certain studies that have had findings in opposition to these consensus statements. Even with use of uninterrupted antithrombotic therapy with clopidogrel and aspirin, risk of significant bleeding was found to be minimal or nonsignificant as compared to holding therapy[95-97]. A risk/benefit discussion should be held with patients who have a higher risk of thromboembolism such as those with coronary artery disease and drug eluting stent placement within the past twelve months or bare stent placement within the past month. A loading dose of thienopyridine can be considered on recontinuation in these patients as well[2,20,83,91-94].

For patients on anticoagulation, patients with higher risk of thromboembolism are those with thrombophilia conditions, deep venous thrombosis within past three months, atrial fibrillation with mitral valve stenosis or prosthetic valve, and metal mitral valve. Warfarin should be discontinued five days before gastrostomy placement. In high risk patients, low molecular weight heparin (LMWH) can be substituted to bridge the patient, with a dose withheld on the morning of the procedure. In low risk patients, INR should be checked to ensure it is less than 1.8 pre-procedure. Warfarin can then be resumed the evening of the procedure. DOACs such as apixaban should be discontinued in high risk patients for the appropriate drug-specific interval[20] and be resumed one to three days after. For heparin products prior to procedure, unfractionated heparin should be withheld six hours before, prophylactic LMWH should be held one dose before, and therapeutic LMWH should be held two doses before[2,20,83,91-94]. Use of uninterrupted heparin products were shown to be independent predictors of bleeding[96,97].

Prior to procedure, platelets, INR, aPTT should the checked. INR should be corrected to a range of 1.5-1.8 and platelets should be corrected to at least 50 x $10^9$/L. There is no consensus on correcting aPTT, though there is a trend towards correcting for values 1.5 x above normal limits. In chronic liver disease

patients, fibrinogen levels should be checked as well. INR should be corrected to below 2.5, platelets should be corrected to above 30x10^9/L, and fibrinogen should be corrected to above 100 mg/dL[92, 93].

## AES AND APPROACH TO PREVENTION AND MANAGEMENT

Gastrostomy tubes are associated with various potential AEs. There are various measures which can be taken to mitigate these, as discussed hereinafter.

### *Aspiration*

Aspiration related to the gastrostomy tube procedure occurs in about 0.3%-1% of cases, and was associated with supine position, deeper sedation, advanced age, and neurologic impairment[20,46,98]. The endoscopist should avoid excessive sedation, have prior evaluation by a sedation team, aspirate all gastric contents before gastrostomy tube placement, suction all insufflated air after gastrostomy tube is placed, and minimize procedural time[78].

### *Bleeding*

Acute bleeding is a rare AE, which occurs roughly 1%. Of these, less than 0.5% requires blood transfusion and laparotomy due to bleeding[87,99-101]. The endoscopist should consider blood transfusion and temporarily holding anticoagulation per guidelines mentioned in prior section. Additionally, if the patient is particularly prone to bleeding, the pull technique should be considered over the introducer technique[38]. Cutaneous puncture should be performed lateral to the rectus muscle. Puncture of anterior gastric wall should be performed at the mid to distal body of the stomach and equidistant from the lesser and greater curvatures to avoid arterial injury[102,103]. Underlying lesions that can cause bleeding (*i.e.* ulcer, erosion, or angioma) should also be assessed.

### *Perforation and pneumoperitoneum*

Inadvertent perforation of the intestines is a rare but potentially fatal AE. The endoscopist can minimize this, among other means, by performing a safe track maneuver to ensure no intervening loops of the bowel[2]. With high intragastric insufflation pressure during endoscopy, air may escape during gastrostomy tube insertion or needle puncture leading to pneumoperitoneum. Transient subclinical pneumoperitoneum is a common benign finding that is usually asymptomatic, but a minority of patients can have signs and symptoms of peritonitis. Carbon dioxide rather than ambient air may be used for insufflation to significantly reduce the severity of pneumoperitoneum[78,104]. Internal bolster placement below the upper body of the stomach can be used to prevent pneumoperitoneum[102].

### *Peristomal infection*

Infection of the peristomal site can be prevented with appropriate pre-procedural antibiotic prophylaxis as described prior. Patients who have comorbid diabetes, obesity, poor nutritional status, or long-term corticosteroid administration have not only a higher incidence of mortality[105] but also infection risk [106]. Additionally, patients with diabetes, chronic kidney disease, pulmonary tuberculosis, or alcoholism could be at risk for the rare development of necrotizing fasciitis around the ostomy site[107-109]. Particular attention should be paid to patients with such comorbid conditions to prevent infection. Standard infection control measures such as aseptic surgical field preparation and preprocedural hand disinfection[78]. As expanded upon in the next sections, introducer technique has been associated with reports of intraperitoneal abscess[87]. The transoral approach has risks as well since it can drag oropharyngeal flora along with the tube, leading to increased peristomal infection rate[42]. If transoral technique is used in high risk chronically hospitalized patients, nasopharyngeal decolonization of MRSA and mouthwash with oral chlorhexidine solution can be considered to reduce peristomal infection[20,78].

### *Fungal tube degradation*

Degradation of PEG tube by fungal colonization has been shown to cause PEG tube failure up to 37% of the time by 250 d and 70% of the time up to 450 d[110]. Fungal growth leads to brittleness, cracking, and obstruction of tube. Though there is no definitive management, the endoscopist should consider polyurethane tubing over silicone tubing to increase resistance to degradation[111,112].

### *Buried bumper syndrome*

Buried bumper syndrome is a partial or complete growth of gastric mucosa over the internal bumper in the stomach. This could lead to migration of the bumper through the gastric wall and gastrostomy tract, which can cause abscess formation, leakage around the gastrostomy site, immobile gastrostomy tube, abdominal pain, and possible resistance to formula infusion. Risk factors include poor wound healing, malnutrition, significant weight gain due to successful nutrition, placement of internal bumper in the

upper gastric body, and excess tension between the internal and external bumpers[2,102].

To reduce the risk of buried bumper, the endoscopist should place the outer bumper tight enough to ensure proper gastropexy but loose enough to allow room for post-procedural tissue swelling. The external bumper should be subjected to a very low traction without tension. The next day, the outer bumper should be loosened and rotated to allow back and forth movement at least 1 cm with minimum resistance. The tube should also be covered to prevent inadvertent tugging. The tube needs to be rotated daily and moved inward from 2 to 10 cm once the gastrostomy tract is healed around 7-10 d. Subsequent restricted movement, pain or leakage around the site should be evaluated for buried bumper as early endoscopic intervention can preserve the feeding tube[78,113,114]. The most common signs of buried bumper syndrome is an inability to move the PEG tube inward[78].

### Ulceration

Ulceration or erosion from PEG tube can be found up to 1.2% of all cases. This is usually caused by friction of the gastric wall opposite to or underneath the internal bumper[20,87,100,115]. Similar to preventing buried bumper syndrome, the endoscopist should avoid excess tension between the internal and external bumpers, rotate the tube daily, and move the tube inward after the gastrostomy tract is healed[78]. The mucosa under the internal bumper should be visualized after placement, and excess lateral traction on the tube should be avoided[2].

### Colonic injury and fistulae

Excessive gastric and small bowel insufflation can lead to bowel transposition and gastric rotation[80]. If the colon is accidentally punctured or cannulated, fistulous tracts can later form between stomach, colon, and skin. Many patients are asymptomatic but can develop severe diarrhea after feeding, fecal discharge around the tube, and even peritonitis and sepsis[78]. If the gastrostomy tube is replaced into a gastrocolocutaneous fistula, the tube could miss the gastrostomy and enter the colon creating a new colocutaneous fistula. The proceduralist can mitigate such AEs with safe track technique to avoid initial puncture of colon. Reverse Trendelenburg positioning, proper transillumination, and finger imprinting may help. If misplaced gastrostomy tube is suspected, radiographic imaging (CT) should be performed with subsequent removal of the misplaced tube[2,116].

### Liver injury

Similar to colonic interposition, the lateral segment of the liver can interpose between the abdominal wall and stomach, leading to possible injury during gastrostomy placement. Injuries may be associated with bleeding but could be asymptomatic. As mentioned previously, caudal edge of the liver should be identified with physical exam before puncture[78].

### Gastric outlet obstruction

Gastric outlet obstruction is usually seen in pediatric patients due to migration of the internal bumper and obstruction of the pyloric channel. It can occur in adults if catheter with internal balloon is used, and the balloon migrates into the pylorus or proximal small bowel. This can be prevented by reducing the length of tube inserted into the gastric lumen, though caution must be taken to avoid excess tension at the gastrostomy tube site[80].

### Tube dislodgement and removal

Maturation of the gastrostomy tract usually occurs within the first seven to ten days after placement but can take weeks longer if there is concurrent malnutrition, ascites, or steroid treatment. If gastrostomy tube is removed during this period, it should be replaced endoscopically or radiographically as an immature tract can result in free perforation. Altered mental status including delirium and dementia increase the risk for accidental tube removal. Additionally, internal bolster placement in the upper body of the stomach increases risk of dislodgement[102]. Measures should be taken to reduce such events, such as using abdominal binders or elastic bandage to restrict access, gastropexy devices at time of tube placement, proper gastrostomy site choice, and use of low-profile gastrostomy button with detachable extension tubing. The latter is already used in the pediatric population to reduce risk of dislodgement [78,117].

### Tube occlusion

Tube occlusion when feeding can be caused by obstruction of the internal lumen or mechanical tube failure. Smaller bore feeding tubes (less than 10-12 French) are more prone to occlusion with repeated gastric residual aspiration[118]. The endoscopist should consider placing larger bore tubes if possible [119].

### Gastrostomy tract tumor seeding

Transoral approach of PEG tube placement may increase risk of tumor seeding in patients with head and neck malignancy due to contact with malignant cells during tube insertion[43-47]. Thus, transabdominal methods such as the introducer, SLiC, PRG, and LAPEG techniques should be highly

considered in these patients.

## CONCLUSION

PEG has gained increasing acceptance as a safe and effective technique to provide enteral nutrition for a wide variety of indications. However, the preprocedural evaluation and selection of patients remains paramount to provide optimal benefit while reducing risk of AEs. The endoscopist should examine indications, contraindications, ethical considerations, and comorbidities of patients referred for gastrostomy placement. Additionally, the endoscopist should consider whether radiologic or surgical tube placement may be more appropriate, and whether a transoral or transabdominal technique is best. If gastrostomy placement appears indicated, physical exam, imaging, and other interventions should be performed to reduce procedure-related AEs.

## FOOTNOTES

**Author contributions:** Rajan AV drafted the manuscript; Wangrattanapranee P designed the illustrations and provided revisions; Kessler J provided revisions; Kidambi T provided revisions; Tabibian J provided revisions and supervision; and All authors have read and approve the final manuscript.

**Conflict-of-interest statement:** All the Authors have no conflict of interest related to the manuscript.



**Country/Territory of origin:** United States

**ORCID number:** Anand Rajan 0000-0003-0738-6236; Peerapol Wangrattanapranee 0000-0002-0805-5001; Jonathan Kessler 0000-0002-0126-2200; Trilokesh Dey Kidambi 0000-0002-1138-2492; James H Tabibian 0000-0001-9104-1702.

**S-Editor:** Ma YJ
**L-Editor:** A
**P-Editor:** Ma YJ

## REFERENCES

1 **Westaby D**, Young A, O'Toole P, Smith G, Sanders DS. The provision of a percutaneously placed enteral tube feeding service. *Gut* 2010; **59**: 1592-1605 [PMID: 21071581 DOI: 10.1136/gut.2009.204982]
2 **Itkin M**, DeLegge MH, Fang JC, McClave SA, Kundu S, d'Othee BJ, Martinez-Salazar GM, Sacks D, Swan TL, Towbin RB, Walker TG, Wojak JC, Zuckerman DA, Cardella JF; Society of Interventional Radiology; American Gastroenterological Association Institute; Canadian Interventional Radiological Association; Cardiovascular and Interventional Radiological Society of Europe. Multidisciplinary practical guidelines for gastrointestinal access for enteral nutrition and decompression from the Society of Interventional Radiology and American Gastroenterological Association (AGA) Institute, with endorsement by Canadian Interventional Radiological Association (CIRA) and Cardiovascular and Interventional Radiological Society of Europe (CIRSE). *Gastroenterology* 2011; **141**: 742-765 [PMID: 21820533 DOI: 10.1053/j.gastro.2011.06.001]
3 **ASGE Technology Committee**, Kwon RS, Banerjee S, Desilets D, Diehl DL, Farraye FA, Kaul V, Mamula P, Pedrosa MC, Rodriguez SA, Varadarajulu S, Song LM, Tierney WM. Enteral nutrition access devices. *Gastrointest Endosc* 2010; **72**: 236-248 [PMID: 20541746 DOI: 10.1016/j.gie.2010.02.008]
4 **Stein DJ**, Moore MB, Hoffman G, Feuerstein JD. Improving All-Cause Inpatient Mortality After Percutaneous Endoscopic Gastrostomy. *Dig Dis Sci* 2021; **66**: 1593-1599 [PMID: 32556970 DOI: 10.1007/s10620-020-06396-y]
5 **Lucendo AJ**, Friginal-Ruiz AB. Percutaneous endoscopic gastrostomy: An update on its indications, management, complications, and care. *Rev Esp Enferm Dig* 2014; **106**: 529-539 [PMID: 25544410]
6 **Ponsky JL**, Gauderer MW. Percutaneous endoscopic gastrostomy: a nonoperative technique for feeding gastrostomy. *Gastrointest Endosc* 1981; **27**: 9-11 [PMID: 6783471 DOI: 10.1016/S0016-5107(81)73133-X]
7 **Gauderer MW**, Ponsky JL, Izant RJ Jr. Gastrostomy without laparotomy: a percutaneous endoscopic technique. *J Pediatr Surg* 1980; **15**: 872-875 [PMID: 6780678 DOI: 10.1016/S0022-3468(80)80296-X]
8 **Sacks BA**, Vine HS, Palestrant AM, Ellison HP, Shropshire D, Lowe R. A nonoperative technique for establishment of a gastrostomy in the dog. *Invest Radiol* 1983; **18**: 485-487 [PMID: 6642944 DOI: 10.1097/00004424-198309000-00015]
9 **Hogan RB**, DeMarco DC, Hamilton JK, Walker CO, Polter DE. Percutaneous endoscopic gastrostomy--to push or pull. A prospective randomized trial. *Gastrointest Endosc* 1986; **32**: 253-258 [PMID: 3743977 DOI:

10.1016/s0016-5107(86)71841-5]
10 **Russell TR**, Brotman M, Norris F. Percutaneous gastrostomy. A new simplified and cost-effective technique. *Am J Surg* 1984; **148**: 132-137 [PMID: 6430111 DOI: 10.1016/0002-9610(84)90300-3]
11 **Dormann AJ**, Wejda B, Kahl S, Huchzermeyer H, Ebert MP, Malfertheiner P. Long-term results with a new introducer method with gastropexy for percutaneous endoscopic gastrostomy. *Am J Gastroenterol* 2006; **101**: 1229-1234 [PMID: 16771943 DOI: 10.1111/j.1572-0241.2006.00541.x]
12 **Sabnis A**, Liu R, Chand B, Ponsky J. SLiC technique. A novel approach to percutaneous gastrostomy. *Surg Endosc* 2006; **20**: 256-262 [PMID: 16362472 DOI: 10.1007/s00464-005-0383-3]
13 **McClave SA**. Techniques in Enteral Access. In: Clinical Gastrointestinal Endoscopy. Elsevier; 2019: 467-487.e2
14 **Bosco JJ**, Barkun AN, Isenberg GA, Nguyen CC, Petersen BT, Silverman WB, Slivka A, Taitelbaum G, Ginsberg GG; ASGE Technology Assessment Committee. Endoscopic enteral nutritional access devices. *Gastrointest Endosc* 2002; **56**: 796-802 [PMID: 12447288 DOI: 10.1016/S0016-5107(02)70350-7]
15 **Preshaw RM**. A percutaneous method for inserting a feeding gastrostomy tube. *Surg Gynecol Obstet* 1981; **152**: 658-660 [PMID: 6784260]
16 **Brown AS**, Mueller PR, Ferrucci JT Jr. Controlled percutaneous gastrostomy: nylon T-fastener for fixation of the anterior gastric wall. *Radiology* 1986; **158**: 543-545 [PMID: 2934763 DOI: 10.1148/radiology.158.2.2934763]
17 **Coleman CC**, Coons HG, Cope C, Derauf BJ, Krenzel C, Epstein DH, Schlam BW, Castaneda F, Hough JP, Moradian GP. Percutaneous enterostomy with the Cope suture anchor. *Radiology* 1990; **174**: 889-891 [PMID: 2406788 DOI: 10.1148/radiology.174.3.2406788]
18 **Laasch HU**, Wilbraham L, Bullen K, Marriott A, Lawrance JA, Johnson RJ, Lee SH, England RE, Gamble GE, Martin DF. Gastrostomy insertion: comparing the options--PEG, RIG or PIG? *Clin Radiol* 2003; **58**: 398-405 [PMID: 12727170 DOI: 10.1016/S0009-9260(03)00058-8]
19 **Ahmed O**, Jilani D, Sheth S, Giger M, Funaki B. Radiologically Guided Placement of Mushroom-retained Gastrostomy Catheters: Long-term Outcomes of Use in 300 Patients at a Single Center. *Radiology* 2015; **276**: 588-596 [PMID: 25775194 DOI: 10.1148/radiol.15141327]
20 **Selby D**, Nolen A, Sittambalam C, Johansen K, Pugash R. Percutaneous Transesophageal Gastrostomy (PTEG): A Safe and Well-Tolerated Procedure for Palliation of End-Stage Malignant Bowel Obstruction. *J Pain Symptom Manage* 2019; **58**: 306-310 [PMID: 31071424 DOI: 10.1016/j.jpainsymman.2019.04.031]
21 **Oishi H**, Shindo H, Shirotani N, Kameoka S. A nonsurgical technique to create an esophagostomy for difficult cases of percutaneous endoscopic gastrostomy. *Surg Endosc* 2003; **17**: 1224-1227 [PMID: 12739113 DOI: 10.1007/s00464-002-8948-x]
22 **Mackey R**, Chand B, Oishi H, Kameoka S, Ponsky JL. Percutaneous transesophageal gastrostomy tube for decompression of malignant obstruction: report of the first case and our series in the US. *J Am Coll Surg* 2005; **201**: 695-700 [PMID: 16256911 DOI: 10.1016/j.jamcollsurg.2005.05.036]
23 **Udomsawaengsup S**, Brethauer S, Kroh M, Chand B. Percutaneous transesophageal gastrostomy (PTEG): a safe and effective technique for gastrointestinal decompression in malignant obstruction and massive ascites. *Surg Endosc* 2008; **22**: 2314-2318 [PMID: 18622539 DOI: 10.1007/s00464-008-9984-y]
24 **Murakami M**, Nishino K, Takaoka Y, Murakami S, Mori K, Murakami B, Azuma M, Tanabe S, Kida M, Koizumi W. Endoscopically assisted percutaneous transesophageal gastrotubing: a retrospective pilot study. *Eur J Gastroenterol Hepatol* 2013; **25**: 989-995 [PMID: 23652910 DOI: 10.1097/MEG.0b013e3283614ae1]
25 **Singal AK**, Dekovich AA, Tam AL, Wallace MJ. Percutaneous transesophageal gastrostomy tube placement: an alternative to percutaneous endoscopic gastrostomy in patients with intra-abdominal metastasis. *Gastrointest Endosc* 2010; **71**: 402-406 [PMID: 20152318 DOI: 10.1016/j.gie.2009.10.037]
26 **Murayama KM**, Schneider PD, Thompson JS. Laparoscopic gastrostomy: a safe method for obtaining enteral access. *J Surg Res* 1995; **58**: 1-5 [PMID: 7830397 DOI: 10.1006/jsre.1995.1001]
27 **Bolder U**, Scherer MN, Schmidt T, Hornung M, Schlitt HJ, Vogel P. Percutaneous laparoscopic assisted gastrostomy (PLAG)--a new technique for cases of pharyngoesophageal obstruction. *Langenbecks Arch Surg* 2010; **395**: 1107-1113 [PMID: 20213460 DOI: 10.1007/s00423-010-0612-7]
28 **Serrano Aguayo P**, Gros Herguido N, Parejo Campos J, Barranco Moreno A, Tous Romero MDC, Pereira Cunill JL, Alarcón Del Agua I, Socas Macias M, García Luna PP, Morales Conde S. New laparoscopic assisted percutaneous gastrostomy. Description and comparison with others gastrostomy types. *Clin Nutr ESPEN* 2016; **16**: 24-29 [PMID: 28531451 DOI: 10.1016/j.clnesp.2016.08.004]
29 **Ha L**, Hauge T. Percutaneous endoscopic gastrostomy (PEG) for enteral nutrition in patients with stroke. *Scand J Gastroenterol* 2003; **38**: 962-966 [PMID: 14531533 DOI: 10.1080/00365520310005190]
30 **Thaker AM**, Sedarat A. Laparoscopic-Assisted Percutaneous Endoscopic Gastrostomy. *Curr Gastroenterol Rep* 2016; **18**: 46 [PMID: 27422123 DOI: 10.1007/s11894-016-0520-2]
31 **Raaf JH**, Manney M, Okafor E, Gray L, Chari V. Laparoscopic placement of a percutaneous endoscopic gastrostomy (PEG) feeding tube. *J Laparoendosc Surg* 1993; **3**: 411-414 [PMID: 8268516 DOI: 10.1089/Lps.1993.3.411]
32 **Smitherman S**, Pimpalwar A. Laparoendoscopic gastrostomy tube placement: our all-in-one technique. *J Laparoendosc Adv Surg Tech A* 2009; **19**: 119-123 [PMID: 19196093 DOI: 10.1089/lap.2007.0210]
33 **Lopes G**, Salcone M, Neff M. Laparoscopic-assisted percutaneous endoscopic gastrostomy tube placement. *JSLS* 2010; **14**: 66-69 [PMID: 20529530 DOI: 10.4293/108680810X12674612014662]
34 **Croshaw RL**, Nottingham JM. Laparoscopic-assisted percutaneous endoscopic gastrostomy: its role in providing enteric access when percutaneous endoscopic gastrostomy is not possible. *Am Surg* 2006; **72**: 1222-1224 [PMID: 17216824 DOI: 10.1177/000313480607201215]
35 **Currie BM**, Getrajdman GI, Covey AM, Alago W Jr, Erinjeri JP, Maybody M, Boas FE. Push versus pull gastrostomy in cancer patients: A single center retrospective analysis of complications and technical success rates. *Diagn Interv Imaging* 2018; **99**: 547-553 [PMID: 29716845 DOI: 10.1016/j.diii.2018.04.005]

36 **Sutcliffe J**, Wigham A, Mceniff N, Dvorak P, Crocetti L, Uberoi R. CIRSE Standards of Practice Guidelines on Gastrostomy. *Cardiovasc Intervent Radiol* 2016; **39**: 973-987 [PMID: 27184363 DOI: 10.1007/s00270-016-1344-z]

37 **Köhler G**, Kalcher V, Koch OO, Luketina RR, Emmanuel K, Spaun G. Comparison of 231 patients receiving either "pull-through" or "push" percutaneous endoscopic gastrostomy. *Surg Endosc* 2015; **29**: 170-175 [PMID: 24993173 DOI: 10.1007/s00464-014-3673-9]

38 **Retes FA**, Kawaguti FS, de Lima MS, da Costa Martins B, Uemura RS, de Paulo GA, Pennacchi CM, Gusmon C, Ribeiro AV, Baba ER, Geiger SN, Sorbello MP, Kulcsar MA, Ribeiro U Jr, Maluf-Filho F. Comparison of the pull and introducer percutaneous endoscopic gastrostomy techniques in patients with head and neck cancer. *United European Gastroenterol J* 2017; **5**: 365-373 [PMID: 28507748 DOI: 10.1177/2050640616662160]

39 **Kulvatunyou N**, Zimmerman SA, Sadoun M, Joseph BA, Friese RS, Gries LM, O'Keeffe T, Tang AL. Comparing Outcomes Between "Pull" Versus "Push" Percutaneous Endoscopic Gastrostomy in Acute Care Surgery: Under-Reported Pull Percutaneous Endoscopic Gastrostomy Incidence of Tube Dislodgement. *J Surg Res* 2018; **232**: 56-62 [PMID: 30463774 DOI: 10.1016/j.jss.2018.06.011]

40 **Timratana P**, El-Hayek K, Shimizu H, Kroh M, Chand B. Percutaneous endoscopic gastrostomy (PEG) with T-fasteners obviates the need for emergent replacement after early tube dislodgement. *Surg Endosc* 2012; **26**: 3541-3547 [PMID: 22648113 DOI: 10.1007/s00464-012-2348-7]

41 **Prathanvanich P**, Chand B. Novel methods of enteral access. *Tech Gastrointest Endosc* 2013; **15**: 216-223 [DOI: 10.1016/j.tgie.2013.07.001]

42 **Maetani I**, Tada T, Ukita T, Inoue H, Sakai Y, Yoshikawa M. PEG with introducer or pull method: a prospective randomized comparison. *Gastrointest Endosc* 2003; **57**: 837-841 [PMID: 12776029 DOI: 10.1016/S0016-5107(03)70017-0]

43 **Tucker AT**, Gourin CG, Ghegan MD, Porubsky ES, Martindale RG, Terris DJ. 'Push' versus 'pull' percutaneous endoscopic gastrostomy tube placement in patients with advanced head and neck cancer. *Laryngoscope* 2003; **113**: 1898-1902 [PMID: 14603043 DOI: 10.1097/00005537-200311000-00007]

44 **Foster JM**, Filocamo P, Nava H, Schiff M, Hicks W, Rigual N, Smith J, Loree T, Gibbs JF. The introducer technique is the optimal method for placing percutaneous endoscopic gastrostomy tubes in head and neck cancer patients. *Surg Endosc* 2007; **21**: 897-901 [PMID: 17180272 DOI: 10.1007/s00464-006-9068-9]

45 **Cappell MS**. Risk factors and risk reduction of malignant seeding of the percutaneous endoscopic gastrostomy track from pharyngoesophageal malignancy: a review of all 44 known reported cases. *Am J Gastroenterol* 2007; **102**: 1307-1311 [PMID: 17488255 DOI: 10.1111/j.1572-0241.2007.01227.x]

46 **Teriaky A**, Gregor J, Chande N. Percutaneous endoscopic gastrostomy tube placement for end-stage palliation of malignant gastrointestinal obstructions. *Saudi J Gastroenterol* 2012; **18**: 95-98 [PMID: 22421713 DOI: 10.4103/1319-3767.93808]

47 **Fung E**, Strosberg DS, Jones EL, Dettorre R, Suzo A, Meara MP, Narula VK, Hazey JW. Incidence of abdominal wall metastases following percutaneous endoscopic gastrostomy placement in patients with head and neck cancer. *Surg Endosc* 2017; **31**: 3623-3627 [PMID: 28039644 DOI: 10.1007/s00464-016-5394-8]

48 **Oakley RJ**, Donnelly R, Freeman L, Wong T, McCarthy M, Calman F, O'Connell M, Jeannon JP, Simo R. An audit of percutaneous endoscopic gastrostomy insertion in patients undergoing treatment for head and neck cancer: reducing the incidence of peri-operative airway events by the introduction of a tumour assessment protocol. *Ann R Coll Surg Engl* 2009; **91**: 249-254 [PMID: 19220948 DOI: 10.1308/003588409X391857]

49 **Yip D**, Vanasco M, Funaki B. Complication rates and patency of radiologically guided mushroom gastrostomy, balloon gastrostomy, and gastrojejunostomy: a review of 250 procedures. *Cardiovasc Intervent Radiol* 2004; **27**: 3-8 [PMID: 15109220 DOI: 10.1007/s00270-003-0108-8]

50 **Horiuchi A**, Nakayama Y, Tanaka N, Fujii H, Kajiyama M. Prospective randomized trial comparing the direct method using a 24 Fr bumper-button-type device with the pull method for percutaneous endoscopic gastrostomy. *Endoscopy* 2008; **40**: 722-726 [PMID: 18773341 DOI: 10.1055/s-2008-1077490]

51 **Ogino H**, Akiho H. Usefulness of percutaneous endoscopic gastrostomy for supportive therapy of advanced aerodigestive cancer. *World J Gastrointest Pathophysiol* 2013; **4**: 119-125 [PMID: 24244880 DOI: 10.4291/wjgp.v4.i4.119]

52 **Kozarek RA**, Ball TJ, Ryan JA Jr. When push comes to shove: a comparison between two methods of percutaneous endoscopic gastrostomy. *Am J Gastroenterol* 1986; **81**: 642-646 [PMID: 3090872]

53 **Akkersdijk WL**, van Bergeijk JD, van Egmond T, Mulder CJ, van Berge Henegouwen GP, van der Werken C, van Erpecum KJ. Percutaneous endoscopic gastrostomy (PEG): comparison of push and pull methods and evaluation of antibiotic prophylaxis. *Endoscopy* 1995; **27**: 313-316 [PMID: 7555937 DOI: 10.1055/s-2007-1005699]

54 **Wollman B**, D'Agostino HB, Walus-Wigle JR, Easter DW, Beale A. Radiologic, endoscopic, and surgical gastrostomy: an institutional evaluation and meta-analysis of the literature. *Radiology* 1995; **197**: 699-704 [PMID: 7480742 DOI: 10.1148/radiology.197.3.7480742]

55 **Neeff M**, Crowder VL, McIvor NP, Chaplin JM, Morton RP. Comparison of the use of endoscopic and radiologic gastrostomy in a single head and neck cancer unit. *ANZ J Surg* 2003; **73**: 590-593 [PMID: 12887525 DOI: 10.1046/j.1445-2197.2003.t01-1-02695.x]

56 **Kohli DR**, Kennedy KF, Desai M, Sharma P. Safety of endoscopic gastrostomy tube placement compared with radiologic or surgical gastrostomy: nationwide inpatient assessment. *Gastrointest Endosc* 2021; **93**: 1077-1085.e1 [PMID: 32931781 DOI: 10.1016/j.gie.2020.09.012]

57 **Galaski A**, Peng WW, Ellis M, Darling P, Common A, Tucker E. Gastrostomy tube placement by radiological versus endoscopic methods in an acute care setting: a retrospective review of frequency, indications, complications and outcomes. *Can J Gastroenterol* 2009; **23**: 109-114 [PMID: 19214286 DOI: 10.1155/2009/801925]

58 **Silas AM**, Pearce LF, Lestina LS, Grove MR, Tosteson A, Manganiello WD, Bettmann MA, Gordon SR. Percutaneous radiologic gastrostomy versus percutaneous endoscopic gastrostomy: a comparison of indications, complications and outcomes in 370 patients. *Eur J Radiol* 2005; **56**: 84-90 [PMID: 16168268 DOI: 10.1016/j.ejrad.2005.02.007]

59 **Yang B**, Shi X. Percutaneous endoscopic gastrostomy versus fluoroscopic gastrostomy in amyotrophic lateral sclerosis

(ALS) sufferers with nutritional impairment: A meta-analysis of current studies. *Oncotarget* 2017; **8**: 102244-102253 [PMID: 29254240 DOI: 10.18632/oncotarget.22288]

60 **Clayton S**, DeClue C, Lewis T, Rodriguez A, Kolkhorst K, Syed R, Kumar A, Davis C, Brady P. Radiologic versus Endoscopic Placement of Gastrostomy Tube: Comparison of Indications and Outcomes at a Tertiary Referral Center. *South Med J* 2019; **112**: 39-44 [PMID: 30608631 DOI: 10.14423/SMJ.0000000000000916]

61 **Park SK**, Kim JY, Koh SJ, Lee YJ, Jang HJ, Park SJ; Small Intestine and Nutrition Research Group of the Korean Association for the Study of Intestinal Diseases (KASID). Complications of percutaneous endoscopic and radiologic gastrostomy tube insertion: a KASID (Korean Association for the Study of Intestinal Diseases) study. *Surg Endosc* 2019; **33**: 750-756 [PMID: 30132209 DOI: 10.1007/s00464-018-6339-1]

62 **Bankhead RR**, Fisher CA, Rolandelli RH. Gastrostomy tube placement outcomes: comparison of surgical, endoscopic, and laparoscopic methods. *Nutr Clin Pract* 2005; **20**: 607-612 [PMID: 16306297 DOI: 10.1177/0115426505020006607]

63 **Hermanowicz A**, Matuszczak E, Komarowska M, Jarocka-Cyrta E, Wojnar J, Debek W, Matysiak K, Klek S. Laparoscopy-assisted percutaneous endoscopic gastrostomy enables enteral nutrition even in patients with distorted anatomy. *World J Gastroenterol* 2013; **19**: 7696-7700 [PMID: 24282357 DOI: 10.3748/wjg.v19.i43.7696]

64 **Chang WK**, McClave SA, Yu CY, Huang HH, Chao YC. Positioning a safe gastric puncture point before percutaneous endoscopic gastrostomy. *Int J Clin Pract* 2007; **61**: 1121-1125 [PMID: 17343669 DOI: 10.1111/j.1742-1241.2006.01106.x]

65 **Petrosyan M**, Khalafallah AM, Franklin AL, Doan T, Kane TD. Laparoscopic Gastrostomy Is Superior to Percutaneous Endoscopic Gastrostomy Tube Placement in Children Less Than 5 years of Age. *J Laparoendosc Adv Surg Tech A* 2016; **26**: 570-573 [PMID: 27268954 DOI: 10.1089/lap.2016.0099]

66 **Lantz M**, Hultin Larsson H, Arnbjörnsson E. Literature review comparing laparoscopic and percutaneous endoscopic gastrostomies in a pediatric population. *Int J Pediatr* 2010; **2010**: 507616 [PMID: 20300186 DOI: 10.1155/2010/507616]

67 **Haskins IN**, Strong AT, Baginsky M, Sharma G, Karafa M, Ponsky JL, Rodriguez JH, Kroh MD. Comparison of laparoscopic jejunostomy tube to percutaneous endoscopic gastrostomy tube with jejunal extension: long-term durability and nutritional outcomes. *Surg Endosc* 2018; **32**: 2496-2504 [PMID: 29218657 DOI: 10.1007/s00464-017-5954-6]

68 **Van Rosendaal GM**, Verhoef MJ, Kinsella TD. How are decisions made about the use of percutaneous endoscopic gastrostomy for long-term nutritional support? *Am J Gastroenterol* 1999; **94**: 3225-3228 [PMID: 10566719 DOI: 10.1111/j.1572-0241.1999.01522.x]

69 **Stathopoulos P**, Karamanolis G, Papanikolaou IS, Polymeros D, Papadopoulos AA, Triantafyllou K. Percutaneous endoscopic gastrostomy: Patients' outcomes, adequacy and quality of information given to decision-makers and procedure acceptance. *Ann Gastroenterol* 2011; **24**: 29-34 [PMID: 24714245]

70 **DeLegge MH**, McClave SA, DiSario JA, Baskin WN, Brown RD, Fang JC, Ginsberg GG; ASGE Task Force on Enteral Nutrition. Ethical and medicolegal aspects of PEG-tube placement and provision of artificial nutritional therapy. *Gastrointest Endosc* 2005; **62**: 952-959 [PMID: 16301043 DOI: 10.1016/j.gie.2005.08.024]

71 **Magnuson JS**, Durst J, Rosenthal EL, Carroll WR, Ritchie CS, Kilgore ML, Locher JL. Increased likelihood of long-term gastrostomy tube dependence in head and neck cancer survivors without partners. *Head Neck* 2013; **35**: 420-425 [PMID: 22505332 DOI: 10.1002/hed.22996]

72 **Angus F**, Burakoff R. The percutaneous endoscopic gastrostomy tube. medical and ethical issues in placement. *Am J Gastroenterol* 2003; **98**: 272-277 [PMID: 12591040 DOI: 10.1111/j.1572-0241.2003.07267.x]

73 **Rabeneck L**, McCullough LB, Wray NP. Ethically justified, clinically comprehensive guidelines for percutaneous endoscopic gastrostomy tube placement. *Lancet* 1997; **349**: 496-498 [PMID: 9040591 DOI: 10.1016/S0140-6736(96)07369-2]

74 **Kuraoka Y**, Nakayama K. Factors influencing decision regret regarding placement of a PEG among substitute decision-makers of older persons in Japan: a prospective study. *BMC Geriatr* 2017; **17**: 134 [PMID: 28659137 DOI: 10.1186/s12877-017-0524-2]

75 **Rosenberger LH**, Newhook T, Schirmer B, Sawyer RG. Late accidental dislodgement of a percutaneous endoscopic gastrostomy tube: an underestimated burden on patients and the health care system. *Surg Endosc* 2011; **25**: 3307-3311 [PMID: 21533968 DOI: 10.1007/s00464-011-1709-y]

76 **Kurien M**, Andrews RE, Tattersall R, McAlindon ME, Wong EF, Johnston AJ, Hoeroldt B, Dear KL, Sanders DS. Gastrostomies Preserve But Do Not Increase Quality of Life for Patients and Caregivers. *Clin Gastroenterol Hepatol* 2017; **15**: 1047-1054 [PMID: 27840184 DOI: 10.1016/j.cgh.2016.10.032]

77 **Callahan CM**, Haag KM, Buchanan NN, Nisi R. Decision-making for percutaneous endoscopic gastrostomy among older adults in a community setting. *J Am Geriatr Soc* 1999; **47**: 1105-1109 [PMID: 10484254 DOI: 10.1111/j.1532-5415.1999.tb05235.x]

78 **Boeykens K**, Duysburgh I. Prevention and management of major complications in percutaneous endoscopic gastrostomy. *BMJ Open Gastroenterol* 2021; **8** [PMID: 33947711 DOI: 10.1136/bmjgast-2021-000628]

79 **Pruijsen JM**, de Bruin A, Sekema G, Koetse HA, van Rheenen PF. Abdominal plain film before gastrostomy tube placement to predict success of percutaneous endoscopic procedure. *J Pediatr Gastroenterol Nutr* 2013; **56**: 186-190 [PMID: 22922374 DOI: 10.1097/MPG.0b013e31826f750a]

80 **Singh A**, Gelrud A. Adverse events associated with percutaneous enteral access. *Gastrointest Endosc Clin N Am* 2015; **25**: 71-82 [PMID: 25442959 DOI: 10.1016/j.giec.2014.09.003]

81 **Chang WK**, Hsieh TY. Safety of percutaneous endoscopic gastrostomy in high-risk patients. *J Gastroenterol Hepatol* 2013; **28** Suppl 4: 118-122 [PMID: 24251717 DOI: 10.1111/jgh.12300]

82 **Gutjahr CJ**, Iverson EP, Walker ST, Johnson JD, Shukla UC, Terrell W. Utility of pre-procedural CT and abdominal radiography before percutaneous radiologic gastrostomy placement. *Abdom Radiol (NY)* 2020; **45**: 571-575 [PMID: 31797024 DOI: 10.1007/s00261-019-02352-1]

83 **Eisen GM**, Baron TH, Dominitz JA, Faigel DO, Goldstein JL, Johanson JF, Mallery JS, Raddawi HM, Vargo JJ 2nd, Waring JP, Fanelli RD, Wheeler-Harbough J; American Society for Gastrointestinal Endoscopy. Guideline on the management of anticoagulation and antiplatelet therapy for endoscopic procedures. *Gastrointest Endosc* 2002; **55**: 775-

779 [PMID: 12024126 DOI: 10.1016/S0016-5107(02)70402-1]
84 **Gossner L**, Keymling J, Hahn EG, Ell C. Antibiotic prophylaxis in percutaneous endoscopic gastrostomy (PEG): a prospective randomized clinical trial. *Endoscopy* 1999; **31**: 119-124 [PMID: 10223359 DOI: 10.1055/s-1999-13658]
85 **Lipp A**, Lusardi G. Systemic antimicrobial prophylaxis for percutaneous endoscopic gastrostomy. *Cochrane Database Syst Rev* 2013; CD005571 [PMID: 24234575 DOI: 10.1002/14651858.CD005571.pub3]
86 **Campoli PM**, de Paula AA, Alves LG, Turchi MD. Effect of the introducer technique compared with the pull technique on the peristomal infection rate in PEG: a meta-analysis. *Gastrointest Endosc* 2012; **75**: 988-996 [PMID: 22365441 DOI: 10.1016/j.gie.2012.01.003]
87 **Petersen TI**, Kruse A. Complications of percutaneous endoscopic gastrostomy. *Eur J Surg* 1997; **163**: 351-356 [PMID: 9195168]
88 **Adachi Y**, Akino K, Mita H, Kikuchi T, Yamashita K, Sasaki Y, Arimura Y, Endo T. Systemic Prophylactic Antibiotics for the Modified Introducer Method for Percutaneous Endoscopic Gastrostomy: A Prospective, Randomized, Double-Blind Study. *J Clin Gastroenterol* 2016; **50**: 727-732 [PMID: 26756107 DOI: 10.1097/MCG.0000000000000470]
89 **ASGE Standards of Practice Committee**, Banerjee S, Shen B, Baron TH, Nelson DB, Anderson MA, Cash BD, Dominitz JA, Gan SI, Harrison ME, Ikenberry SO, Jagannath SB, Lichtenstein D, Fanelli RD, Lee K, van Guilder T, Stewart LE. Antibiotic prophylaxis for GI endoscopy. *Gastrointest Endosc* 2008; **67**: 791-798 [PMID: 18374919 DOI: 10.1016/j.gie.2008.02.068]
90 **Blomberg J**, Lagergren P, Martin L, Mattsson F, Lagergren J. Novel approach to antibiotic prophylaxis in percutaneous endoscopic gastrostomy (PEG): randomised controlled trial. *BMJ* 2010; **341**: c3115 [PMID: 20601414 DOI: 10.1136/bmj.c3115]
91 **Malloy PC**, Grassi CJ, Kundu S, Gervais DA, Miller DL, Osnis RB, Postoak DW, Rajan DK, Sacks D, Schwartzberg MS, Zuckerman DA, Cardella JF; Standards of Practice Committee with Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Endorsement. Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. *J Vasc Interv Radiol* 2009; **20**: S240-S249 [PMID: 19394868 DOI: 10.1016/j.jvir.2008.11.027]
92 **Patel IJ**, Davidson JC, Nikolic B, Salazar GM, Schwartzberg MS, Walker TG, Saad WE; Standards of Practice Committee, with Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Endorsement; Standards of Practice Committee of the Society of Interventional Radiology. Addendum of newer anticoagulants to the SIR consensus guideline. *J Vasc Interv Radiol* 2013; **24**: 641-645 [PMID: 23622037 DOI: 10.1016/j.jvir.2012.12.007]
93 **Patel IJ**, Rahim S, Davidson JC, Hanks SE, Tam AL, Walker TG, Wilkins LR, Sarode R, Weinberg I. Society of Interventional Radiology Consensus Guidelines for the Periprocedural Management of Thrombotic and Bleeding Risk in Patients Undergoing Percutaneous Image-Guided Interventions-Part II: Recommendations: Endorsed by the Canadian Association for Interventional Radiology and the Cardiovascular and Interventional Radiological Society of Europe. *J Vasc Interv Radiol* 2019; **30**: 1168-1184.e1 [PMID: 31229333 DOI: 10.1016/j.jvir.2019.04.017]
94 **Davidson JC**, Rahim S, Hanks SE, Patel IJ, Tam AL, Walker TG, Weinberg I, Wilkins LR, Sarode R. Society of Interventional Radiology Consensus Guidelines for the Periprocedural Management of Thrombotic and Bleeding Risk in Patients Undergoing Percutaneous Image-Guided Interventions-Part I: Review of Anticoagulation Agents and Clinical Considerations: Endorsed by the Canadian Association for Interventional Radiology and the Cardiovascular and Interventional Radiological Society of Europe. *J Vasc Interv Radiol* 2019; **30**: 1155-1167 [PMID: 31229332 DOI: 10.1016/j.jvir.2019.04.016]
95 **Lucendo AJ**, Sánchez-Casanueva T, Redondo O, Tenías JM, Arias Á. Risk of bleeding in patients undergoing percutaneous endoscopic gastrotrostomy (PEG) tube insertion under antiplatelet therapy: a systematic review with a meta-analysis. *Rev Esp Enferm Dig* 2015; **107**: 128-136 [PMID: 25733036]
96 **Thosani N**, Rashtak S, Kannadath BS, Munjal A, Meriwether M, Yoon ED, Hermann A, Ali S, Haddad PG, Patil P, Ramireddy S, Badillo R, DaVee RT, Guha S. Bleeding Risk and Mortality Associated With Uninterrupted Antithrombotic Therapy During Percutaneous Endoscopic Gastrostomy Tube Placement. *Am J Gastroenterol* 2021; **116**: 1868-1875 [PMID: 34158462 DOI: 10.14309/ajg.0000000000001348]
97 **Singh D**, Laya AS, Vaidya OU, Ahmed SA, Bonham AJ, Clarkston WK. Risk of bleeding after percutaneous endoscopic gastrostomy (PEG). *Dig Dis Sci* 2012; **57**: 973-980 [PMID: 22138961 DOI: 10.1007/s10620-011-1965-7]
98 **Grant JP**. Percutaneous endoscopic gastrostomy. Initial placement by single endoscopic technique and long-term follow-up. *Ann Surg* 1993; **217**: 168-174 [PMID: 8439214 DOI: 10.1097/00000658-199302000-00011]
99 **Rabeneck L**, Wray NP, Petersen NJ. Long-term outcomes of patients receiving percutaneous endoscopic gastrostomy tubes. *J Gen Intern Med* 1996; **11**: 287-293 [PMID: 8725977 DOI: 10.1007/BF02598270]
100 **Amann W**, Mischinger HJ, Berger A, Rosanelli G, Schweiger W, Werkgartner G, Fruhwirth J, Hauser H. Percutaneous endoscopic gastrostomy (PEG). 8 years of clinical experience in 232 patients. *Surg Endosc* 1997; **11**: 741-744 [PMID: 9214323 DOI: 10.1007/s004649900440]
101 **Mamel JJ**. Percutaneous endoscopic gastrostomy. *Am J Gastroenterol* 1989; **84**: 703-710 [PMID: 2500845]
102 **Lee SP**, Lee KN, Lee OY, Lee HL, Jun DW, Yoon BC, Choi HS, Kim SH. Risk factors for complications of percutaneous endoscopic gastrostomy. *Dig Dis Sci* 2014; **59**: 117-125 [PMID: 24142070 DOI: 10.1007/s10620-013-2891-7]
103 **Shin JH**, Park AW. Updates on percutaneous radiologic gastrostomy/gastrojejunostomy and jejunostomy. *Gut Liver* 2010; **4** Suppl 1: S25-S31 [PMID: 21103291 DOI: 10.5009/gnl.2010.4.S1.S25]
104 **Murphy CJ**, Adler DG, Cox K, Sommers DN, Fang JC. Insufflation with carbon dioxide reduces pneumoperitoneum after percutaneous endoscopic gastrostomy (PEG): a randomized controlled trial. *Endosc Int Open* 2016; **4**: E292-E295 [PMID: 27004246 DOI: 10.1055/s-0042-100192]
105 **Calton WC**, Martindale RG, Gooden SM. Complications of percutaneous endoscopic gastrostomy. *Mil Med* 1992; **157**: 358-360 [PMID: 1528471 DOI: 10.1093/milmed/157.7.358]
106 **Lee JH**, Kim JJ, Kim YH, Jang JK, Son HJ, Peck KR, Rhee PL, Paik SW, Rhee JC, Choi KW. Increased risk of peristomal wound infection after percutaneous endoscopic gastrostomy in patients with diabetes mellitus. *Dig Liver Dis* 2002; **34**: 857-861 [PMID: 12643294 DOI: 10.1016/S1590-8658(02)80256-0]

107 **Person JL**, Brower RA. Necrotizing fasciitis/myositis following percutaneous endoscopic gastrostomy. *Gastrointest Endosc* 1986; **32**: 309 [PMID: 3743994 DOI: 10.1016/S0016-5107(86)71867-1]

108 **Korula J**, Rice HE. Necrotizing fasciitis and percutaneous endoscopic gastrostomy. *Gastrointest Endosc* 1987; **33**: 335-336 [PMID: 3653662 DOI: 10.1016/S0016-5107(87)71622-8]

109 **Cave DR**, Robinson WR, Brotschi EA. Necrotizing fasciitis following percutaneous endoscopic gastrostomy. *Gastrointest Endosc* 1986; **32**: 294-296 [PMID: 2943631 DOI: 10.1016/S0016-5107(86)71852-X]

110 **Iber FL**, Livak A, Patel M. Importance of fungus colonization in failure of silicone rubber percutaneous gastrostomy tubes (PEGs). *Dig Dis Sci* 1996; **41**: 226-231 [PMID: 8565761 DOI: 10.1007/BF02208608]

111 **Sartori S**, Trevisani L, Nielsen I, Tassinari D, Ceccotti P, Abbasciano V. Longevity of silicone and polyurethane catheters in long-term enteral feeding *via* percutaneous endoscopic gastrostomy. *Aliment Pharmacol Ther* 2003; **17**: 853-856 [PMID: 12641508 DOI: 10.1046/j.1365-2036.2003.01538.x]

112 **Blacka J**, Donoghue J, Sutherland M, Martincich I, Mitten-Lewis S, Morris P, Meredith G. Dwell time and functional failure in percutaneous endoscopic gastrostomy tubes: a prospective randomized-controlled comparison between silicon polymer and polyurethane percutaneous endoscopic gastrostomy tubes. *Aliment Pharmacol Ther* 2004; **20**: 875-882 [PMID: 15479359 DOI: 10.1111/j.1365-2036.2004.02191.x]

113 **Ma MM**, Semlacher EA, Fedorak RN, Lalor EA, Duerksen DR, Sherbaniuk RW, Chalpelsky CE, Sadowski DC. The buried gastrostomy bumper syndrome: prevention and endoscopic approaches to removal. *Gastrointest Endosc* 1995; **41**: 505-508 [PMID: 7615232 DOI: 10.1016/S0016-5107(05)80012-4]

114 **McClave SA**, Jafri NS. Spectrum of morbidity related to bolster placement at time of percutaneous endoscopic gastrostomy: buried bumper syndrome to leakage and peritonitis. *Gastrointest Endosc Clin N Am* 2007; **17**: 731-746 [PMID: 17967378 DOI: 10.1016/j.giec.2007.07.011]

115 **Rimon E**. The safety and feasibility of percutaneous endoscopic gastrostomy placement by a single physician. *Endoscopy* 2001; **33**: 241-244 [PMID: 11293757 DOI: 10.1055/s-2001-12800]

116 **Foutch PG**, Talbert GA, Waring JP, Sanowski RA. Percutaneous endoscopic gastrostomy in patients with prior abdominal surgery: virtues of the safe tract. *Am J Gastroenterol* 1988; **83**: 147-150 [PMID: 3124605]

117 **Cortez AR**, Warren PW, Goddard GR, Jenkins TM, Sauser JA, Gerrein BT, Rymeski BA. Primary Placement of a Low-Profile Gastrostomy Button Is Safe and Associated With Improved Outcomes in Children. *J Surg Res* 2020; **249**: 156-162 [PMID: 31958600 DOI: 10.1016/j.jss.2019.11.027]

118 **Powell KS**, Marcuard SP, Farrior ES, Gallagher ML. Aspirating gastric residuals causes occlusion of small-bore feeding tubes. *JPEN J Parenter Enteral Nutr* 1993; **17**: 243-246 [PMID: 8505829 DOI: 10.1177/0148607193017003243]

119 **Blumenstein I**, Shastri YM, Stein J. Gastroenteric tube feeding: techniques, problems and solutions. *World J Gastroenterol* 2014; **20**: 8505-8524 [PMID: 25024606 DOI: 10.3748/wjg.v20.i26.8505]

120 **Pothuri B**, Montemarano M, Gerardi M, Shike M, Ben-Porat L, Sabbatini P, Barakat RR. Percutaneous endoscopic gastrostomy tube placement in patients with malignant bowel obstruction due to ovarian carcinoma. *Gynecol Oncol* 2005; **96**: 330-334 [PMID: 15661217 DOI: 10.1016/j.ygyno.2004.09.058]

121 **Kawata N**, Kakushima N, Tanaka M, Sawai H, Imai K, Hagiwara T, Takao T, Hotta K, Yamaguchi Y, Takizawa K, Matsubayashi H, Ono H. Percutaneous endoscopic gastrostomy for decompression of malignant bowel obstruction. *Dig Endosc* 2014; **26**: 208-213 [PMID: 23772988 DOI: 10.1111/den.12139]

122 **Thampy S**, Najran P, Mullan D, Laasch HU. Safety and Efficacy of Venting Gastrostomy in Malignant Bowel Obstruction: A Systematic Review. *J Palliat Care* 2020; **35**: 93-102 [PMID: 31448682 DOI: 10.1177/0825859719864915]

123 **Inaba Y**, Yamaura H, Sato Y, Kashima M, Kato M, Inoue D, Kurinobu T, Sato T. Percutaneous radiologic gastrostomy in patients with malignant pharyngoesophageal obstruction. *Jpn J Clin Oncol* 2013; **43**: 713-718 [PMID: 23698854 DOI: 10.1093/jjco/hyt069]

124 **Laval G**, Marcelin-Benazech B, Guirimand F, Chauvenet L, Copel L, Durand A, Francois E, Gabolde M, Mariani P, Rebischung C, Servois V, Terrebonne E, Arvieux C; French Society for Palliative Care; French Society for Digestive Surgery; French Society for Gastroenterology; French Association for Supportive Care in Oncology; French Society for Digestive Cancer. Recommendations for bowel obstruction with peritoneal carcinomatosis. *J Pain Symptom Manage* 2014; **48**: 75-91 [PMID: 24798105 DOI: 10.1016/j.jpainsymman.2013.08.022]

125 **Kubrak C**, Olson K, Jha N, Jensen L, McCargar L, Seikaly H, Harris J, Scrimger R, Parliament M, Baracos VE. Nutrition impact symptoms: key determinants of reduced dietary intake, weight loss, and reduced functional capacity of patients with head and neck cancer before treatment. *Head Neck* 2010; **32**: 290-300 [PMID: 19626639 DOI: 10.1002/hed.21174]

126 **Jager-Wittenaar H**, Dijkstra PU, Vissink A, van der Laan BF, van Oort RP, Roodenburg JL. Critical weight loss in head and neck cancer--prevalence and risk factors at diagnosis: an explorative study. *Support Care Cancer* 2007; **15**: 1045-1050 [PMID: 17277925 DOI: 10.1007/s00520-006-0212-9]

127 **Dawson ER**, Morley SE, Robertson AG, Soutar DS. Increasing dietary supervision can reduce weight loss in oral cancer patients. *Nutr Cancer* 2001; **41**: 70-74 [PMID: 12094631 DOI: 10.1080/01635581.2001.9680614]

128 **Strom T**, Trotti AM, Kish J, Rao NG, McCaffrey J, Padhya TA, Lin HY, Fulp W, Caudell JJ. Risk factors for percutaneous endoscopic gastrostomy tube placement during chemoradiotherapy for oropharyngeal cancer. *JAMA Otolaryngol Head Neck Surg* 2013; **139**: 1242-1246 [PMID: 24136493 DOI: 10.1001/jamaoto.2013.5193]

129 **Jack DR**, Dawson FR, Reilly JE, Shoaib T. Guideline for prophylactic feeding tube insertion in patients undergoing resection of head and neck cancers. *J Plast Reconstr Aesthet Surg* 2012; **65**: 610-615 [PMID: 22137826 DOI: 10.1016/j.bjps.2011.11.018]

130 **Kramer S**, Newcomb M, Hessler J, Siddiqui F. Prophylactic versus reactive PEG tube placement in head and neck cancer. *Otolaryngol Head Neck Surg* 2014; **150**: 407-412 [PMID: 24381015 DOI: 10.1177/0194599813517081]

131 **Wright GP**, Foster SM, Chung MH. Esophagectomy in patients with prior percutaneous endoscopic gastrostomy tube placement. *Am J Surg* 2014; **207**: 361-5; discussion 364 [PMID: 24418181 DOI: 10.1016/j.amjsurg.2013.10.012]

132 **Grilo A**, Santos CA, Fonseca J. Percutaneous endoscopic gastrostomy for nutritional palliation of upper esophageal cancer

unsuitable for esophageal stenting. *Arq Gastroenterol* 2012; **49**: 227-231 [PMID: 23011248 DOI: 10.1590/S0004-28032012000300012]

133 **Volkmer K**, Meyer T, Sailer M, Fein M. [Metastasis of an esophageal carcinoma at a PEG site--case report and review of the literature]. *Zentralbl Chir* 2009; **134**: 481-485 [PMID: 19757350 DOI: 10.1055/s-0028-1098769]

134 **Saeed SM**, Fontaine JP, Dam AN, Hoffe SE, Cameron M, Frakes J, Mehta R, Gurd E, Pimiento JM. Is Preoperative G-Tube Use Safe for Esophageal Cancer Patients? *J Am Coll Nutr* 2020; **39**: 301-306 [PMID: 31397638 DOI: 10.1080/07315724.2019.1646168]

135 **Mahawongkajit P**, Techagumpuch A, Limpavitayaporn P, Kanlerd A, Sriussadaporn E, Juntong J, Tongyoo A, Mingmalairak C. Comparison of Introducer Percutaneous Endoscopic Gastrostomy with Open Gastrostomy in Advanced Esophageal Cancer Patients. *Dysphagia* 2020; **35**: 117-120 [PMID: 31025103 DOI: 10.1007/s00455-019-10017-w]

136 **Song JH**, Ko J, Min YW, Kim K, Lee H, Min BH, Lee JH, Rhee PL, Kim JJ. Comparison between Percutaneous Gastrostomy and Self-Expandable Metal Stent Insertion for the Treatment of Malignant Esophageal Obstruction, after Propensity Score Matching. *Nutrients* 2020; **12** [PMID: 32927691 DOI: 10.3390/nu12092756]

137 **Allen K**, Hoffman L. Enteral Nutrition in the Mechanically Ventilated Patient. *Nutr Clin Pract* 2019; **34**: 540-557 [PMID: 30741491 DOI: 10.1002/ncp.10242]

138 **Altintas ND**, Aydin K, Türkoğlu MA, Abbasoğlu O, Topeli A. Effect of enteral versus parenteral nutrition on outcome of medical patients requiring mechanical ventilation. *Nutr Clin Pract* 2011; **26**: 322-329 [PMID: 21531737 DOI: 10.1177/0884533611405790]

139 **Seron-Arbeloa C**, Zamora-Elson M, Labarta-Monzon L, Mallor-Bonet T. Enteral nutrition in critical care. *J Clin Med Res* 2013; **5**: 1-11 [PMID: 23390469 DOI: 10.4021/jocmr1210w]

140 **Artinian V**, Krayem H, DiGiovine B. Effects of early enteral feeding on the outcome of critically ill mechanically ventilated medical patients. *Chest* 2006; **129**: 960-967 [PMID: 16608945 DOI: 10.1378/chest.129.4.960]

141 **Grant JP**. Nutrition care of patients with acute and chronic respiratory failure. *Nutr Clin Pract* 1994; **9**: 11-17 [PMID: 8159135 DOI: 10.1177/011542659400900111]

142 **Farina N**, Nordbeck S, Montgomery M, Cordwin L, Blair F, Cherry-Bukowiec J, Kraft MD, Pleva MR, Raymond E. Early Enteral Nutrition in Mechanically Ventilated Patients With COVID-19 Infection. *Nutr Clin Pract* 2021; **36**: 440-448 [PMID: 33651909 DOI: 10.1002/ncp.10629]

143 **Goyal H**, Perisetti A, Tharian B. Percutaneous Endoscopic Gastrostomy tube placement in COVID-19 patients: Multidisciplinary approach. *Dig Endosc* 2021; **33**: 209 [PMID: 33063878 DOI: 10.1111/den.13873]

144 **Oberg CL**, Keyes C, Panchabhai TS, Sajawal Ali M, Oh SS, Grogan TR, Mojica J, Auchincloss H, Pulido N, Brait K, Folch EE. Combined Percutaneous Tracheostomy and Endoscopic Gastrostomy Tubes in COVID-19: A Prospective Series of Patient Outcomes. *J Intensive Care Med* 2021; **36**: 1340-1346 [PMID: 34424096 DOI: 10.1177/08850666211038875]

145 **Volkert D**, Berner YN, Berry E, Cederholm T, Coti Bertrand P, Milne A, Palmblad J, Schneider S, Sobotka L, Stanga Z; DGEM (German Society for Nutritional Medicine), Lenzen-Grossimlinghaus R, Krys U, Pirlich M, Herbst B, Schütz T, Schröer W, Weinrebe W, Ockenga J, Lochs H; ESPEN (European Society for Parenteral and Enteral Nutrition). ESPEN Guidelines on Enteral Nutrition: Geriatrics. *Clin Nutr* 2006; **25**: 330-360 [PMID: 16735082 DOI: 10.1016/j.clnu.2006.01.012]

146 **Jauch EC**, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW Jr, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; **44**: 870-947 [PMID: 23370205 DOI: 10.1161/STR.0b013e318284056a]

147 **Wirth R**, Smoliner C, Jäger M, Warnecke T, Leischker AH, Dziewas R; DGEM Steering Committee*. Guideline clinical nutrition in patients with stroke. *Exp Transl Stroke Med* 2013; **5**: 14 [PMID: 24289189 DOI: 10.1186/2040-7378-5-14]

148 **Kim DS**, Jones RN, Shireman TI, Kluger BM, Friedman JH, Akbar U. Trends and outcomes associated with gastrostomy tube placement in common neurodegenerative disorders. *Clin Park Relat Disord* 2021; **4**: 100088 [PMID: 34316666 DOI: 10.1016/j.prdoa.2020.100088]

149 **Lex KM**, Kundt FS, Lorenzl S. Using tube feeding and levodopa-carbidopa intestinal gel application in advanced Parkinson's disease. *Br J Nurs* 2018; **27**: 259-262 [PMID: 29517331 DOI: 10.12968/bjon.2018.27.5.259]

150 **Ishibashi Y**, Shimo Y, Yube Y, Oka S, Egawa H, Kohira Y, Kaji S, Kanda S, Oyama G, Hatano T, Hattori N, Fukunaga T. Technique and outcome of percutaneous endoscopic transgastric jejunostomy for continuous infusion of levodopa-carbidopa intestinal gel for treatment of Parkinson's disease. *Scand J Gastroenterol* 2019; **54**: 787-792 [PMID: 31125265 DOI: 10.1080/00365521.2019.1619830]

151 **Epstein M**, Johnson DA, Hawes R, Schmulewitz N, Vanagunas AD, Gossen ER, Robieson WZ, Eaton S, Dubow J, Chatamra K, Benesh J. Long-Term PEG-J Tube Safety in Patients With Advanced Parkinson's Disease. *Clin Transl Gastroenterol* 2016; **7**: e159 [PMID: 27030949 DOI: 10.1038/ctg.2016.19]

152 **Katzberg HD**, Benatar M. Enteral tube feeding for amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database Syst Rev* 2011; CD004030 [PMID: 21249659 DOI: 10.1002/14651858.CD004030.pub3]

153 **Grandidge L**, Chotiyarnwong C, White S, Denning J, Nair KPS. Survival following the placement of gastrostomy tube in patients with multiple sclerosis. *Mult Scler J Exp Transl Clin* 2020; **6**: 2055217319900907 [PMID: 32002190 DOI: 10.1177/2055217319900907]

154 **Civan HA**, Bektas G, Dogan AE, Ozdener F. Percutaneous Endoscopic Gastrostomy Feeding in Children with Cerebral Palsy. *Neuropediatrics* 2021; **52**: 326-332 [PMID: 34192785 DOI: 10.1055/s-0041-1731007]

155 **Akkersdijk WL**, Roukema JA, van der Werken C. Percutaneous endoscopic gastrostomy for patients with severe cerebral injury. *Injury* 1998; **29**: 11-14 [PMID: 9659473 DOI: 10.1016/S0020-1383(97)00108-3]

156 **Godil A**, Chen YK. Percutaneous endoscopic gastrostomy for nutrition support in pregnancy associated with hyperemesis gravidarum and anorexia nervosa. *JPEN J Parenter Enteral Nutr* 1998; **22**: 238-241 [PMID: 9661126 DOI:

10.1177/0148607198022004238]
157 **Irving PM**, Howell RJ, Shidrawi RG. Percutaneous endoscopic gastrostomy with a jejunal port for severe hyperemesis gravidarum. *Eur J Gastroenterol Hepatol* 2004; **16**: 937-939 [PMID: 15316422 DOI: 10.1097/00042737-200409000-00021]
158 **Serrano P**, Velloso A, García-Luna PP, Pereira JL, Fernádez Z, Ductor MJ, Castro D, Tejero J, Fraile J, Romero H. Enteral nutrition by percutaneous endoscopic gastrojejunostomy in severe hyperemesis gravidarum: a report of two cases. *Clin Nutr* 1998; **17**: 135-139 [PMID: 10205331 DOI: 10.1016/S0261-5614(98)80008-3]
159 **Senadhi V**, Chaudhary J, Dutta S. Percutaneous endoscopic gastrostomy placement during pregnancy in the critical care setting. *Endoscopy* 2010; **42** Suppl 2: E358-E359 [PMID: 21181630 DOI: 10.1055/s-0030-1256052]
160 **Wood MF**, Sapala JA, Sapala MA, Schuhknecht MP, Flake TM. Micropouch gastric bypass: indications for gastrostomy tube placement in the bypassed stomach. *Obes Surg* 2000; **10**: 413-419 [PMID: 11054245 DOI: 10.1381/096089200321594273]
161 **Nosher JL**, Bodner LJ, Girgis WS, Brolin R, Siegel RL, Gribbin C. Percutaneous gastrostomy for treating dilatation of the bypassed stomach after bariatric surgery for morbid obesity. *AJR Am J Roentgenol* 2004; **183**: 1431-1435 [PMID: 15505316 DOI: 10.2214/ajr.183.5.1831431]
162 **Baltz JG**, Argo CK, Al-Osaimi AM, Northup PG. Mortality after percutaneous endoscopic gastrostomy in patients with cirrhosis: a case series. *Gastrointest Endosc* 2010; **72**: 1072-1075 [PMID: 20855067 DOI: 10.1016/j.gie.2010.06.043]
163 **Shah I**, Bhurwal A, Mehta H, Maas D, Koneru G, Cohen AS, Kadkhodayan KS. Trends and outcomes of percutaneous endoscopic gastrostomy in hospitalized patients with malignant and nonmalignant ascites: a nationwide population study. *Ann Gastroenterol* 2020; **33**: 656-660 [PMID: 33162742 DOI: 10.20524/aog.2020.0531]
164 **Wilmskoetter J**, Simpson KN, Bonilha HS. Hospital Readmissions of Stroke Patients with Percutaneous Endoscopic Gastrostomy Feeding Tubes. *J Stroke Cerebrovasc Dis* 2016; **25**: 2535-2542 [PMID: 27423366 DOI: 10.1016/j.jstrokecerebrovasdis.2016.06.034]
165 **Geeganage C**, Beavan J, Ellender S, Bath PM. Interventions for dysphagia and nutritional support in acute and subacute stroke. *Cochrane Database Syst Rev* 2012; **10**: CD000323 [PMID: 23076886 DOI: 10.1002/14651858.CD000323.pub2]
166 **Joundi RA**, Saposnik G, Martino R, Fang J, Porter J, Kapral MK. Outcomes among patients with direct enteral vs nasogastric tube placement after acute stroke. *Neurology* 2018; **90**: e544-e552 [PMID: 29367443 DOI: 10.1212/WNL.0000000000004962]
167 **Gauvin G**, Do-Nguyen CC, Lou J, O'Halloran EA, Selesner LT, Handorf E, Collins ME, Farma JM. Gastrostomy Tube for Nutrition and Malignant Bowel Obstruction in Patients With Cancer. *J Natl Compr Canc Netw* 2021; **19**: 48-56 [PMID: 33406493 DOI: 10.6004/jnccn.2020.7604]
168 **McCann RM**, Hall WJ, Groth-Juncker A. Comfort care for terminally ill patients. The appropriate use of nutrition and hydration. *JAMA* 1994; **272**: 1263-1266 [PMID: 7523740 DOI: 10.1001/jama.272.16.1263]
169 **Oterdoom LH**, Marinus Oterdoom DL, Ket JCF, van Dijk JMC, Scholten P. Systematic review of ventricular peritoneal shunt and percutaneous endoscopic gastrostomy: a safe combination. *J Neurosurg* 2017; **127**: 899-904 [PMID: 27911231 DOI: 10.3171/2016.8.JNS152701]
170 **Kim JS**, Park YW, Kim HK, Cho YS, Kim SS, Youn NR, Chae HS. Is percutaneous endoscopic gastrostomy tube placement safe in patients with ventriculoperitoneal shunts? *World J Gastroenterol* 2009; **15**: 3148-3152 [PMID: 19575495 DOI: 10.3748/wjg.15.3148]
171 **Gieniusz M**, Sinvani L, Kozikowski A, Patel V, Nouryan C, Williams MS, Kohn N, Pekmezaris R, Wolf-Klein G. Percutaneous Feeding Tubes in Individuals with Advanced Dementia: Are Physicians "Choosing Wisely"? *J Am Geriatr Soc* 2018; **66**: 64-69 [PMID: 28975616 DOI: 10.1111/jgs.15125]
172 **Finucane TE**, Christmas C, Travis K. Tube feeding in patients with advanced dementia: a review of the evidence. *JAMA* 1999; **282**: 1365-1370 [PMID: 10527184 DOI: 10.1001/jama.282.14.1365]
173 **Teno JM**, Gozalo P, Mitchell SL, Kuo S, Fulton AT, Mor V. Feeding tubes and the prevention or healing of pressure ulcers. *Arch Intern Med* 2012; **172**: 697-701 [PMID: 22782196 DOI: 10.1001/archinternmed.2012.1200]
174 **Higaki F**, Yokota O, Ohishi M. Factors predictive of survival after percutaneous endoscopic gastrostomy in the elderly: is dementia really a risk factor? *Am J Gastroenterol* 2008; **103**: 1011-6; quiz 1017 [PMID: 18177448 DOI: 10.1111/j.1572-0241.2007.01719.x]
175 **Finucane TE**, Bynum JP. Use of tube feeding to prevent aspiration pneumonia. *Lancet* 1996; **348**: 1421-1424 [PMID: 8937283 DOI: 10.1016/S0140-6736(96)03369-7]
176 **Murphy LM**, Lipman TO. Percutaneous endoscopic gastrostomy does not prolong survival in patients with dementia. *Arch Intern Med* 2003; **163**: 1351-1353 [PMID: 12796072 DOI: 10.1001/archinte.163.11.1351]
177 **Nakanishi M**, Hattori K. Percutaneous endoscopic gastrostomy (PEG) tubes are placed in elderly adults in Japan with advanced dementia regardless of expectation of improvement in quality of life. *J Nutr Health Aging* 2014; **18**: 503-509 [PMID: 24886737 DOI: 10.1007/s12603-014-0011-9]
178 **Ayman AR**, Khoury T, Cohen J, Chen S, Yaari S, Daher S, Benson AA, Mizrahi M. PEG Insertion in Patients With Dementia Does Not Improve Nutritional Status and Has Worse Outcomes as Compared With PEG Insertion for Other Indications. *J Clin Gastroenterol* 2017; **51**: 417-420 [PMID: 27505401 DOI: 10.1097/MCG.0000000000000624]
179 **van Bruchem-Visser RL**, Mattace-Raso FUS, de Beaufort ID, Kuipers EJ. Percutaneous endoscopic gastrostomy in older patients with and without dementia: Survival and ethical considerations. *J Gastroenterol Hepatol* 2019; **34**: 736-741 [PMID: 30551264 DOI: 10.1111/jgh.14573]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 April 27; 14(4): 304-314

DOI: 10.4240/wjgs.v14.i4.304

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

# Laparoscopic-assisted *vs* open transhiatal gastrectomy for Siewert type II adenocarcinoma of the esophagogastric junction: A retrospective cohort study

Qi-Ying Song, Xiong-Guang Li, Li-Yu Zhang, Di Wu, Shuo Li, Ben-Long Zhang, Zi-Yao Xu, Ri-Li-Ge Wu, Xin Guo, Xin-Xin Wang

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): A
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Heath OM, United Kingdom; Levine Y, Israel; Ozawa S, Japan

**Received:** December 7, 2021
**Peer-review started:** December 7, 2021
**First decision:** January 12, 2022
**Revised:** January 15, 2022
**Accepted:** March 26, 2022
**Article in press:** March 26, 2022
**Published online:** April 27, 2022

**Qi-Ying Song, Li-Yu Zhang, Di Wu, Shuo Li, Ben-Long Zhang, Zi-Yao Xu,** Medical School of Chinese People's Liberation Army, Chinese People's Liberation Army General Hospital, Beijing 100853, China

**Xiong-Guang Li,** School of Medicine, Nankai University, Tianjin 300071, China

**Ri-Li-Ge Wu,** Medical Big Data Research Center, Chinese PLA General Hospital, Beijing 100853, China

**Xin Guo,** Air Force Medical University Xijing Hospital, Xi'an 710000, Shaanxi Province, China

**Xin-Xin Wang,** Department of General Surgery, Chinese People's Liberation Army General Hospital, Beijing 100853, China

**Corresponding author:** Xin-Xin Wang, MD, PhD, Assistant Professor, Chief Doctor, Department of General Surgery, Chinese People's Liberation Army General Hospital, No. 28 Fuxing Road, Haidian District, Beijing 100853, China. 301wxx@sina.com

## Abstract

### *BACKGROUND*

The studies of laparoscopic-assisted transhiatal gastrectomy (LTG) in patients with Siewert type II adenocarcinoma of the esophagogastric junction (AEG) are scarce.

### *AIM*

To compare the surgical efficiency of LTG with the open transhiatal gastrectomy (OTG) for patients with Siewert type II AEG.

### *METHODS*

We retrospectively evaluated a total of 578 patients with Siewert type II AEG who have undergone LTG or OTG at the First Medical Center of the Chinese People's Liberation Army General Hospital from January 2014 to December 2019. The short-term and long-term outcomes were compared between the LTG ($n$ = 382) and OTG ($n$ = 196) groups.

***RESULTS***

Compared with the OTG group, the LTG group had a longer operative time but less blood loss, shorter length of abdominal incision and an increased number of harvested lymph nodes ($P$ < 0.05). Patients in the LTG group were able to eat liquid food, ambulate, expel flatus and discharge sooner than the OTG group ($P$ < 0.05). No significant differences were found in postoperative complications and R0 resection. The 3-year overall survival and disease-free survival performed better in the LTG group compared with that in the OTG group (88.2% *vs* 79.2%, $P$ = 0.011; 79.7% *vs* 73.0%, $P$ = 0.002, respectively). In the stratified analysis, both overall survival and disease-free survival were better in the LTG group than those in the OTG group for stage II/III patients ($P$ < 0.05) but not for stage I patients.

***CONCLUSION***

For patients with Siewert type II AEG, LTG is associated with better short-term outcomes and similar oncology safety. In addition, patients with advanced stage AEG may benefit more from LTG in the long-term outcomes.

**Key Words:** Adenocarcinoma of the esophagogastric junction; Siewert type II; Laparoscopic-assisted transhiatal gastrectomy; Open transhiatal gastrectomy



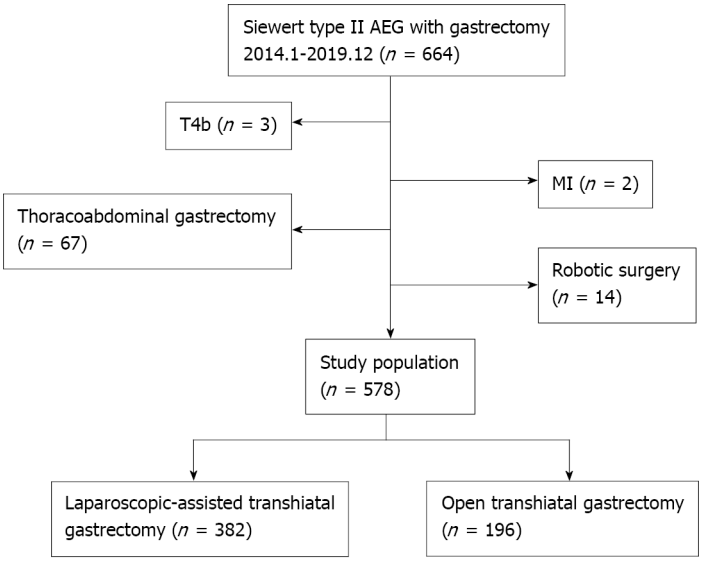
**Core Tip:** Our objective was to compare the surgical efficiency of laparoscopic-assisted transhiatal gastrectomy (LTG) with the open transhiatal gastrectomy in patients with Siewert type II adenocarcinoma of the esophagogastric junction. We found that LTG was associated with better short-term outcomes and similar oncology safety. In addition, patients with advanced stage adenocarcinoma of the esophagogastric junction may benefit more from LTG in 3-year overall survival and disease-free survival.

**Citation:** Song QY, Li XG, Zhang LY, Wu D, Li S, Zhang BL, Xu ZY, Wu RLG, Guo X, Wang XX. Laparoscopic-assisted *vs* open transhiatal gastrectomy for Siewert type II adenocarcinoma of the esophagogastric junction: A retrospective cohort study. *World J Gastrointest Surg* 2022; 14(4): 304-314
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i4/304.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i4.304

## INTRODUCTION

In recent decades, the global incidence of gastric cancer has declined annually while the incidence of adenocarcinoma of the esophagogastric junction (AEG) has presented an upward trend, especially in Asian countries[1-5]. Although there are many controversies concerning the optimal treatment for AEG patients, surgery is still the cornerstone of therapeutic strategies[6]. According to the results of the nationwide clinical trial (JCOG 9502) in Japan, the transhiatal approach is recommended for Siewert type II/III AEG patients with esophageal invasion within 3 cm[7,8]. Since the first report of laparoscopic-assisted transhiatal gastrectomy (LTG) by Kitano *et al*[9] in 1994, LTG has developed rapidly worldwide. With the improvement of laparoscopic technology and the optimization of equipment, a large number of countries have successively carried out LTG for gastric cancer because it provides not only better short-term outcomes but also comparable oncologic safety and survival in comparison with open transhiatal gastrectomy (OTG), especially in early-stage and distal gastric cancer[10-13]. Conversely, due to the lack of scientific evidence, the feasibility of LTG in proximal gastric cancer is still controversial. Moreover, peripheral lymphatic drainage pathways of Siewert type II AEG are more complicated as the particularity of the anatomical location, and LTG surgery with D2 lymphadenectomy remains more challenging than other gastric cancer sites[14,15].

At present, the studies on the short-term and long-term clinical effects of Siewert type II AEG regarding LTG and OTG are limited[16-20]. Thus, this study retrospectively analyzed the clinical data of Siewert type II AEG patients in our hospital, compared the short-term and long-term outcomes of LTG and traditional OTG and aimed to explore the feasibility of LTG treatment of Siewert type II AEG.




**DOI:** 10.4240/wjgs.v14.i4.304 

**Figure 1 Flow chart of patient selection.** AEG: Adenocarcinoma of the esophagogastric junction.

## MATERIALS AND METHODS

### Patients

This work retrospectively reviewed patients with Siewert II AEG who have undergone gastrectomy at the First Medical Center of Chinese PLA General Hospital in China from January 2014 to December 2019. The inclusion criteria contained: (1) Histologically proven Siewert type II AEG; (2) Surgery *via* either OTG or LTG with total or proximal gastrectomy with D2 lymphadenectomy; (3) Staging T1-4a, N0-3, M0 (according to the 8$^{th}$ edition of the TNM staging system of the American Joint Committee on Cancer)[21]; and (4) Esophageal invasion < 3 cm. The exclusion criteria were presented as following: (1) Patients with a secondary malignancy within 5 years; (2) American Society of Anesthesiologists physical status score > 3; (3) Only underwent palliative resection or combined organ resection; and (4) Received preoperative chemotherapy of radiotherapy. Finally, a total of 578 patients were pooled into the study (LTG = 382, OTG = 196).

This study has been registered on Clinical-Trial.gov (ChiCTR2100053647) and approved by the Ethics Committee of Chinese PLA General Hospital.

### Surgical procedures

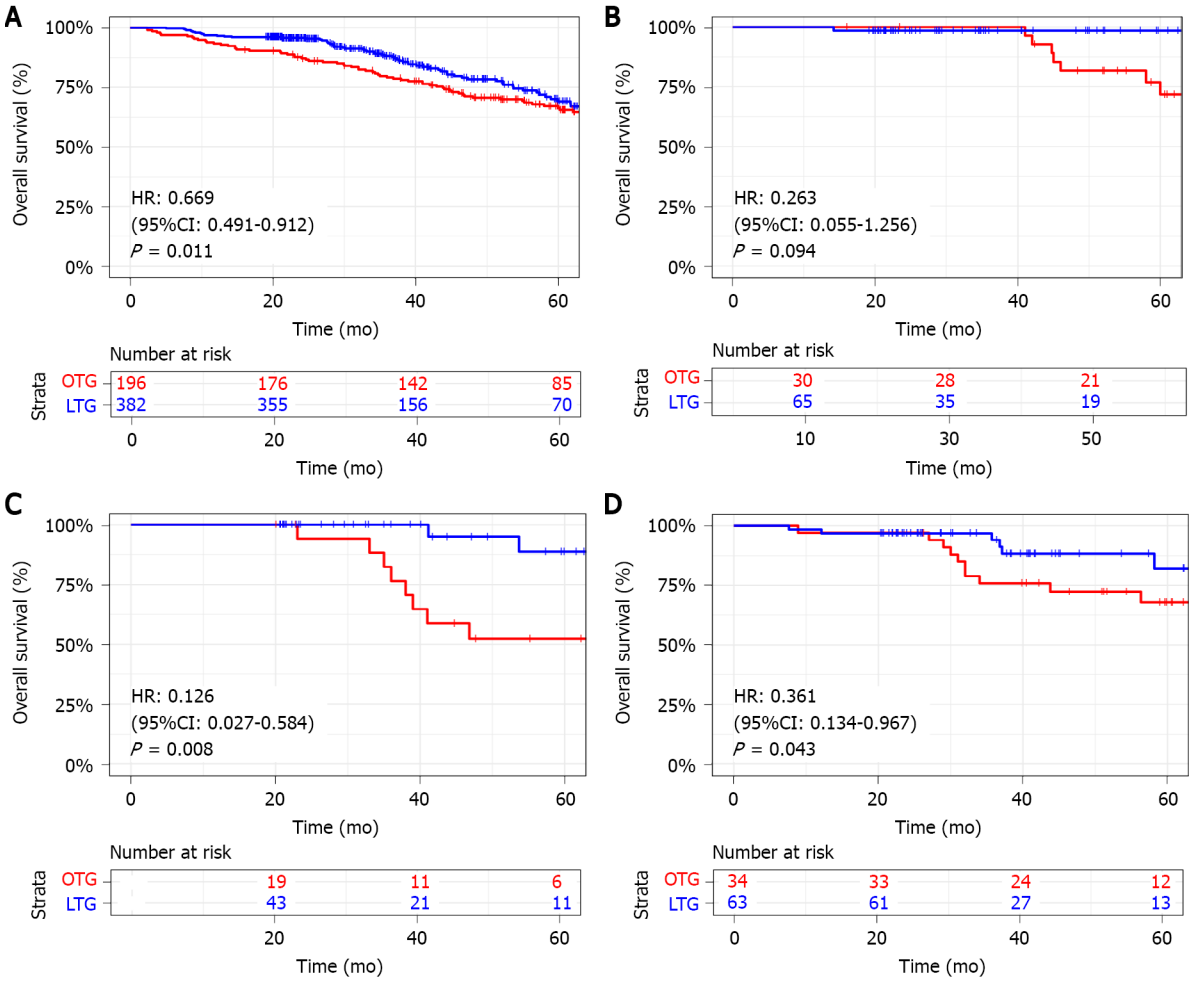
**LTG:** The patient was placed in a supine position and given general anesthesia by employing a 5-hole method. After exploring the relevant positions of various tissues in the abdominal cavity and the location and size of the tumor, a radical total and proximal gastrectomy was performed in this study. Gastrectomy and D2-lymphadenectomy were completed. Then, a small incision was made in the middle of the abdomen to reconstruct the digestive tract. Gastric tube construction and esophagogastrostomy were often performed after proximal gastrectomy. After total gastrectomy, most patients underwent esophagojejunostomy and jejunojejunostomy (Roux-en-Y reconstruction).

**OTG:** The positioning and anesthesia of the patients remained the same as those of the LTG group. An incision was made in the middle of the abdomen to enter the abdominal cavity. Other operative details such as gastrectomy, lymphadenectomy and reconstruction were the same as those in the LTG group.

### Clinical parameters and follow-up

We retrospectively collected the following clinical and pathological factors available in our clinical database: Age, sex, body mass index, smoking/drinking history, American Society of Anesthesiologists score, tumor size, histopathological grade, TNM stage, operation time, intraoperative blood loss, length of abdominal incision, length of proximal margin, number of harvested lymph nodes (LNs), number of positive LNs, resection status (R-status) of margin, postoperative recovery (the time to liquid diet, ambulation, first flatus or defecation and discharge) and postoperative complications (anastomotic leakage, anastomotic stenosis, abdominal abscess, pneumonia, arrhythmia and wound infection). All postoperative complications were classified with the application of the Clavien-Dindo grading system [22].

In addition, postoperative patients were periodically followed up with blood tests, physical examinations and chest/abdominal computed tomography scans through outpatient visits. The follow-up




**DOI:** 10.4240/wjgs.v14.i4.304 

**Figure 2 Comparison of overall survival rates between the laparoscopic-assisted transhiatal gastrectomy and open transhiatal gastrectomy groups.** A. Comparison of overall survival rates between the laparoscopic-assisted transhiatal gastrectomy (LTG) and open transhiatal gastrectomy (OTG) groups for all patients; B: Comparison of overall survival rates between the LTG and OTG groups for stage I patients; C: Comparison of overall survival rates between the LTG and OTG groups for stage II patients; D: Comparison of overall survival rates between the LTG and OTG groups for stage III patients. CI: Confidence interval; HR: Hazard ratio.

interval was every 3–6 mo for the first 2 years and every 6–12 mo for the subsequent 3 years. All surviving patients were followed up annually thereafter until death. Overall survival (OS) was calculated from the time of surgery to death due to any cause or latest follow-up. Disease-free survival (DFS) was calculated as the time from surgery to first recurrence or death because of any reason.

### *Statistical analysis*

Continuous data were presented as mean ± standard deviation with *t* test if normally distributed or as the median (interquartile range) with Mann-Whitney *U* test if not normally distributed. Dichotomous variables were compared with the $\chi^2$ test or Fisher test. Survival analysis was performed by the Kaplan-Meier curves based on the log-rank test. Statistical analysis was done by IBM SPSS (version 26.0.0.0). The figures were plotted with RStudio (version 1.4.1717). Bilateral $P < 0.05$ was considered to be statistically significant.

## RESULTS

### *Clinicopathological characteristics*

As shown in Figure 1, a total of 578 patients were eligible (512 male and 66 female) for our study, of which 382 (66.1%) patients underwent LTG and 196 (33.9%) patients underwent OTG. The demographic information of the participants was presented in Table 1. No significant difference could be observed in the distribution of baseline features between the two groups.

**Table 1 Clinicopathological characteristics for patients in two cohorts**

| Characteristics | LTG, *n* = 382 | OTG, *n* = 196 | *P* value |
|---|---|---|---|
| Age in yr | 64 (58, 69) | 63 (59, 69) | 0.816[a] |
| Sex, *n* (%) | | | |
| Female | 44 (11.5) | 22 (11.2) | 1.000 |
| Male | 338 (88.5) | 174 (88.8) | |
| BMI (kg/m$^2$) | 24.45 (22.10, 26.70) | 24.40 (22.50, 27.25) | 0.389[a] |
| Smoking history, *n* (%) | | | 0.635 |
| No | 280 (73.3) | 148 (75.5) | |
| Yes | 102 (26.7) | 48 (24.5) | |
| Drinking history, *n* (%) | | | 0.773 |
| No | 212 (55.5) | 112 (57.1) | |
| Yes | 170 (44.5) | 84 (42.9) | |
| ASA, *n* (%) | | | |
| 1 | 201 (52.6) | 100 (51.0) | 0.396 |
| 2 | 164 (42.9) | 82 (41.8) | |
| 3 | 17 (4.5) | 14 (7.1) | |
| Tumor size (cm) | 3.49 ± 1.60 | 3.69 ± 1.62 | 0.161 |
| Grade, *n* (%) | | | 0.267 |
| 1-2 | 132 (34.6) | 58 (29.6) | |
| 3-4 | 250 (65.4) | 138 (70.4) | |
| T stage, *n* (%) | | | 0.860 |
| T1-T2 | 129 (33.8) | 64 (32.7) | |
| T3-4a | 253 (66.2) | 132 (67.3) | |
| N stage, *n* (%) | | | 0.602 |
| N0 | 168 (44.0) | 81 (41.3) | |
| N1-N3 | 214 (56.0) | 115 (58.7) | |
| TNM stage, *n* (%) | | | 0.544 |
| I | 107 (28.0) | 49 (25.0) | |
| II | 120 (31.4) | 70 (35.7) | |
| III | 155 (40.6) | 77 (39.3) | |

[a]Mann-Whitney *U* test. ASA: American Society of Anesthesiologists; BMI: Body mass index; LTG: Laparoscopic-assisted transhiatal gastrectomy; OTG: Open transhiatal gastrectomy.

### *Perioperative outcomes*

Perioperative outcomes are shown in Table 2. The LTG group experienced a significantly longer operation time (230.14 ± 58.92 min *vs* 198.4 ± 56.76 min, $P < 0.001$) but significantly decreased blood loss (200.42 ± 304.34 mL *vs* 275.77 ± 384.72 mL, $P = 0.010$) and significantly shorter abdominal incision (9.66 ± 1.73 cm *vs* 18.12 ± 3.92 cm, $P < 0.001$) in comparison with the OTG group. Patients with LTG were sooner able to take a liquid diet (3.65 ± 2.56 d *vs* 4.62 ± 2.59 d, $P < 0.001$) and expel flatus or defecation (3.87 ± 2.17 d *vs* 5.62 ± 2.35 d, $P < 0.001$) after the operation, indicating the restoration of the intestinal function. Additionally, patients in the LTG group were able to ambulate after 2.93 ± 2.04 d, which is fewer days than the OTG group required (4.13 ± 2.55 d) ($P < 0.001$). In addition, the duration of postoperative hospitalization of the LTG group was significantly shorter than that in OTG groups [9 (8, 11) d *vs* 10 (9, 12) d, $P < 0.001$].

Postoperative complications occurred in 5.0% of patients after LTG and in 4.6% of patients after OTG ($P = 0.840$). There existed no significant difference between the two groups in terms of anastomotic leakage, anastomotic stenosis, abdominal abscess, pneumonia, arrhythmia or wound infection ($P > 0.05$).

**Table 2 Perioperative outcomes (mean ± SD)/median (interquartile range)**

| | LTG, *n* = 382 | OTG, *n* = 196 | *P* value |
|---|---|---|---|
| Operation time in min | 230.14 ± 58.92 | 198.4 ± 56.76 | < 0.001 |
| Blood loss in m | 200.42 ± 304.34 | 275.77 ± 384.72 | 0.010 |
| Length of abdominal incision in cm | 9.66 ± 1.73 | 18.12 ± 3.92 | < 0.001 |
| Length of proximal margin in cm | 1.15 ± 0.72 | 1.16 ± 0.77 | 0.986 |
| R-status, *n* (%) | | | 0.879 |
| R0 | 380 (99.5) | 194 (99.0) | |
| R1/2 | 2 (0.5) | 2 (1.0) | |
| Number of harvested LNs | 28.81 ± 12.16 | 26.20 ± 12.23 | 0.015 |
| Number of positive LNs | 3.72 ± 6.33 | 3.61 ± 5.30 | 0.842 |
| Time to liquid diet in d | 3.65 ± 2.56 | 4.62 ± 2.49 | < 0.001 |
| Time to first flatus or defecation in d | 3.87 ± 2.17 | 5.62 ± 2.35 | < 0.001 |
| Time to ambulation in d | 2.93 ± 2.04 | 4.13 ± 2.55 | < 0.001 |
| Postoperative hospitalization in d | 9 (8, 11) | 10 (9, 12) | < 0.001[a] |
| Postoperative complication, *n* (%) | 19 (5.0) | 9 (4.6) | 0.840 |
| Clavien–Dindo ≥ IIIa | 18 (4.7) | 8 (4.1) | 0.729 |
| Anastomotic leakage | 13 (3.4) | 5 (2.6) | 0.577 |
| Abdominal abscess | 2 (0.5) | 1 (0.5) | 1.000 |
| Anastomotic stenosis | 2 (0.5) | 1 (0.5) | 1.000 |
| Pneumonia | 0 | 1 (0.5) | 0.339[b] |
| Arrhythmia | 1 (0.3) | 0 | 1.000[b] |
| Wound infection | 1 (0.3) | 1 (0.5) | 1.000[b] |
| Mortality | 0 | 0 | |

[a]Mann-Whitney *U* test.
[b]Fisher's test.
LNs: Lymph nodes; LTG: Laparoscopic-assisted transhiatal gastrectomy; OTG: Open transhiatal gastrectomy.

Furthermore, the complications of Clavien-Dindo grade III or higher were comparable in both groups ($P$ = 0.729). No mortality existed within 30 d postoperatively in either group. Further details are presented in Table 2.

According to the histopathological analysis, the rate of complete tumor resection (R0) could be achieved in 99.5% in the LTG group and 99.0% in the OTG group ($P$ = 0.879). The number of the harvested LNs was significantly higher in the LTG groups (28.81 ± 12.16 *vs* 26.20 ± 12.23, $P$ = 0.015). In addition, the number of positive LNs was similar in the two groups ($P$ > 0.05). Apart from that, the length of the proximal margin was also comparable between the two groups ($P$ = 0.597).

### Survival

The median follow-up time was 38.94 mo (Interquartile range: 23.28-59.93) for all patients. In comparison with the OTG group, the LTG group showed a better 3-year OS (88.2% *vs* 79.2%, $P$ = 0.011) (Figure 2A). Then, we performed a stratified analysis of survival according to the TNM stage. For patients with stage I, there existed no significant difference in 3-year OS between the two groups, but patients in the LTG group with stage II and stage III had a better 3-year OS compared with that of the OTG group [Stage II: hazard ratio (HR): 0.126, 95% confidence interval (CI): 0.027-0.584, $P$ = 0.008; Stage III: HR: 0.361, 95%CI: 0.134-0.967, $P$ = 0.043] (Figure 2B-D).

### Recurrence

The rate of recurrence presented no significant difference in the LTG and OTG groups (12.8% *vs* 10.7%, $P$ = 0.547). The patterns of recurrence were listed in Table 3. Distributions of recurrence for LTG were similar to that for OTG, and there existed no differences in organ metastasis (liver, lung, bone, brain, pancreas), anastomotic recurrence, peritoneal dissemination, lymph node metastasis or others ($P$ > 0.05).

**Table 3 Patterns of recurrence**

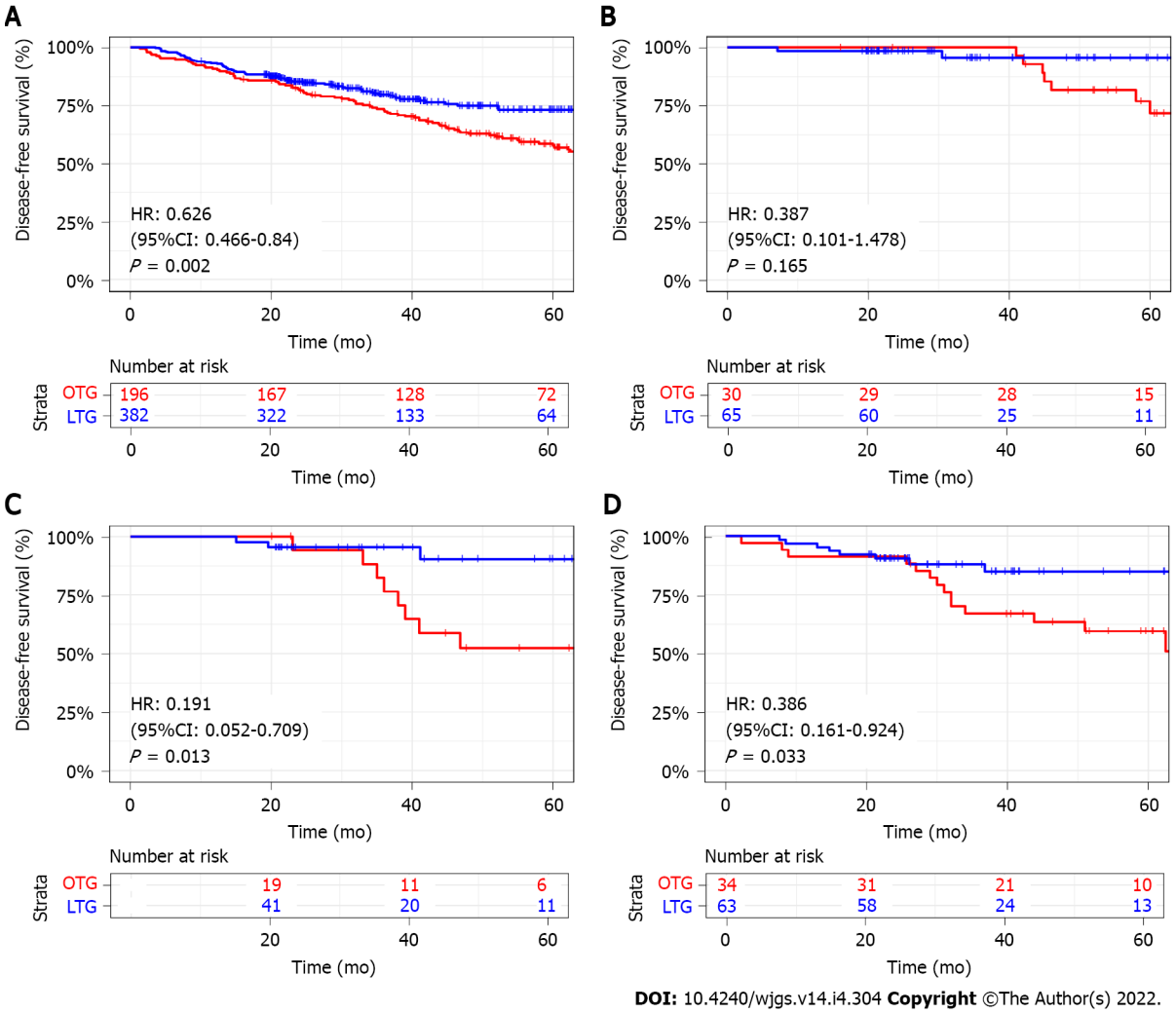
| | LTG, *n* = 382 | OTG, *n* = 196 | *P* value |
|---|---|---|---|
| Recurrence, *n* (%) | | | |
| No | 333 (87.2) | 175 (89.3) | 0.547 |
| Yes | 49 (12.8) | 21 (10.7) | |
| Liver metastasis, *n* (%) | | | |
| No | 372 (97.4) | 193 (98.5) | 0.590 |
| Yes | 10 (2.6) | 3 (1.5) | |
| Lung metastasis, *n* (%) | | | |
| No | 376 (98.4) | 192 (98.0) | 0.941 |
| Yes | 6 (1.6) | 4 (2.0) | |
| Bone metastasis, *n* (%) | | | |
| No | 377 (98.7) | 193 (98.5) | 1.000 |
| Yes | 5 (1.3) | 3 (1.5) | |
| Brain metastasis, *n* (%) | | | |
| No | 380 (99.5) | 193 (98.5) | 0.445 |
| Yes | 2 (0.5) | 3 (1.5) | |
| Pancreas metastasis, *n* (%) | | | |
| No | 381 (99.7) | 194 (99.0) | 0.555 |
| Yes | 1 (0.3) | 2 (1.0) | |
| Anastomotic recurrence, *n* (%) | | | |
| No | 369 (96.6) | 189 (96.4) | 1.000 |
| Yes | 13 (3.4) | 7 (3.6) | |
| Peritoneal dissemination, *n* (%) | | | |
| No | 377 (98.7) | 196 (100.0) | 0.257 |
| Yes | 5 (1.3) | 0 (0.0) | |
| Lymph node metastasis, *n* (%) | | | |
| No | 377 (98.7) | 196 (100.0) | 0.257 |
| Yes | 5 (1.3) | 0 (0.0) | |
| Others, *n* (%) | | | |
| No | 378 (99.0) | 196 (100.0) | 0.364 |
| Yes | 4 (1.0) | 0 (0.0) | |

LTG: Laparoscopic-assisted transhiatal gastrectomy; OTG: Open transhiatal gastrectomy.

The 3-year DFS was significantly better in the LTG group than that in the OTG group (79.7% *vs* 73.0%, *P* = 0.002) (Figure 3A). After stratification by TNM stage, the 3-year DFS was similar between the two groups in stage I patients. However, for stage II and stage III patients, the 3-year DFS was better in the LTG group compared with that of OTG group with significant difference (Stage II: HR: 0.191, 95%CI: 0.052-0.709, *P* = 0.013; Stage III: HR: 0.386, 95%CI: 0.161-0.924, *P* = 0.033) (Figure 3B-D).

## DISCUSSION

Recently, the prevalence of Siewert type II AEG has risen rapidly, and most patients are diagnosed as an advanced stage with a poor prognosis at the first visit[23]. Complete removal of the tumor and adequate regional LN resection remains the only curative treatment for AEG[6]. Since the first report of laparoscopic-assisted gastrectomy, laparoscopic techniques have developed quickly in gastrointestinal tumors




**DOI:** 10.4240/wjgs.v14.i4.304 

**Figure 3 Comparison of disease-free survival rates between the laparoscopic-assisted transhiatal gastrectomy and open transhiatal gastrectomy groups.** A: Comparison of disease-free survival rates between the laparoscopic-assisted transhiatal gastrectomy (LTG) and open transhiatal gastrectomy (OTG) groups for all patients; B: Comparison of disease-free survival rates between the LTG and OTG groups for stage I patients; C: Comparison of disease-free survival rates between the LTG and OTG groups for stage II patients; D: Comparison of disease-free survival rates between the LTG and OTG groups for stage III patients. CI: Confidence interval; HR: Hazard ratio.

[9,24]. However, due to the lack of scientific evidence, the safety and feasibility of LTG in the treatment of Siewert type II AEG still remain controversial[16,17]. In the present study, LTG for Siewert type II AEG showed longer operation times but less blood loss, shorter abdominal incision and faster recovery compared with OTG. The obtained results were similar to the previous studies[17,18,20]. A large number of studies have demonstrated that LTG was comparable for morbidity and mortality to OTG for gastric cancer while few of them were focused on AEG[25-28]. In this study, no significant difference was observed in postoperative complications between the LTG group and OTG group for Siewert type II AEG. Apart from that, the complications of Clavien-Dindo grade III or higher were comparable in both groups. These results suggested that LTG can be safely performed and provide better short-term outcomes for patients diagnosed with Siewert type II AEG.

Ensuring the safety of oncology is critical to the choice of surgical strategy. Shi *et al*[17] compared 132 patients with LTG and 264 patients with OTG. After propensity score matching, the number of harvested LNs showed no significant difference for AEG. By contrast, Sugita *et al*[18] suggested an increased number of dissected LNs in the LTG group compared with OTG for Siewert type II AEG[18]. In the current work, there existed a higher number of harvested LNs in the LTG group than that in the OTG group. The previous studies reported that the number of harvested LNs is an important prognostic factor for patients with AEG[29,30]. In addition, other oncological parameters in terms of length of proximal margin, R0 resection and the number of positive LNs were comparable between the two groups. As a result, the oncological safety of LTG is equivalent to OTG.

Regarding the long-term outcomes, we found that the distribution of recurrence patterns was similar in the two groups. Shi *et al*[17] reported that there existed no significant difference for OS between the LTG and OTG groups[17]. Nevertheless, their study population included not only Siewert type II but

also type III AEG. In addition, Huang *et al*[19] and Sugita *et al*[16] suggested that Siewert type II patients in the LTG group had significantly better OS than that in the OTG group[16,19]. The existing limitations included short observation period and small population, respectively. We observed a better 3-year OS and DFS of LTG for Siewert type II AEG patients compared with those treated with OTG. Moreover, we conducted a stratified analysis based on the TNM stage. Patients with stage I exhibited no survival benefit from LTG, while patients with stage II and III also revealed better survival outcomes in the LTG group.

Undoubtedly, our study has some limitations. First, this study was a single-center, retrospective cohort study. In addition, the follow-up compliance of patients is limited, and the specific death and the patterns of recurrence of some patients remain unknown. Thus, prospective randomized controlled studies are still needed.

## CONCLUSION

In conclusion, LTG is a safe and feasible treatment for Siewert type II AEG. Meanwhile, patients with advanced stage AEG may benefit more from LTG in the long-term outcomes.

## ARTICLE HIGHLIGHTS

### *Research background*

Due to the lack of scientific evidence, the feasibility of laparoscopic-assist transhiatal gastrectomy (LTG) in patients with Siewert type II adenocarcinoma of the esophagogastric junction (AEG) is still controversial.

### *Research motivation*

To compare the feasibility of LTG with the traditional open transhiatal gastrectomy (OTG) in patients with Siewert type II AEG.

### *Research objectives*

We retrospectively evaluated and compared the short-term and long-term outcomes for patients with Siewert type II AEG treated with LTG and OTG and aimed to explore the feasibility of LTG treatment of Siewert type II AEG.

### *Research methods*

We retrospectively evaluated 578 patients with Siewert type II AEG who have undergone LTG or OTG at the First Medical Center of the Chinese People's Liberation Army General Hospital from January 2014 to December 2019. The short-term and long-term outcomes were compared between the LTG ($n$ = 382) and OTG ($n$ = 196) groups.

### *Research results*

Compared with the OTG group, the LTG group had less surgical trauma and a faster recovery after surgery. No significant difference was present between the two groups regarding oncological safety. The 3-year overall survival and disease-free survival were better in the LTG group than those in the OTG group (88.2% *vs* 79.2%, $P$ = 0.011; 79.7% *vs* 73.0%, $P$ = 0.002, respectively). In the stratified analysis, both overall survival and disease-free survival were better in the LTG group than those in the OTG group for stage II/III patients ($P$ < 0.05) but not for stage I patients.

### *Research conclusions*

For patients with Siewert type II AEG, LTG is associated with better short-term outcomes and similar oncology safety. In addition, patients with advanced stage AEG may benefit more from LTG in the long-term outcomes.

### *Research perspectives*

Well-designed multicenter prospective randomized controlled studies are still needed.

## FOOTNOTES

**Author contributions:** Song QY, Li XG and Zhang LY contributed equally to this article; Song QY and Wang XX designed the experiment; Li XG and Zhang LY performed the experiment; Li S and Zhang BL collected data; Wu D and Xu ZY analyzed the data; Song QY and Wu RLG created the tables and figures based on the data; Song QY, Li

XG and Zhang LY wrote the initial draft; Guo X and Wang XX modified the draft.

**Institutional review board statement:** The study was reviewed and approved by the Ethics Committee of Chinese PLA General Hospital, No. S-2021-593-01.

**Conflict-of-interest statement:** All authors declare that there is no conflict of interest.

**Data sharing statement:** No additional data are available.

**STROBE statement:** The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.



**Country/Territory of origin:** China

**ORCID number:** Qi-Ying Song 0000-0003-4953-9683; Xiong-Guang Li 0000-0002-9039-4562; Li-Yu Zhang 0000-0001-8599-155X; Di Wu 0000-0003-1620-2224; Shuo Li 0000-0002-1631-6654; Ben-Long Zhang 0000-0002-2844-9964; Zi-Yao Xu 0000-0002-3837-082X; Ri-Lige Wu 0000-0002-5293-0782; Xin Guo 0000-0002-9658-1887; Xin-Xin Wang 0000-0001-2492-4932.

**S-Editor:** Fan JR
**L-Editor:** Filipodia
**P-Editor:** Fan JR

## REFERENCES

1 **Colquhoun A**, Arnold M, Ferlay J, Goodman KJ, Forman D, Soerjomataram I. Global patterns of cardia and non-cardia gastric cancer incidence in 2012. *Gut* 2015; **64**: 1881-1888 [PMID: 25748648 DOI: 10.1136/gutjnl-2014-308915]
2 **Imamura Y**, Watanabe M, Toihata T, Takamatsu M, Kawachi H, Haraguchi I, Ogata Y, Yoshida N, Saeki H, Oki E, Taguchi K, Yamamoto M, Morita M, Mine S, Hiki N, Baba H, Sano T. Recent Incidence Trend of Surgically Resected Esophagogastric Junction Adenocarcinoma and Microsatellite Instability Status in Japanese Patients. *Digestion* 2019; **99**: 6-13 [PMID: 30554205 DOI: 10.1159/000494406]
3 **Dubecz A**, Solymosi N, Stadlhuber RJ, Schweigert M, Stein HJ, Peters JH. Does the Incidence of Adenocarcinoma of the Esophagus and Gastric Cardia Continue to Rise in the Twenty-First Century? *J Gastrointest Surg* 2013 [PMID: 24234242 DOI: 10.1007/s11605-013-2345-8]
4 **Brown LM**, Devesa SS, Chow WH. Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age. *J Natl Cancer Inst* 2008; **100**: 1184-1187 [PMID: 18695138 DOI: 10.1093/jnci/djn211]
5 **Buas MF**, Vaughan TL. Epidemiology and risk factors for gastroesophageal junction tumors: understanding the rising incidence of this disease. *Semin Radiat Oncol* 2013; **23**: 3-9 [PMID: 23207041 DOI: 10.1016/j.semradonc.2012.09.008]
6 **Hashimoto T**, Kurokawa Y, Mori M, Doki Y. Surgical Treatment of Gastroesophageal Junction Cancer. *J Gastric Cancer* 2018; **18**: 209-217 [PMID: 30275998 DOI: 10.5230/jgc.2018.18.e28]
7 **Sasako M**, Sano T, Yamamoto S, Sairenji M, Arai K, Kinoshita T, Nashimoto A, Hiratsuka M; Japan Clinical Oncology Group (JCOG9502). Left thoracoabdominal approach versus abdominal-transhiatal approach for gastric cancer of the cardia or subcardia: a randomised controlled trial. *Lancet Oncol* 2006; **7**: 644-651 [PMID: 16887481 DOI: 10.1016/s1470-2045(06)70766-5]
8 **Kurokawa Y**, Sasako M, Sano T, Yoshikawa T, Iwasaki Y, Nashimoto A, Ito S, Kurita A, Mizusawa J, Nakamura K; Japan Clinical Oncology Group (JCOG9502). Ten-year follow-up results of a randomized clinical trial comparing left thoracoabdominal and abdominal transhiatal approaches to total gastrectomy for adenocarcinoma of the oesophagogastric junction or gastric cardia. *Br J Surg* 2015; **102**: 341-348 [PMID: 25605628 DOI: 10.1002/bjs.9764]
9 **Kitano S**, Iso Y, Moriyama M, Sugimachi K. Laparoscopy-assisted Billroth I gastrectomy. *Surg Laparosc Endosc* 1994; **4**: 146-148 [PMID: 8180768]
10 **Lee MS**, Lee JH, Park DJ, Lee HJ, Kim HH, Yang HK. Comparison of short- and long-term outcomes of laparoscopic-assisted total gastrectomy and open total gastrectomy in gastric cancer patients. *Surg Endosc* 2013; **27**: 2598-2605 [PMID: 23539255 DOI: 10.1007/s00464-013-2796-8]
11 **Lee JH**, Lee CM, Son SY, Ahn SH, Park DJ, Kim HH. Laparoscopic versus open gastrectomy for gastric cancer: long-term oncologic results. *Surgery* 2014; **155**: 154-164 [PMID: 24238126 DOI: 10.1016/j.surg.2013.06.015]
12 **Hu Y**, Huang C, Sun Y, Su X, Cao H, Hu J, Xue Y, Suo J, Tao K, He X, Wei H, Ying M, Hu W, Du X, Chen P, Liu H, Zheng C, Liu F, Yu J, Li Z, Zhao G, Chen X, Wang K, Li P, Xing J, Li G. Morbidity and Mortality of Laparoscopic Versus Open D2 Distal Gastrectomy for Advanced Gastric Cancer: A Randomized Controlled Trial. *J Clin Oncol* 2016; **34**: 1350-1357 [PMID: 26903580 DOI: 10.1200/JCO.2015.63.7215]
13 **Kim HI**, Hur H, Kim YN, Lee HJ, Kim MC, Han SU, Hyung WJ. Standardization of D2 lymphadenectomy and surgical quality control (KLASS-02-QC): a prospective, observational, multicenter study [NCT01283893]. *BMC Cancer* 2014; **14**:

209 [PMID: 24646327 DOI: 10.1186/1471-2407-14-209]
14 **Kurokawa Y**, Takeuchi H, Doki Y, Mine S, Terashima M, Yasuda T, Yoshida K, Daiko H, Sakuramoto S, Yoshikawa T, Kunisaki C, Seto Y, Tamura S, Shimokawa T, Sano T, Kitagawa Y. Mapping of Lymph Node Metastasis From Esophagogastric Junction Tumors: A Prospective Nationwide Multicenter Study. *Ann Surg* 2021; **274**: 120-127 [PMID: 31404008 DOI: 10.1097/SLA.0000000000003499]
15 **Duan XF**, Yue J, Tang P, Shang XB, Jiang HJ, Yu ZT. Lymph node dissection for Siewert II esophagogastric junction adenocarcinoma: A retrospective study of 3 surgical procedures. *Medicine (Baltimore)* 2017; **96**: e6120 [PMID: 28207537 DOI: 10.1097/MD.0000000000006120]
16 **Sugita S**, Kinoshita T, Kuwata T, Tokunaga M, Kaito A, Watanabe M, Tonouchi A, Sato R, Nagino M. Long-term oncological outcomes of laparoscopic versus open transhiatal resection for patients with Siewert type II adenocarcinoma of the esophagogastric junction. *Surg Endosc* 2021; **35**: 340-348 [PMID: 32025923 DOI: 10.1007/s00464-020-07406-w]
17 **Shi Y**, Li L, Xiao H, Guo S, Wang G, Tao K, Dong J, Zong L. Feasibility of laparoscopic gastrectomy for patients with Siewert-type II/III adenocarcinoma of the esophagogastric junction: A propensity score matching analysis. *PloS One* 2018; **13**: e0203125 [PMID: 30256806 DOI: 10.1371/journal.pone.0203125]
18 **Sugita S**, Kinoshita T, Kaito A, Watanabe M, Sunagawa H. Short-term outcomes after laparoscopic versus open transhiatal resection of Siewert type II adenocarcinoma of the esophagogastric junction. *Surg Endosc* 2018; **32**: 383-390 [PMID: 28656339 DOI: 10.1007/s00464-017-5687-6]
19 **Huang CM**, Lv CB, Lin JX, Chen QY, Zheng CH, Li P, Xie JW, Wang JB, Lu J, Cao LL, Lin M, Tu RH. Laparoscopic-assisted versus open total gastrectomy for Siewert type II and III esophagogastric junction carcinoma: a propensity score-matched case-control study. *Surg Endosc* 2017; **31**: 3495-3503 [DOI: 10.1007/s00464-016-5375-y]
20 **Zhao Y**, Zhang J, Yang D, Tang Z, Wang Q. Feasibility of laparoscopic total gastrectomy for advanced Siewert type II and type III esophagogastric junction carcinoma: A propensity score-matched case-control study. *Asian J Surg* 2019; **42**: 805-813 [PMID: 30685144 DOI: 10.1016/j.asjsur.2018.12.014]
21 **Amin MB**, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR, Winchester DP. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin* 2017; **67**: 93-99 [PMID: 28094848 DOI: 10.3322/caac.21388]
22 **Dindo D**, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205-213 [PMID: 15273542 DOI: 10.1097/01.sla.0000133083.54934.ae]
23 **Huang Q**, Sun Q, Fan XS, Zhou D, Zou XP. Recent advances in proximal gastric carcinoma. *J Dig Dis* 2016; **17**: 421-432 [PMID: 27129018 DOI: 10.1111/1751-2980.12355]
24 **Lee Y**, Min SH, Park KB, Park YS, Ahn SH, Park DJ, Kim HH. Long-term Outcomes of Laparoscopic Versus Open Transhiatal Approach for the Treatment of Esophagogastric Junction Cancer. *J Gastric Cancer* 2019; **19**: 62-71 [PMID: 30944759 DOI: 10.5230/jgc.2019.19.e1]
25 **Fan Y**, Liu M, Li S, Yu J, Qi X, Tan F, Xu K, Zhang N, Yao Z, Yang H, Zhang C, Xing J, Wang Z, Cui M, Su X. Surgical and oncological efficacy of laparoscopic-assisted total gastrectomy versus open total gastrectomy for gastric cancer by propensity score matching: a retrospective comparative study. *J Cancer Res Clin Oncol* 2021; **147**: 2153-2165 [PMID: 33415526 DOI: 10.1007/s00432-020-03503-4]
26 **Yoshikawa T**, Cho H, Rino Y, Yamamoto Y, Kimura M, Fukunaga T, Hasegawa S, Yamada T, Aoyama T, Tsuburaya A. A prospective feasibility and safety study of laparoscopy-assisted distal gastrectomy for clinical stage I gastric cancer initiated by surgeons with much experience of open gastrectomy and laparoscopic surgery. *Gastric Cancer* 2013; **16**: 126-132 [PMID: 22527185 DOI: 10.1007/s10120-012-0157-2]
27 **Shehzad K**, Mohiuddin K, Nizami S, Sharma H, Khan IM, Memon B, Memon MA. Current status of minimal access surgery for gastric cancer. *Surg Oncol* 2007; **16**: 85-98 [PMID: 17560103 DOI: 10.1016/j.suronc.2007.04.012]
28 **Choi YY**, Bae JM, An JY, Hyung WJ, Noh SH. Laparoscopic gastrectomy for advanced gastric cancer: are the long-term results comparable with conventional open gastrectomy? *J Surg Oncol* 2013; **108**: 550-556 [PMID: 24115104 DOI: 10.1002/jso.23438]
29 **Zhu M**, Cao B, Li X, Li P, Wen Z, Ji J, Min L, Zhang S. Risk factors and a predictive nomogram for lymph node metastasis of superficial esophagogastric junction cancer. *J Gastroenterol Hepatol* 2020; **35**: 1524-1531 [PMID: 32023349 DOI: 10.1111/jgh.15004]
30 **Xu J**, Cao J, Wang L, Wang Z, Wang Y, Wu Y, Lv W, Hu J. Prognostic performance of three lymph node staging schemes for patients with Siewert type II adenocarcinoma of esophagogastric junction. *Sci Rep* 2017; **7**: 10123 [PMID: 28860457 DOI: 10.1038/s41598-017-09625-z]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 April 27; 14(4): 315-328

DOI: 10.4240/wjgs.v14.i4.315

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

# How to examine anastomotic integrity intraoperatively in totally laparoscopic radical gastrectomy? Methylene blue testing prevents technical defect-related anastomotic leaks

Chun Deng, Yang Liu, Zhen-Yu Zhang, Heng-Duo Qi, Zhi Guo, Xu Zhao, Xiao-Jun Li

**Specialty type:** Surgery

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Surlin VM, Romania; van Helsdingen CP, Netherlands

**Received:** November 11, 2021
**Peer-review started:** November 11, 2021
**First decision:** January 9, 2022
**Revised:** January 20, 2022
**Accepted:** April 4, 2022
**Article in press:** April 4, 2022
**Published online:** April 27, 2022

**Chun Deng, Yang Liu, Zhen-Yu Zhang, Heng-Duo Qi, Zhi Guo, Xu Zhao, Xiao-Jun Li,** Department of General Surgery, Shaanxi Provincial People's Hospital, Xi'an 710068, Shaanxi Province, China

**Corresponding author:** Xiao-Jun Li, MD, Professor, Surgeon, Department of General Surgery, Shaanxi Provincial People's Hospital, No. 256 Youyi West Road, Xi'an 710068, Shaanxi Province, China. lixiaojun20040912@163.com

## Abstract

### *BACKGROUND*

Intraoperative methylene blue testing (IMBT), air leak testing, or endoscopy is used to assess the anastomotic integrity of esophagojejunostomy during open total gastrectomy for gastric cancer. Totally laparoscopic radical gastrectomy has been widely used to treat gastric cancer in the last few decades. However, reports on testing anastomotic integrity in totally laparoscopic radical gastrectomy are limited.

### *AIM*

To explore the effects of IMBT on the incidence of postoperative anastomotic leaks (PALs) and identify the risk factors for PALs in totally laparoscopic radical gastrectomy.

### *METHODS*

From January 2017 to December 2019, patients who underwent totally laparoscopic radical gastrectomy at the Shaanxi Provincial People's Hospital were retrospectively analyzed. According to whether or not they experienced an IMBT, the patients were divided into an IMBT group and a control group. If the IMBT was positive, an intraoperative suture was required to reinforce the anastomosis. The difference in the incidence of PALs was compared, and the risk factors were investigated.

### *RESULTS*

This study consisted of 513 patients, 211 in the IMBT group and 302 in the control group. Positive IMBT was shown in seven patients (3.3%) in the IMBT group, and no PAL occurred in these patients after suture reinforcement. Multivariate analysis showed that risk factors for predicting positive IMBT were body mass

index (BMI) > 25 kg/m² (hazard ratio [HR] = 8.357, *P* = 0.009), operation time > 4 h (HR = 55.881, *P* = 0.002), and insufficient surgical experience (HR = 15.286, *P* = 0.010). Moreover, 15 patients (2.9%) developed PALs in 513 patients, and the rates of PALs were significantly lower in the IMBT group than in the control group [2 of 211 patients (0.9%) *vs* 13 of 302 patients (4.3%), *P* = 0.0026]. Further analysis demonstrated that preoperative complications (HR = 13.128, *P* = 0.017), totally laparoscopic total gastrectomy (HR = 9.075, *P* = 0.043), and neoadjuvant chemotherapy (HR = 7.150, *P* = 0.008) were independent risk factors for PALs.

***CONCLUSION***

IMBT is an effective method to evaluate the integrity of anastomosis during totally laparoscopic radical gastrectomy, thus preventing technical defect-related anastomotic leaks. Preoperative complications, totally laparoscopic total gastrectomy, and neoadjuvant chemotherapy are independent risk factors for PALs.

**Key Words:** Anastomotic leak; Gastric neoplasms; Totally laparoscopic radical gastrectomy; Methylene blue; Risk factors



**Core Tip:** We reviewed the outcomes of 513 consecutive patients with gastric cancer who underwent totally laparoscopic radical gastrectomy with and without intraoperative methylene blue testing at Shaanxi Provincial People's Hospital from January 2017 to December 2019. We found that intraoperative methylene blue testing is an effective method to evaluate the integrity of anastomosis during totally laparoscopic radical gastrectomy and could reduce the incidence of postoperative anastomotic leaks. Preoperative complications, totally laparoscopic total gastrectomy, and neoadjuvant chemotherapy are independent risk factors for postoperative anastomotic leaks.

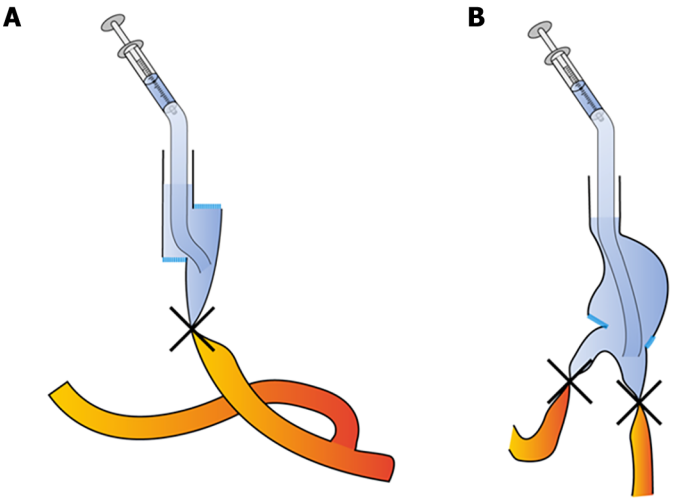
**Citation:** Deng C, Liu Y, Zhang ZY, Qi HD, Guo Z, Zhao X, Li XJ. How to examine anastomotic integrity intraoperatively in totally laparoscopic radical gastrectomy? Methylene blue testing prevents technical defect-related anastomotic leaks. *World J Gastrointest Surg* 2022; 14(4): 315-328
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i4/315.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i4.315

## INTRODUCTION

Gastric cancer is one of the most common cancers worldwide, ranking fifth in incidence and third in mortality[1]. Totally laparoscopic radical gastrectomy has been widely used to treat gastric cancer[2-4]. Postoperative anastomotic leak (PAL) is a severe complication, and occurs in 1.7%-5.7% of patients with gastric cancer[5-7]. These complications could prolong hospital stay, increase medical expenses, cause poor quality of life, and subsequently worsen the long-term survival of patients[8-10].

It is well known that the defects of intraoperative anastomotic techniques are closely related to PALs [11-13]. Therefore, some PALs might be avoided if insufficiently integral anastomoses were immediately reinforced. Intraoperative methylene blue testing (IMBT), intraoperative air leak test, or intraoperative endoscopy has been used to assess the anastomotic integrity of esophagojejunostomy during open total gastrectomy for gastric cancer[6,14-15]. However, to the best of our knowledge, no study has assessed the integrity of anastomosis during totally laparoscopic radical gastrectomy. Compared with open surgery, totally laparoscopic radical gastrectomy has the disadvantages of two-dimensional images, poor hand-eye coordination, limited operating space, fulcrum effect, and lack of haptic feedback[16-17]. Furthermore, according to the ERAS guidelines, abdominal drains should not routinely be placed after gastrectomy, which requires high-quality anastomosis[18-19]. Thus, a reliable anastomosis leak test is vital during totally laparoscopic radical gastrectomy.

In this study, we used IMBT to check the anastomotic integrity of esophagojejunostomy or gastrojejunostomy during totally laparoscopic radical gastrectomy. This is the first study to assess the anastomotic integrity during totally laparoscopic radical gastrectomy. We aimed to explore the effects of IMBT on the incidence and risk factors for PALs.




**DOI:** 10.4240/wjgs.v14.i4.315 

**Figure 1 Schematic representation of intraoperative methylene blue testing.** A: Overlap anastomosis; B: Billroth-II anastomosis.

## MATERIALS AND METHODS

### *Patients*

We performed a retrospective review of patients who underwent totally laparoscopic radical gastrectomy from January 2017 to December 2019. In our department, some surgeons think that IMBT is useful, while others are skeptical regarding its effects. Thus, two groups were formed: An IMBT group and a control group. Staging of the tumor was performed following the eighth edition of the AJCC Guidelines for gastric cancer[20]. This study was approved by the Ethics Committee of Shaanxi Provincial People's Hospital.

The inclusion criteria were: (1) Patients who underwent totally laparoscopic radical gastrectomy for gastric cancer and adenocarcinoma of the gastroesophageal junction from January 2017 to December 2019; (2) Gastric cancer or adenocarcinoma of the gastroesophageal junction diagnosed *via* endoscopy and pathological identification; and (3) Patients whose surgical and demographic data were complete and reliable. The exclusion criteria were: (1) Patients who underwent totally laparoscopic distal gastrectomy that used Billroth-I anastomosis; (2) Those who were converted to open surgery; (3) Those who were found to have distant metastases intraoperatively; (4) Those who did not undergo radical resection; and (5) Those who gave up treatment or were transferred to another hospital.

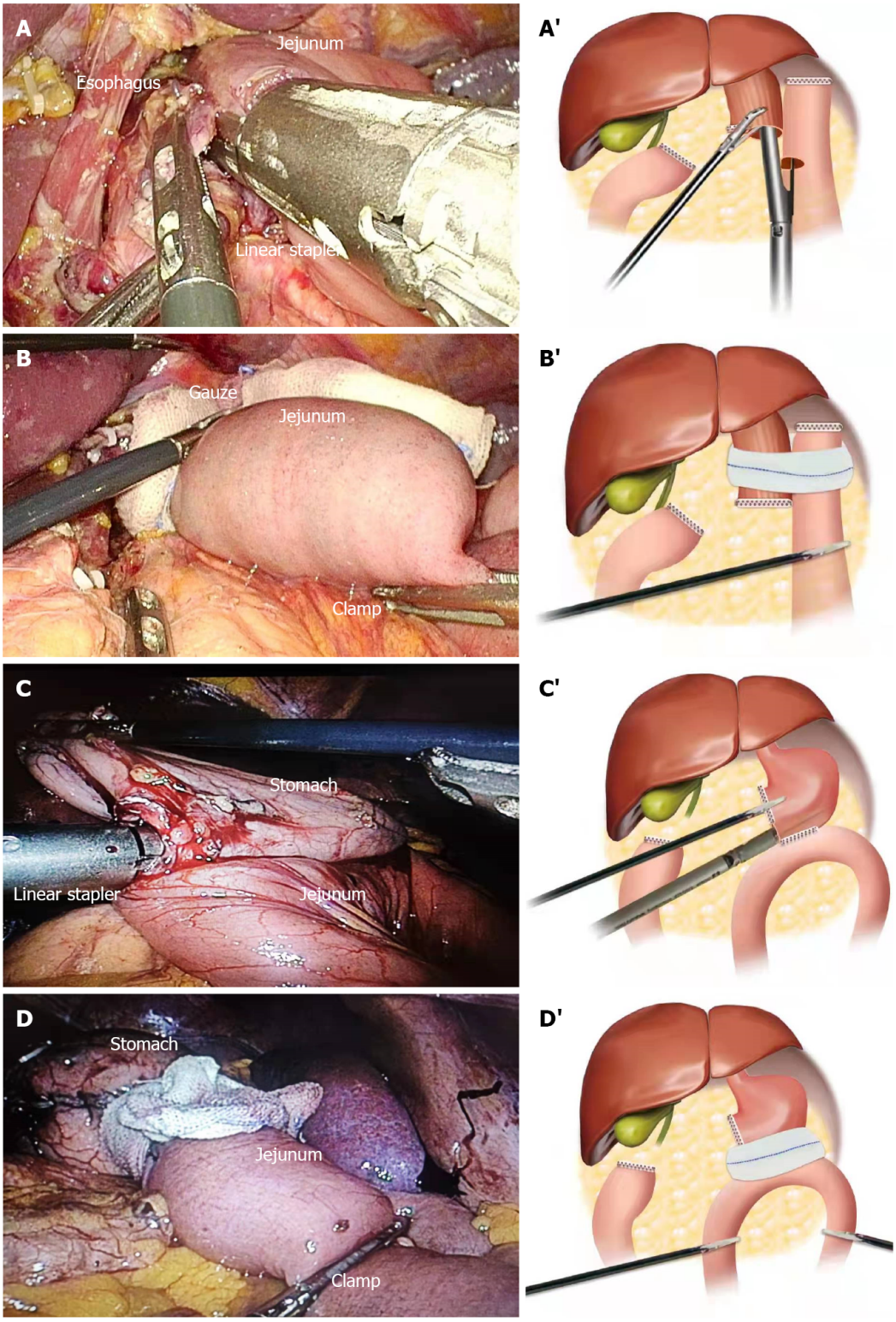
### *Surgical methods and postoperative management*

All surgeries were performed laparoscopically. Totally laparoscopic total gastrectomy was reconstructed *via* an overlap anastomosis[21], and totally laparoscopic distal gastrectomy was reconstructed *via* a Billroth-II anastomosis[22]. Lymph node dissection was performed according to the Japanese Gastric Cancer Treatment Guidelines 2014 (ver. 4)[23]. This study used a 45-mm linear stapler (Johnson Company, United States) for the overlap anastomosis and a 60-mm linear stapler (Johnson Company, United States) for the Billroth-II anastomosis. In our department, we preferred the Billroth II anastomosis and Roux-en-Y esophagojejunostomy rather than the Billroth I anastomosis. A Billroth I anastomosis needs to preserve a large residual stomach, leading to insufficient tumor margins and significant anastomotic tension when the tumor location is relatively high and the diameter is large. In China, most gastric cancer cases are found in advanced stages, and the diameter of the tumor is often large compared to Japan and Korea[24-26]. In addition, Billroth I anastomosis has a greater risk of remnant gastritis and reflux esophagitis[27-28].

Postoperative management was conducted according to the Japanese Gastric Cancer Treatment Guidelines (ver.4)[23]: The nasogastric tube was removed on postoperative day 1, and the abdominal drainage tube removed on postoperative day 5 without symptoms or inflammatory reactions. Abdominal CT, gastrointestinal tract angiography, or endoscopy was performed when an anastomotic leak was suspected.

### *Methylene blue testing technique*

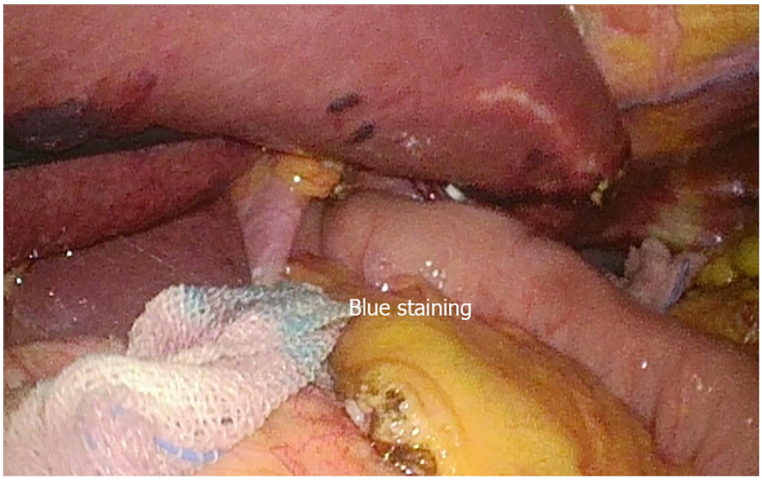
For the patients that underwent totally laparoscopic total gastrectomy, we performed IMBT as follows (Figure 1A): After the digestive tract reconstruction (Figure 2A and A'), the nasogastric tube (18F) was delivered 5 cm from the distal end of the anastomotic stoma, gauze was wrapped around the anastomosis, and then the jejunum was clamped using an intestinal clamp 5 cm distal to the anastomosis. Next, normal saline was injected through the nasogastric tube to rinse and observe




**DOI:** 10.4240/wjgs.v14.i4.315 

**Figure 2 Surgery pictures and schematic pictures of intraoperative methylene blue testing.** A: Surgery picture of esophagojejunostomy (overlap method); A': Schematic picture of esophagojejunostomy (overlap method); B: Surgery picture of intraoperative methylene blue testing in totally laparoscopic total gastrectomy; B': Schematic picture of intraoperative methylene blue testing in totally laparoscopic total gastrectomy; C: Surgery picture of Billroth-II anastomosis; C': Schematic picture of Billroth-II anastomosis; D: Surgery picture of intraoperative methylene blue testing in totally laparoscopic distal gastrectomy; D': Schematic picture of intraoperative methylene blue testing in totally laparoscopic distal gastrectomy.

whether continuous bright red liquid flowed out of the nasogastric tube when pumping back. If the liquid was detected, we looked for and stopped the bleeding and then flushed repeatedly until the clear liquid was pumped back out. Next, we dissolved 2 mL (20 mg) of methylene blue into 50 mL of normal saline and injected it through the nasogastric tube in order to make the methylene blue liquid disperse evenly around the anastomosis (Figure 2B and B′). Finally, we observed whether the gauze around the




**DOI:** 10.4240/wjgs.v14.i4.315 

**Figure 3 Positive results of intraoperative methylene blue testing.**

anastomosis was stained blue; if there was blue staining (Figure 3), we identified the leak according to the blue-stained site, sutured it, and then changed the gauze and repeated the process.

For the patients who underwent totally laparoscopic distal gastrectomy, IMBT was performed as follows (Figure 1B): The nasogastric tube (18F) was indwelled 5 cm from the distal end of the anastomotic stoma after the digestive tract reconstruction (Figure 2C and C′). Next, we wrapped the anastomosis with gauze, and closed it with clamps 5 cm distal to the anastomosis. Then, the anastomosis was flushed with normal saline through the nasogastric tube; the needle was pumped back to observe whether there was bright red liquid flowing out of the nasogastric tube. If red liquid was present, we looked for and stopped the bleeding. The flushing was repeated until the clear liquid was extracted from the nasogastric tube. Next, 5 mL (50 mg) of methylene blue was dissolved into 500 mL of normal saline and injected through the nasogastric tube in order to evenly distribute the methylene blue liquid around the anastomosis (Figure 2D and D′). Finally, if blue liquid was present, we repeated the above procedures.

### *Definitions*

We defined preoperative complications as one or more of the following: Anemia, malnutrition, diabetes, or pulmonary dysfunction. The World Health Organization's definition of anemia was used to define anemia: Hb concentration of < 12 g/dL in women and < 13 g/dL in men[29]. Malnutrition was defined by the European Society of Clinical Nutrition and Metabolism (ESPEN) criteria[30], which suggested two methods used to diagnose malnutrition: Method one: Body mass index (BMI) < 18.5 kg/m$^2$; method two: Unintentional weight loss combined with a low age-related BMI (< 20 kg/m$^2$ in subjects < 70 years or < 22 kg/m$^2$ in those ≥ 70 years) or low fat-free mass index (FFMI) (< 17 kg/m$^2$ in men and < 15 kg/m$^2$ in women). Positive IMBT was defined as the visualization of methylene blue on the gauze surrounding the anastomosis. PAL was defined as meeting one of the following criteria: (1) Gastrointestinal contents or bile-like fluid drained from the abdominal drainage tube; (2) Gastrointestinal radiography showed leakage of the contrast medium from the drainage tube; (3) Methylene blue was extracted from the abdominal drainage tube after the oral administration of methylene blue; (4) Abdominal CT examination showed that the gastrointestinal wall was incomplete, revealing gas and fluid leaks around the anastomosis; and (5) Anastomotic leaks were found under endoscopy after surgery.

### *Statistical analysis*

Analyses were performed with statistic software SPSS for Windows Version 25.0 (SPSS Inc., Chicago, Illinois, United States). Measurement data are expressed as the mean ± SD (normal distribution) or median (non-normal distribution). Count data are expressed as cases (rate). Univariate analysis was performed by the Chi-square test or a Fisher's exact test when appropriate. Variables with $P < 0.05$ in the univariate analysis were included in multivariate analysis, which was conducted using the logistic regression model. $P < 0.05$ was considered statistically significant.

## RESULTS

From January 2017 to December 2019, a total of 513 patients that underwent totally laparoscopic radical gastrectomy were analyzed retrospectively (211 patients in the IMBT group and 302 patients in the

**Table 1 Demographic, surgical, and tumor characteristics of patients according to whether an intraoperative methylene blue testing was performed or not**

| Variable | | IMBT group (211 cases) | Control group (302 cases) | $\chi^2$ | *P* value |
|---|---|---|---|---|---|
| Gender | Male | 130 | 182 | 0.095 | 0.759 |
| | Female | 81 | 120 | | |
| Age (yr) | < 75 | 143 | 196 | 0.457 | 0.499 |
| | ≥ 75 | 68 | 106 | | |
| BMI (kg/m$^2$) | < 25 | 155 | 211 | 0.784 | 0.376 |
| | ≥ 25 | 56 | 91 | | |
| Preoperative complications | Present absent | 88123 | 111191 | 1.282 | 0.257 |
| Neoadjuvant chemotherapy | Present absent | 43168 | 61241 | 0.003 | 0.960 |
| Degree of tumor differentiation | High | 72 | 92 | 0.785 | 0.672 |
| | Medium | 95 | 142 | | |
| | Low | 44 | 68 | | |
| Postoperative tumor pathological stage[1] | I | 32 | 62 | 3.298 | 0.192 |
| | II | 62 | 94 | | |
| | III | 117 | 146 | | |
| Surgeon's experience | < 50 cases | 21 | 24 | 0.624 | 0.429 |
| | ≥ 50 cases | 190 | 278 | | |
| Mode of surgery | TLTG | 101 | 146 | 0.025 | 0.875 |
| | TLDG | 111 | 156 | | |
| Operation time | < 4h | 143 | 189 | 1.465 | 0.226 |
| | ≥ 4h | 68 | 113 | | |
| Amount of bleeding ≥ 400 mL | Present | 79 | 100 | 1.024 | 0.312 |
| | Absent | 132 | 202 | | |

[1]According to the 8th AJCC TNM staging system for gastric cancer. IMBT: Intraoperative methylene blue testing; TLTG: Totally laparoscopic total gastrectomy; BMI: Body mass index; TLDG: Totally laparoscopic distal gastrectomy.

control group). Complete data of the intraoperative and postoperative findings are shown in Figure 4. The baseline data of the patients in the two groups are consistent, as shown in Table 1.

### *Risk factors for positive IMBT*

Seven patients (3.3%) had positive IMBT in the IMBT group, as detailed in Table 2. These cases were managed by additional suturing, none had a PAL, and the mean postoperative hospital stay was 10.3 ± 1.1 d. Univariate analysis showed that surgeons with insufficient surgical experience (< 50 cases of totally laparoscopic radical gastrectomy) were associated with a higher rate of positive IMBT (14.3% *vs* 2.1%, $P = 0.021$). Other risk factors included operation time > 4 h, neoadjuvant chemotherapy, and a body mass index (BMI) > 25 kg/m$^2$ ($P = 0.008$, 0.033, and 0.021, respectively), as shown in Tables 3 and 4. Multivariate analysis identified BMI > 25 kg/m$^2$, operation time > 4 h, and insufficient surgical experience as independent risk factors for positive IMBT ($P = 0.009$, 0.002, and 0.010, respectively), as detailed in Table 5.

### *Comparison of incidence of PALs*

PAL occurred in 15 (2.9%) patients, including 2 in the IMBT group and 13 in the control group. The rate of PALs was significantly lower in the IMBT group than in the control group [2 of 211 patients (0.9%) *vs* 13 of 302 patients (4.3%), $P = 0.0026$].

### *Risk factors for PALs*

The clinical characteristics of the patients with anastomotic leaks are shown in Table 6. The diagnosis time of PALs was 5.8 ± 2.0 d after surgery, postoperative hospital stay was 19.3 ± 3.5 d, and the

**Table 2 Characteristics of positive intraoperative methylene blue testing**

| Patient No. | Location of leak on anastomotic wall | Operation model | Dehiscence | Management | PAL | Postoperative hospital stays (d) |
|---|---|---|---|---|---|---|
| 1 | Posterior wall | TLTG | Present | Suturing | No | 10 |
| 2 | Posterior wall | TLTG | Absent | Suturing | No | 9 |
| 3 | Posterior wall | TLTG | Absent | Suturing | No | 11 |
| 4 | Joint opening | TLTG | Absent | Suturing | No | 10 |
| 5 | Joint opening | TLTG | Absent | Suturing | No | 11 |
| 6 | Left wall | TLDG | Absent | Suturing | No | 12 |
| 7 | Left wall | TLDG | Present | Suturing | No | 9 |

IMBT: Intraoperative methylene blue testing; PAL: Postoperative anastomotic leak; TLTG: Totally laparoscopic total gastrectomy; TLDG: Totally laparoscopic distal gastrectomy.

**Table 3 Clinicopathological characteristics of the patients according to the results of intraoperative methylene blue testing and postoperative anastomotic leaks**

| Variable | IMBT group | IMBT | | *P* value | Control group | PAL | | *P* value |
|---|---|---|---|---|---|---|---|---|
| | | Negative | Positive (%) | | | Negative | Positive (%) | |
| Cases | 211 | 204 | 7 (3.3) | - | 302 | 289 | 13(4.3) | - |
| Gender | | | | | | | | |
| Male | 130 | 126 | 4 (3.1) | 1.0 | 182 | 173 | 9 (4.9) | 0.575 |
| Female | 81 | 78 | 3 (3.7) | | 120 | 116 | 4 (3.3) | |
| Age (yr) | | | | | | | | |
| < 75 | 143 | 139 | 4 (2.8) | 0.541 | 196 | 191 | 5 (2.6) | 0.70 |
| ≥ 75 | 68 | 65 | 3 (4.4) | | 106 | 98 | 8 (7.5) | |
| BMI (kg/m$^2$) | | | | | | | | |
| < 25 | 155 | 153 | 2 (1.3) | 0.021 | 211 | 206 | 5 (2.4) | 0.025 |
| ≥ 25 | 56 | 51 | 5 (8.9) | | 91 | 83 | 8 (8.8) | |
| Preoperative complications | | | | | | | | |
| Absent | 123 | 120 | 3 (2.4) | 0.454 | 191 | 187 | 4 (2.0) | 0.018 |
| Present | 88 | 84 | 4 (4.5) | | 111 | 102 | 9 (8.1) | |
| Neoadjuvant chemotherapy | | | | | | | | |
| Absent | 168 | 165 | 3 (1.8) | 0.033 | 241 | 234 | 7 (2.9) | 0.028 |
| Present | 43 | 39 | 4 (9.3) | | 61 | 55 | 6 (9.8) | |
| Degree of tumor differentiation | | | | | | | | |
| High | 72 | 70 | 2 (2.8) | 0.784 | 92 | 88 | 4 (4.3) | 1.000 |
| Medium | 95 | 92 | 3 (3.2) | | 142 | 136 | 6 (4.2) | |
| Low | 44 | 42 | 2 (4.5) | | 68 | 65 | 3 (4.6) | |
| Postoperative tumor pathological stage[1] | | | | | | | | |
| I | 32 | 30 | 2 (6.3) | 0.493 | 62 | 59 | 3 (4.8) | 0.754 |
| II | 62 | 60 | 2 (3.2) | | 94 | 89 | 5 (5.3) | |
| III | 117 | 114 | 3 (2.6) | | 146 | 141 | 5 (3.4) | |

[1]According to the 8th AJCC TNM staging system for gastric cancer. IMBT: Intraoperative methylene blue testing; PAL: Postoperative anastomotic leak; BMI: Body mass index.

**Table 4 Surgical variables according to the results of intraoperative methylene blue testing and postoperative anastomotic leaks**

| Variable | IMBT group | IMBT | | *P* value | Control group | PAL | | *P* value |
|---|---|---|---|---|---|---|---|---|
| | | Negative | Positive (%) | | | Negative | Positive (%) | |
| Cases | 211 | 204 | 7 (3.3) | - | 302 | 289 | 13 (4.3) | - |
| Operation time (h) | | | | | | | | |
| < 4 | 143 | 142 | 1 (0.7) | 0.008 | 184 | 177 | 7 (4.0) | 0.577 |
| ≥ 4 | 68 | 62 | 6 (8.8) | | 118 | 112 | 6 (5.1) | |
| Amount of bleeding (mL) | | | | | | | | |
| < 400 | 132 | 130 | 2 (1.5) | 0.136 | 202 | 194 | 8 (4.0) | 0.765 |
| ≥ 400 | 79 | 74 | 5 (6.3) | | 100 | 95 | 5 (5.0) | |
| Mode of operation | | | | | | | | |
| TLTG | 100 | 95 | 5 (5.0) | 0.200 | 146 | 136 | 10 (6.8) | 0.046 |
| TLDG | 111 | 109 | 2 (1.8) | | 156 | 153 | 3 (1.9) | |
| Surgeon's experience (cases) | | | | | | | | |
| < 50 | 21 | 18 | 3(14.3) | 0.021 | 24 | 21 | 3 (12.5) | 0.074 |
| ≥ 50 | 190 | 186 | 4 (2.1) | | 278 | 268 | 10 (3.6) | |

IMBT: Intraoperative methylene blue testing; PAL: Postoperative anastomotic leak; TLTG: Totally laparoscopic total gastrectomy; TLDG: Totally laparoscopic distal gastrectomy.

abdominal drainage tube placement time was 17.3 ± 3.2 d. All 15 patients improved and were discharged from the hospital, and no one died. In the univariate analysis, patients with BMI > 25 kg/m$^2$ (8.8% *vs* 2.4%, $P = 0.025$), preoperative complications (8.1% *vs* 2.0%, $P = 0.018$), totally laparoscopic total gastrectomy (6.8% *vs* 1.9%, $P = 0.046$), and neoadjuvant chemotherapy (9.8% *vs* 2.9%, $P = 0.028$) were associated with PALs, as shown in Tables 3 and 4. Multivariate analysis showed that preoperative complications (hazard ratio [HR] = 13.128, $P = 0.017$), totally laparoscopic total gastrectomy (HR = 9.075, $P = 0.043$), and neoadjuvant chemotherapy (HR = 7.150, $P = 0.008$) were independent risk factors for PALs (Table 5).

## DISCUSSION

Anastomotic leaks are among the most common and severe complications after totally laparoscopic radical gastrectomy and are the main risk factor for patients' postoperative death[8-10]. The integrity of the anastomosis, which is closely related to the anastomotic technique, is a prerequisite for tissue healing and is essential for preventing anastomotic leaks[6,12]. In totally laparoscopic radical gastrectomy, we used IMBT to check the integrity of the anastomosis. The results showed that IMBT reduces the incidence of PALs, which is consistent with the IMBT results in open total gastrectomy[14].

Several methods are available to assess the integrity of the anastomosis. An intraoperative air leak test was proposed by Kanaji to check anastomotic integrity during open radical gastrectomy[6] and showed that this test reduces the occurrence of postoperative anastomotic leaks; however, the intraoperative air leak test did not show the exact site of the leaks and only depicted the approximate area. Celik *et al*[14] showed a low incidence of anastomotic leaks in the methylene blue testing group (3.7% *vs* 14.4%, $P = 0.007$) in which methylene blue is injected *via* a nasogastric tube to check the integrity of the anastomosis during an open total gastrectomy. Some researchers[31] who performed an intraoperative endoscopic examination during laparoscopic gastric bypass surgery showed a low incidence of anastomotic leaks (0 *vs* 8%, $P = 0.0412$) and a low reoperation rate (0 *vs* 8%, $P = 0.0412$). However, it is a challenge to find gastroscopic instruments as well as an experienced endoscopist. Our study confirmed that IMBT is an important method for assessing anastomotic integrity in totally laparoscopic radical gastrectomy, which detects anastomoses and pinpoints the areas of the leaks. Furthermore, we examined the anastomosis during totally laparoscopic distal gastrectomy, whereas previous studies focused on esophagojejunal

**Table 5 Risk factors for positive intraoperative methylene blue testing and postoperative anastomotic leaks analyzed by multivariate analysis**

| Variable | B | Standard deviation | Wald | Exp(B) | Odds ratio (95%CI) | | *P* value |
|---|---|---|---|---|---|---|---|
| | | | | | Lower limit | Upper limit | |
| IMBT | | | | | | | |
| BMI ≥ 25 kg/m$^2$ | 2.123 | 0.810 | 6.862 | 8.357 | 1.707 | 40.922 | 0.009 |
| Neoadjuvant chemotherapy | 1.326 | 0.805 | 2.715 | 3.767 | 0.778 | 18.245 | 0.099 |
| Operation time ≥ 4 h | 4.023 | 1.319 | 9.303 | 55.881 | 4.212 | 741.381 | 0.002 |
| Inexperienced surgeons | 2.727 | 1.052 | 6.719 | 15.286 | 1.944 | 120.167 | 0.010 |
| PAL | | | | | | | |
| BMI > 25 kg/m$^2$ | 1.289 | 0.858 | 2.259 | 3.630 | 0.676 | 19.498 | 0.133 |
| Preoperative complications | 2.575 | 1.081 | 5.671 | 13.128 | 1.577 | 109.268 | 0.017 |
| Neoadjuvant chemotherapy | 1.967 | 0.740 | 7.063 | 7.150 | 1.676 | 30.506 | 0.008 |
| TLTG | 2.206 | 1.091 | 4.083 | 9.075 | 1.069 | 77.070 | 0.043 |

IMBT: Intraoperative methylene blue testing; PAL: Postoperative anastomotic leak; BMI: Body mass index; TLTG: Totally laparoscopic total gastrectomy.

anastomotic leaks after total gastrectomy.

This study found seven IMBT-positive patients whose anastomosis was reinforced with sutures, and none of them developed PALs. Our study indicated that patients with an operative time > 4 h, those with a BMI > 25 kg/m$^2$, and insufficient surgical experience were associated with a higher risk of positive IMBT. Previous studies have shown that technically relevant factors such as prolonged operative time, excessive BMI, and inexperience of the surgeon are strongly associated with the occurrence of PALs[6,32-33]. Therefore, we recommend performing IMBT in patients with these high-risk factors.

However, two patients (0.9%) with negative IMBT developed PALs in this study, meaning that the cause of the anastomotic leaks is complex. This study found that patients with preoperative complications, totally laparoscopic total gastrectomy, and neoadjuvant chemotherapy are at a higher risk for PALs. Previous studies have indicated that anemia, malnutrition, and pulmonary insufficiency are also strongly associated with the occurrence of PALs[13,32,34], and are consistent with the results of our study. Kawamura *et al*[35] showed that the rate of anastomotic leaks is significantly higher in the laparoscopic total gastrectomy group (5.0 %) than in the laparoscopic distal gastrectomy group (1.2%), which is consistent with our study. However, there is still controversy about whether neoadjuvant chemotherapy leads to PALs. Gorur *et al*[36] reported that chemotherapy affects cell proliferation and the formation of collagenous fiber, which is a key component of anastomotic healing. Some studies reported that neoadjuvant chemotherapy does not increase the risk of PALs[37,38]. Our study suggested that neoadjuvant chemotherapy is a risk factor for PALs. We hypothesized that patients undergoing neoadjuvant chemotherapy have increased tissue toughness and adhesion within the abdominal cavity, resulting in increased surgical damage, thus leading to PALs. Therefore, we should pay close attention to patients with the above-mentioned risk factors.

This study has its limitations. First, it is a single-center retrospective study, which needs to be further confirmed by a multicenter, randomized controlled study with a larger sample size. Second, our study did not compare the IMBT, intraoperative air leak test, and intraoperative endoscopy. Finally, the methylene blue testing could not prevent PALs caused by non-technical factors.

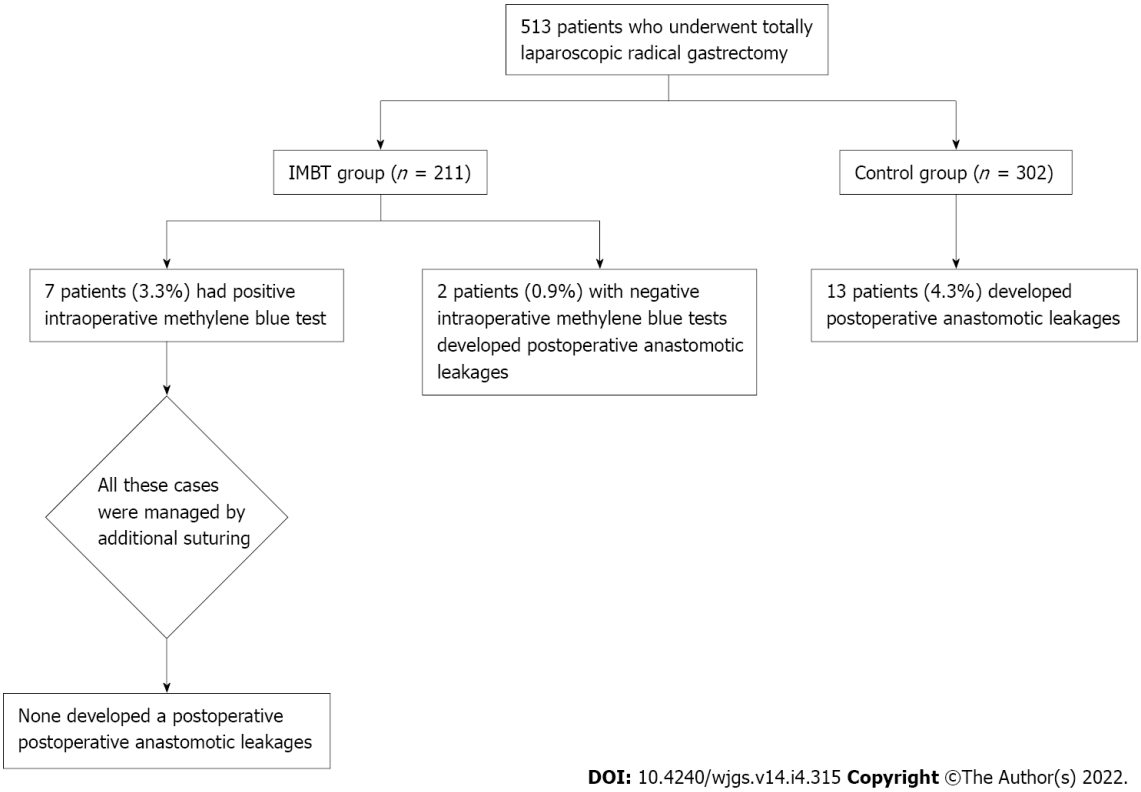
## CONCLUSION

In summary, IMBT can find technical defects within an anastomosis, and suturing can reduce the incidence of anastomotic leaks after totally laparoscopic radical gastrectomy. Independent risk factors associated with PALs include preoperative complications, totally laparoscopic total gastrectomy, and neoadjuvant chemotherapy.

**Table 6 Characteristics of postoperative anastomotic leaks**

| Patient No. | Group | Day of diagnosis after surgery (d) | TLTG or TLDG | Tumor staging[1] | Procedure used for patients | Time of placement of abdominal drainage tube (d) | Postoperative Hospital stays (d) |
|---|---|---|---|---|---|---|---|
| 1 | IMBT group | 6 | TLTG | IIB | Drainage | 15 | 16 |
| 2 | IMBT group | 8 | TLTG | IIIA | Second surgery + Drainage | 20 | 21 |
| 3 | Control group | 4 | TLTG | IA | Drainage | 18 | 19 |
| 4 | Control group | 5 | TLTG | IIA | Drainage | 13 | 15 |
| 5 | Control group | 9 | TLTG | IIB | Drainage | 19 | 21 |
| 6 | Control group | 8 | TLTG | IIB | Drainage | 12 | 14 |
| 7 | Control group | 5 | TLTG | IIIC | Drainage | 18 | 20 |
| 8 | Control group | 3 | TLTG | IIIC | Drainage | 16 | 18 |
| 9 | Control group | 8 | TLTG | IIB | Second surgery + Drainage | 21 | 24 |
| 10 | Control group | 7 | TLTG | IIIB | Second surgery + Drainage | 22 | 25 |
| 11 | Control group | 7 | TLTG | IIIC | Second surgery + Drainage | 17 | 21 |
| 12 | Control group | 5 | TLDG | IIIA | Drainage | 12 | 14 |
| 13 | Control group | 3 | TLDG | IIA | Second surgery + Drainage | 17 | 18 |
| 14 | Control group | 3 | TLDG | IIIA | Second surgery + Drainage | 19 | 20 |
| 15 | Control group | 6 | TLDG | IIIC | Second surgery + Drainage | 20 | 23 |

[1]According to the 8th AJCC TNM staging system for gastric cancer. PAL: Postoperative anastomotic leak; TLTG: Totally laparoscopic total gastrectomy; TLDG: Totally laparoscopic distal gastrectomy.




**DOI:** 10.4240/wjgs.v14.i4.315 

**Figure 4 Schematic representation of study protocol and results.** IMBT: Intraoperative methylene blue testing.

## ARTICLE HIGHLIGHTS

### *Research background*

We hypothesized that intraoperative methylene blue testing (IMBT) could reduce the incidence of postoperative anastomotic leaks (PALs) in totally laparoscopic radical gastrectomy.

### *Research motivation*

IMBT, air leak testing, or endoscopy is used to assess the anastomotic integrity of esophagojejunostomy during open total gastrectomy for gastric cancer. To the best of our konwledge, this is the first study to assess the anastomotic integrity during totally laparoscopic radical gastrectomy.

### *Research objectives*

To explore the effects of IMBT on the incidence of PALs and identify the risk factors for PALs in totally laparoscopic radical gastrectomy.

### *Research methods*

The difference in the incidence of PALs was compared between the IMBT group and the control group. Logistic regression analysis was used to clarify the risk factor for positive IMBT and PALs.

### *Research results*

Positive IMBT was shown in 7 patients (3.3%) in the IMBT group, and no PAL occurred in these patients after suture reinforcement. Moreover, 15 patients (2.9%) developed PALs, and the rate of PALs was significantly lower in the IMBT group than in the control group [2 of 211 patients (0.9%) *vs* 13 of 302 patients (4.3%), $P = 0.0026$]. Further analysis demonstrated that preoperative complications (hazard ratio [HR] = 13.128, $P = 0.017$), totally laparoscopic total gastrectomy (HR = 9.075, $P = 0.043$), and neoadjuvant chemotherapy (HR = 7.150, $P = 0.008$) were independent risk factors for PALs.

### *Research conclusions*

IMBT can find technical defects within an anastomosis, and suturing can reduce the incidence of PALs in totally laparoscopic radical gastrectomy. Independent risk factors associated with PAL include preoperative complications, totally laparoscopic total gastrectomy, and neoadjuvant chemotherapy.

### *Research perspectives*

Randomized controlled trials are expected to be conducted to measure the effects of IMBT.

## ACKNOWLEDGEMENTS

We thank Zhu JF for his review of our statistics.

## FOOTNOTES

**Author contributions:** Deng C designed and performed the research and wrote the paper; Liu Y, Zhang ZY, and Qi HD designed the research and supervised the report; Guo Z and Zhao X provided clinical advice; Li XJ designed and performed the research and supervised the report.

**Institutional review board statement:** This study was reviewed and approved by the Ethics Committee of the Shaanxi Provincial People's Hospital.

**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

**Conflict-of-interest statement:** We have no financial relationships to disclose.

**Data sharing statement:** No additional data are available.



**Country/Territory of origin:** China

**ORCID number:** Chun Deng 0000-0002-6517-9924; Yang Liu 0000-0003-1047-7454; Zhen-Yu Zhang 0000-0002-9891-6716; Heng-Duo Qi 0000-0002-2093-4711; Xu Zhao 0000-0002-5407-2400; Xiao-Jun Li 0000-0002-3355-6529.

**S-Editor:** Wu YXJ
**L-Editor:** Wang TQ
**P-Editor:** Wu YXJ

## REFERENCES

1 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]

2 **Lee JH**, Nam BH, Ryu KW, Ryu SY, Park YK, Kim S, Kim YW. Comparison of outcomes after laparoscopy-assisted and open total gastrectomy for early gastric cancer. *Br J Surg* 2015; **102**: 1500-1505 [PMID: 26398912 DOI: 10.1002/bjs.9902]

3 **Kim W**, Kim HH, Han SU, Kim MC, Hyung WJ, Ryu SW, Cho GS, Kim CY, Yang HK, Park DJ, Song KY, Lee SI, Ryu SY, Lee JH, Lee HJ; Korean Laparo-endoscopic Gastrointestinal Surgery Study (KLASS) Group. Decreased Morbidity of Laparoscopic Distal Gastrectomy Compared With Open Distal Gastrectomy for Stage I Gastric Cancer: Short-term Outcomes From a Multicenter Randomized Controlled Trial (KLASS-01). *Ann Surg* 2016; **263**: 28-35 [PMID: 26352529 DOI: 10.1097/SLA.0000000000001346]

4 **Ajani JA**, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P, Denlinger CS, Enzinger PC, Fanta P, Farjah F, Gerdes H, Gibson M, Glasgow RE, Hayman JA, Hochwald S, Hofstetter WL, Ilson DH, Jaroszewski D, Johung KL, Keswani RN, Kleinberg LR, Leong S, Ly QP, Matkowskyj KA, McNamara M, Mulcahy MF, Paluri RK, Park H, Perry KA, Pimiento J, Poultsides GA, Roses R, Strong VE, Wiesner G, Willett CG, Wright CD, McMillian NR, Pluchino LA. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2019; **17**: 855-883 [PMID: 31319389 DOI: 10.6004/jnccn.2019.0033]

5 **Hyung WJ**, Yang HK, Han SU, Lee YJ, Park JM, Kim JJ, Kwon OK, Kong SH, Kim HI, Lee HJ, Kim W, Ryu SW, Jin SH, Oh SJ, Ryu KW, Kim MC, Ahn HS, Park YK, Kim YH, Hwang SH, Kim JW, Cho GS. A feasibility study of laparoscopic total gastrectomy for clinical stage I gastric cancer: a prospective multi-center phase II clinical trial, KLASS 03. *Gastric Cancer* 2019; **22**: 214-222 [PMID: 30128720 DOI: 10.1007/s10120-018-0864-4]

6 **Kanaji S**, Ohyama M, Yasuda T, Sendo H, Suzuki S, Kawasaki K, Tanaka K, Fujino Y, Tominaga M, Kakeji Y. Can the intraoperative leak test prevent postoperative leakage of esophagojejunal anastomosis after total gastrectomy? *Surg Today* 2016; **46**: 815-820 [PMID: 26354031 DOI: 10.1007/s00595-015-1243-y]

7 **Katai H**, Mizusawa J, Katayama H, Kunisaki C, Sakuramoto S, Inaki N, Kinoshita T, Iwasaki Y, Misawa K, Takiguchi N, Kaji M, Okitsu H, Yoshikawa T, Terashima M; Stomach Cancer Study Group of Japan Clinical Oncology Group. Single-arm confirmatory trial of laparoscopy-assisted total or proximal gastrectomy with nodal dissection for clinical stage I gastric cancer: Japan Clinical Oncology Group study JCOG1401. *Gastric Cancer* 2019; **22**: 999-1008 [PMID: 30788750 DOI: 10.1007/s10120-019-00929-9]

8 **Aurello P**, Cinquepalmi M, Petrucciani N, Moschetta G, Antolino L, Felli F, Giulitti D, Nigri G, D'Angelo F, Valabrega S, Ramacciato G. Impact of Anastomotic Leakage on Overall and Disease-free Survival After Surgery for Gastric Carcinoma: A Systematic Review. *Anticancer Res* 2020; **40**: 619-624 [PMID: 32014902 DOI: 10.21873/anticanres.13991]

9 **Sierzega M**, Kolodziejczyk P, Kulig J; Polish Gastric Cancer Study Group. Impact of anastomotic leakage on long-term survival after total gastrectomy for carcinoma of the stomach. *Br J Surg* 2010; **97**: 1035-1042 [PMID: 20632269 DOI: 10.1002/bjs.7038]

10 **Yoo HM**, Lee HH, Shim JH, Jeon HM, Park CH, Song KY. Negative impact of leakage on survival of patients undergoing curative resection for advanced gastric cancer. *J Surg Oncol* 2011; **104**: 734-740 [PMID: 21792945 DOI: 10.1002/jso.22045]

11 **Kim SH**, Son SY, Park YS, Ahn SH, Park DJ, Kim HH. Risk Factors for Anastomotic Leakage: A Retrospective Cohort Study in a Single Gastric Surgical Unit. *J Gastric Cancer* 2015; **15**: 167-175 [PMID: 26468414 DOI: 10.5230/jgc.2015.15.3.167]

12 **Trapani R**, Rausei S, Reddavid R, Degiuli M; ITALIAN RESEARCH GROUP FOR GASTRIC CANCER (GIRCG) Clinical Investigators. Risk factors for esophago-jejunal anastomosis leakage after total gastrectomy for cancer. A multicenter retrospective study of the Italian research group for gastric cancer. *Eur J Surg Oncol* 2020; **46**: 2243-2247 [PMID: 32703713 DOI: 10.1016/j.ejso.2020.06.035]

13 **Migita K**, Takayama T, Matsumoto S, Wakatsuki K, Enomoto K, Tanaka T, Ito M, Nakajima Y. Risk factors for esophagojejunal anastomotic leakage after elective gastrectomy for gastric cancer. *J Gastrointest Surg* 2012; **16**: 1659-1665 [PMID: 22688419 DOI: 10.1007/s11605-012-1932-4]

14 **Celik S**, Almalı N, Aras A, Yılmaz Ö, Kızıltan R. Intraoperatively Testing the Anastomotic Integrity of Esophagojejunostomy Using Methylene Blue. *Scand J Surg* 2017; **106**: 62-67 [PMID: 26929288 DOI: 10.1177/1457496916630652]

15 **Nishikawa K**, Yanaga K, Kashiwagi H, Hanyuu N, Iwabuchi S. Significance of intraoperative endoscopy in total gastrectomy for gastric cancer. *Surg Endosc* 2010; **24**: 2633-2636 [PMID: 20354882 DOI: 10.1007/s00464-010-1007-0]

16 **Alkatout I**, Dhanawat J, Ackermann J, Freytag D, Peters G, Maass N, Mettler L, Pape JM. Video Feedback and Video Modeling in Teaching Laparoscopic Surgery: A Visionary Concept from Kiel. *J Clin Med* 2021; **10** [PMID: 33466531 DOI: 10.3390/jcm10010163]

17 **Pinzon D**, Byrns S, Zheng B. Prevailing Trends in Haptic Feedback Simulation for Minimally Invasive Surgery. *Surg Innov* 2016; **23**: 415-421 [PMID: 26839212 DOI: 10.1177/1553350616628680]

18 **Mortensen K**, Nilsson M, Slim K, Schäfer M, Mariette C, Braga M, Carli F, Demartines N, Griffin SM, Lassen K; Enhanced Recovery After Surgery (ERAS®) Group. Consensus guidelines for enhanced recovery after gastrectomy: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *Br J Surg* 2014; **101**: 1209-1229 [PMID: 25047143 DOI: 10.1002/bjs.9582]

19 **Liu H**, Jin P, Quan X, Xie YB, Ma FH, Ma S, Li Y, Kang WZ, Tian YT. Feasibility of totally laparoscopic gastrectomy without prophylactic drains in gastric cancer patients. *World J Gastroenterol* 2021; **27**: 4236-4245 [PMID: 34326622 DOI: 10.3748/wjg.v27.i26.4236]

20 **Son T**, Sun J, Choi S, Cho M, Kwon IG, Kim HI, Cheong JH, Choi SH, Noh SH, Woo Y, Fong Y, Park S, Hyung WJ. Multi-institutional validation of the 8th AJCC TNM staging system for gastric cancer: Analysis of survival data from high-volume Eastern centers and the SEER database. *J Surg Oncol* 2019; **120**: 676-684 [PMID: 31338834 DOI: 10.1002/jso.25639]

21 **Ko CS**, Choi NR, Kim BS, Yook JH, Kim MJ. Totally laparoscopic total gastrectomy using the modified overlap method and conventional open total gastrectomy: A comparative study. *World J Gastroenterol* 2021; **27**: 2193-2204 [PMID: 34025073 DOI: 10.3748/wjg.v27.i18.2193]

22 **Yanagimoto Y**, Omori T, Fujiwara Y, Demura K, Jeong-Ho M, Shinno N, Yamamoto K, Sugimura K, Miyata H, Ushigome H, Takahashi Y, Nishimura J, Yasui M, Asukai K, Yamada D, Wada H, Takahashi H, Ohue M, Yano M, Sakon M. Comparison of the intracorporeal triangular and delta-shaped anastomotic techniques in totally laparoscopic distal gastrectomy for gastric cancer: an analysis with propensity score matching. *Surg Endosc* 2020; **34**: 2445-2453 [PMID: 31385072 DOI: 10.1007/s00464-019-07025-0]

23 **Japanese Gastric Cancer Association**. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer* 2017; **20**: 1-19 [PMID: 27342689 DOI: 10.1007/s10120-016-0622-4]

24 **Hatta W**, Gotoda T, Oyama T, Kawata N, Takahashi A, Yoshifuku Y, Hoteya S, Nakamura K, Hirano M, Esaki M, Matsuda M, Ohnita K, Shimoda R, Yoshida M, Dohi O, Takada J, Tanaka K, Yamada S, Tsuji T, Ito H, Hayashi Y, Nakamura T, Shimosegawa T. Is radical surgery necessary in all patients who do not meet the curative criteria for endoscopic submucosal dissection in early gastric cancer? *J Gastroenterol* 2017; **52**: 175-184 [PMID: 27098174 DOI: 10.1007/s00535-016-1210-4]

25 **Park JY**, Kim YJ. Uncut Roux-en-Y Reconstruction after Laparoscopic Distal Gastrectomy Can Be a Favorable Method in Terms of Gastritis, Bile Reflux, and Gastric Residue. *J Gastric Cancer* 2014; **14**: 229-237 [PMID: 25580354 DOI: 10.5230/jgc.2014.14.4.229]

26 **GBD 2017 Stomach Cancer Collaborators**. The global, regional, and national burden of stomach cancer in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease study 2017. *Lancet Gastroenterol Hepatol* 2020; **5**: 42-54 [PMID: 31648970 DOI: 10.1016/S2468-1253(19)30328-0]

27 **Nakamura M**, Nakamori M, Ojima T, Iwahashi M, Horiuchi T, Kobayashi Y, Yamade N, Shimada K, Oka M, Yamaue H. Randomized clinical trial comparing long-term quality of life for Billroth I *vs* Roux-en-Y reconstruction after distal gastrectomy for gastric cancer. *Br J Surg* 2016; **103**: 337-347 [PMID: 26840944 DOI: 10.1002/bjs.10060]

28 **Kim MS**, Kwon Y, Park EP, An L, Park H, Park S. Revisiting Laparoscopic Reconstruction for Billroth 1 Versus Billroth 2 Versus Roux-en-Y After Distal Gastrectomy: A Systematic Review and Meta-Analysis in the Modern Era. *World J Surg* 2019; **43**: 1581-1593 [PMID: 30756163 DOI: 10.1007/s00268-019-04943-x]

29 World Health Organization Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity. [cited 21 June 2021]; Available from: https://www.who.int/vmnis/indicators/haemoglobin/en/

30 **Cederholm T**, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, Muscaritoli M, Nyulasi I, Ockenga J, Schneider SM, de van der Schueren MA, Singer P. Diagnostic criteria for malnutrition - An ESPEN Consensus Statement. *Clin Nutr* 2015; **34**: 335-340 [PMID: 25799486 DOI: 10.1016/j.clnu.2015.03.001]

31 **Valenzuela-Salazar C**, Rojano-Rodríguez ME, Romero-Loera S, Trejo-Ávila ME, Bañuelos-Mancilla J, Delano-Alonso R, Moreno-Portillo M. Intraoperative endoscopy prevents technical defect related leaks in laparoscopic Roux-en-Y gastric bypass: A randomized control trial. *Int J Surg* 2018; **50**: 17-21 [PMID: 29278753 DOI: 10.1016/j.ijsu.2017.12.024]

32 **Deguchi Y**, Fukagawa T, Morita S, Ohashi M, Saka M, Katai H. Identification of risk factors for esophagojejunal anastomotic leakage after gastric surgery. *World J Surg* 2012; **36**: 1617-1622 [PMID: 22415758 DOI: 10.1007/s00268-012-1559-3]

33 **Chen HN**, Chen XZ, Zhang WH, Yang K, Chen XL, Zhang B, Chen ZX, Chen JP, Zhou ZG, Hu JK. The Impact of Body Mass Index on the Surgical Outcomes of Patients With Gastric Cancer: A 10-Year, Single-Institution Cohort Study. *Medicine (Baltimore)* 2015; **94**: e1769 [PMID: 26496304 DOI: 10.1097/MD.0000000000001769]

34 **Gong W**, Li J. Combat with esophagojejunal anastomotic leakage after total gastrectomy for gastric cancer: A critical review of the literature. *Int J Surg* 2017; **47**: 18-24 [PMID: 28935529 DOI: 10.1016/j.ijsu.2017.09.019]

35 **Kawamura Y**, Satoh S, Suda K, Ishida Y, Kanaya S, Uyama I. Critical factors that influence the early outcome of laparoscopic total gastrectomy. *Gastric Cancer* 2015; **18**: 662-668 [PMID: 24906557 DOI: 10.1007/s10120-014-0392-9]

36 **Gorur M**, Sozutek A, Irkorucu O, Karakaya B. The influence of platelet-rich plasma (PRP) on colonic anastomosis healing impaired by intraperitoneal 5-flourouracil application. An experimental study. *Acta Cir Bras* 2020; **35**: e202000504 [PMID: 32638844 DOI: 10.1590/s0102-865020200050000004]

37 **Haskins IN**, Kroh MD, Amdur RL, Ponksy JL, Rodriguez JH, Vaziri K. The Effect of Neoadjuvant Chemoradiation on Anastomotic Leak and Additional 30-Day Morbidity and Mortality in Patients Undergoing Total Gastrectomy for Gastric Cancer. *J Gastrointest Surg* 2017; **21**: 1577-1583 [PMID: 28744744 DOI: 10.1007/s11605-017-3496-9]

38 **Schuhmacher C**, Gretschel S, Lordick F, Reichardt P, Hohenberger W, Eisenberger CF, Haag C, Mauer ME, Hasan B, Welch J, Ott K, Hoelscher A, Schneider PM, Bechstein W, Wilke H, Lutz MP, Nordlinger B, Van Cutsem E, Siewert JR, Schlag PM. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. *J Clin Oncol* 2010; **28**: 5210-5218 [PMID: 21060024 DOI: 10.1200/JCO.2009.26.6114]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 April 27; 14(4): 329-340

DOI: 10.4240/wjgs.v14.i4.329

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

# Clinical outcomes of endoscopic resection of superficial nonampullary duodenal epithelial tumors: A 10-year retrospective, single-center study

Joon Hyun Cho, Ki Young Lim, Eun Jung Lee, Si Hyung Lee

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

**P-Reviewer:** Dutta AK, India; Furukawa M, Japan

**Received:** December 18, 2021
**Peer-review started:** December 18, 2021
**First decision:** January 27, 2022
**Revised:** February 9, 2022
**Accepted:** March 26, 2022
**Article in press:** March 26, 2022
**Published online:** April 27, 2022

**Joon Hyun Cho, Ki Young Lim, Eun Jung Lee, Si Hyung Lee,** Division of Gastroenterology and Hepatology, Department of Internal Medicine, Yeungnam University College of Medicine, Daegu 42415, South Korea

**Corresponding author:** Si Hyung Lee, MD, Professor, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, South Korea. dr9696@gmail.com

## Abstract

### *BACKGROUND*

Although premalignant duodenal lesions such as adenomas are uncommon, the incidences of these lesions have increased in recent times, and thus, the demand for minimally invasive treatments such as endoscopic resection (ER) has also increased. However, ER in the duodenum is more challenging than ER in other locations of the gastrointestinal tract.

### *AIM*

To evaluate the safety and efficacy of ER for superficial nonampullary duodenal epithelial tumors (SNADETs)

### *METHODS*

We performed a retrospective observational study on 56 consecutive patients (58 lesions) diagnosed with SNADETs that underwent ER from January 2011 to December 2020 at Yeungnam University Hospital. Patient demographics, lesion characteristics, and procedural and technical data were collected, and clinical outcomes, including procedure-related complications, completeness of resection, and recurrence were analyzed.

### *RESULTS*

Median patient age was 57 years [range, 26–77, 30 (53.6%) men]. Endoscopic mucosal resection (EMR) was performed on 57 lesions (98.3%) and snare polypectomy on one (1.7%). Lesions consisted of 52 adenomas with low-grade dysplasia (89.7%), 3 adenomas with high-grade dysplasia (5.2%), and 3 intramucosal adenocarcinomas (5.2%). There were 16 cases of intraprocedural bleeding (27.6%) and 1 case of delayed bleeding (1.7%), and all these 17 cases were successfully managed endoscopically. No perforation or procedure-related death

occurred. Larger lesion size was associated with an increased risk of EMR-related bleeding ($P$ = 0.033). During a median follow-up period of 23 mo (range 6–100 mo), no local recurrence occurred, despite the fact one-third of the patients (19 lesions, 32.8%) underwent piecemeal resection and 3 patients (3 lesions, 5.2%) that underwent *en bloc* resection had a pathologically determined positive lateral margin. No patient died from a primary duodenal neoplasm.

***CONCLUSION***

The majority of SNADETs can be safely and curatively resected by EMR, and thus, based on consideration of the high incidence of fatal complications attributable to ESD, we conclude EMR, including piecemeal resection, should be considered the treatment of first choice for SNADETs.

**Key Words:** Duodenum; Adenoma; Endoscopic mucosal resection; Endoscopic resection; Superficial nonampullary duodenal epithelial tumor



**Core Tip:** This long-term retrospective observational study shows that superficial nonampullary duodenal epithelial tumors (SNADETs) can be safely and curatively managed by endoscopic mucosal resection (EMR), even after piecemeal resection. Therefore, based on consideration of the high incidence of fatal complications attributable to endoscopic submucosal dissection in duodenum, we recommend that EMR, including piecemeal resection, be considered the treatment of first choice for SNADETs. However, we caution that because of its technical difficulty, EMR on duodenum should only be performed by highly skilled endoscopists. In addition, we emphasize that more attention is required during EMR of a large duodenal tumor because lesion size is positively associated with the risk of EMR-related bleeding.

**Citation:** Cho JH, Lim KY, Lee EJ, Lee SH. Clinical outcomes of endoscopic resection of superficial nonampullary duodenal epithelial tumors: A 10-year retrospective, single-center study. *World J Gastrointest Surg* 2022; 14(4): 329-340

**URL:** https://www.wjgnet.com/1948-9366/full/v14/i4/329.htm

**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i4.329

## INTRODUCTION

Superficial nonampullary duodenal epithelial tumors (SNADETs) such as primary duodenal adenomas and adenocarcinomas are rare compared with other gastrointestinal (GI) tract cancers. However, as the use of screening endoscopy continues to increase and endoscopic skills and technology improve, small early SNADETs are being diagnosed more frequently[1]. The adenoma-carcinoma sequence is also accepted for lesions in the small bowel[2,3], and reported malignant transformation rates of duodenal adenoma range from 30% to 85%[4,5]. Therefore, once diagnosed, surgical excision and endoscopic resection (ER) are the initial considerations, and ER is generally preferred over operative interventions because of its less invasive nature.

However, the duodenum is the most challenging location in the GI tract for ER. Several anatomic features of the duodenum contribute to these difficulties, such as a narrow lumen, a ''C-loop'' that reduces endoscope stability, the presence of Brunner's glands in the deep mucosal and submucosal layers that stiffen the wall and lead to poor mucosal lifting, a thin deep muscle layer that increases the risk of complications like perforation, and difficulties associated with accessing sites if emergency or salvage surgery becomes necessary[6-8].

Endoscopic submucosal dissection (ESD) is regularly performed at expert centers in South Korea for superficial lesions of the esophagus, stomach, or colorectum. ESD has a high *en bloc* resection rate, which enables accurate histopathological assessments. However, we refrain from aggressive duodenal ESD because the procedure is technically difficult and associated with a higher incidence of consequential perforation than at other sites in the GI tract[9-11]. Although endoscopic mucosal resection (EMR) is a safer, easier, and quicker procedure than ESD, EMR results in fewer *en bloc* resections[12-18]. Even though debate continues as to which ER method is preferable, EMR is currently recognized as the standard procedure for the endoscopic treatment of SNADETs.

Duodenal lesions that require ER are limited in number, and thus, although several reports have been published, little information is available on the long-term clinical outcomes of ER for SNADETs. In this study, we evaluated the safety and efficacy of ER for the treatment of SNADETs and associated factors using a 10-year follow-up.

## MATERIALS AND METHODS

### Patients

We retrospectively analyzed our institutional database for patients that underwent duodenal ER between January 2011 and December 2020. During this period, 56 consecutive patients with 58 lesions underwent ER for SNADETs. In all cases, these were primary tumors without a previous history. Patients with polyposis syndrome, an ampullary duodenal tumor, or a neuroendocrine tumor were excluded. Written informed consent was obtained from all patients before they underwent ER, and the study protocol was reviewed and approved beforehand by the Institutional Review Board of Yeungnam University Hospital (IRB No. 2021-10-045).

Patient demographics, lesion characteristics, and procedural descriptions were collected from the institutional database and electronic medical records. Data on the use of antiplatelet or anticoagulant medication or nonsteroidal anti-inflammatory drugs (NSAIDs) were also obtained for analysis. Follow-up was defined as time between ER and recurrence, death, or loss to follow-up. If none of these events was documented, the end of the follow-up period was defined as the time of last patient contact before June 30, 2021.

### Endoscopic procedure and follow-up

Suitability for ER was determined based on endoscopic appearance as determined by high-definition white light endoscopy and narrow-band imaging in patients with histologically confirmed adenoma or adenocarcinoma confined to mucosa. Suspected invasive neoplasia was deemed unsuitable for endoscopic resection. Patients on antiplatelet and/or anticoagulant medications were instructed to consult with their prescribing physicians for permission to withhold medications before ER. EMR was carried out by highly skilled endoscopists. With patients under propofol and midazolam sedation and cardiorespiratory function monitoring, conventional EMR was performed using a snare-assisted technique with submucosal injection of methylene blue-tinted normal saline containing a small amount of epinephrine (0.01 mg/mL) using a single-use 21-gauge needle (Olympus, Japan). Two types of oval electrosurgical snares were used of diameter 15 or 25 mm (Olympus). In one case, standard snare polypectomy was performed without submucosal injection.

The EMR technique was individualized on a case-by-case basis. *En bloc* resection was attempted if a lesion had a largest diameter of < 2.0 cm and < 25% of the luminal circumference. Piecemeal resection was conducted for larger lesions and when there was endoscopic evidence of residual tumor after an *en bloc* resection attempt. Adjunctive coagulation using a hot-biopsy forceps (Boston Scientific, Natick, MA, USA) or an argon plasma coagulation (APC) unit (ERBE, Elektromedizin, Tuebingen, Germany) was sometimes used to reduce the risk posed by any residual tumor, based on endoscopist judgment when the residual portion was too small to remove using a snare. Prophylactic clip placement was performed to reduce the risk of delayed bleeding and perforation when technically possible, depending on lesion location and size, and endoscope stability[9,13,16,19]. EMR was performed only after hospital admission.

After endoscopic treatment, routine chest and abdominal radiography were performed to evaluate possible adverse events, such as perforation and aspiration pneumonia. Routine second-look endoscopy was performed 1 d after EMR. After discharge, follow-up endoscopy was performed at 6 and 12 mo post-EMR during the first year and annually thereafter. If recurrence was suspected, forceps tissue sampling was performed, and further endoscopic treatment such as EMR, and/or ablation were performed at the discretion of the endoscopist.

### Clinical outcomes and adverse events

Outcomes were classified as short- or long-term. Short-term outcomes included ER success, which included *en bloc* resection and complete resection rates, and procedure-related complications, which included bleeding and perforation. *En bloc* resection was defined as lesion resection as a single piece, and piecemeal resection as resection resulting in multiple pieces. Complete resection was defined as resection with no endoscopic or histologic evidence of residual tumor tissue at resection sites, irrespective of whether *en bloc* resection was undertaken. EMR-related bleeding was categorized as intraprocedural or delayed bleeding requiring directed intervention. Intraprocedural bleeding was defined as persistent bleeding during the procedure that did not cease spontaneously and required endoscopic intervention involving the injection of diluted epinephrine solution (1:10000), snare-tip soft coagulation, coagulation forceps, or hemoclip placement. Delayed bleeding was defined as any bleeding that prompted medical intervention after the procedure. Perforation was diagnosed endoscopically during procedures or based on the presence of free air in post-procedural chest or abdomen radiographs.

Long-term outcomes included local recurrence and disease-specific survival rates of patients followed for > 6 mo. Incomplete follow-up data were retrieved in various ways, such as by telephone contact or correspondence with patients, families, or referring physicians. Local recurrence was defined as the presence of a tumor on or adjacent to a previous endoscopic resection scar.

### Statistical analysis

Data were analyzed using SPSS version 20.0 for Windows (SPSS Inc, Chicago, IL, United States). All variables are presented as mean ± SD, medians and ranges, or absolute numbers and proportions. For univariate analyses, categorical variables were analyzed using the chi-square test or Fisher's exact test. A multivariable logistic regression model was used to identify independent predictors of outcomes and adverse events. Significant variables (*P*-values < 0.05) by univariate analysis and variables with clinical correlations were included in the multivariate model. Multivariate comparisons are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). All statistical tests were two-sided and statistical significance was accepted for *P* values < 0.05.

## RESULTS

### Patient characteristics

Over the ten-year study period, 56 patients underwent 57 EMR and 1 snare polypectomy procedures. Two patients had two duodenal adenomas, and all lesions were treated simultaneously. The baseline clinicopathologic characteristics of the study population are summarized in Table 1. The patients included 30 men (53.6%) and 26 women of median age 57 years (range 26-77 years). Six patients (10.7%) were on at least 1 antiplatelet medication, and no patient was taking an anticoagulant or NSAID. Nine lesions (15.5%) were located in the duodenal bulb, 47 (81.0%) in the 2$^{nd}$ portion, and 2 (3.4%) in the 3$^{rd}$ portion. Colonoscopy was performed in 69.6% of the patients with SNADETs, and colorectal adenomas were found in 46.2% of these patients. Macroscopic types were classified as Is in 24 patients (41.4%), IIa or IIb in 24 (41.4%), and Ip in 10 (17.2%). Based on the pathologies of biopsy specimens before EMR, there were 55 (94.8%) low-grade dysplasia (LGD) lesions, 2 (3.4%) high-grade dysplasia (HGD) lesions, and 1 (1.7%) adenocarcinoma.

### EMR and complications

*En bloc* resection was achieved successfully for 39 lesions (67.2%), and 19 lesions (32.8%) were resected piecemeal, which resulted in two resected specimens in each case (Table 2). Lesion sizes was categorized into 4 groups for further analysis, that is, a < 10 mm group [*n* = 20 (34.5%)], a ≥ 10 to < 15 mm group [*n* = 26 (44.8%)], a ≥ 15 to < 20 mm group [*n* = 7 (12.1%)], and a ≥ 20 mm group [*n* = 5 lesions (8.6%)]. Twenty-nine lesions (50.0%, 10 lesions that underwent *en bloc* resection and all of 19 lesions treated by piecemeal resection) underwent adjunctive coagulation by hot biopsy or APC to eliminate residual tumor risk. Immediate closure after EMR was performed for 48 lesions (82.8%) by prophylactic clip placement.

Sixteen lesions (27.6%) developed EMR-related bleeding; 15 were intraprocedural and 1 was delayed. All intraprocedural bleedings were successfully controlled endoscopically. Ten of these patients underwent endoscopic hemostasis with hemoclips and electrocoagulation. Only electrocoagulation was needed for five patients with bleeding. Delayed bleeding occurred in 1 EMR case despite prophylactic clipping and was successfully managed endoscopically with hemoclips and electrocoagulation. No patient required further surgical or radiological treatment. Neither perforation nor procedure-related mortality occurred.

### Histopathological results

The pathologic results of ER specimens are summarized in Table 3. Median tumor size as determined by histopathology was 12 mm (range 4-20 mm). There were 52 adenomas with LGD, 3 adenomas with HGD, and 3 intramucosal adenocarcinomas. Lateral margins were estimated pathologically to be negative for 36 (62.1%), positive for 3 (5.2%), and inconclusive for 19 (32.8%) lesions, and vertical margins were negative for 50 (86.2%), positive for 0 (0 %), and inconclusive for 8 (13.8%) lesions.

### Factors associated with EMR-related bleeding

Increasing lesion size was significantly associated with a higher risk of EMR-related bleeding (*P* = 0.033) (Table 4), but antiplatelet use, piecemeal resection, tumor location, macroscopic type, and pathology were not found to be associated with bleeding risk. Multivariate logistic regression analysis to identify independent predictors of EMR-related bleeding could not preformed due to only 17 events.

### Long-term outcomes

Six of the 56 patients followed for less than 6 mo were excluded from the analysis of long-term outcomes. All 22 patients (22 lesions) with a histopathologic result of an inconclusive or positive resection margin were followed for more than 6 mo (median follow-up duration 28 mo; range 12–101 mo). Clinicopathologic data and the outcomes of 3 cases of incomplete resection are summarized in Table 5, and long-term outcomes are summarized in Table 6. All 3 lesions of incomplete resection with a positive lateral margin were those that had undergone adjunctive coagulation. Of the 50 patients (52 lesions) followed for more than 6 mo, 2 died and 48 survived, but these deaths were not ascribed to a

**Table 1 Baseline characteristics of the study subjects**

| | |
|---|---|
| **Patients** | **56** |
| Median age, yr (range) | 57 (26-77) |
| Male, *n* (%) | 30 (53.6) |
| Number of lesions, *n* (%) | |
| 1 | 54 (96.4) |
| 2 | 2 (3.6) |
| Medications, *n* (%) | |
| Aspirin | 3 (5.3) |
| Clopidogrel | 1 (1.8) |
| Dual antiplatelets | 2 (3.6) |
| Anticoagulants | 0 |
| NSAIDs | 0 |
| Patients that underwent colonoscopy | 39 (69.6) |
| Colonoscopy positive for adenoma | 18 (46.2) |
| **Lesions** | **58** |
| Location, *n* (%) | |
| Bulb | 9 (15.5) |
| Second portion | 47 (81.0) |
| Third portion | 2 (3.4) |
| Macroscopic type, *n* (%) | |
| Ip | 10 (17.2) |
| Is | 24 (41.4) |
| IIa or IIb | 24 (41.4) |
| Biopsy diagnosis, *n* (%) | |
| Adenoma/LGD | 55 (94.8) |
| Adenoma/HGD | 2 (3.4) |
| Adenocarcinoma | 1 (1.7) |

NSAID: Nonsteroidal anti-inflammatory drug; LGD: Low-grade dysplasia; HGD: High-grade dysplasia.

primary duodenal tumor. One patient succumbed to aspiration pneumonia and the other patient to colon cancer with multiple liver metastases. In addition, none of the 50 patients experienced local recurrence during follow-up (median follow-up duration 23 mo; range 6–100 mo).

## DISCUSSION

In this 10-year retrospective study, we investigated the safety and efficacy of EMR for SNADETs. The results obtained suggest that the prognoses of patients treated by EMR are excellent. In the present study, no death was attributable to a primary duodenal tumor. Furthermore, no local recurrence occurred, although one-third of the patients underwent piecemeal EMR, and no perforation or procedure-related mortality occurred. These findings affirm that EMR of SNADETs has excellent safety and efficacy profiles.

The oncologic long-term outcomes of patients with tumors that are not resected in an *en bloc* fashion are of considerable importance. In the present study, *en bloc* resection was achieved in 67.2%, piecemeal resection in 32.8%, and complete (R0) resection in 62.1%. Due to the risks associated with ESD, endoscopists at our institute chose EMR or polypectomy for all 58 lesions, even for lesions > 20 mm. Considering the effects of *en bloc* resection on oncologic outcomes, this low proportion is obviously unsatisfactory. However, it was largely the result of attempting to minimize mucosal defects due to

**Table 2 Endoscopic treatment and complications for the 58 lesions**

| | |
|---|---|
| Treatment methods, *n* (%) | |
| EMR | 57 (98.3) |
| Snare polypectomy | 1 (1.7) |
| Lesion size, mm, *n* (%) | |
| Size < 10 | 20 (34.5) |
| 10 ≤ size < 15 | 26 (44.8) |
| 15 ≤ size < 20 | 7 (12.1) |
| 20 ≤ size | 5 (8.6) |
| Results of resection, *n* (%) | |
| *En bloc* | 39 (67.2) |
| Piecemeal | 19 (32.8) |
| Adjunctive coagulation, *n* (%) | 29 (50.0) |
| Prophylactic clip placement, *n* (%) | 48 (82.8) |
| Complication, *n* (%) | |
| Intraprocedural bleeding | 16 (27.6) |
| Delayed bleeding | 1 (1.7) |
| Perforation | 0 (0) |

EMR: Endoscopic mucosal resection.

**Table 3 Histopathologic results for the 58 lesions**

| | |
|---|---|
| Tumor size, mm, median (range) | 12 (4–20) |
| Final pathology, *n* (%) | 57 (98.3) |
| Adenoma/LGD | 52 (89.7) |
| Adenoma/HGD | 3 (5.2) |
| Intramucosal adenocarcinoma | 3 (5.2) |
| Lateral margin, *n* (%) | |
| Negative | 36 (62.1) |
| Positive | 3 (5.2) |
| Inconclusive | 19 (32.8) |
| Vertical margin, *n* (%) | |
| Negative | 50 (86.2) |
| Positive | 0 (0) |
| Inconclusive | 8 (13.8) |
| Complete (R0) resection | 36 (62.1) |

LGD: Low-grade dysplasia; HGD: High-grade dysplasia.

concerns about perforation and bleeding and to enable prophylactic clipping. Fortunately, no local recurrences or death attributable to primary duodenal tumors occurred even after a median follow-up of 23 mo.

Median tumor size (12 mm) in this study was smaller than the 22 to 25 mm sizes reported in Western studies, which also reported higher incidences of local recurrence (14.4%-30.8%) after EMR (*en bloc* rates varied from 23.5% to 31.0%)[20,21]. On the other hand, other studies on smaller lesions have reported local recurrence incidence rates between 5.8% and 8.3% and *en bloc* rates of 69.2%-82% (R0 30%-59%) for

**Table 4 Factors associated with endoscopic mucosal resection -related bleeding**

| | Bleeding (+) (*n* = 17) | Bleeding (-) (*n* = 41) | *P* value |
|---|---|---|---|
| Antiplatelet use | | | 0.661 |
| Yes | 1 (14.3) | 6 (85.7) | |
| No | 16 (31.4) | 35 (68.6) | |
| Lesion size, mm, *n* (%) | | | **0.033** |
| Size < 10 | 1 (5.0) | 19 (95.0) | |
| 10 ≤ size < 15 | 8 (30.8) | 18 (69.2) | |
| 15 ≤ size < 20 | 4 (57.1) | 3 (42.9) | |
| 20 ≤ size | 4 (80.0) | 1 (20.0) | |
| Results of resection, *n* (%) | | | 0.218 |
| *En bloc* | 9 (23.1) | 30 (76.9) | |
| Piecemeal | 8 (42.1) | 11 (57.9) | |
| Location, *n* (%) | | | 0.855 |
| Bulb | 2 (22.2) | 7 (77.8) | |
| Second portion | 15 (31.9) | 32 (68.1) | |
| Third portion | 0 (0) | 2 (100) | |
| Macroscopic type, *n* (%) | | | 0.950 |
| Ip | 2 (20.0) | 8 (80.0) | |
| Is | 7 (29.2) | 17 (70.8) | |
| IIa or IIb | 8 (33.3) | 16 (66.7) | |
| Final pathology | | | 0.345 |
| Adenoma/LGD | 14 (26.9) | 38 (73.1) | |
| Adenoma/HGD and adenocarcinoma | 3 (50.0) | 3 (50.0) | |

LGD: Low-grade dysplasia; HGD: High-grade dysplasia

**Table 5 Clinicopathologic data and outcomes for 3 cases of incomplete resection**

| Patient | Age (yr) | Location | Tumor Size | Pathology | Resection type | Treatment method | Vertical/lateral margin | Result of follow-up biopsy | Follow-up (mo) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 72 | Bulb | 20 | Intramucosal adenocarcinoma | *En bloc* | EMR | -/+ | - | 29 |
| 2 | 71 | Bulb | 20 | LGD | *En bloc* | EMR | -/+ | - | 27 |
| 3 | 75 | 2nd portion | 10 | LGD | *En bloc* | EMR | -/+ | - | 17 |

LGD: Low-grade dysplasia; EMR: Endoscopic mucosal resection.

lesions of approximately 10 mm[18,22,23]. Tomizawa *et al*[24] reported adenoma size, incomplete snare resection, and piecemeal resection were associated with duodenal adenoma recurrence by univariate analysis (multivariate analysis was not performed). Incomplete snare resection and piecemeal resection are likely consequences of larger lesions. However, others have reported incomplete resection, including piecemeal resection, was not associated with the long-term recurrence of SNADETs[25,26]. In the present study, one-third of patients underwent piecemeal EMR, but no recurrence was observed during follow-up. In a study on 75 duodenal adenomas treated by EMR, the residual tumor rate was 14.5% and the recurrence rate over a median follow-up of 59 mo was 10.9%[27]. However, all but one of these recurrences were successfully treated endoscopically and achieved favorable long-term outcomes.

**Table 6 Long-term outcomes (*n* = 50 patients and 52 lesions)**

| | |
|---|---|
| Recurrence, *n* (%) | 0 (0%) |
| Death by duodenal neoplasm | 0 (0%) |
| All-cause mortality | 2 (3.6%) |
| Follow-up period median (range) | 23 (6-100) mo |
| No. of follow-up endoscopies | |
| 2 | 9 |
| 3 or 4 | 28 |
| 5 ≤ | 13 |

Although it is not clear how much effect piecemeal resection has on local recurrence, it appears piecemeal resection may not have a significant negative effect on the long-term outcomes of duodenal adenomas. Therefore, we believe that EMR, including EMR with piecemeal resection, offers an acceptable alternative to ESD for the treatment of duodenal adenoma.

Despite considerable technical advances in ER for superficial neoplasms of the GI tract, duodenal endoscopic treatment is considered a high-risk procedure that is more challenging than ER in other GI tract locations for several reasons[6-8]; (1) Endoscope and accessory maneuverability are restricted by the small-caliber, angulated, and fixed-in-place duodenal lumen; (2) Rich vascularity poses a bleeding risk; and (3) The risk of perforation is increased by a thin duodenal wall, retroperitoneal location, and surrounding structures. Although EMR techniques have not been standardized for SNADETs, the approach used should be similar to that adopted for polyps in other parts of the GI tract with added consideration of the thin duodenal wall. However, it is sometimes difficult to obtain successful results by conventional EMR due to insufficient lifting after submucosal injection. A new technique, underwater endoscopic mucosal resection (UEMR) was developed recently in the United States for the treatment of SNADETs, and its usefulness has been reported[28]. Subsequently, several studies were performed in Japan[29-31] to remove SNADETs of less than 20 mm by *en bloc* resection and to reduce treatment-related complications. During UEMR, superficial lesions float up into the snare as protruding lesions, and thus, are easily snared and removed, even when lesions are flat or sessile and difficult to remove by conventional EMR[32]. Theoretically, UEMR is safe because the underwater procedure decreases thermal damage to the duodenal wall and submucosa is cut shallower than during EMR. Additionally, post-UEMR defects are small and soft, and defects are easily closed using endoclips[32]. A retrospective observational study[33] on two different types of subjects, that is, prospectively collected consecutive 104 UEMR cases and 204 EMR cases as historical controls, demonstrated that the technical success rate of UEMR was significantly higher than that of EMR. However, *en bloc* resection and R0 resection rates of UEMR were significantly lower than those of EMR, and no significant difference in adverse events was observed. Further prospective study is warranted to evaluate the efficacy of UEMR.

Duodenal lesions of > 20 mm cannot usually be removed *en bloc* by EMR. Several recent studies of the efficacy of ESD for the treatment of SNADETs have reported *en bloc* and complete resection rates of 80%–100%[6,10,11,22]. However, even experts have reported duodenal ESD complication rates of 6.6% to 31.6% for intraprocedural perforation, 0% to 14.3% for delayed perforation, and 0% to 18.4 % for delayed bleeding[10,11,22,34]. Furthermore, reported emergency surgery rates range from 3.3 to 14.3 % in this technically difficult and dangerous situation. Of course, it is preferable to resect such lesions *en bloc* using ESD but performing duodenal ESD is exceptionally difficult, as evidenced by higher complication incidences. In contrast, EMR is recognized as a safer, easier, quicker procedure, with considerably lower risks of intraprocedural perforation (0%-2.7 %), delayed perforation (0%-2.0%), and emergency surgery (2.7%-4.0 %)[12-16,18]. In addition, several other factors should be borne in mind. (1) Mucosal resection–related perforations are not as easily recognized in duodenum as in other parts of the GI tract[35], any delay in the diagnosis of iatrogenic perforation increases the risk of subsequent surgery [26]; (2) Perforation of the duodenum, particularly of the 2$^{nd}$ portion, requires immediate surgery because bile and pancreatic juice have the deleterious effects on surrounding organs; and (3) The risk of delayed perforation in duodenum is also high[9,36], and this can result in serious consequences in the absence of prompt diagnosis and surgery. Thus, the risks of perforation associated with ESD require careful consideration. Furthermore, no head-to-head comparison of the long-term adenoma recurrence–free rates of ESD and EMR has been performed to date. In our opinion, the risks associated with ESD are greater than the benefits of *en bloc* resection in some cases. Given the considerable technical skills and time required for ESD, it is not routinely recommended for the endoscopic treatment of duodenal tumors, particularly for lesions < 20 mm.

Reported bleeding rates during or after ER of SNADETs vary, in part, because of the different definitions of bleeding used, but nevertheless, are consistently greater than those reported for ER of colorectal adenomas. Ahmad *et al*[37] reported a bleeding frequency of 33% for duodenal EMR, and Lé

pilliez *et al*[16] reported a frequency of 25%. In the present study, clinically significant bleeding, which was defined as any bleeding that requires intervention, occurred in 29.3% of lesions, which is similar to the results mentioned above. Klein *et al*[21] reported a higher EMR-related bleeding rate of 43%, which was probably due to a greater proportion of large lesions (29 lesions > 40 mm) in their cohort. Most of the bleeding cases (15/16) in the present study were intraprocedural bleedings. The thin muscular layer of the duodenum is easily perforated by transmural thermal injury during hemostasis procedures, and intraprocedural bleeding is generally considered an undesirable complication. However, Lépilliez *et al* [16] did not consider it a true complication, because it can often be controlled by endoscopic clip application, ablative therapy, or adrenaline injection without serious complication. In addition, as there is no standardized definition for intraprocedural bleeding, it is difficult to determine whether reported bleeding cases in various studies were clinically significant, and therefore, discussions on the management of intraprocedural bleeding during duodenal EMR tend to subjective. Our analysis showed lesion size was significantly associated with a higher risk of EMR-related bleeding, although multivariate analysis could not preformed because there were only 17 events. Even though patients that experienced bleeding required additional hospitalization, all bleeding cases were successfully managed endoscopically, and neither surgical intervention nor interventional radiology was required.

Furthermore, no case of intraprocedural or delayed perforation was encountered, and delayed bleeding occurred only in 1 case (1.7%), which had undergone prophylactic clip placement. Forty-eight lesions (82.8%) underwent prophylactic clip placement based on perceived higher risk because we believe clip placement reduces complications by protecting mucosal defects from pancreatic juice and bile[6,13,16,18,19]. Yamamoto *et al*[22] also reported the absence of bleeding after prophylactic clipping during duodenal ER. Although a larger study is required to precisely determine the effect of prophylactic clipping, results published to date support its use based on considerations of technical difficulties associated with location, size, or scope instability[9,16,18].

Previous studies have shown that 4.8–13.5% of cases in which lesions were initially diagnosed as duodenal adenoma by biopsy were finally diagnosed as adenocarcinoma after resection[13,16]. Okada *et al*[38] reported that HGD in biopsy samples and a lesion diameter of > 2 cm predict progression to adenocarcinoma and suggested that erythematous lesions and lesions with surface nodularity present the risk of progression and recommended their removal. In the present study, EMR resulted in 1.8% of lesions (1/55) being upgraded from LGD to HGD and 3.6% of lesions (2/55) being upgraded from LGD to intramucosal adenocarcinoma. This discrepancy between biopsy samples and resected specimens suggests that relatively large adenoma lesions and adenoma lesions exhibiting surface changes are better to treated by EMR rather than APC.

The major strength of our study is that it covers a 10-year span and benefits from meticulous, long-term follow-up in terms of determining clinical outcomes regarding the safety and efficacy of EMR for SNADETs and natural history after EMR. Our findings reinforce notions that the vast majority of SNADETs can be safely and curatively resected by EMR, even when resection is piecemeal, and that larger lesions size are associated with EMR-related bleeding, which has implications for risk management and surveillance strategies.

The limitations of our study are that it was a single center, retrospective study with a relatively small sample size, and some patients were lost during follow-up to other institutions. Nevertheless, the study documents both short-term outcomes, including complications, and long-term outcomes after EMR for SNADETs.

## CONCLUSION

Summarizing, most SNADETs can be safely and effectively managed by EMR undertaken by an expert endoscopist, and EMR may be considered a first-line treatment for SNADETs due to the high incidence of fatal complications attributable to ESD in duodenum. We believe the risks of performing *en bloc* resection by ESD exceed its benefits in some cases, therefore, even piecemeal resection by EMR is a better proposition based on the excellent prognoses observed in this study.

## ARTICLE HIGHLIGHTS

### *Research background*

Superficial nonampullary duodenal epithelial tumors (SNADETs) are uncommon, but small early SNADETs are now being diagnosed more frequently, and thus, the demand for endoscopic resection (ER) has increased. However, the duodenum is the most challenging location in the gastrointestinal tract for ER.

### *Research motivation*

Duodenal lesions that require ER are limited in number, and thus, although several reports have been

published on the topic, little information is available on the long-term clinical outcomes of ER for SNADETs.

### Research objectives

The objective of this investigation was to evaluate the safety and efficacy of ER for the treatment of SNADETs and associated factors using a 10-year follow-up.

### Research methods

This retrospective analysis was conducted on 56 consecutive patients with 58 lesions who underwent endoscopic mucosal resection (EMR; 57 lesions), and snare polypectomy (one lesion) for SNADETs from January 2011 to December 2020. Patient demographics, lesion characteristics, and procedural and technical data were collected, and clinical outcomes, including procedure-related complications, completeness of resection, and recurrence were analyzed.

### Research results

Lesions consisted of 52 adenomas with low-grade dysplasia, 3 adenomas with high-grade dysplasia, and 3 intramucosal adenocarcinomas. There were 16 cases of intraprocedural bleeding (27.6%) and 1 case of delayed bleeding (1.7%), and these 17 cases were successfully managed endoscopically. No perforation or procedure-related death occurred. Larger lesion size was associated with an increased risk of EMR-related bleeding. During a median follow-up period of 23 mo (range 6–100 mo) no local recurrence occurred, despite the fact one-third of the patients (19 lesions, 32.8%) underwent piecemeal resection and 3 patients (3 lesions, 5.2%) that underwent *en bloc* resection had a pathologically determined positive lateral margin.

### Research conclusions

The majority of SNADETs can be safely and curatively resected by EMR, even when resection is piecemeal. However, larger lesions are associated with EMR-related bleeding, which has implications for risk management and surveillance strategies.

### Research perspectives

This study covers a 10-year period and benefits from meticulous, long-term follow-up in terms of determining clinical outcomes that reflect the safety and efficacy of EMR for SNADETs and natural history after EMR. Further larger-scale studies are needed to determine the long-term outcomes of ER for SNADETs.

## FOOTNOTES

**Author contributions:** Cho JH and Lee SH designed the study; Cho JH, Lim KY, and Lee EJ performed the research; Cho JH, Lim KY, and Lee EJ analyzed the data; Cho JH wrote the paper; Lee SH and Cho JH revised the manuscript.

**Institutional review board statement:** This study was performed in accordance with the Helsinki Declaration. The protocol and informed consent form used were approved beforehand by the Institutional Review Board of Yeungnam University Hospital (IRB No. 2021-10-045).

**Conflict-of-interest statement:** The authors have no conflict of interest to declare.

**Data sharing statement:** No additional data is available.



**Country/Territory of origin:** South Korea

**ORCID number:** Joon Hyun Cho 0000-0002-3584-6300; Ki Young Lim 0000-0002-9928-2559; Eun Jung Lee 0000-0003-0231-2596; Si Hyung Lee 0000-0001-7221-7506.

**S-Editor:** Ma YJ
**L-Editor:** A
**P-Editor:** Ma YJ

## REFERENCES


1 **Lim CH**, Cho YS. Nonampullary duodenal adenoma: Current understanding of its diagnosis, pathogenesis, and clinical management. *World J Gastroenterol* 2016; **22**: 853-861 [PMID: 26811631 DOI: 10.3748/wjg.v22.i2.853]
2 **Sellner F**. Investigations on the significance of the adenoma-carcinoma sequence in the small bowel. *Cancer* 1990; **66**: 702-715 [PMID: 2167140 DOI: 10.1002/1097-0142(19900815)66:4<702::aid-cncr2820660419>3.0.co;2-z]
3 **Seifert E**, Schulte F, Stolte M. Adenoma and carcinoma of the duodenum and papilla of Vater: a clinicopathologic study. *Am J Gastroenterol* 1992; **87**: 37-42 [PMID: 1728122]
4 **Galandiuk S**, Hermann RE, Jagelman DG, Fazio VW, Sivak MV. Villous tumors of the duodenum. *Ann Surg* 1988; **207**: 234-239 [PMID: 3345110 DOI: 10.1097/00000658-198803000-00002]
5 **Miller JH**, Gisvold JJ, Weiland LH, McIlrath DC. Upper gastrointestinal tract: villous tumors. *AJR Am J Roentgenol* 1980; **134**: 933-936 [PMID: 6768268 DOI: 10.2214/ajr.134.5.933]
6 **Honda T**, Yamamoto H, Osawa H, Yoshizawa M, Nakano H, Sunada K, Hanatsuka K, Sugano K. Endoscopic submucosal dissection for superficial duodenal neoplasms. *Dig Endosc* 2009; **21**: 270-274 [PMID: 19961529 DOI: 10.1111/j.1443-1661.2009.00908.x]
7 **Seo JY**, Hong SJ, Han JP, Jang HY, Myung YS, Kim C, Lee YN, Ko BM. Usefulness and safety of endoscopic treatment for nonampullary duodenal adenoma and adenocarcinoma. *J Gastroenterol Hepatol* 2014; **29**: 1692-1698 [PMID: 24720570 DOI: 10.1111/jgh.12601]
8 **Gaspar JP**, Stelow EB, Wang AY. Approach to the endoscopic resection of duodenal lesions. *World J Gastroenterol* 2016; **22**: 600-617 [PMID: 26811610 DOI: 10.3748/wjg.v22.i2.600]
9 **Inoue T**, Uedo N, Yamashina T, Yamamoto S, Hanaoka N, Takeuchi Y, Higashino K, Ishihara R, Iishi H, Tatsuta M, Takahashi H, Eguchi H, Ohigashi H. Delayed perforation: a hazardous complication of endoscopic resection for non-ampullary duodenal neoplasm. *Dig Endosc* 2014; **26**: 220-227 [PMID: 23621427 DOI: 10.1111/den.12104]
10 **Jung JH**, Choi KD, Ahn JY, Lee JH, Jung HY, Choi KS, Lee GH, Song HJ, Kim DH, Kim MY, Bae SE, Kim JH. Endoscopic submucosal dissection for sessile, nonampullary duodenal adenomas. *Endoscopy* 2013; **45**: 133-135 [PMID: 23364841 DOI: 10.1055/s-0032-1326178]
11 **Matsumoto S**, Miyatani H, Yoshida Y. Endoscopic submucosal dissection for duodenal tumors: a single-center experience. *Endoscopy* 2013; **45**: 136-137 [PMID: 22930172 DOI: 10.1055/s-0032-1310123]
12 **Abbass R**, Rigaux J, Al-Kawas FH. Nonampullary duodenal polyps: characteristics and endoscopic management. *Gastrointest Endosc* 2010; **71**: 754-759 [PMID: 20363416 DOI: 10.1016/j.gie.2009.11.043]
13 **Alexander S**, Bourke MJ, Williams SJ, Bailey A, Co J. EMR of large, sessile, sporadic nonampullary duodenal adenomas: technical aspects and long-term outcome (with videos). *Gastrointest Endosc* 2009; **69**: 66-73 [PMID: 18725157 DOI: 10.1016/j.gie.2008.04.061]
14 **Apel D**, Jakobs R, Spiethoff A, Riemann JF. Follow-up after endoscopic snare resection of duodenal adenomas. *Endoscopy* 2005; **37**: 444-448 [PMID: 15844023 DOI: 10.1055/s-2005-861287]
15 **Fanning SB**, Bourke MJ, Williams SJ, Chung A, Kariyawasam VC. Giant laterally spreading tumors of the duodenum: endoscopic resection outcomes, limitations, and caveats. *Gastrointest Endosc* 2012; **75**: 805-812 [PMID: 22305507 DOI: 10.1016/j.gie.2011.11.038]
16 **Lépilliez V**, Chemaly M, Ponchon T, Napoleon B, Saurin JC. Endoscopic resection of sporadic duodenal adenomas: an efficient technique with a substantial risk of delayed bleeding. *Endoscopy* 2008; **40**: 806-810 [PMID: 18828076 DOI: 10.1055/s-2008-1077619]
17 **Sohn JW**, Jeon SW, Cho CM, Jung MK, Kim SK, Lee DS, Son HS, Chung IK. Endoscopic resection of duodenal neoplasms: a single-center study. *Surg Endosc* 2010; **24**: 3195-3200 [PMID: 20490557 DOI: 10.1007/s00464-010-1114-y]
18 **Maruoka D**, Arai M, Kishimoto T, Matsumura T, Inoue M, Nakagawa T, Watanabe Y, Katsuno T, Tsuyuguchi T, Imazeki F, Yokosuka O. Clinical outcomes of endoscopic resection for nonampullary duodenal high-grade dysplasia and intramucosal carcinoma. *Endoscopy* 2013; **45**: 138-141 [PMID: 23322475 DOI: 10.1055/s-0032-1325799]
19 **Endo M**, Abiko Y, Oana S, Kudara N, Chiba T, Suzuki K, Koizuka H, Uesugi N, Sugai T. Usefulness of endoscopic treatment for duodenal adenoma. *Dig Endosc* 2010; **22**: 360-365 [PMID: 21175499 DOI: 10.1111/j.1443-1661.2010.01014.x]
20 **Singh A**, Siddiqui UD, Konda VJ, Whitcomb E, Hart J, Xiao SY, Ruiz MG, Koons A, Waxman I. Safety and efficacy of EMR for sporadic, nonampullary duodenal adenomas: a single U.S. center experience (with video). *Gastrointest Endosc* 2016; **84**: 700-708 [PMID: 27063918 DOI: 10.1016/j.gie.2016.03.1467]
21 **Klein A**, Nayyar D, Bahin FF, Qi Z, Lee E, Williams SJ, Byth K, Bourke MJ. Endoscopic mucosal resection of large and giant lateral spreading lesions of the duodenum: success, adverse events, and long-term outcomes. *Gastrointest Endosc* 2016; **84**: 688-696 [PMID: 26975231 DOI: 10.1016/j.gie.2016.02.049]
22 **Yamamoto Y**, Yoshizawa N, Tomida H, Fujisaki J, Igarashi M. Therapeutic outcomes of endoscopic resection for superficial non-ampullary duodenal tumor. *Dig Endosc* 2014; **26** Suppl 2: 50-56 [PMID: 24750149 DOI: 10.1111/den.12273]
23 **Nonaka S**, Saito Y, Takisawa H, Kim Y, Kikuchi T, Oda I. Safety of carbon dioxide insufflation for upper gastrointestinal tract endoscopic treatment of patients under deep sedation. *Surg Endosc* 2010; **24**: 1638-1645 [PMID: 20108154 DOI: 10.1007/s00464-009-0824-5]
24 **Tomizawa Y**, Ginsberg GG. Clinical outcome of EMR of sporadic, nonampullary, duodenal adenomas: a 10-year retrospective. *Gastrointest Endosc* 2018; **87**: 1270-1278 [PMID: 29317270 DOI: 10.1016/j.gie.2017.12.026]
25 **Na HK**, Kim DH, Ahn JY, Lee JH, Jung KW, Choi KD, Song HJ, Lee GH, Jung HY. Clinical Outcomes following Endoscopic Treatment for Sporadic Nonampullary Duodenal Adenoma. *Dig Dis* 2020; **38**: 364-372 [PMID: 32516770 DOI: 10.1159/000504249]
26 **Nonaka S**, Oda I, Tada K, Mori G, Sato Y, Abe S, Suzuki H, Yoshinaga S, Nakajima T, Matsuda T, Taniguchi H, Saito Y, Maetani I. Clinical outcome of endoscopic resection for nonampullary duodenal tumors. *Endoscopy* 2015; **47**: 129-135 [PMID: 25314330 DOI: 10.1055/s-0034-1390774]

27 **Valerii G**, Tringali A, Landi R, Boškoski I, Familiari P, Bizzotto A, Perri V, Petruzziello L, Costamagna G. Endoscopic mucosal resection of non-ampullary sporadic duodenal adenomas: a retrospective analysis with long-term follow-up. *Scand J Gastroenterol* 2018; **53**: 490-494 [PMID: 29458293 DOI: 10.1080/00365521.2018.1438508]

28 **Binmoeller KF**, Shah JN, Bhat YM, Kane SD. "Underwater" EMR of sporadic laterally spreading nonampullary duodenal adenomas (with video). *Gastrointest Endosc* 2013; **78**: 496-502 [PMID: 23642790 DOI: 10.1016/j.gie.2013.03.1330]

29 **Iwagami H**, Takeuchi Y, Yamasaki Y, Nakagawa K, Ohmori M, Matsuno K, Inoue S, Iwatsubo T, Nakahira H, Matsuura N, Shichijo S, Maekawa A, Kanesaka T, Higashino K, Uedo N, Ishihara R. Feasibility of underwater endoscopic mucosal resection and management of residues for superficial non-ampullary duodenal epithelial neoplasms. *Dig Endosc* 2020; **32**: 565-573 [PMID: 31550394 DOI: 10.1111/den.13541]

30 **Shibukawa G**, Irisawa A, Sato A, Abe Y, Yamabe A, Arakawa N, Takasaki Y, Maki T, Yoshida Y, Igarashi R, Yamamoto S, Ikeda T, Hojo H. Endoscopic Mucosal Resection Performed Underwater for Nonampullary Duodenal Epithelial Tumor: Evaluation of Feasibility and Safety. *Gastroenterol Res Pract* 2018; **2018**: 7490961 [PMID: 30158967 DOI: 10.1155/2018/7490961]

31 **Yamasaki Y**, Uedo N, Takeuchi Y, Higashino K, Hanaoka N, Akasaka T, Kato M, Hamada K, Tonai Y, Matsuura N, Kanesaka T, Arao M, Suzuki S, Iwatsubo T, Shichijo S, Nakahira H, Ishihara R, Iishi H. Underwater endoscopic mucosal resection for superficial nonampullary duodenal adenomas. *Endoscopy* 2018; **50**: 154-158 [PMID: 28962044 DOI: 10.1055/s-0043-119214]

32 **Yamasaki Y**, Uedo N, Takeuchi Y, Ishihara R, Okada H, Iishi H. Current Status of Endoscopic Resection for Superficial Nonampullary Duodenal Epithelial Tumors. *Digestion* 2018; **97**: 45-51 [PMID: 29393159 DOI: 10.1159/000484112]

33 **Kiguchi Y**, Kato M, Nakayama A, Sasaki M, Mizutani M, Tsutsumi K, Akimoto T, Takatori Y, Mutaguchi M, Takabayashi K, Ochiai Y, Maehata T, Kanai T, Yahagi N. Feasibility study comparing underwater endoscopic mucosal resection and conventional endoscopic mucosal resection for superficial non-ampullary duodenal epithelial tumor < 20 mm. *Dig Endosc* 2020; **32**: 753-760 [PMID: 31498932 DOI: 10.1111/den.13524]

34 **Hoteya S**, Yahagi N, Iizuka T, Kikuchi D, Mitani T, Matsui A, Ogawa O, Yamashita S, Furuhata T, Yamada A, Kimura R, Nomura K, Kuribayashi Y, Kaise M. Endoscopic submucosal dissection for nonampullary large superficial adenocarcinoma/adenoma of the duodenum: feasibility and long-term outcomes. *Endosc Int Open* 2013; **1**: 2-7 [PMID: 26135505 DOI: 10.1055/s-0033-1359232]

35 **Bourke MJ**. Endoscopic resection in the duodenum: current limitations and future directions. *Endoscopy* 2013; **45**: 127-132 [PMID: 23364840 DOI: 10.1055/s-0032-1326177]

36 **Kakushima N**, Kanemoto H, Tanaka M, Takizawa K, Ono H. Treatment for superficial non-ampullary duodenal epithelial tumors. *World J Gastroenterol* 2014; **20**: 12501-12508 [PMID: 25253950 DOI: 10.3748/wjg.v20.i35.12501]

37 **Ahmad NA**, Kochman ML, Long WB, Furth EE, Ginsberg GG. Efficacy, safety, and clinical outcomes of endoscopic mucosal resection: a study of 101 cases. *Gastrointest Endosc* 2002; **55**: 390-396 [PMID: 11868015 DOI: 10.1067/mge.2002.121881]

38 **Okada K**, Fujisaki J, Kasuga A, Omae M, Kubota M, Hirasawa T, Ishiyama A, Inamori M, Chino A, Yamamoto Y, Tsuchida T, Nakajima A, Hoshino E, Igarashi M. Sporadic nonampullary duodenal adenoma in the natural history of duodenal cancer: a study of follow-up surveillance. *Am J Gastroenterol* 2011; **106**: 357-364 [PMID: 21139577 DOI: 10.1038/ajg.2010.422]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 April 27; 14(4): 341-351

DOI: 10.4240/wjgs.v14.i4.341

ISSN 1948-9366 (online)

CASE REPORT

# Subacute liver and respiratory failure after segmental hepatectomy for complicated hepatolithiasis with secondary biliary cirrhosis: A case report

Wen-Juan Fan, Xiao-Jing Zou

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

**P-Reviewer:** Kanno H, Japan; Ker CG, Taiwan; Mansilla-Vivar R, Chile

**Received:** November 26, 2021
**Peer-review started:** November 26, 2021
**First decision:** January 8, 2022
**Revised:** January 17, 2022
**Accepted:** March 27, 2022
**Article in press:** March 27, 2022
**Published online:** April 27, 2022

**Wen-Juan Fan,** Department of Gastroenterology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China

**Xiao-Jing Zou,** Emergency Department/Intensive Care Unit, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China

**Corresponding author:** Xiao-Jing Zou, MD, Associate Chief Physician, Emergency Department/Intensive Care Unit, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 1095 Jiefang District, Wuhan 430030, Hubei Province, China.
ph.ggto@163.com

## Abstract

### *BACKGROUND*

Despite being a benign disease, hepatolithiasis has a poor prognosis because of its intractable nature and frequent recurrence. Nonsurgical treatment is associated with high incidences of residual and recurrent stones. Consequently, surgery *via* hepatic lobectomy or segmental hepatectomy has become the main treatment modality. Clinical management and resolution of complicated hepatolithiasis with bilateral or diffuse intrahepatic stones remain very difficult and challenging. Repeated cholangitis and calculous obstruction may result in secondary biliary cirrhosis, a limiting factor in the treatment of hepatolithiasis.

### *CASE SUMMARY*

A 53-year-old woman with a 5-year history of intermittent abdominal pain and fever was admitted to the hepatopancreatobiliary surgery department following worsening symptoms over a 3-d period. Blood tests revealed elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and total bilirubin, as well as anemia. Magnetic resonance cholangiopancreatography showed dilatation of the intrahepatic, left and right hepatic, common hepatic, and common bile ducts, and multiple short T2 signals in the intrahepatic and common bile ducts. Abdominal computed tomography showed splenomegaly and splenic varices. The diagnosis was bilateral hepatolithiasis and choledocholithiasis with cholangitis. Surgical treatment included hepatectomy of segments II and III, cholangioplasty, left hepaticolithotomy, second biliary duct exploration, choledocholithotomy, T-tube drainage, and accretion lysis. Surgical and pathological

findings confirmed secondary biliary cirrhosis. Liver-protective therapy and anti-infectives were administered. The patient developed liver and respiratory failure, severe abdominal infection, and septicemia. Eventually, her family elected to discontinue treatment.

*CONCLUSION*
Liver transplantation, rather than hepatectomy, might be a treatment option for complicated bilateral hepatolithiasis with secondary liver cirrhosis.

**Key Words:** Hepatolithiasis; Hepatectomy; Liver failure; Biliary cirrhosis; Septicemia; Case report



**Core Tip:** Treatment of complicated hepatolithiasis with bilateral intrahepatic stones is challenging. In this case of complicated hepatolithiasis with diffuse intrahepatic stones, liver imaging before surgery showed a normal morphology, but nodular and atrophic changes observed during segmental hepatectomy indicated cirrhosis. Preoperatively, the patient's liver function was Child-Pugh class B, and the presence of splenomegaly indicated decompensated liver cirrhosis. Postoperatively, the patient experienced persisting elevated total bilirubin and worsened coagulation function. The patient ultimately experienced liver failure, respiratory failure, and septicemia resulting from severe biliary infection. Further treatment was discontinued at the family's request.

**Citation:** Fan WJ, Zou XJ. Subacute liver and respiratory failure after segmental hepatectomy for complicated hepatolithiasis with secondary biliary cirrhosis: A case report. *World J Gastrointest Surg* 2022; 14(4): 341-351
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i4/341.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i4.341

## INTRODUCTION

Hepatolithiasis is defined by the presence of gallstones in all bile ducts peripheral to the confluence of the right and left hepatic ducts, regardless of the coexistence of gallstones in other parts of the biliary tract[1]. It is prevalent primarily in Southeast Asia and in the southeastern coastal regions of China[2]. Obstruction caused by stones can lead to serious complications, including bile duct inflammation, liver cirrhosis, liver atrophy, or malignant transformation, and these contribute to hepatolithiasis being the most common cause of death among the nonmalignant diseases of the biliary tract[3]. As such, aggressive treatment is needed for all cases.

Although nonsurgical techniques are effective in resolving cholestasis and providing temporary relief (*via* removal) of stones, they cannot completely clear a sclerotic hepatobiliary system and may predispose the patient to subsequent recurrence. Hepatectomy has become a primary treatment for hepatolithiasis, applied most often to unilobar, particularly left-sided, hepatolithiasis[4]. Despite recent improvements in surgical and nonsurgical management of hepatolithiasis, difficulties remain in the treatment of complicated hepatolithiasis with bilateral stones. Surgery is still the mainstay of the treatment for complex hepatolithiasis cases. However, secondary biliary cirrhosis develops in 6.0%-7.4% of patients, and more than half experience moderate to severe Child-Pugh class B or C liver dysfunction [5]. The secondary biliary cirrhosis itself may further complicate treatment of the underlying hepatolithiasis. Herein, we present a patient with complicated bilateral hepatolithiasis and secondary biliary cirrhosis who failed treatment after undergoing segmental hepatectomy.

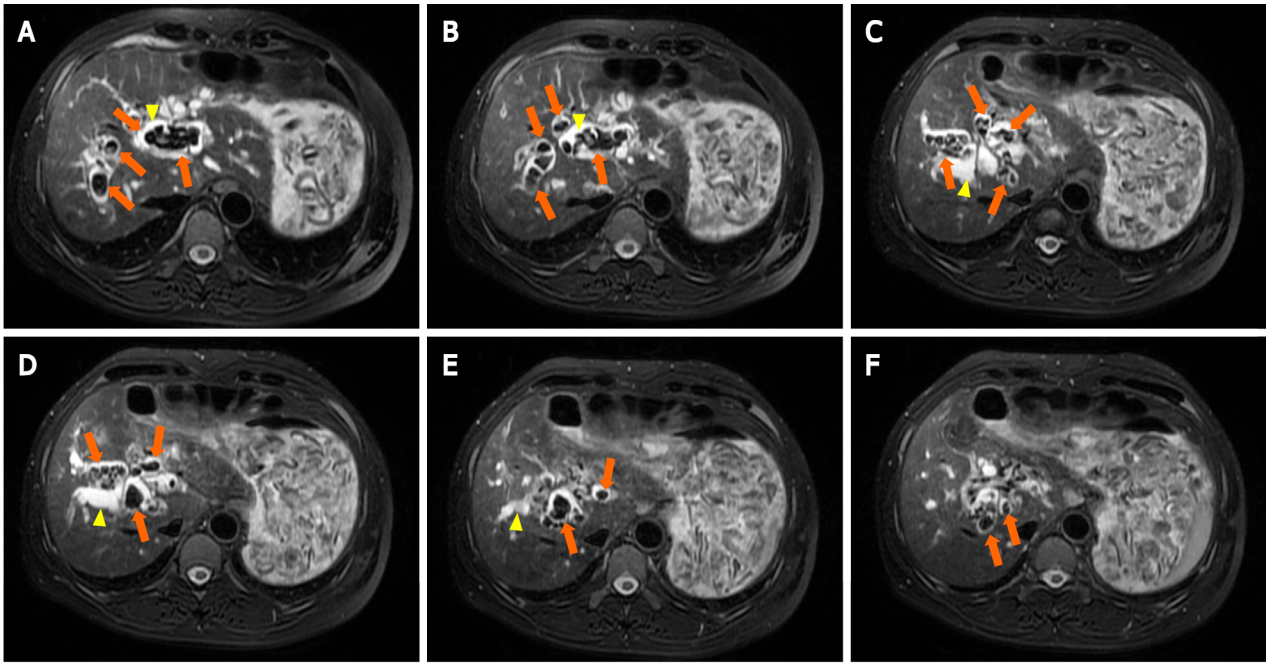
## CASE PRESENTATION

### *Chief complaints*

On July 30, 2021, a 53-year-old woman presented at the hepatopancreatobiliary surgery department of our hospital, complaining of intermittent abdominal pain with fever that she had experienced for 5 years but which had worsened over the previous 3 d.

### *History of present illness*

The patient reported having developed intermittent abdominal pain with fever 5 years previously, describing the symptoms as having appeared every 2 or 3 mo over that time. She denied nausea, vomiting, or diarrhea during that time. In the immediate 3 d before her admission to our department,




**DOI:** 10.4240/wjgs.v14.i4.341 

**Figure 1 Preoperative magnetic resonance cholangiopancreatography.** A-C: Representative multiple short T2 signals in the intrahepatic and common bile ducts (orange arrows), and obvious intrahepatic duct, left and right hepatic duct dilatation (yellow arrows); D-F: Representative multiple short T2 signals in the intrahepatic and common bile ducts (orange arrows), and obvious intrahepatic duct and left and right hepatic duct dilatation (yellow arrows).

her symptoms had worsened, presenting with hyperpyrexia and chills that were accompanied by jaundice.

### History of past illness

The patient had undergone a cholecystectomy 8 years prior. She had no history of other chronic diseases.

### Personal and family history

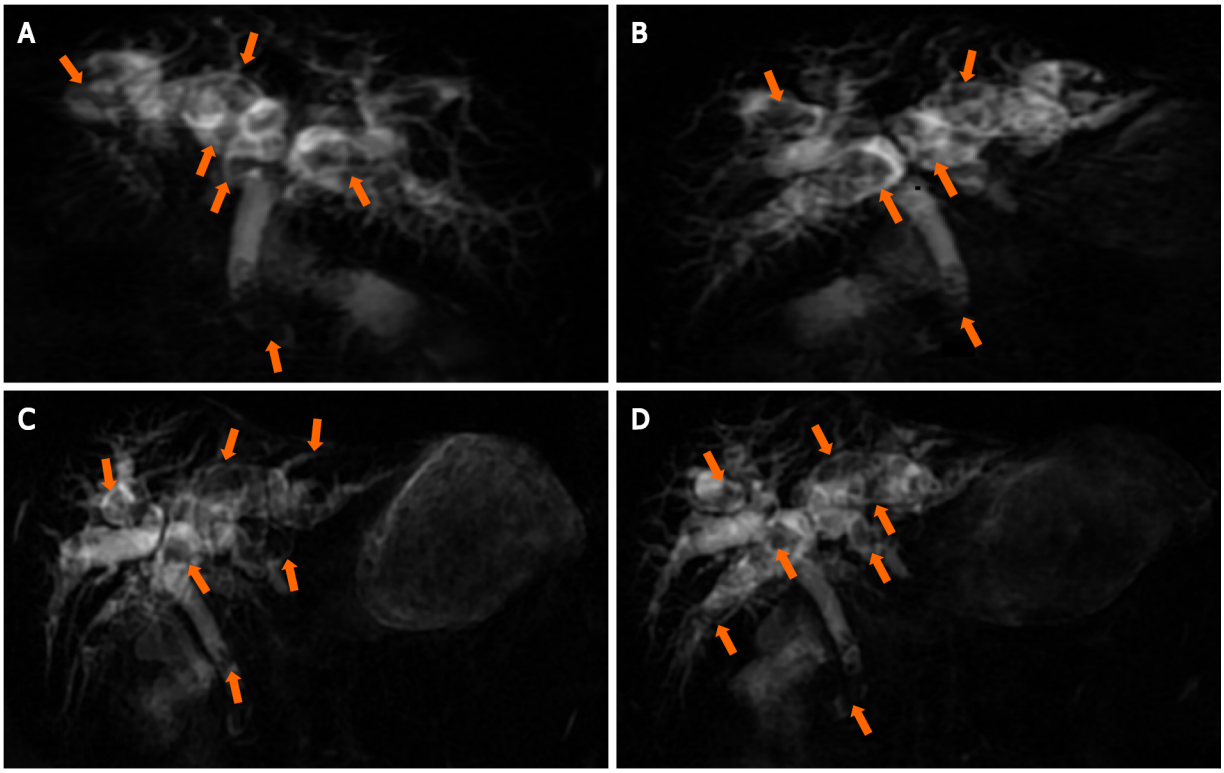
The patient had no history of smoking or drinking. She denied a history of allergies and her family history was unremarkable.

### Physical examination

At admission, the patient's temperature was 39.0 °C, heart rate was 104 beats *per* min, respiratory rate was 21 breaths *per* min, and blood pressure was 117/85 mmHg. She had a yellow coloration to her overall skin and sclera. Abdominal examination revealed tenderness in the right quadrant, without rebound tenderness. Lung and heart examinations were normal.

### Laboratory examinations

Blood workup in anticipation of surgical intervention revealed a normal white blood cell (WBC) count ($4.01 \times 10^9$ cells/L), moderate anemia (hemoglobin of 80.0 g/L; normal range: 115.0-150.0 g/L), hypoproteinemia (25.3 g/L; normal range: 35.0-52.0 g/L), and elevated levels of alanine aminotransferase (ALT) (39 U/L; normal range: ≤ 33 U/L), aspartate aminotransferase (AST) (141 U/L; normal range: ≤ 32 U/L), total bilirubin (TBIL) (185.4 μmol/L; normal range: ≤ 21 μmol/L), direct bilirubin (DBIL) (146.3 μmol/L; normal range: ≤ 8 μmol/L), alkaline phosphatase (ALP) (162 U/L; normal range: 35-102 U/L), and γ-glutamyl transpeptidase (γ-GT) (135 U/L; normal range: 6-42 U/L). The coagulation markers were within normal range [prothrombin time (PT), 13.6 s; normal range: 11.5-14.5 s] and tests for hepatitis B and C were negative. The patient's Child-Pugh score was 7, indicating class B. Six days after surgery (August 12, 2021), her TBIL reached a peak of 357 μmol/L; her DBIL was 255.5 μmol/L, ALP was 167 U/L, and γ-GT was 47 U/L. Eight days after surgery (August 14, 2021), arterial blood gas analysis showed a pH of 7.410, $PaO_2$ of 66.3 mmHg, and $PaCO_2$ of 43.9 mmHg, indicating acute respiratory distress syndrome. Ten days after surgery (August 16, 2021), the WBC count reached a peak of $29.81 \times 10^9$/L, with 90.7% of neutrophils, and elevated high-sensitivity C-reactive protein (103.7 mg/L; normal range: < 1 mg/L) was detected. Sixteen days after surgery (August 22, 2021), PT reached a peak of 19.5 s; her prothrombin activity (PTA) (normal range: 75.0%-125.0%) was 51%, international normalized ratio (INR) (normal range: 0.80-1.20) was 1.69, and activated partial thromboplastin time was 23.7 s (normal




**DOI:** 10.4240/wjgs.v14.i4.341 

**Figure 2 Preoperative multiplanar reconstruction magnetic resonance cholangiopancreatography.** A and B: Representative multiple short T2 signals in the intrahepatic duct common bile duct (orange arrows); C and D: Representative multiple short T2 signals in the intrahepatic duct common bile duct (orange arrows).

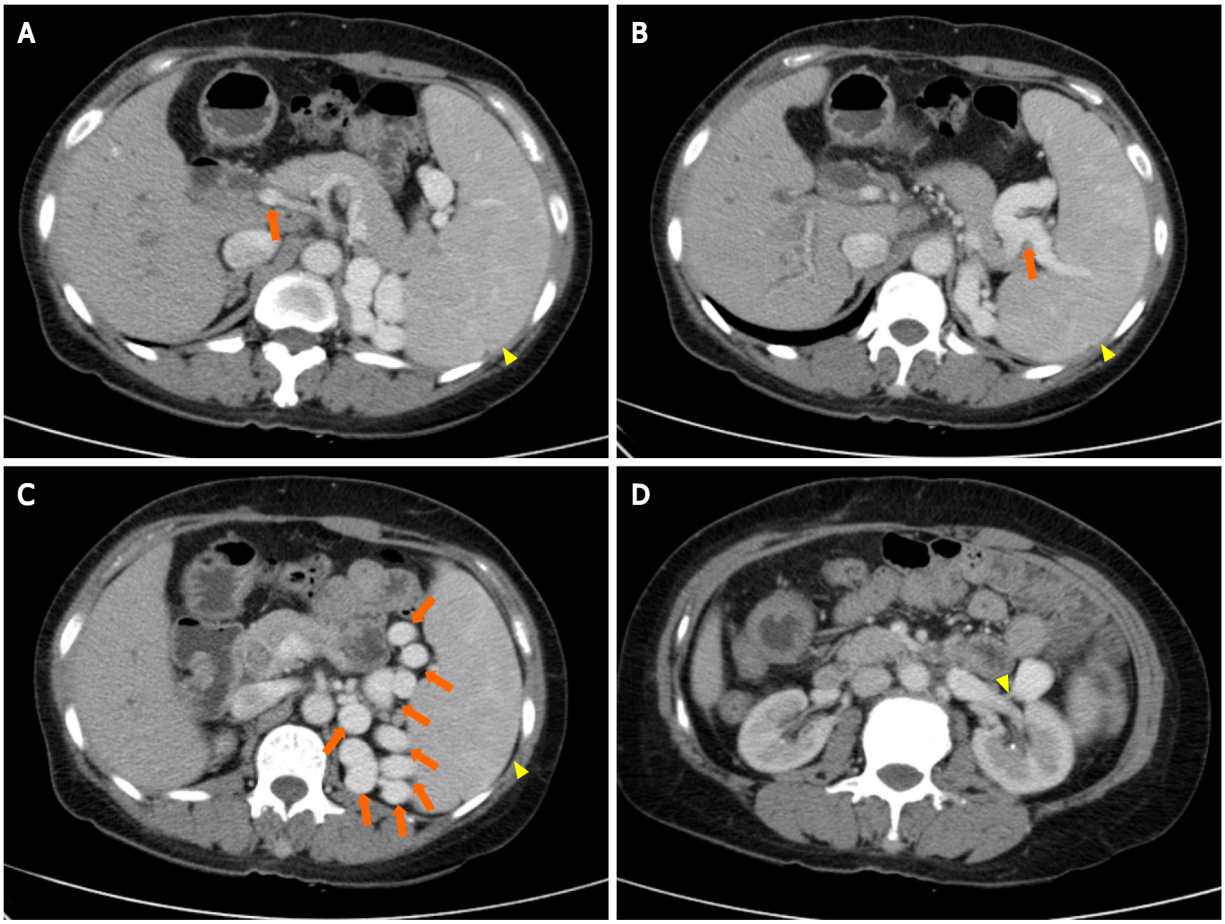
range: 29.0-42.0 s). Autoimmune hepatitis-associated antibody tests were negative for anti-mitochondrial antibody and weakly positive for anti-soluble liver antigen antibody. T-tube drainage fluid was Rivalta (+), with a karyocyte count of 1600 × $10^6$ cells/L and neutrophil percentage of 62%. Twenty-five days after surgery (August 31, 2021), her blood ammonia level peaked, at 70 μmol/L.

Eleven days after surgery (August 17, 2021), the T-tube drainage fluid and subcutaneous drainage fluid cultures tested positive for *Enterococcus faecalis* and *Candida parapsilosis*; sputum cultures were also positive for *Candida parapsilosis*. Eighteen days after surgery (August 24, 2021), cultures of sputum and catheter fluid (sensitive to piperacillin/tazobactam and amikacin) and blood (sensitive to piperacillin/tazobactam and cefepime) were positive for *Pseudomonas aeruginosa*.

### *Imaging examinations*

Magnetic resonance cholangiopancreatography in anticipation of surgical intervention showed normal liver volume and left-to-right lobe proportion but splenomegaly and splenic varices. The gallbladder (removed 8 years prior) was absent from the imaging view, and the pancreas appeared normal. Magnetic resonance imaging revealed dilatation of the intrahepatic, left and right hepatic, common hepatic, and common bile ducts, and multiple short T2 signals in the intrahepatic and common bile ducts. Figure 1 shows the intrahepatic duct dilatation and multiple short T2 signals in the intrahepatic duct, which indicated multiple stones. Multiplanar reconstruction also showed multiple short T2 signals in the intrahepatic and common bile ducts (Figure 2). Abdominal and pelvic contrast-enhanced computed tomography (CT) showed multiple nodular high-density shadows in the intrahepatic and extrahepatic bile ducts, with the largest ones up to 8 mm in length. Contrast-enhanced CT also showed intrahepatic and extrahepatic bile ducts dilatation, portal vein narrowing, splenomegaly (Figure 3A), splenic varices (Figure 3B), collateral circulation expansion (Figure 3C), and spontaneous spleno-renal shunting (Figure 3D).

At day 6 postoperatively (August 12, 2021), abdominal CT showed multiple nodular high-density shadows in the right hepatic and common bile ducts with intrahepatic and extrahepatic bile duct dilatation (Figure 4). Eight days after surgery (August 14, 2021), a bedside chest X-ray showed bilateral pulmonary diffuse patchy high-density shadows and bilateral pleural effusion, which indicated bilateral pulmonary infection (Figure 5A). Fourteen days after surgery (August 20, 2021), chest CT showed bilateral pulmonary nodular and patchy shadows and left pulmonary atelectasis, indicating pulmonary infection (Figure 5B–D). Pathology findings following evaluation of a 13 cm × 6.5 cm × 5 cm liver specimen included dilatation of multiple intrahepatic ducts, with a maximum diameter of 2 cm and




**DOI:** 10.4240/wjgs.v14.i4.341 

**Figure 3 Preoperative abdominal and pelvic contrast-enhanced computed tomography images.** A: Narrowed portal vein (orange arrow) and splenomegaly (yellow arrow); B: Splenic varices (orange arrow) and splenomegaly (yellow arrow); C: Collateral circulation expansion (orange arrows) and splenomegaly (yellow arrow); D: Spontaneous spleno-renal shunt (yellow arrow).

containing multiple, brown stones. Histopathology included intrahepatic duct dilatation with stones and inflammatory cell infiltration of the bile duct walls (Figure 6). Proliferation of fibrous tissue in portal tracts divided the liver parenchyma into irregular regenerative nodules (pseudolobules) that had lost the normal architecture and central veins (Figure 7A–C). Hepatic cords were poorly arranged in foci, with two layers of cells and enlarged cells that included binucleate forms (Figure 7D–F).

## MULTIDISCIPLINARY EXPERT CONSULTATION

### *Doctor Yu, Associate Chief Physician, MD, Respiratory Department*

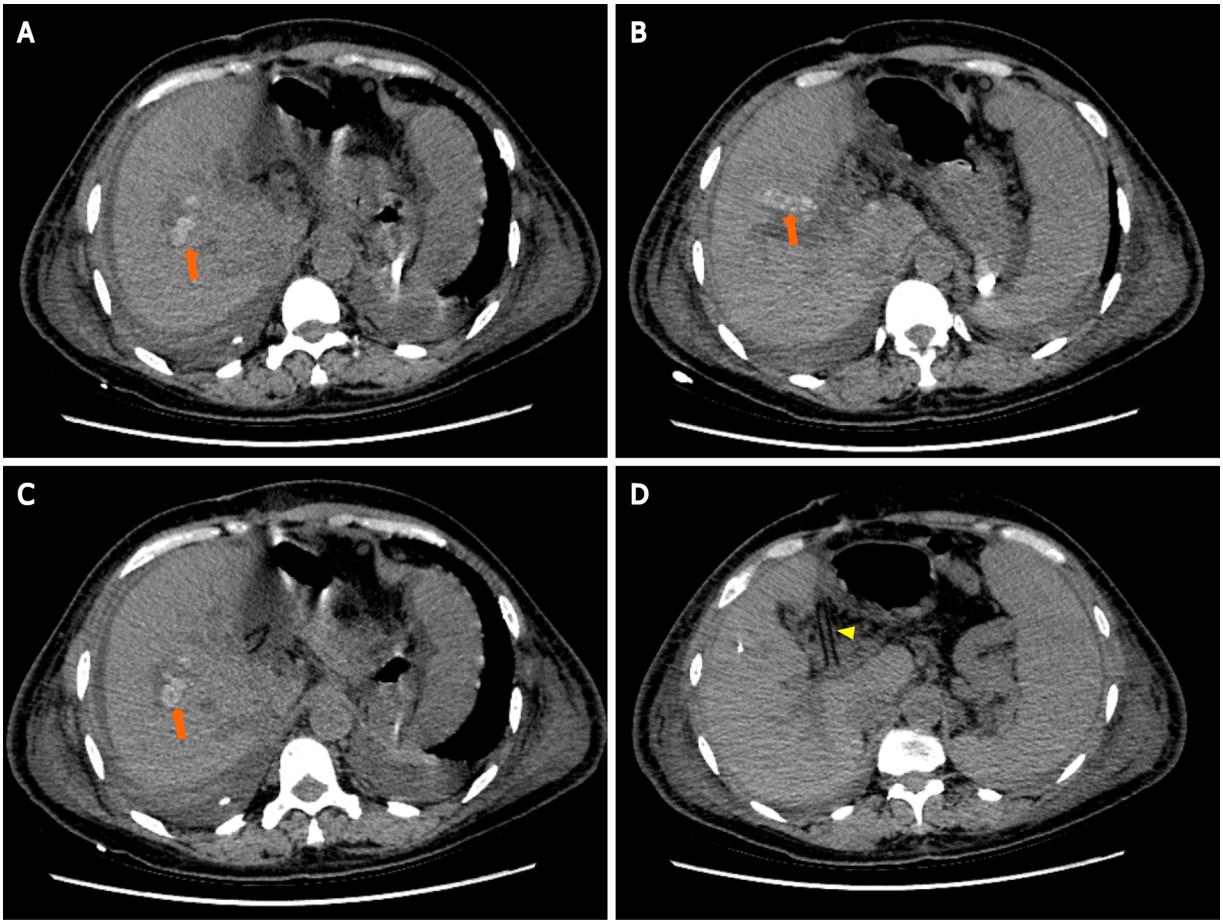
The systemic infection is severe, the current anti-infective treatments are effective, and respiratory support therapy should be continued.

### *Doctor Ding, Associate Chief Physician, MD, Infectious Disease Department*

The patient's TBIL has not declined with treatment and the pulmonary infection is severe, indicating a poor prognosis. Sputum, catheter, and blood cultures are positive for *Pseudomonas aeruginosa*, indicating hematogenous spread. The catheter should be replaced. If the infection cannot be controlled, fosfomycin can be added. The persisting elevated TBIL is related to surgery, biliary tract infection, and obstruction. Percutaneous transhepatic cholangial drainage may be useful.

### *Doctor Zhu, Chief Physician, MD, Hepatopancreatobiliary Surgery Department*

The T-tube is open and the current drug treatments should be continued. There is no indication for a second surgery.




**DOI:** 10.4240/wjgs.v14.i4.341 

**Figure 4 Postoperative abdominal computed tomography images.** A-C: Representative multiple nodular high-density shadows in the right hepatic duct (orange arrows); D: Drainage tube (yellow arrow).

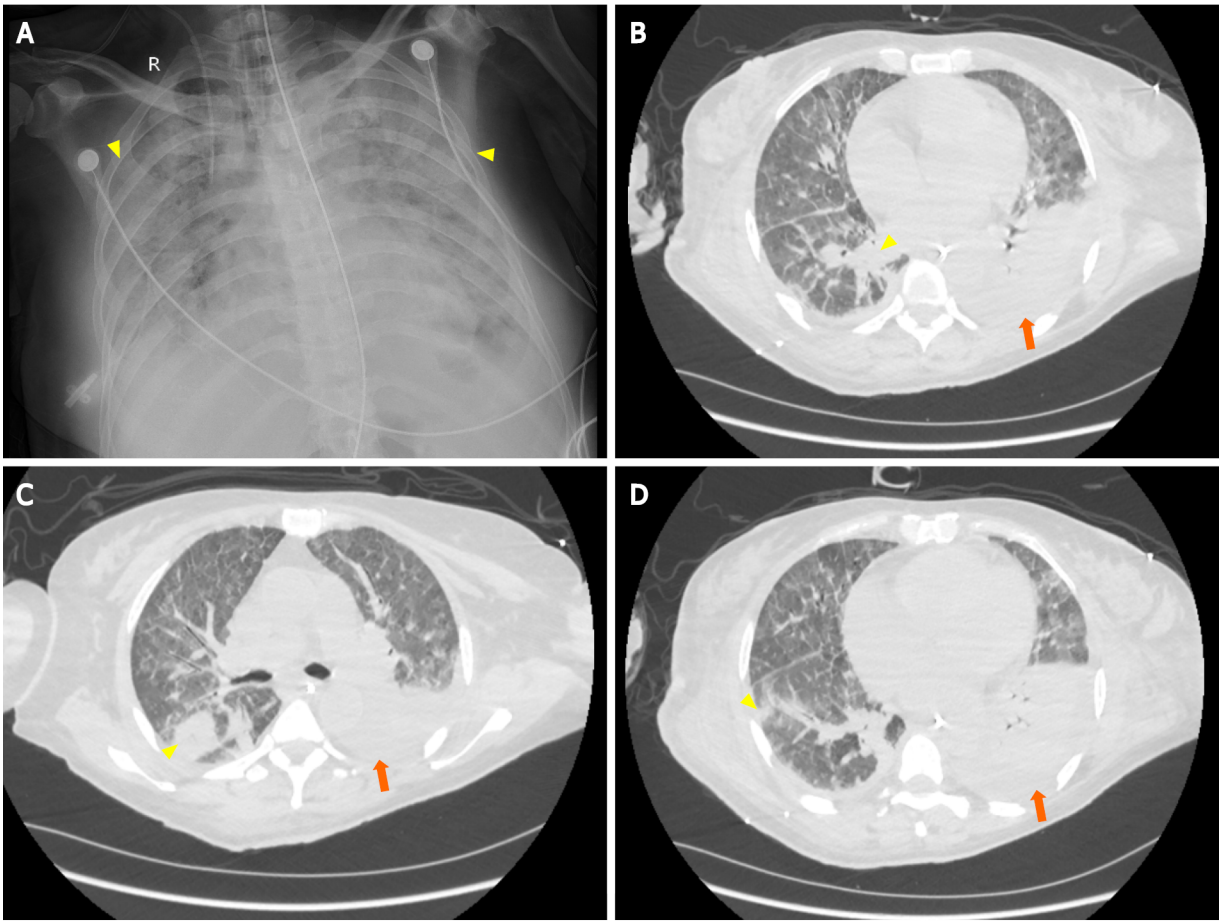
## FINAL DIAGNOSIS

Bilateral hepatolithiasis and choledocholithiasis with cholangitis (after partial hepatectomy), subacute liver failure, secondary biliary cirrhosis, splenomegaly, splenic varices, type 1 respiratory failure, severe pneumonia, septicemia (*Pseudomonas aeruginosa*), abdominal infection, anemia, and hypoproteinemia.

## TREATMENT

After admission, polyene phosphatidylcholine (465 mg), ademetionine 1,4-butanedisulfonate (1 g), and glycine cysteine sodium chloride (200 mL) were given once a day (QD) as liver-protective therapy. Ceftriaxone sodium and tazobactam sodium (2 g) were given two times a day (BID) for 3 d as anti-infective treatment. On August 6, 2021, hepatectomy of segments II and III, cholangioplasty, left hepaticolithotomy, second biliary duct exploration, choledocholithotomy, T-tube drainage, and accretion lysis were performed. During surgery, stones were palpable in the common bile duct and left lateral lobe of the liver. The liver showed nodular and atrophic changes, which indicated cirrhosis. After surgery, hepatocyte growth-promoting factor (60 μg), acetylcysteine (8 g), and reduced glutathione (1.8 g) were given QD for liver protection. Ambroxol hydrochloride (60 mg) and doxofylline (0.3 g) were given BID to promote expectoration drainage. Imipenem and cilastatin sodium [0.5 g every 8 h (q8h)] and linezolid and glucose [0.6 g every 12 h (q12h)] were given as anti-infective treatment from August 7-10, 2021 and were then switched to meropenem (1 g) and tigecycline (50 mg q8h) from August 11-13, 2021.

On August 10, 2021, the patient developed dyspnea, decreased oxygen saturation, and a continuously increasing level of TBIL. Considering pulmonary infection and liver failure, the patient was transferred to the infectious disease department on August 13, 2021. The anti-infective treatments were changed to meropenem (1 g q8h), teicoplanin (400 mg QD), and voriconazole (0.2 g q12h). On August 14, 2021, the patient developed tachypnea with bilateral moist rales. The arterial $PaO_2$ dropped to 66.3 mmHg and the $PaCO_2$ increased to 43.9 mmHg. Tracheal intubation was performed, and the patient was transferred to the intensive care unit (ICU). A single dose of methylprednisolone (40 mg) was given, and fiberoptic




**DOI:** 10.4240/wjgs.v14.i4.341 

**Figure 5 Postoperative pulmonary imaging.** A: Bedside chest X-ray (August 14, 2021) showing bilateral pulmonary diffuse patchy high-density shadows (yellow arrows) and bilateral pleural effusion, indicating bilateral pulmonary infection; B-D: Representative chest computed tomography (August 20, 2021) images showing bilateral pulmonary nodular and patchy shadows (yellow arrows) and left pulmonary atelectasis (orange arrows), indicating pulmonary infection.

bronchoscopy was performed to aspirate sputum. In the ICU, anti-infective treatment included meropenem (1 g q8h) given from August 15-17, 2021, imipenem and cilastatin sodium (0.5 g q8h) given from August 17-22, 2021, piperacillin sodium and tazobactam sodium (4.5 g q6h) given from August 24-28, 2021, amikacin (0.4 g q12h) given from August 24-29, 2021, ceftazidime (1 g q8h) given from August 28 to September 1, 2021, polymyxin B sulfate (75 wu q12h) given from August 29 to September 1, 2021, tigecycline (50 mg q8h) given from August 15 to 23, 2021, vancocin (1000 mg BID) given from August 22 to 30, 2021, voriconazole (0.2 g q12h) given from August 18 to 24, 2021, and micafungin sodium (100 mg QD) given from August 24 to September 1, 2021. Ventilator support was provided, and the patient was given packed red blood cell and fresh frozen plasma transfusions; noradrenaline bitartrate was given to maintain blood pressure.

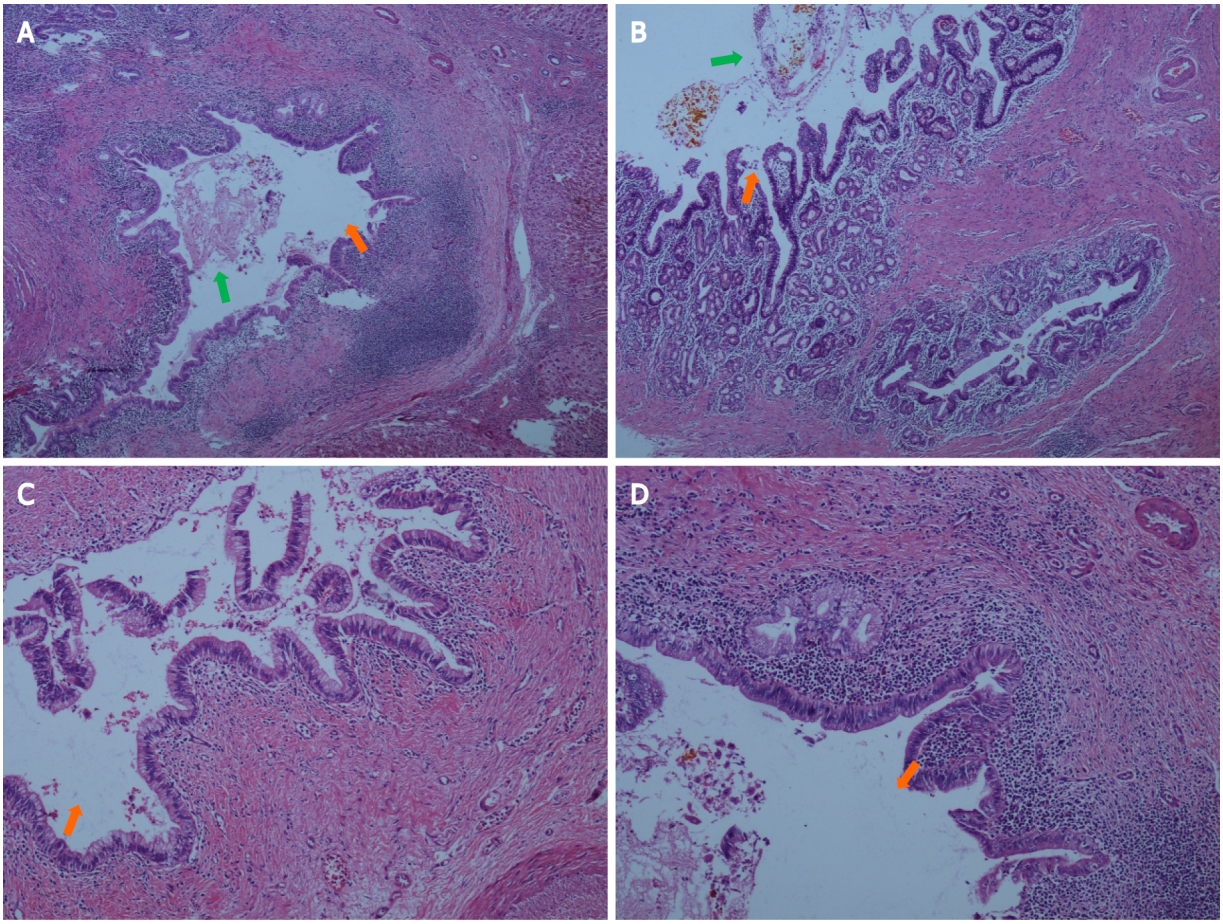
On August 25, 2021, the patient was successfully extubated and given high flow nasal oxygen. On August 26, 2021, artificial liver support therapy and plasmapheresis were performed. On August 27, 2021, the patient was reintubated because of disturbance of consciousness and decreased oxygen saturation.

## OUTCOME AND FOLLOW-UP

Sputum, catheter fluid, and blood cultures were positive for *Pseudomonas aeruginosa*. The patient's TBIL continued to increase after surgery and her coagulation function worsened. Her family elected to discontinue treatment because of severe infection, septicemia, and liver and respiratory failure.

## DISCUSSION

Hepatolithiasis is a disease of unknown etiology that seriously impacts patient health and quality of life,



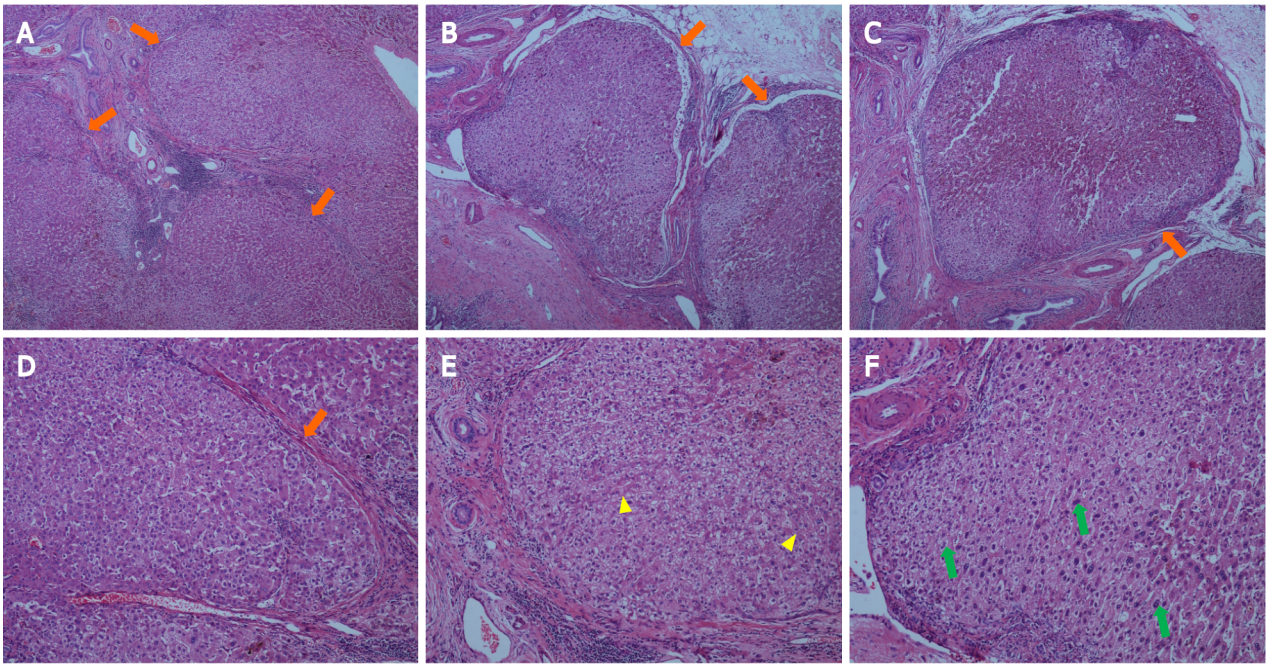

**DOI:** 10.4240/wjgs.v14.i4.341 **Copyright** ©The Author(s) 2022.

**Figure 6 Histopathological findings of the resected liver (intrahepatic duct).** A and B: Representative specimens showing intrahepatic duct dilatation (orange arrows) with stones (green arrows) and inflammatory cell infiltration in bile duct walls (hematoxylin and eosin staining; 40 ×); C and D: Representative specimens showing intrahepatic duct dilatation (orange arrows) with stones and inflammatory cell infiltration in bile duct walls (hematoxylin and eosin staining; 100 ×).

with a reported morbidity of 20%–50% in patients who undergo cholecystectomy[6]. Our patient had undergone cholecystectomy 8 years prior to presentation at our department. Since her autoimmune hepatitis-associated antibodies were not sufficiently elevated to support a diagnosis of autoimmune liver disease, we hypothesize that the etiology of her presenting hepatolithiasis may have been related to her history of cholecystectomy.

Complete stone clearance, restoration of normal bile flow, and excision of diseased hepatic parenchyma are the goals of hepatolithiasis treatment. In the last decade, advances in nonsurgical and surgical treatments have resulted in improvement of the management of the disease, but such nonsurgical treatments as percutaneous transhepatic and peroral cholangioscopic lithotripsy are associated with high rates of residual and recurrent stones[7]. Hepatectomy, mainly segmental hepatectomy, is an effective surgical treatment that can remove stones, diseased bile ducts, and damaged hepatic parenchyma[8]. However, hepatectomy is applied most often to cases of unilobar, particularly left-sided, hepatolithiasis[4]. Hepatolithiasis involving two or more lobes is challenging because diffuse intrahepatic stones in bilateral intrahepatic ducts are difficult to clear, strictures may be present in the remaining liver, and calculus extraction may be incomplete. Hepatectomy for bilateral hepatolithiasis is controversial, as patients may not tolerate resection of multiple liver segments. Therefore, bile duct exploration and choledochoscopic lithotomy combined with a reduced hepatectomy were essential. Some studies have reported resection of the dominantly-affected side, followed by postoperative cholangioscopic lithotomy[9]. Right hepatic lobectomy is usually avoided because of the increased risk involved. Our patient was treated with a left-sided segmental hepatectomy, and stones remaining in the right hepatic duct after surgery can be seen in Figure 4. Bilateral hepatolithiasis deserves to be considered as a distinct disease.

Although imaging evaluation showed that the patient's liver morphology was relatively normal, splenomegaly and splenic varices indirectly indicated portal hypertension. The surgical and pathological findings confirmed secondary biliary cirrhosis. Established liver cirrhosis has been reported in 10%–15% of patients with hepatolithiasis at the initial presentation[10], and secondary biliary cirrhosis has been reported to develop 7 years after the onset of obstruction and 4.5 years after a




**DOI:** 10.4240/wjgs.v14.i4.341 

**Figure 7 Histopathological findings in the resected liver (liver parenchyma).** A-C: Representative specimens showing proliferation of fibrous tissue in portal tracts dividing the liver parenchyma into irregular regenerative nodules (pseudolobules, orange arrows) that have lost the normal structure, and central veins (hematoxylin and eosin staining; 40 ×); D-F: Representative specimens showing pseudolobules (orange arrow) hepatic cords arranged irregularly, with foci of two layers of cells (yellow arrows), and large, occasionally binucleate cells (green arrows; hematoxylin and eosin staining; 100 ×).

calculous obstruction[11]. Our patient had intermittent abdominal pain with fever for 5 years and her liver function on admission was Child-Pugh class B (*i.e.* decompensated liver cirrhosis), which was consistent with the reported prognosis. Patients with secondary biliary cirrhosis may be prone to postoperative sepsis and at increased risk of postprocedural complications. Previous studies have reported that 10%–30% of patients with cirrhosis developed bacterial infections after abdominal surgery [12], which may have been related to impaired immune defense mechanisms of the liver. As the prognosis is better and the feasibility of aggressive management is greater in patients with Child-Pugh class A than class B or C status, we believe that hepatolithiasis should be managed early, before the development of secondary biliary cirrhosis. Hepatolithiasis combined with secondary biliary cirrhosis was frequently found and we have to pay attention and try to prevent the occurrence of hepatic failure after surgery especially in the jaundiced patient.

There are no widely accepted guidelines for treating patients with terminal hepatolithiasis. According to the classification described by Feng *et al*[13], our patient had Type IIc disease with diffuse stones, biliary cirrhosis, and portal hypertension. Liver transplantation is recommended for such patients[13]. The indications for liver transplantation include end-stage decompensated liver cirrhosis and/or liver failure, compensated cirrhosis or non-cirrhosis in patients with diffusely distributed intrahepatic calculi, and/or multiple hepatobiliary stenoses that cannot be cured by other surgical and nonsurgical procedures[14]. Our patient was suitable for liver transplantation, which has a reported 1-year survival of 100% and 5-year survival of 73%[15]. However, because of the critical shortage of cadaveric livers, grafts are preferentially provided to those with the highest likelihood of death without transplantation. Owing to the limited understanding of patients and doctors about liver transplantation for hepatolithiasis, few patients have received liver transplants[15]. Terminal hepatolithiasis, especially when combined with portal hypertension and previous right upper quadrant surgery, may make the transplantation procedure difficult. Thus, selecting patients for transplantation before they reach end-stage disease is important. However, the imaging before surgery did not show signs of liver cirrhosis and it was until the surgery that surgeons found that the liver showed nodular and atrophic changes indicating cirrhosis. Besides, in China, liver transplantation was mostly for end-stage liver cirrhosis and it was not easy to get access to liver donors since the patient's general conditions were relatively good compared to patients with end-stage liver cirrhosis. Therefore, the surgeons did not discuss liver transplantation with the patient before surgery.

Surgery failed to rescue our patient. One of the reasons was infection. The patient suffered from abdominal infection derived from bile duct and pulmonary infection, resulting in respiratory failure and septicemia. The primary cause of death after hepatectomy is reported to be uncontrollable septicemia [7], and positive bile cultures have been reported in 83.3% of patients with hepatolithiasis[12], which is higher than the incidence of surgical site infections after hepatectomy for hepatocellular carcinoma[12].

Sepsis must thus be effectively controlled before hepatectomy in patients with hepatolithiasis. Another reason for patient death is liver failure. The maximum TBIL of our patient was 10-times higher than the upper limit of normal and her maximum INR was 1.69. The guidelines for diagnosis and treatment of liver failure suggest that patients with a TBIL level of more than 10-times normal and a PTA ≤ 40% or an INR ≥ 1.5 can be diagnosed with liver failure[16]. The reasons for liver failure in our patient were related to liver resection and the abnormal function of the remaining liver.

## CONCLUSION

The management of complicated bilateral hepatolithiasis is challenging, and segmental hepatectomy is unable to completely remove all the intrahepatic ductal stones. It is important to effectively control biliary tract infection before surgical procedures. Liver transplantation rather than hepatectomy may be considered as an option in complicated bilateral hepatolithiasis with secondary liver cirrhosis.

## FOOTNOTES

**Author contributions:** Fan WJ reviewed the literature and contributed to manuscript drafting and imaging data interpretation; Zou XJ was responsible for revising the manuscript for important intellectual content; all authors provided approval of the final version for submission and publication.

**Informed consent statement:** Informed written consent was obtained from family members of the patient for publication of this report and any accompanying images.

**Conflict-of-interest statement:** The authors declare that they have no conflicting interests to disclose.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).



**Country/Territory of origin:** China

**ORCID number:** Wen-Juan Fan 0000-0002-2927-9266; Xiao-Jing Zou 0000-0002-2897-0709.

**S-Editor:** Fan JR
**L-Editor:** Wang TQ
**P-Editor:** Fan JR

## REFERENCES

1 **Liu B**, Cao PK, Wang YZ, Wang WJ, Tian SL, Hertzanu Y, Li YL. Modified percutaneous transhepatic papillary balloon dilation for patients with refractory hepatolithiasis. *World J Gastroenterol* 2020; **26**: 3929-3937 [PMID: 32774067 DOI: 10.3748/wjg.v26.i27.3929]
2 **Kim HJ**, Kim JS, Joo MK, Lee BJ, Kim JH, Yeon JE, Park JJ, Byun KS, Bak YT. Hepatolithiasis and intrahepatic cholangiocarcinoma: A review. *World J Gastroenterol* 2015; **21**: 13418-13431 [PMID: 26730152 DOI: 10.3748/wjg.v21.i48.13418]
3 **Cheon YK**, Cho YD, Moon JH, Lee JS, Shim CS. Evaluation of long-term results and recurrent factors after operative and nonoperative treatment for hepatolithiasis. *Surgery* 2009; **146**: 843-853 [PMID: 19744434 DOI: 10.1016/j.surg.2009.04.009]
4 **Nuzzo G**, Clemente G, Giovannini I, De Rose AM, Vellone M, Sarno G, Marchi D, Giuliante F. Liver resection for primary intrahepatic stones: a single-center experience. *Arch Surg* 2008; **143**: 570-3; discussion 574 [PMID: 18559750 DOI: 10.1001/archsurg.143.6.570]
5 **You MS**, Lee SH, Kang J, Choi YH, Choi JH, Shin BS, Huh G, Paik WH, Ryu JK, Kim YT, Jang DK, Lee JK. Natural Course and Risk of Cholangiocarcinoma in Patients with Recurrent Pyogenic Cholangitis: A Retrospective Cohort Study. *Gut Liver* 2019; **13**: 373-379 [PMID: 30600674 DOI: 10.5009/gnl18339]
6 **Catena M**, Aldrighetti L, Finazzi R, Arzu G, Arru M, Pulitanò C, Ferla G. Treatment of non-endemic hepatolithiasis in a Western country. The role of hepatic resection. *Ann R Coll Surg Engl* 2006; **88**: 383-389 [PMID: 16834860 DOI: 10.1308/003588406X98711]
7 **Jan YY**, Chen MF, Wang CS, Jeng LB, Hwang TL, Chen SC. Surgical treatment of hepatolithiasis: long-term results.

*Surgery* 1996; **120**: 509-514 [PMID: 8784405 DOI: 10.1016/s0039-6060(96)80071-7]

8 **Qiao O**, Hu P, Jin Y. Hepatic lobectomy and segmental resection of liver for hepatolithiasis. *West Indian Med J* 2014; **63**: 176-178 [PMID: 25303254 DOI: 10.7727/wimj.2013.015]

9 **Uenishi T**, Hamba H, Takemura S, Oba K, Ogawa M, Yamamoto T, Tanaka S, Kubo S. Outcomes of hepatic resection for hepatolithiasis. *Am J Surg* 2009; **198**: 199-202 [PMID: 19249730 DOI: 10.1016/j.amjsurg.2008.08.020]

10 **Strong RW**, Chew SP, Wall DR, Fawcett J, Lynch SV. Liver transplantation for hepatolithiasis. *Asian J Surg* 2002; **25**: 180-183 [PMID: 12376243 DOI: 10.1016/S1015-9584(09)60170-6]

11 **Scheuer PJ**. Biliary disease and cholestasis. In: Scheuer PJ, editor. Liver biopsy interpretation. 4th ed. London: Baillere Tindall, 1988: 40-65

12 **Uchiyama K**, Ueno M, Ozawa S, Kiriyama S, Kawai M, Hirono S, Tani M, Yamaue H. Risk factors for postoperative infectious complications after hepatectomy. *J Hepatobiliary Pancreat Sci* 2011; **18**: 67-73 [PMID: 20676699 DOI: 10.1007/s00534-010-0313-1]

13 **Feng X**, Zheng S, Xia F, Ma K, Wang S, Bie P, Dong J. Classification and management of hepatolithiasis: A high-volume, single-center's experience. *Intractable Rare Dis Res* 2012; **1**: 151-156 [PMID: 25343089 DOI: 10.5582/irdr.2012.v1.4.151]

14 **Ali JM**, See TC, Wiseman O, Griffiths WJ, Jah A. Salvage of liver transplant with hepatolithiasis by percutaneous transhepatic cholangioscopic hepatolithotomy. *Transpl Int* 2014; **27**: e126-e128 [PMID: 24964398 DOI: 10.1111/tri.12387]

15 **Chen ZY**, Yan LN, Zeng Y, Wen TF, Li B, Zhao JC, Wang WT, Yang JY, Xu MQ, Ma YK, Wu H. Preliminary experience with indications for liver transplantation for hepatolithiasis. *Transplant Proc* 2008; **40**: 3517-3522 [PMID: 19100427 DOI: 10.1016/j.transproceed.2008.07.142]

16 **Liver Failure and Artificial Liver Group Group**, Chinese Society of Infectious Diseases, Chinese Medical Association; Severe Liver Disease and Artificial Liver Group, Chinese Society of Hepatology, Chinese Medical Association; Chinese Society of Infectious Diseases, Chinese Medical Association; Severe Liver Disease and Artificial Liver Group, Chinese Society of Hepatology, Chinese Medical Association. [Guideline for diagnosis and treatment of liver failure]. *Zhonghua Gan Zang Bing Za Zhi* 2019; **27**: 18-26 [PMID: 30685919 DOI: 10.3760/cma.j.issn.1007-3418.2019.01.006]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 April 27; 14(4): 352-361

DOI: 10.4240/wjgs.v14.i4.352

ISSN 1948-9366 (online)

CASE REPORT

# Surgical timing for primary encapsulating peritoneal sclerosis: A case report and review of literature

Peng Deng, Long-Xin Xiong, Ping He, Jian-Hua Hu, Qi-Xu Zou, Shi-Lian Le, Sen-Lin Wen

**Specialty type:** Surgery

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Bairwa DBL, India; Mohammed F, Sudan

**Received:** November 28, 2021
**Peer-review started:** November 28, 2021
**First decision:** December 26, 2021
**Revised:** January 6, 2022
**Accepted:** March 26, 2022
**Article in press:** March 26, 2022
**Published online:** April 27, 2022

**Peng Deng, Long-Xin Xiong, Ping He, Qi-Xu Zou, Shi-Lian Le, Sen-Lin Wen,** Department of General Surgery, The First Hospital of Nanchang, Nanchang 330008, Jiangxi Province, China

**Jian-Hua Hu,** Department of Emergency Surgery, The First Hospital of Nanchang, Nanchang 330008, Jiangxi Province, China

**Corresponding author:** Long-Xin Xiong, MD, Chief Doctor, Professor, Department of General Surgery, The First Hospital of Nanchang, No. 128 Xiangshan Road, Nanchang 330008, Jiangxi Province, China. xlx20211027@126.com

## Abstract

### *BACKGROUND*

Primary encapsulating peritoneal sclerosis (EPS) is a rare but devastating disease that causes fibrocollagenous cocoon-like encapsulation of the bowel, resulting in bowel obstruction. The pathogenesis, prevention, and treatment strategies of EPS remain unclear so far. Since most patients are diagnosed during exploratory laparotomy, for the non-surgically diagnosed patients with primary EPS, the surgical timing is also uncertain.

### *CASE SUMMARY*

A 44-year-old female patient was referred to our center on September 6, 2021, with complaints of abdominal distention and bilious vomiting for 2 d. Physical examination revealed that the vital signs were stable, and the abdomen was slightly distended. Computerized tomography scan showed a conglomerate of multiple intestinal loops encapsulated in a thick sac-like membrane, which was surrounded by abdominal ascites. The patient was diagnosed with idiopathic EPS. Recovery was observed after abdominal paracentesis, and the patient was discharged on September 13 after the resumption of a normal diet. This case raised a question: When should an exploratory laparotomy be performed on patients who are non-surgically diagnosed with EPS. As a result, we conducted a review of the literature on the clinical manifestations, intraoperative findings, surgical methods, and therapeutic effects of EPS.

### *CONCLUSION*

Recurrent intestinal obstructions and abdominal mass combined with the imaging of encapsulated bowel are helpful in diagnosing idiopathic EPS. Small intestinal resection should be avoided.

**Key Words:** Primary encapsulating peritoneal sclerosis; Abdominal cocoon; Intestinal obstruction; Case report



**Core Tip:** Primary encapsulating peritoneal sclerosis (EPS), also called an abdominal cocoon, is so rare that the etiology, pathogenesis, treatment strategies of primary EPS remain vague. We reported a case of primary EPS and carried out a comprehensive literature analysis. The data indicated for the first time that recurrent intestinal obstructions and abdominal mass combined with the imaging of encapsulated bowel are helpful in diagnosing primary EPS. Surgical treatments are promising, but care should be taken to avoid small intestinal resection. Elective abdominal exploration might decrease complications of patients with primary EPS, but further research is required to substantiate this.

**Citation:** Deng P, Xiong LX, He P, Hu JH, Zou QX, Le SL, Wen SL. Surgical timing for primary encapsulating peritoneal sclerosis: A case report and review of literature. *World J Gastrointest Surg* 2022; 14(4): 352-361
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i4/352.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i4.352

## INTRODUCTION

Encapsulating peritoneal sclerosis (EPS) is a rare but chronic syndrome, clinically presenting as acute and subacute intestinal obstruction, with abdominal pain, distention, vomiting, and constipation. EPS can be classified as primary (idiopathic) and secondary (cases where causes for the disease have been identified)[1]. Secondary EPS cases are reported to be associated with peritoneal dialysis (PD), tuberculosis, β-adrenergic blocker usage, endometriosis, *etc*[2-5]. With the broader applications of PD, the cases of PD-related EPS have increased up to 0.7%[6]. The pathogenesis, prevention, and treatment strategies of secondary EPS have been well established[7-9]. The term primary EPS, which is also called idiopathic EPS, was first used by Foo *et al*[8] in 1978 to describe EPS cases of unknown origin in young women residing in tropical or subtropical countries. However, primary EPS has since been found to develop in elderly men. The etiology, pathogenesis, and treatment strategies for primary EPS remain vague. This paper reports a patient diagnosed with primary EPS and compiles 63 primary EPS cases reported in the literature.

## CASE PRESENTATION

### *Chief complaints*

A 44-year-old female patient was admitted to the emergency department of our institution on September 6, 2021, with complaints of abdominal distention and bilious vomiting for 2 d.

### *History of present illness*

The patient had experienced abdominal distension and bilious vomiting the day before with no obvious precipitating factors. She had no fever, abdominal pain, constipation, and normal menstruation. She was treated with fasting and parenteral nutrition; the patient ceased vomiting, but abdominal distention continued.

### *History of past illness*

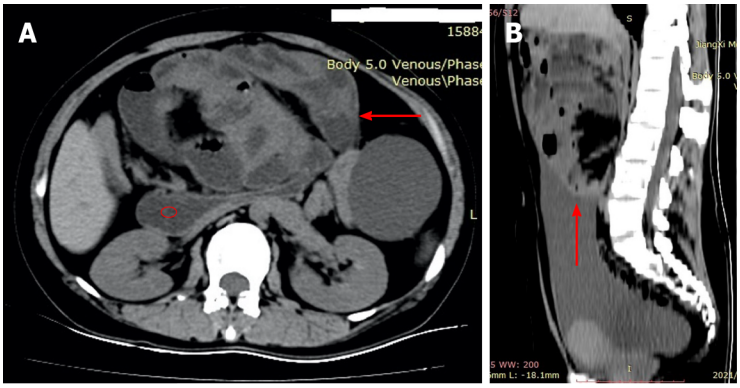
She had three episodes of abdominal pain, abdominal distention, and bilious vomiting. The last episode occurred 3 years before, with abdominal distention and massive ascites. The patient recovered after abdominal paracentesis, which indicated bloody ascites. A year ago, she had schizophrenia and took aripiprazole orally (10 mg QD). She had untreated menstrual cramps when she was young, and her menstruation is regular. No weight loss was observed before.

### *Personal and family history*

There was no unremarkable personal or family history.

### *Physical examination*

The patient's vital signs were stable and the abdomen was slightly distended. There was mild




**DOI:** 10.4240/wjgs.v14.i4.352 **Copyright** ©The Author(s) 2022.

**Figure 1 Computerized tomography of transverse plane and sagittal plane.** A: Computerized tomography (CT) of transverse plane: A conglomerate of multiple intestinal loops encapsulated in a thick sac-like membrane (arrow), and dilated duodenum (red cycle); B: CT of sagittal plane: Epigastric mass floating in ascites.

tenderness in the right upper abdomen, but there was no rebound tenderness. A palpable, soft, low mobility mass (6 cm × 8 cm) was detected in the upper right abdomen, and the abdomen ascites sign was positive.

### *Laboratory examinations*

Leukocyte count: 5.66 × $10^9$/L, percentage of neutrophils (NEU%): 65.2%; Hemoglobin: 122 g/L; C-reactive protein: 14.3 mg/L; carcinoembryonic antigen: 2.1 ng/mL; and tuberculosis antibody and T.Spot-TB tests were negative.

### *Imaging examinations*

Computerized tomography (CT) scan showed a conglomerate of multiple intestinal loops encapsulated in a thick sac-like membrane, which was surrounded by abdominal ascites (Figure 1). "Gourd sign" (Figure 1A) was also observed in this case, which refers to the expansion of the horizontal part of the duodenum caused by an abdominal cocoon.

## FINAL DIAGNOSIS

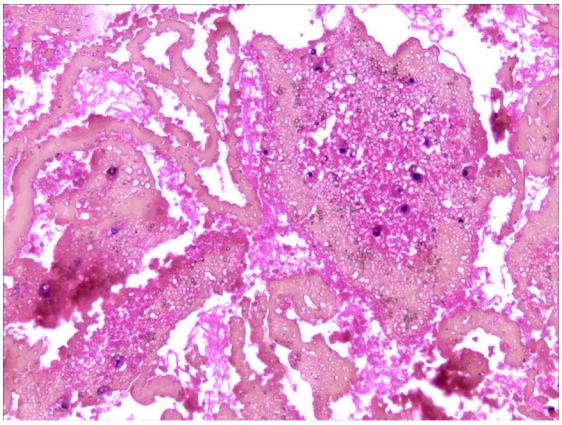
According to the clinical manifestations of recurrent intestinal obstruction, abdominal mass, and imaging features of encased bowel, this case was clinically diagnosed as primary EPS.

## TREATMENT

Laparoscopic exploration was proposed but was not accepted by the patient and her husband. Abdominal drainage was performed for 3 d, and a total of 2200 mL of blood liquid was removed. No carcinoma cells were found in the centrifugal cytology of ascites (Figure 2).

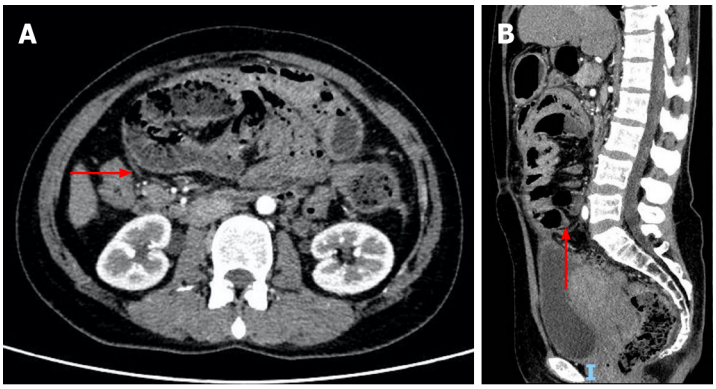
## OUTCOME AND FOLLOW-UP

After this, the patient felt well, her abdominal distention was completely relieved, and she was put on a semi-liquid diet. After abdominal ultrasound confirmed the absence of ascites in the abdominal cavity, an abdominal contrast-enhanced CT (CECT) (September 9, 2021) scan was arranged, which revealed that the entire small intestine was dilated, clustered, and wrapped in an enhancing sac, separating the intestine from ascending colon, descending colon, and sigmoid colon (Figure 3). She was discharged on September 13 after resuming a normal diet, with no recurrence of symptoms in the following month.



**DOI:** 10.4240/wjgs.v14.i4.352 **Copyright** ©The Author(s) 2022.

**Figure 2 Exfoliative cytology of ascites (hematoxylin and eosin stain, × 40).** A large number of red blood cells, including scattered inflammatory cells.




**DOI:** 10.4240/wjgs.v14.i4.352 **Copyright** ©The Author(s) 2022.

**Figure 3 Contrast-enhanced computerized tomography of transverse plane and sagittal plane.** A: Transverse plane; B: Sagittal plane. Intestinal loops were encapsulated in a thick sac-like membrane (arrow).

## DISCUSSION

### *Literature review*

A systematic search of the literature, focusing on article titles and abstracts of publications in the English language using the PubMed database, was performed; the publication date of these articles was from January 2004 to September 2021. The search was executed utilizing the following keywords: "abdominal cocoon", "encapsulating peritoneal sclerosis", "sclerosing encapsulating peritonitis", and "peritoneal encapsulation". Manual searches of reference lists of the publications were performed to supplement the electronic search.

Case series without clinical details were excluded. Case reports with features of EPS that might be associated with PD, including abdominal tuberculosis, abdominal surgery, recurrent peritonitis, ventriculoperitoneal or peritoneovenous shunts, liver transplantation, abdominal trauma, beta-blocker treatment (practolol or propranolol), intraperitoneal chemotherapy, endometrioid carcinomas, intraperitoneal povidone-iodine use, liver cirrhosis, carcinomatous peritonitis, fibrogenic foreign material, systemic lupus erythematosus, and parasitic infection, were determined to be secondary EPS and were excluded.

Two investigators independently read the articles. The following information was extracted from the reports: Country (of the author), year (of publication), age/sex (of the patient), major syndrome, past history, major symptoms (of peritonitis and abdominal mass), radiologic tools, ascites characteristics, operations, intraoperative findings, histopathology, curative effect, and follow-up status. A total of 52 reports[10-61] from January 2004 to September 2021 with data of 63 patients was reviewed (Table 1). A total of 14 females with the median age of 38 years (range: 12-64 years) and 49 males with the median age of 45.5 years (range: 7-82 years) were reported; the difference of age between female and male patients was statistically significant (rank-sum test). Recurrent abdominal distention, abdominal pain or colicky pain, nausea, vomiting or bilious vomiting, anal defecation, and dehydration or malnutrition were among the symptoms reported by the patients. Also, 68.25% of the cases reported chronic

**Table 1 The information of reviewed cases about primary encapsulating peritoneal sclerosis**

| Aspects of case description | | Male, *n* = 49 | Female, *n* = 14 | Frequency as %, Z, $\chi^2$ | |
|---|---|---|---|---|---|
| Age | | R (7-82), M = 45.5 | R (12-64), M = 38 | Z = 4.833 | |
| Duration of symptoms | > 2 mo | 37 | 6 | 68.25 | $\chi^2 = 8.625$, $P < 0.01$ |
| | < 2 mo | 3 | 0 | 4.76 | |
| | ≤ 1 mo | 9 | 8 | 26.98 | |
| Sign of peritonitis | Not mentioned | 12 | 5 | 26.98 | $\chi^2 = 0.484$, $P > 0.5$ |
| | Soft | 12 | 4 | 25.40 | |
| | Tenderness | 23 | 4 | 42.86 | |
| | Rebound tenderness | 2 | 1 | 4.76 | |
| Abdominal mass | | 15 | 7 | 34.92 | |
| Ascites | | 2 | 3 | 7.94 | |
| Classification | Not mentioned | 2 | 1 | 4.76 | $\chi^2 = 9.422$, $P < 0.01$ |
| | Type I | 13 | 2 | 23.81 | |
| | Type II | 26 | 5 | 49.21 | |
| | Type III | 8 | 6 | 22.22 | |
| Lack greater omentum | | 6 | 0 | 9.52 | |
| Operation | Non surgery | 2 | 1 | 4.76 | $\chi^2 = 12.21$, $P < 0.01$ |
| | Laparotomy | 1 | 4 | 7.94 | |
| | Dissection + adhesionlysis | 39 | 9 | 76.19 | |
| | Partial resection | 7 | 0 | 11.11 | |
| Histopathology (of the membrane) | | 30 | 4 | 53.97 | |
| Curative effect | Not mentioned | 4 | 1 | 7.94 | $\chi^2 = 0.635$, $P > 0.5$ |
| | Uneventful recover | 37 | 11 | 76.19 | |
| | Prolonged recover | 6 | 2 | 12.70 | |
| | Leakage | 2 | 0 | 3.17 | |

Dissection: Dissection of membrane; Not mentioned: Not mentioned in the report; Partial resection: Partial resection of small intestine.

symptoms, with the duration of the syndrome being more than 2 mo. Moreover, there were significant differences in the distribution of symptoms between male and female patients, with female patients exhibiting more acute symptoms. There were only 4.76% of the cases with the peritonitis symptom of rebound tenderness. Abdominal mass was palpable in 34.92% of cases, and only five patients (7.94%) were noted with ascites.

The intraoperative findings were analyzed and the cases were divided into the following three types according to the classification of primary EPS[8,9]: Type I: A segment of the small intestine is wrapped by a fibrous capsule; Type II: All intestines are encapsulated by fibers; and Type III: All small intestines and other organs are encapsulated by fibers. Type III and II EPS were more common in females than males, while only three male patients were noted with the absence of greater omentum. Nonoperative treatment was performed in three patients; exploratory surgery was performed in five patients; dissection of membrane and adhesiolysis was performed successfully in 76.19% of patients, and the partial resection of the small intestine was performed only in seven patients (11.11%).

The pathological description data were available for 53% of the cases. Most of the cases were pathologically reported as fibroconnective tissue proliferation with chronic inflammatory infiltration. Most of the patients (76.19%) recovered eventually, except for two patients who developed anastomotic leakage after partial resection of the intestine.

## Discussion

The conditions of intestinal membrane encapsulation have been described using a variety of terms. Akbulut[9] emphasized the correct usage of terms, such as peritoneal encapsulation (PE), abdominal cocoon, idiopathic EPS, and secondary EPS. PE is a rare congenital anomaly characterized by an

accessory peritoneal membrane derived from the yolk sac peritoneum in the early stages of fetal life [62]; it is not the consequence of chronic inflammation. Unlike PE, EPS is an acquired disease and is associated with chronic peritoneal inflammation that might be provoked by various factors[63]. Depending on the underlying triggering factors and the properties of the fibrocollagenous membrane, EPS can be classified as primary (idiopathic) or secondary[64]. The primary form (EPS of unknown origin) is also known as an abdominal cocoon and was first described by Foo *et al*[8] in 1978.

Primary EPS was thought to be present in tropical and subtropical areas, leading to theories of gynecologic infection or retrograde menstruation as the cause[65]. Although several studies have confirmed the equatorial predilection of primary EPS, men are more vulnerable to EPS than women [66]; however, female patients are younger than men when they develop symptoms.

The diagnosis of EPS was based on clinical manifestations and imaging findings, and most patients were diagnosed during explorative laparotomy. Recurrent intestinal obstructions characterize the clinical manifestation of primary EPS. In a large case series of primary EPS, the average duration of symptoms was 3.9 years before malnourishment symptoms developed[66]. In our study, 68.25% of the patients had a history of recurrent intestinal obstructions for more than 3 mo. While some patients with idiopathic EPS had no symptoms, the majority had abdominal pain, distention, nausea, vomiting or bilious vomiting, constipation, appetite loss, weight loss, dehydration, and malnutrition.

In this study, the physical examination of EPS patients revealed a higher occurrence of mild tenderness (42.86%) compared to rebound tenderness. The abdominal mass was palpable in 34.9% of patients, which is inconsistent with the literature report[8]. This may be due to the difference in case selection methods. Massive ascites was rare and did not seem to indicate a serious condition. There were five patients with massive ascites in the reports reviewed; one case improved by paracentesis, and four cases reported an uneventful recovery after the operation. Bloody ascites was rarer but found in both male ($n$ = 15) and female ($n$ = 21) patients, which questions theories of retrograde menstruation. Therefore, there may be a different cause for the massive bloody ascites in patients with primary EPS.

Blood tests did not report abnormal values, except for some patients with dehydration, electrolyte disorder, and malnutrition. The various imaging tools available for diagnosing EPS are erect abdominal X-ray, ultrasonography, barium meal, and CT or CECT. The air-fluid levels of dilated small bowel of EPS patients are visible in erect abdominal X-rays but are non-specific[28]. Ultrasound may show peritoneal thickening, ascites, and dilated bowel loops enclosed within a membrane; barium meal studies of the small intestine are useful in detecting clumped small bowel loops in the abdomen, which is also known as the cauliflower sign. CT or CECT may be the first choice for preoperative diagnosis of idiopathic EPS by providing the following image features: (1) Thickened jejunal and ileal loops encased in a thick fibrocollagenous membrane[27]; (2) "cauliflower-like" sign[67] or abdominal cystic masses with intestines freely floating in the fluid; and (3) "bottle gourd" sign[29] or dilated duodenum in patients with abdominal cocoon due to jejunal obstruction. Out of these, feature one is more common and specific.

Although the diagnosis of primary EPS is facilitated by the patient`s past history, existing symptoms, physical signs, radiological imaging, and above all, high-level clinical suspicion are major factors contributing to proper detection of the disease[47]. In this study, the preoperative diagnosis rate of primary EPS was low, and most patients were diagnosed in exploratively laparotomy or laparoscopy [11,17].

Presently, the management strategy of secondary EPS associated with PD is well established. However, very few reports suggest the surgical timing for patients who are non-surgically diagnosed with idiopathic EPS. Whether non-surgical management, such as tamoxifen, is efficacious for idiopathic EPS[15]. Célicout *et al*[68] believed non-surgical treatment is required in ascites and subacute intestinal obstruction.

Primary EPS could be categorized into three types according to the extent of bowel encapsulated by the membrane. Type II refers to all types of intestines encapsulated by a membrane and is the most common. In this study, the greater omentum was absent in six male patients[17,18,32,41,56,59], with age ranging from 19 years to 69 years. These cases may be diagnosed as PE or primary EPS, as both are accompanied by embryonic abnormalities[58], such as the absence of greater omentum or greater omentum dysplasia.

Dissection of membrane and adhesiolysis should be performed to all encased intestinal segments by concentrating on the following tips: (1) operate softly and lightly to avoid damaging the bowel and causing iatrogenic bowel perforation[46,54]; (2) resection of the intestine should be performed only when the bowel is nonviable; (3) anastomosis should not be the primary choice as it may increase the incidence of anastomotic leakage[25,47,68]; (4) prophylactic appendectomy is worth recommending because it is difficult to surgically treat acute appendicitis that may occur later[41]; (5) in order to reduce the complication of postoperative adhesive intestinal obstruction, it is recommended that nasointestinal obstruction tube should be installed during the operation[32]; and (6) application of an anti-adhesive substance may help prevent the patients from developing early postoperative small bowel obstruction [41,54].

Thirty-four reports describe the pathological features of the cases. The characteristic histopathological features were fibrocollagenous tissue proliferation, moderate chronic inflammatory infiltrate, and lymphatic endothelial cells[10,14,20]; some cases were accompanied by calcification[30] and hyalin-

ization[36].

Of the 63 cases we reviewed, three patients were discharged after non-surgical treatment, five patients underwent exploratory laparotomy only, while membrane dissection and adhesiolysis were successfully performed on 76.19% of cases. Partial resection of the small bowel was performed for seven cases, two of which developed leakage, resulting in one death[47]. Early postoperative small bowel obstruction[59] was common and difficult to manage, leading to the delayed recovery of eight cases. Total parenteral nutrition with complete gastrointestinal rest was proposed[69], while reoperation was recommended. Other complications, such as poorly healed incision[21], were the cause of the prolonged recovery of one case. However, in general, the surgical effect of primary EPS seems optimistic, which is in contrast with that of secondary EPS associated PD[70].

## CONCLUSION

Owing to the uncommon nature of primary EPS, its etiology, pathogenesis, and treatment strategies remain unclear. This paper presents a case of non-surgically diagnosed primary EPS, treated with paracentesis, and her CT scan with and without ascites. Recurrent intestinal obstructions and abdominal mass combined with the imaging of encapsulated bowel help diagnose primary EPS. The surgical effect of excision of membrane and adhesiolysis seems optimistic; however, small intestinal resection should be avoided as it could lead to anastomotic leakage. Elective abdominal exploration might decrease the complications of primary EPS patients with the recurrent syndrome, but further research is required to substantiate this.

## FOOTNOTES

**Author contributions:** Deng P, Xiong LX, and He P wrote the main manuscript text; Deng P, He P, and Wen SL reviewed the literature; Zhou QX prepared Figures 1-3; Hu JH prepared Table 1; all authors edited, read, and approved the final manuscript.

**Supported by** the Key Projects of Support Plan of Nanchang Science and Technology Bureau, Jiangxi Province, China, No. [2020]153.

**Informed consent statement:** Written informed consent was obtained from the patient and her husband for treatment and the publication of this case and any accompanying images.

**Conflict-of-interest statement:** The authors declare having no potential conflicts of interest.

**CARE Checklist (2016) statement:** The manuscript was revised according to the CARE Checklist (2016).



**Country/Territory of origin:** China

**ORCID number:** Peng Deng 0000-0003-0283-7368; Long-Xin Xiong 0000-0002-3691-3173; Ping He 0000-0002-3548-2607; Jian-Hua Hu 0000-0003-0296-6004; Qi-Xu Zou 0000-0001-7035-3782; Shi-Lian Le 0000-0003-0377-5533; Sen-Lin Wen 0000-0003-3508-7882.

**S-Editor:** Yan JP
**L-Editor:** Filipodia
**P-Editor:** Yan JP

## REFERENCES

1 **Dave A**, McMahon J, Zahid A. Congenital peritoneal encapsulation: A review and novel classification system. *World J Gastroenterol* 2019; **25**: 2294-2307 [PMID: 31148901 DOI: 10.3748/wjg.v25.i19.2294]

2 **Ulmer C**, Braun N, Rieber F, Latus J, Hirschburger S, Emmel J, Alscher MD, Steurer W, Thon KP. Efficacy and morbidity of surgical therapy in late-stage encapsulating peritoneal sclerosis. *Surgery* 2013; **153**: 219-224 [PMID: 22981361 DOI: 10.1016/j.surg.2012.07.033]

3 **Singal R**, Satyashree B, Mittal A, Sharma BP, Singal S, Zaman M, Shardha P. Tubercular abdominal cocoon in children - a

single centre study in remote area of northern India. *Clujul Med* 2017; **90**: 179-184 [PMID: 28559702 DOI: 10.15386/cjmed-725]
4 **Noh SH**, Ye BD, So H, Kim YS, Suh DJ, Yoon SN. Sclerosing encapsulating peritonitis in a long-term propranolol user. *Intest Res* 2016; **14**: 375-378 [PMID: 27799890 DOI: 10.5217/ir.2016.14.4.375]
5 **Katz CB**, Diggory RT, Samee A. Abdominal cocoon. *BMJ Case Rep* 2014; **2014** [PMID: 24682136 DOI: 10.1136/bcr-2013-203102]
6 **Rigby RJ**, Hawley CM. Sclerosing peritonitis: the experience in Australia. *Nephrol Dial Transplant* 1998; **13**: 154-159 [PMID: 9481732 DOI: 10.1093/ndt/13.1.154]
7 **Kawaguchi Y**, Saito A, Kawanishi H, Nakayama M, Miyazaki M, Nakamoto H, Tranaeus A. Recommendations on the management of encapsulating peritoneal sclerosis in Japan, 2005: diagnosis, predictive markers, treatment, and preventive measures. *Perit Dial Int* 2005; **25** Suppl 4: S83-S95 [PMID: 16300277]
8 **Foo KT**, Ng KC, Rauff A, Foong WC, Sinniah R. Unusual small intestinal obstruction in adolescent girls: the abdominal cocoon. *Br J Surg* 1978; **65**: 427-430 [PMID: 656764 DOI: 10.1002/bjs.1800650617]
9 **Akbulut S**. Accurate definition and management of idiopathic sclerosing encapsulating peritonitis. *World J Gastroenterol* 2015; **21**: 675-687 [PMID: 25593498 DOI: 10.3748/wjg.v21.i2.675]
10 **Bhatta OP**, Verma R, Shrestha G, Sharma D, Dahal R, Kansakar PBS. An unusual case of intestinal obstruction due to abdominal cocoon: A case report. *Int J Surg Case Rep* 2021; **85**: 106282 [PMID: 34388909 DOI: 10.1016/j.ijscr.2021.106282]
11 **Aziz W**, Malik Y, Haseeb S, Mirza RT, Aamer S. Abdominal Cocoon Syndrome: A Laparoscopic Approach. *Cureus* 2021; **13**: e16787 [PMID: 34513394 DOI: 10.7759/cureus.16787]
12 **Yin MY**, Qian LJ, Xi LT, Yu YX, Shi YQ, Liu L, Xu CF. Encapsulating peritoneal sclerosis in an AMA-M2 positive patient: A case report. *World J Clin Cases* 2021; **9**: 6138-6144 [PMID: 34368336 DOI: 10.12998/wjcc.v9.i21.6138]
13 **Ulusoy C**, Nikolovski A, Öztürk NN. Difficult to Diagnose the Cause of Intestinal Obstruction due to Abdominal Cocoon Syndrome. *Eur J Case Rep Intern Med* 2021; **8**: 002588 [PMID: 34123948 DOI: 10.12890/2021_002588]
14 **Saqib SU**, Farooq R, Saleem O, Moeen S, Chawla TU. Acute presentation of cocoon abdomen as septic peritonitis mimicking with strangulated internal herniation: a case report. *Surg Case Rep* 2021; **7**: 93 [PMID: 33851284 DOI: 10.1186/s40792-021-01179-7]
15 **Wetherell J**, Woolley K, Chadha R, Kostka J, Adilovic E, Nepal P. Idiopathic Sclerosing Encapsulating Peritonitis in a Patient with Atypical Symptoms and Imaging Findings. *Case Rep Gastrointest Med* 2021; **2021**: 6695806 [PMID: 33880193 DOI: 10.1155/2021/6695806]
16 **Karona P**, Blevrakis E, Kastanaki P, Tzouganakis A, Kastanakis M. Abdominal Cocoon Syndrome: An Extremely Rare Cause of Small Bowel Obstruction. *Cureus* 2021; **13**: e14351 [PMID: 33972908 DOI: 10.7759/cureus.14351]
17 **Tang H**, Xia R, Xu S, Tao C, Wang C. Sclerosing encapsulating peritonitis presenting with paroxysmal abdominal pain and strangulated mechanical bowel obstruction: A case report. *Medicine (Baltimore)* 2021; **100**: e24794 [PMID: 33663096 DOI: 10.1097/MD.0000000000024794]
18 **Song WJ**, Liu XY, Saad GAA, Khan A, Yang KY, Zhang Y, Liu JY, He LY. Primary abdominal cocoon with cryptorchidism: a case report. *BMC Gastroenterol* 2020; **20**: 334 [PMID: 33054747 DOI: 10.1186/s12876-020-01466-x]
19 **Lasheen O**, ElKorety M. Abdominal Cocoon or Encapsulating Peritoneal Sclerosis: A Rare Cause of Small Bowel Obstruction. *Eur J Case Rep Intern Med* 2020; **7**: 001972 [PMID: 33313011 DOI: 10.12890/2020_001972]
20 **Sivakumar J**, Brown G, Galea L, Choi J. An intraoperative diagnosis of sclerosing encapsulating peritonitis: a case report. *J Surg Case Rep* 2020; **2020**: rjaa329 [PMID: 32934790 DOI: 10.1093/jscr/rjaa329]
21 **Zhang Z**, Zhang M, Li L. Sclerosing encapsulating peritonitis: three case reports and review of the literature. *J Int Med Res* 2020; **48**: 300060520949104 [PMID: 32811273 DOI: 10.1177/0300060520949104]
22 **Kang JH**. A rare case of intestinal obstruction: Sclerosing encapsulating peritonitis of unknown cause. *Turk J Emerg Med* 2020; **20**: 152-155 [PMID: 32832736 DOI: 10.4103/2452-2473.290068]
23 **Zhou H**, Xu J, Xie X, Han J. Idiopathic cocoon abdomen with congenital colon malrotation: a case report and review of the literature. *BMC Surg* 2020; **20**: 124 [PMID: 32517682 DOI: 10.1186/s12893-020-00788-7]
24 **Akbas A**, Hacım NA, Dagmura H, Meric S, Altınel Y, Solmaz A. Two Different Clinical Approaches with Mortality Assessment of Four Cases: Complete and Incomplete Type of Abdominal Cocoon Syndrome. *Case Rep Surg* 2020; **2020**: 4631710 [PMID: 32082687 DOI: 10.1155/2020/4631710]
25 **Park GH**, Lee BC, Hyun DW, Choi JB, Park YM, Jung HJ, Jo HJ. Mechanical intestinal obstruction following laparoscopic inguinal hernia repair in a patient with abdominal cocoon syndrome. *J Surg Case Rep* 2019; **2019**: rjz370 [PMID: 31867099 DOI: 10.1093/jscr/rjz370]
26 **Yue B**, Cui Z, Kang W, Wang H, Xiang Y, Huang Z, Jin X. Abdominal cocoon with bilateral cryptorchidism and seminoma in the right testis: a case report and review of literature. *BMC Surg* 2019; **19**: 167 [PMID: 31711457 DOI: 10.1186/s12893-019-0636-z]
27 **Saqib SU**, Pal I. Sclerosing peritonitis presenting as complete mechanical bowel obstruction: a case report. *J Med Case Rep* 2019; **13**: 310 [PMID: 31623685 DOI: 10.1186/s13256-019-2243-0]
28 **Mohakud S**, Juneja A, Lal H. Abdominal cocoon: preoperative diagnosis on CT. *BMJ Case Rep* 2019; **12** [PMID: 31154350 DOI: 10.1136/bcr-2019-229983]
29 **Sharma V**, Mandavdhare HS, Singh H, Gorsi U. Significance of Bottle Gourd sign on computed tomography in patients with abdominal cocoon: a case series. *Med Pharm Rep* 2019; **92**: 192-194 [PMID: 31086849 DOI: 10.15386/mpr-1147]
30 **Renko AE**, Witte SR, Cooper AB. Abdominal cocoon syndrome: an obstructive adhesiolytic metamorphosis. *BMJ Case Rep* 2019; **12** [PMID: 30975778 DOI: 10.1136/bcr-2018-228593]
31 **Sovatzidis A**, Nikolaidou E, Katsourakis A, Chatzis I, Noussios G. Abdominal Cocoon Syndrome: Two Cases of an Anatomical Abnormality. *Case Rep Surg* 2019; **2019**: 3276919 [PMID: 31073417 DOI: 10.1155/2019/3276919]
32 **Xia J**, Xie W, Chen L, Liu D. Abdominal cocoon with early postoperative small bowel obstruction: A case report and review of literature in China. *Medicine (Baltimore)* 2018; **97**: e11102 [PMID: 29924005 DOI: 10.1097/MD.0000000000011102]

33 **Al-Azzawi M**, Al-Alawi R. Idiopathic abdominal cocoon: a rare presentation of small bowel obstruction in a virgin abdomen. How much do we know? *BMJ Case Rep* 2017; **2017** [PMID: 28684645 DOI: 10.1136/bcr-2017-219918]

34 **Kirshtein B**, Mizrahi S, Sinelnikov I, Lantsberg L. Abdominal cocoon as a rare cause of small bowel obstruction in an elderly man: report of a case and review of the literature. *Indian J Surg* 2011; **73**: 73-75 [PMID: 22211046 DOI: 10.1007/s12262-010-0200-7]

35 **Shah MY**, Gedam BS, Sonarkar R, Gopinath KS. Abdominal cocoon: an unusual cause of subacute intestinal obstruction. *Indian J Surg* 2013; **75**: 391-393 [PMID: 24426626 DOI: 10.1007/s12262-012-0582-9]

36 **Obaid O**, Alhalabi D, Ghonami M. Intestinal Obstruction in a Patient with Sclerosing Encapsulating Peritonitis. *Case Rep Surg* 2017; **2017**: 8316147 [PMID: 28458941 DOI: 10.1155/2017/8316147]

37 **Cheng Y**, Qu L, Li J, Wang B, Geng J, Xing D. Abdominal cocoon accompanied by multiple peritoneal loose body. *Medicine (Baltimore)* 2017; **96**: e6185 [PMID: 28248873 DOI: 10.1097/MD.0000000000006185]

38 **Lim MC**, Chotai NC, Giron DM. Idiopathic Sclerosing Encapsulating Peritonitis: A Rare Cause of Subacute Intestinal Obstruction. *Case Rep Med* 2016; **2016**: 8206894 [PMID: 27642301 DOI: 10.1155/2016/8206894]

39 **Fei X**, Yang HR, Yu PF, Sheng HB, Gu GL. Idiopathic abdominal cocoon syndrome with unilateral abdominal cryptorchidism and greater omentum hypoplasia in a young case of small bowel obstruction. *World J Gastroenterol* 2016; **22**: 4958-4962 [PMID: 27239122 DOI: 10.3748/wjg.v22.i20.4958]

40 **Yang CS**, Kim D. Unusual intestinal obstruction due to idiopathic sclerosing encapsulating peritonitis: a report of two cases and a review. *Ann Surg Treat Res* 2016; **90**: 231-234 [PMID: 27073795 DOI: 10.4174/astr.2016.90.4.231]

41 **Zhang Y**, Liu WD, He JT, Liu Q, Zhai DG. A rare case of abdominal cocoon presenting as umbilical hernia. *Chin Med J (Engl)* 2015; **128**: 1415-1417 [PMID: 25963367 DOI: 10.4103/0366-6999.156815]

42 **Uzunoglu Y**, Altintoprak F, Yalkin O, Gunduz Y, Cakmak G, Ozkan OV, Celebi F. Rare etiology of mechanical intestinal obstruction: Abdominal cocoon syndrome. *World J Clin Cases* 2014; **2**: 728-731 [PMID: 25405199 DOI: 10.12998/wjcc.v2.i11.728]

43 **Frost JH**, Price EE. Abdominal cocoon: idiopathic sclerosing encapsulating peritonitis. *BMJ Case Rep* 2015; **2015** [PMID: 25612756 DOI: 10.1136/bcr-2014-207524]

44 **Solmaz A**, Tokoçin M, Arıcı S, Yiğitbaş H, Yavuz E, Gülçiçek OB, Erçetin C, Çelebi F. Abdominal cocoon syndrome is a rare cause of mechanical intestinal obstructions: a report of two cases. *Am J Case Rep* 2015; **16**: 77-80 [PMID: 25671606 DOI: 10.12659/AJCR.892658]

45 **Rasihashemi SZ**, Ramouz A, Ebrahimi F. An unusual small bowel obstruction (abdominal cocoon): a case report. *Arq Bras Cir Dig* 2014; **27**: 82-83 [PMID: 24676306 DOI: 10.1590/s0102-67202014000100019]

46 **Naniwadekar RG**, Kulkarni SR, Bane P, Agrarwal S, Garje A. Abdominal cocoon: an unusual presentation of small bowel obstruction. *J Clin Diagn Res* 2014; **8**: 173-174 [PMID: 24701524 DOI: 10.7860/JCDR/2014/6514.4049]

47 **Kadow JS**, Fingerhut CJ, Fernandes Vde B, Coradazzi KR, Silva LM, Penachim TJ. Encapsulating peritonitis: computed tomography and surgical correlation. *Radiol Bras* 2014; **47**: 262-264 [PMID: 25741096 DOI: 10.1590/0100-3984.2013.1780]

48 **Cağlar M**, Cetinkaya N, Ozgü E, Güngör T. Persistent ascites due to sclerosing encapsulating peritonitis mimicking ovarian carcinoma: A case report. *J Turk Ger Gynecol Assoc* 2014; **15**: 201-203 [PMID: 25317050 DOI: 10.5152/jtgga.2014.37268]

49 **Al Ani AH**, Al Zayani N, Najmeddine M, Jacob S, Nair S. Idiopathic sclerosing encapsulating peritonitis (abdominal cocoon) in adult male. A case report. *Int J Surg Case Rep* 2014; **5**: 735-738 [PMID: 25217877 DOI: 10.1016/j.ijscr.2014.07.017]

50 **Al-Thani H**, El Mabrok J, Al Shaibani N, El-Menyar A. Abdominal cocoon and adhesiolysis: a case report and a literature review. *Case Rep Gastrointest Med* 2013; **2013**: 381950 [PMID: 23476828 DOI: 10.1155/2013/381950]

51 **Awe JA**. Abdominal cocoon syndrome (idiopathic sclerosing encapsulating peritonitis): how easy is its diagnosis preoperatively? *Case Rep Surg* 2013; **2013**: 604061 [PMID: 23738183]

52 **Sharma D**, Nair RP, Dani T, Shetty P. Abdominal cocoon-A rare cause of intestinal obstruction. *Int J Surg Case Rep* 2013; **4**: 955-957 [PMID: 24055916 DOI: 10.1016/j.ijscr.2013.08.004]

53 **Kayastha K**, Mirza B. Abdominal cocoon simulating acute appendicitis. *APSP J Case Rep* 2012; **3**: 8 [PMID: 22953302]

54 **Meshikhes AW**, Bojal S. A rare cause of small bowel obstruction: Abdominal cocoon. *Int J Surg Case Rep* 2012; **3**: 272-274 [PMID: 22522743 DOI: 10.1016/j.ijscr.2012.03.016]

55 **Bassiouny IE**, Abbas TO. Small bowel cocoon: a distinct disease with a new developmental etiology. *Case Rep Surg* 2011; **2011**: 940515 [PMID: 22606598 DOI: 10.1155/2011/940515]

56 **Gupta RK**, Chandra AS, Bajracharya A, Sah PL. Idiopathic sclerosing encapsulating peritonitis in an adult male with intermittent subacute bowel obstruction, preoperative multidetector-row CT (MDCT) diagnosis. *BMJ Case Rep* 2011; **2011** [PMID: 22689278 DOI: 10.1136/bcr.07.2011.4448]

57 **Jayant M**, Kaushik R. Cocoon within an abdominal cocoon. *J Surg Case Rep* 2011; **2011**: 7 [PMID: 24950587 DOI: 10.1093/jscr/2011.5.7]

58 **Xu P**, Chen LH, Li YM. Idiopathic sclerosing encapsulating peritonitis (or abdominal cocoon): a report of 5 cases. *World J Gastroenterol* 2007; **13**: 3649-3651 [PMID: 17659721 DOI: 10.3748/wjg.v13.i26.3649]

59 **Zheng YB**, Zhang PF, Ma S, Tong SL. Abdominal cocoon complicated with early postoperative small bowel obstruction. *Ann Saudi Med* 2008; **28**: 294-296 [PMID: 18596392 DOI: 10.5144/0256-4947.2008.294]

60 **Mohd Noor NH**, Zaki NM, Kaur G, Naik VR, Zakaria AZ. Abdominal cocoon in association with adenomyosis and leiomyomata of the uterus and endometriotic cyst : unusual presentation. *Malays J Med Sci* 2004; **11**: 81-85 [PMID: 22977364]

61 **Devay AO**, Gomceli I, Korukluoglu B, Kusdemir A. An unusual and difficult diagnosis of intestinal obstruction: The abdominal cocoon. Case report and review of the literature. *World J Emerg Surg* 2006; **1**: 8 [PMID: 16759404 DOI: 10.1186/1749-7922-1-8]

62 **Serter A**, Kocakoç E, Çipe G. Supposed to be rare cause of intestinal obstruction; abdominal cocoon: report of two cases. *Clin Imaging* 2013; **37**: 586-589 [PMID: 23041158 DOI: 10.1016/j.clinimag.2012.08.010]

63 **Browne LP**, Patel J, Guillerman RP, Hanson IC, Cass DL. Abdominal cocoon: a unique presentation in an immunodeficient infant. *Pediatr Radiol* 2012; **42**: 263-266 [PMID: 21713442 DOI: 10.1007/s00247-011-2135-y]

64 **Tannoury JN**, Abboud BN. Idiopathic sclerosing encapsulating peritonitis: abdominal cocoon. *World J Gastroenterol* 2012; **18**: 1999-2004 [PMID: 22563185 DOI: 10.3748/wjg.v18.i17.1999]

65 **Danford CJ**, Lin SC, Smith MP, Wolf JL. Encapsulating peritoneal sclerosis. *World J Gastroenterol* 2018; **24**: 3101-3111 [PMID: 30065556 DOI: 10.3748/wjg.v24.i28.3101]

66 **Li N**, Zhu W, Li Y, Gong J, Gu L, Li M, Cao L, Li J. Surgical treatment and perioperative management of idiopathic abdominal cocoon: single-center review of 65 cases. *World J Surg* 2014; **38**: 1860-1867 [PMID: 24519587 DOI: 10.1007/s00268-014-2458-6]

67 **Ibrarullah M**, Mishra T. Abdominal Cocoon: "Cauliflower Sign" on CT Scan. *Indian J Surg* 2016; **78**: 243-244 [PMID: 27358524 DOI: 10.1007/s12262-016-1487-9]

68 **Célicout B**, Levard H, Hay J, Msika S, Fingerhut A, Pelissier E. Sclerosing encapsulating peritonitis: early and late results of surgical management in 32 cases. French Associations for Surgical Research. *Dig Surg* 1998; **15**: 697-702 [PMID: 9845640 DOI: 10.1159/000018681]

69 **Cheng SP**, Liu CL. Early postoperative small bowel obstruction (Br J Surg 2004; 91: 683-691). *Br J Surg* 2004; **91**: 1382 [PMID: 15382096 DOI: 10.1002/bjs.4827]

70 **Kawanishi H**. Surgical and medical treatments of encapsulation peritoneal sclerosis. *Contrib Nephrol* 2012; **177**: 38-47 [PMID: 22613913 DOI: 10.1159/000336934]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 April 27; 14(4): 362-369

DOI: 10.4240/wjgs.v14.i4.362

ISSN 1948-9366 (online)

CASE REPORT

# Laparoscopic-assisted endoscopic full-thickness resection of a large gastric schwannoma: A case report

Cheng-Hai He, Shi-Hua Lin, Zhen Chen, Wei-Min Li, Chun-Yan Weng, Yun Guo, Guo-Dong Li

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**
Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D, D
Grade E (Poor): 0

**P-Reviewer:** Kung WM, Taiwan; Sharaf MM, Syria; Sperti C, Italy

**Received:** December 8, 2021
**Peer-review started:** December 8, 2021
**First decision:** January 8, 2022
**Revised:** February 24, 2022
**Accepted:** March 27, 2022
**Article in press:** March 27, 2022
**Published online:** April 27, 2022

**Cheng-Hai He, Wei-Min Li, Yun Guo, Guo-Dong Li,** Department of Gastroenterology, The Affiliated Hospital of Hangzhou Normal University, Hangzhou 310000, Zhejiang Province, China

**Shi-Hua Lin,** Department of Internal Medicine, Zhejiang Hospital, Hangzhou 310000, Zhejiang Province, China

**Zhen Chen,** Department of Pathology, The Affiliated Hospital of Hangzhou Normal University, Hangzhou 310000, Zhejiang Province, China

**Chun-Yan Weng,** Department of Gastroenterology, The First Clinical Medical College of Zhejiang Chinese Medical University, Hangzhou 310000, Zhejiang Province, China

**Corresponding author:** Guo-Dong Li, Doctor, Chief Doctor, Department of Gastroenterology, The Affiliated Hospital of Hangzhou Normal University, No. 126 Wenzhou Road, Hangzhou 310000, Zhejiang Province, China. hzseliguodong@sina.com

## Abstract

*BACKGROUND*

Schwannomas, also known as neurinomas, are benign tumors derived from Schwann cells. Gastrointestinal schwannomas are rare and are most frequently reported in the stomach. They are usually asymptomatic and are difficult to diagnose preoperatively; however, endoscopy and imaging modalities can provide beneficial preliminary diagnostic data. There are various surgical options for management. Here, we present a case of a large gastric schwannoma (GS) managed by combined laparoscopic and endoscopic surgery.

*CASE SUMMARY*

A 28-year-old woman presented with a 2-mo history of epigastric discomfort and a feeling of abdominal fullness. On upper gastrointestinal endoscopy and endoscopic ultrasonography, a hypoechogenic submucosal mass was detected in the gastric antrum: It emerged from the muscularis propria and projected intraluminally. Computed tomography showed a nodular lesion (4 cm × 3.5 cm), which exhibited uniform enhancement, on the gastric antrum wall. Based on these findings, a preliminary diagnosis of gastrointestinal stromal tumor was established, with schwannoma as a differential. Considering the large tumor size, we planned to perform endoscopic resection and to convert to laparoscopic treatment, if necessary. Eventually, the patient underwent combined laparoscopic and gastroscopic surgery. Immunohistochemically, the resected specimen showed

positivity for S-100 and negativity for desmin, DOG-1, α-smooth muscle actin, CD34, CD117, and p53. The Ki-67 index was 3%, and a final diagnosis of GS was established.

*CONCLUSION*
Combined laparoscopic and endoscopic surgery is a minimally invasive and effective treatment option for large GSs.

**Key Words:** Gastric schwannoma; Laparoscopy; Gastroscopy; Immunohistochemical staining; Operation method; Case report



**Core Tip:** Gastric schwannomas (GSs) do not have specific clinical and endoscopic characteristics. Therefore, preoperative diagnosis may be difficult, and they can be misdiagnosed as gastrointestinal stromal tumors. In addition, while laparoscopic resection is possible, it is difficult to determine the location of intraluminal tumors. In contrast, endoscopic resection is only suitable for small submucosal tumors. Here, we present a case of a GS excised using laparoscopic-gastroscopic cooperative surgery. Additionally, we performed a literature review on computed tomography findings and surgical interventions used in the management of gastrointestinal stromal tumors and GSs.

**Citation:** He CH, Lin SH, Chen Z, Li WM, Weng CY, Guo Y, Li GD. Laparoscopic-assisted endoscopic full-thickness resection of a large gastric schwannoma: A case report. *World J Gastrointest Surg* 2022; 14(4): 362-369
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i4/362.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i4.362

## INTRODUCTION

Schwannomas are neurogenic tumors that emerge from Schwann cells. The most common site of a gastric schwannoma (GS) is the stomach, followed by the colon and rectum[1]. They usually arise from the muscular layer, with no specific clinical and endoscopic characteristics, and can frequently be misdiagnosed as gastrointestinal stromal tumors (GISTs), which are more common[2].

A GS can be managed by various surgical options, which have their advantages and disadvantages. Here, we report a case of a GS that was resected using combined gastroscopic and laparoscopic surgery.

## CASE PRESENTATION

### *Chief complaints*

A 28-year-old woman presented with a 2-mo history of epigastric discomfort and a feeling of abdominal fullness.

### *History of present illness*

Two months before presentation, the patient developed epigastric discomfort, which was accompanied by a sensation of abdominal fullness. She did not experience abdominal pain, melena, and vomiting and exhibited no other symptoms of discomfort.

### *History of past illness*

The patient was a non-smoker and did not drink alcohol. She reported no known food or drug allergies. Additionally, she had no history of blood transfusion or prior surgical procedure.

### *Personal and family history*

The patient reported no significant family history.

### *Physical examination*

Clinical data on admission were as follows: Body temperature, 36 °C; blood pressure, 120/84 mmHg; heart rate, 80 beats/min; and respiratory rate, 16 breaths/min. The abdomen appeared flat and soft, and the patient did not experience any abdominal tenderness or rebound pain.

### *Laboratory examinations*

Routine blood tests, liver and kidney function tests, and electrolyte assay revealed no marked irregularities, and tumor markers were also negative.

### *Imaging examinations*

On upper gastrointestinal (GI) endoscopy and endoscopic ultrasonography (EUS), we detected a hypoechogenic submucosal mass, which arose from the muscularis propria and projected into the lumen, in the gastric antrum (Figure 1). Computed tomography (CT) images revealed a nodular lesion (4.5 cm × 4 cm) showing homogeneous enhancement on the gastric antrum wall (Figure 2).

### *Initial diagnosis*

A working diagnosis of GIST was established, with schwannoma as a differential.

## FINAL DIAGNOSIS

Histopathological examination confirmed that the tumor was localized within the gastric muscularis propria. The tumor was well circumscribed and comprised fusiform cells. Immunohistochemically, it showed S-100 (+), 3% Ki-67 index, desmin (-), DOG-1 (-), α-smooth muscle actin (-), CD34 (-), CD117 (-), and P53 (-). Accordingly, a final diagnosis of a GS was established (Figure 3).

## TREATMENT

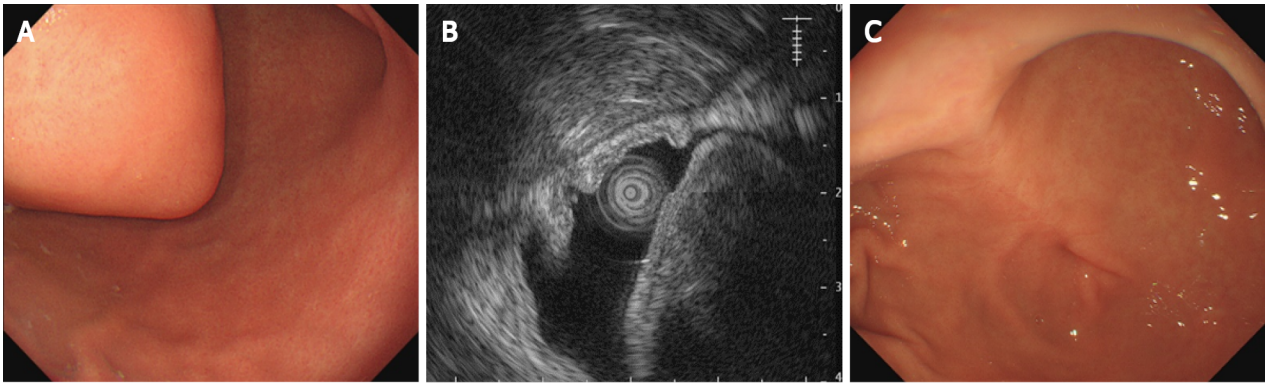
First, endoscopic resection was performed: Endoscopic full-thickness resection (EFTR) was conducted under general anesthesia with endotracheal intubation. A smooth submucosal lesion measuring 5 cm in diameter was observed on the anterior wall of the gastric antrum. We marked the edge of the lesion, injected a solution of methylene blue and saline into the mucosa, and subsequently excised the tumor gradually using a hook knife. Bleeding was minimal and easily controlled with electric hemostatic forceps. Following a successful EFTR, a large full-thickness defect was left on the gastric wall. A supplementary laparoscopic surgery was conducted considering the large defect size and difficulties with endoscopic closure and tumor extraction *via* the esophagus. The patient was placed in a supine position, and a tiny arc-shaped incision was made under the umbilicus. Next, the abdominal cavity was punctured using a pneumoperitoneum (PP) needle and filled with $CO_2$ gas to generate a peak pressure of 1.59 kPa. The PP needle was then removed. Subsequently, a cannula needle was used to puncture the abdominal cavity. The inner core of the cannula was removed, and the needle was placed into a laparoscope. Two trocar punctures were made on the left and right sides of the abdomen using the open technique. A defect measuring 5.5 cm × 5 cm was detected on the anterior wall of the gastric antrum, approximately 2 cm from the pylorus, and surrounded by small amounts of bloody fluid. The large excised tumor measuring 5 cm × 4 cm dropped into the abdominal cavity and was placed in an extraction pouch, which was subsequently removed *via* the main surgical incision. The edge of the defect on the stomach wall was trimmed using an ultrasonic knife. Subsequently, the wound was closed with a 3-0 slippery thread. Finally, we confirmed the absence of bleeding in the abdominal cavity, extracted the laparoscope, checked for appropriate retrieval of all instruments and gauze, and closed the incision and puncture sites with silk thread.

## OUTCOME AND FOLLOW-UP

The patient recovered fully and was discharged on postoperative day 7, and a check-up was performed 3 mo after the surgery. Gastroscopy showed an improvement in the healing of the gastric wall. Figure 4 illustrates the timeline of the clinical course of the patient.

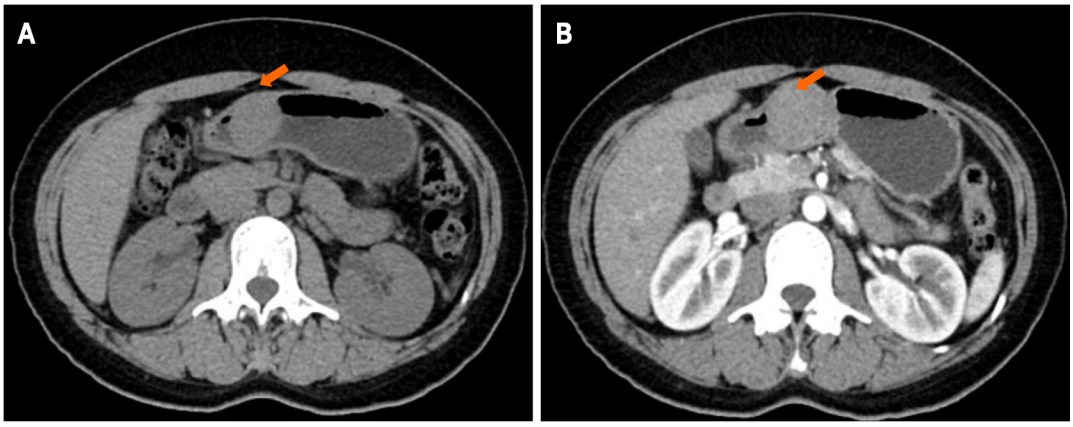
## DISCUSSION

GI mesenchymal tumors comprise a wide range of spindle cell tumors, including GISTs, leiomyomas, leiomyosarcomas, and schwannomas[3]. Furthermore, schwannomas are spindle cell mesenchymal tumors that originate from Schwann cells. GSs originate from the gastrointestinal neural plexus. Most GSs are benign, and only a few malignant cases have been reported in the literature[4,5]. Schwannomas are generally asymptomatic in affected patients; however, they may cause abdominal discomfort, pain, or digestive symptoms in some cases. A palpable mass may be detected if the tumor is large and exophytic. Dysphagia and obstipation are possible symptoms when the lesions originate from the




**DOI:** 10.4240/wjgs.v14.i4.362 **Copyright** ©The Author(s) 2022.

**Figure 1 Preoperative endoscopy and endoscopic ultrasonography.** A: Upper digestive tract endoscopy showing a submucosal tumor along the greater curvature of the anterior gastric antrum wall; B: Endoscopic ultrasonography showing a mass within the gastric antrum, which originated from the muscularis propria; C: Gastroscopy 3 mo after surgery revealing appropriate incision healing.




**DOI:** 10.4240/wjgs.v14.i4.362 **Copyright** ©The Author(s) 2022.

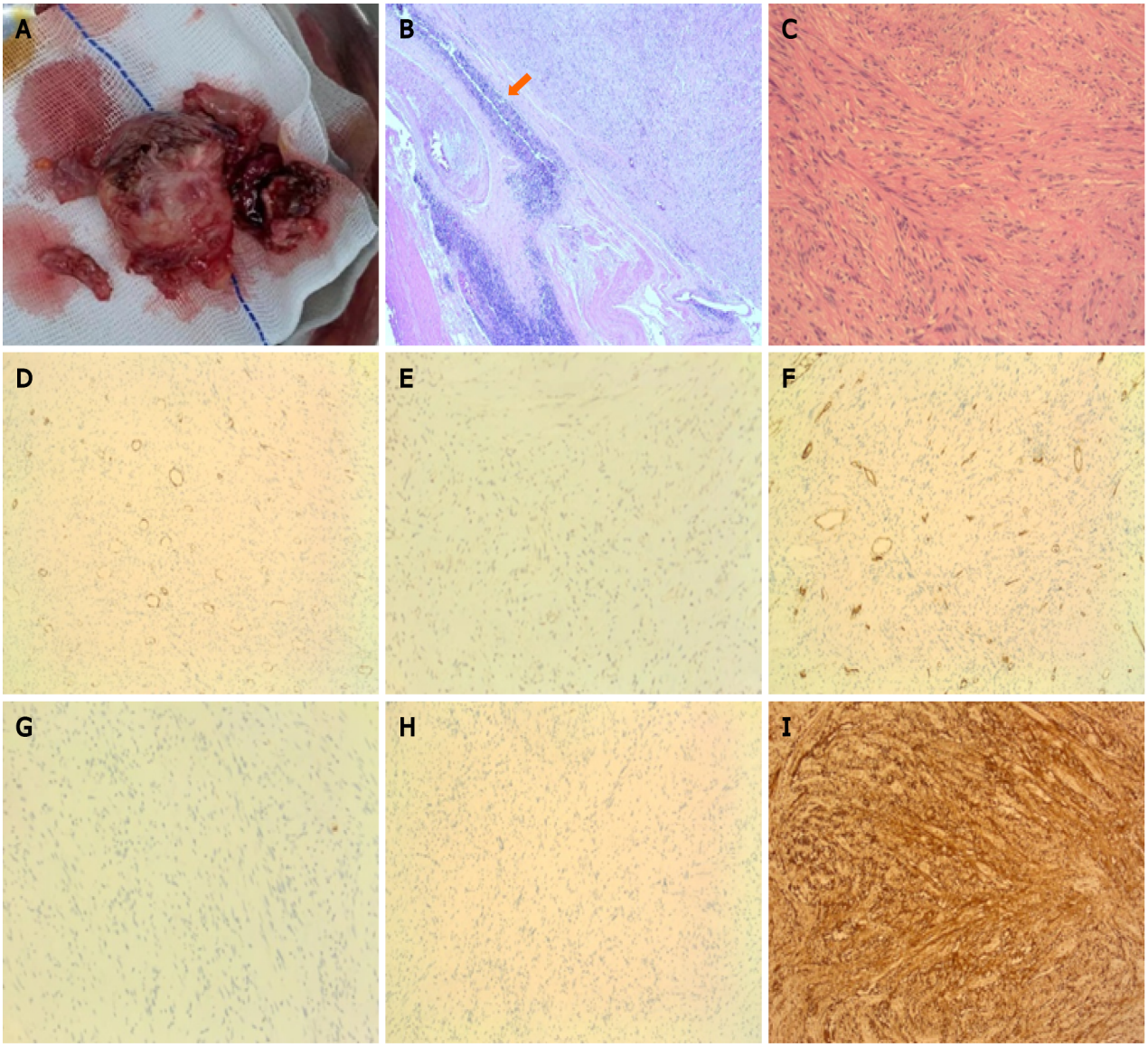
**Figure 2 Computed tomography scan.** A: Computed tomography showing an oval mass in the antrum of the stomach, with intracavitary growth; B: Enhanced computed tomography shows obvious enhancement of the mass in the arterial phase.

esophagus or rectum, respectively. Bleeding may occur if deep ulcerations are present[6,7].

GISTs are the most prevalent mesenchymal tumors of the GI tract, and 60%–70% of cases occur in the stomach. They are similar to GSs in terms of age of onset, clinical manifestations, and gross and histological appearance; however, the prognoses differ. Generally, schwannomas are mostly benign and have a good prognosis, while 10%–30% of cases of GIST are malignant[3]. Therefore, it is essential to distinguish between a GS and GIST and to develop a targeted treatment plan. The diagnostic workup for gastric tumors mainly includes upper GI endoscopy, CT, magnetic resonance imaging, and intracavitary (endoscopic) ultrasound. On endoscopy, both GS and GIST present as elevated submucosal lesions with a firm consistency. On EUS, a GS usually shows a hypoechogenic lesion originating from the muscularis propria[8]. Reports on EUS assessment show that round shape, definite borders, heterogeneous hypoechogenicity or isoechogenicity, and lack of cystic alteration and calcification are crucial markers for GS diagnosis. In contrast, on EUS, a GIST usually shows a hypoechoic or anechoic and slightly heterogeneous tumor. Hyperechogenicity is a potential sign of malignancy. GISTs are usually observed in the third or fourth layer of the gastric wall and rarely in the second layer[8]. Unlike GISTs, on CT, schwannomas appear to be uniform, significantly contrast-enhancing tumors with no evidence of hemorrhage, necrosis, cystic alteration, or calcification[9]. Despite these differences, establishing accurate preoperative diagnoses of GSs and GISTs is challenging.

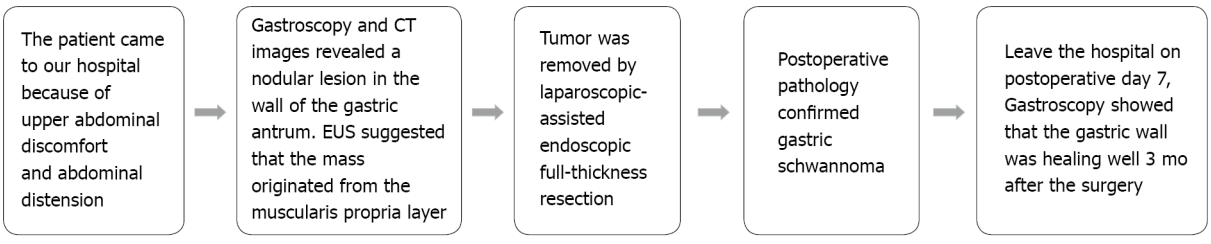
In this patient, the tumor was detected on abdominal CT and was initially thought to be a GIST. Gastroscopic and EUS findings were not contradictory; therefore, the tumor was misdiagnosed as a GIST until a correct diagnosis was established based on the tumor's immunohistochemical profile.

A GS rarely presents with specific clinical features and imaging characteristics. Therefore, preoperative diagnosis is challenging, and definitive diagnosis can only be established after careful pathological examination of the resected specimen. Given these challenges, surgical resection is the optimal treatment approach. Local extirpation, wedge resection, and partial, subtotal, or total




**DOI:** 10.4240/wjgs.v14.i4.362 **Copyright** ©The Author(s) 2022.

**Figure 3 Specimen after surgery, hematoxylin and eosin-stained pathological sections, and immunohistochemistry.** A: The resected tumor; B and C: The tumor comprises intertwined bundles of spindle cells with tapered nuclei; mitotic figures are rare. Lymphocyte infiltration is observed in the tumor tissue, and a characteristic peripheral lymphoid cuff is present (B: 4 × C: 20 ×); D-I: Immunohistochemical staining of the gastric mass confirming a gastric schwannoma with positive staining for S-100 protein (I) and negative staining for α-smooth muscle actin (D), DOG-1 (E), CD34 (F), CD117 (G), and desmin (H).




**DOI:** 10.4240/wjgs.v14.i4.362 **Copyright** ©The Author(s) 2022.

**Figure 4 Timeline of case occurrence**. CT: Computed tomography; EUS: Endoscopic ultrasonography.

gastrectomy are all acceptable approaches. Laparoscopic techniques can also be employed[10].

Submucosal gastric tumor therapies have greatly advanced in recent years, thereby enabling a more frequent use of minimally invasive endoscopic techniques, such as snare polypectomy, endoscopic submucosal dissection, and EFTR. Some studies have shown that EFTR is safe and effective for schwannomas and other tumors originating from the muscularis propria[11,12]. However, for larger

**Table 1 Literature review of laparoscopic endoscopic cooperative surgery for gastric schwannoma resection**

| Ref. | Gender | Age (yr) | No. of cases | Tumor size (cm) | Pathology | Treatment | Hospital stay (d) |
|---|---|---|---|---|---|---|---|
| Eom *et al*[16] | 3 Males; 11 Females | Median 61.0 IQR (51.0–66.8) | 14 | Median 2.6 IQR (2.3–3.7) | 9 GISTs, 2 GS, 3 Leiomyomas | LECS | Median 5.0 IQR (4.0– 5.5) |
| Mahawongkajit *et al*[17] | Female | 50 | 1 | 2.1 | GS | NEWs | NR |
| Sugiyama *et al*[18] | Female | 49 | 1 | 1.7 | GS | NEWS | 5 |
| Matsuda *et al*[19] | 47 Males; 53 Females | mean ± SD: 59.8 ± 13.2 | 100 | mean ± SD: 3.09 ± 1.06 | 75 GISTs; 11 GS; 6 Leiomyomas; 5 Ectopic pancreas; 2 Neuroendocrine tumor; 1 Lymphangioma | LECS | mean ± SD: 8.4 ± 10.2 |
| Mitsui *et al*[15] | Males | 58 | 1 | 2.4 × 2.3 × 1.9 | GS | NEWS | 7 |
| Hiki *et al*[13] | 7 Females | Range 34–66 | 7 | mean ± SD: 4.6 ± 0.3 | 6 GISTs 1 GS | LECS | mean ± SD: 7.4 ± 8.1 |

LECS: Laparoscopy-endoscopy cooperative surgery; NEWS: Non-exposed endoscopic wall-inversion surgery; GISTs: Gastrointestinal stromal tumors; GS: Gastric schwannoma; NR: Not reported; IQR: Interquartile range.

GSs, endoscopic resection should not be indicated without careful consideration because we believe that this could increase the risk of surgery and the incidence of postoperative complications.

Although laparoscopic resection can be used to treat GSs, it is difficult to precisely locate tumors within the gastric lumen with a laparoscope from the serosal surface alone. Consequently, a large portion of the stomach wall may be removed, leading to gastric deformity and outlet obstruction. Laparoscopic endoscopic cooperative surgery (LECS) was first introduced by Hiki *et al*[13] as a surgical intervention for GISTs and is currently classified as "classical LECS." LECS is superior to laparoscopic or robot-assisted wedge resection and partial resection because the gastric serosa resection area is substantially reduced, which lowers the possibility of post-surgical gastric deformity and reduces the negative impact on patients' quality of life[14]. Subsequently, Mitsui *et al*[15] developed another non-exposure technique, known as "non-exposure endoscopic wall-inversion surgery" (NEWS), that can prevent contamination and tumor dissemination into the peritoneal cavity. Only a few studies[13,15-19] have previously reported GS resection using LECS and NEWS (Table 1). Shoji *et al*[20] reported that LECS or NEWS is suitable for submucosal tumors measuring less than 5 cm in diameter. In this case, because the diameter of the gastric tumor reached 5 cm, we considered that endoscopic treatment alone might be complicated by difficulties in closing the gastric wall defect after tumor excision and removing the specimen through the esophagus. Therefore, after discussing with the patient, we decided to remove the tumor endoscopically, and if difficulties arose, laparoscopy would be performed. Accordingly, we could excise the tumor completely without removing a large part of the gastric wall while causing minimal trauma and ensuring safety. The tumor was removed using a gastroscope. The large defect in the gastric wall after tumor resection was difficult to close; therefore, suturing was performed laparoscopically. This combined surgery resulted in complete tumor excision and prevented wound expansion. Although our procedure differed from classical LECS in terms of surgical details, the goal of treatment was still to achieve complete resection of the lesion and avoid the expansion of the incision. Postoperative patient management included gastric acid inhibition, fluid replacement, dietary restriction, and nutritional support. The patient was mobile on postoperative day 1. She recovered completely and was discharged from the hospital 1 wk after surgery. Considering the outcomes of this case, we believe that laparoscopic-assisted endoscopic full-thickness resection can reduce the risk of endoscopic surgery and simultaneously achieve precise resection of lesions, which should be evaluated in future studies.

## CONCLUSION

GSs are uncommon and generally mostly benign. Despite advances in endoscopic and imaging techniques, accurate preoperative diagnosis of a GS is difficult to establish. Final diagnosis requires histopathological and immunohistochemical examinations. Surgical resection is the optimal treatment option, and the emergence of techniques, such as EFTR, has greatly increased the possibility of minimally invasive removal of small tumors. For larger GSs, combined laparoscopic and gastroscopic surgery is recommended for tumor resection.

## ACKNOWLEDGEMENTS

The authors thank Jian-Liang Wu and Li-Wei Sun for assisting in the preparation of this manuscript.

## FOOTNOTES

**Author contributions:** He CH and Lin SH reviewed the literature and contributed to manuscript drafting; Li GD drafted the manuscript and revised manuscript; Chen Z performed the pathology analyses and interpretation and contributed to manuscript drafting; Li WM and Weng CY analyzed and interpreted the imaging findings; Li GD and Guo Y were responsible for the revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

**Supported by** Zhejiang Provincial Natural Science Foundation of China, No. LGF18H160036.

**Informed consent statement:** Informed written consent was obtained from the patient for publication of this report and any accompanying images.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).



**Country/Territory of origin:** China

**ORCID number:** Cheng-Hai He 0000-0001-8322-2669; Shi-Hua Lin 0000-0002-3950-2222; Zhen Chen 0000-0003-1061-0219; Wei-Min Li 0000-0002-4012-5882; Chun-Yan Weng 0000-0003-3618-9629; Yun Guo 0000-0002-9815-0976; Guo-Dong Li 0000-0003-0800-8640.

**S-Editor:** Fan JR
**L-Editor:** A
**P-Editor:** Fan JR

## REFERENCES

1 **Hong HS**, Ha HK, Won HJ, Byun JH, Shin YM, Kim AY, Kim PN, Lee MG, Lee GH, Kim MJ. Gastric schwannomas: radiological features with endoscopic and pathological correlation. *Clin Radiol* 2008; **63**: 536-542 [PMID: 18374717 DOI: 10.1016/j.crad.2007.05.026]
2 **Hsu WH**, Wu TS, Hsieh MS, Kung YM, Wang YK, Wu JY, Yu FJ, Kuo CH, Su YC, Wang JY, Wu DC, Hu HM. Comparison of Endoscopic Submucosal Dissection Application on Mucosal Tumor and Subepithelial Tumor in stomach. *J Cancer* 2021; **12**: 765-770 [PMID: 33403034 DOI: 10.7150/jca.47653]
3 **Nishida T**, Hirota S. Biological and clinical review of stromal tumors in the gastrointestinal tract. *Histol Histopathol* 2000; **15**: 1293-1301 [PMID: 11005253 DOI: 10.14670/HH-15.1293]
4 **Loffeld RJ**, Balk TG, Oomen JL, van der Putten AB. Upper gastrointestinal bleeding due to a malignant Schwannoma of the stomach. *Eur J Gastroenterol Hepatol* 1998; **10**: 159-162 [PMID: 9581994 DOI: 10.1097/00042737-199802000-00012]
5 **Takemura M**, Yoshida K, Takii M, Sakurai K, Kanazawa A. Gastric malignant schwannoma presenting with upper gastrointestinal bleeding: a case report. *J Med Case Rep* 2012; **6**: 37 [PMID: 22277785 DOI: 10.1186/1752-1947-6-37]
6 **Hou YY**, Tan YS, Xu JF, Wang XN, Lu SH, Ji Y, Wang J, Zhu XZ. Schwannoma of the gastrointestinal tract: a clinicopathological, immunohistochemical and ultrastructural study of 33 cases. *Histopathology* 2006; **48**: 536-545 [PMID: 16623779 DOI: 10.1111/j.1365-2559.2006.02370.x]
7 **Lin CS**, Hsu HS, Tsai CH, Li WY, Huang MH. Gastric schwannoma. *J Chin Med Assoc* 2004; **67**: 583-586 [PMID: 15720074]
8 **Nishida T**, Kawai N, Yamaguchi S, Nishida Y. Submucosal tumors: comprehensive guide for the diagnosis and therapy of gastrointestinal submucosal tumors. *Dig Endosc* 2013; **25**: 479-489 [PMID: 23902569 DOI: 10.1111/den.12149]
9 **Levy AD**, Quiles AM, Miettinen M, Sobin LH. Gastrointestinal schwannomas: CT features with clinicopathologic correlation. *AJR Am J Roentgenol* 2005; **184**: 797-802 [PMID: 15728600 DOI: 10.2214/ajr.184.3.01840797]
10 **Basso N**, Rosato P, De Leo A, Picconi T, Trentino P, Fantini A, Silecchia G. Laparoscopic treatment of gastric stromal tumors. *Surg Endosc* 2000; **14**: 524-526 [PMID: 10890957 DOI: 10.1007/s004640000021]
11 **Zhai YQ**, Chai NL, Li HK, Lu ZS, Feng XX, Zhang WG, Liu SZ, Linghu EQ. Endoscopic submucosal excavation and endoscopic full-thickness resection for gastric schwannoma: five-year experience from a large tertiary center in China. *Surg*

*Endosc* 2020; **34**: 4943-4949 [PMID: 31811454 DOI: 10.1007/s00464-019-07285-w]

12 **Jain D**, Mahmood E, Desai A, Singhal S. Endoscopic full thickness resection for gastric tumors originating from muscularis propria. *World J Gastrointest Endosc* 2016; **8**: 489-495 [PMID: 27499831 DOI: 10.4253/wjge.v8.i14.489]

13 **Hiki N**, Yamamoto Y, Fukunaga T, Yamaguchi T, Nunobe S, Tokunaga M, Miki A, Ohyama S, Seto Y. Laparoscopic and endoscopic cooperative surgery for gastrointestinal stromal tumor dissection. *Surg Endosc* 2008; **22**: 1729-1735 [PMID: 18074180 DOI: 10.1007/s00464-007-9696-8]

14 **Hiki N**, Nunobe S. Laparoscopic endoscopic cooperative surgery (LECS) for the gastrointestinal tract: Updated indications. *Ann Gastroenterol Surg* 2019; **3**: 239-246 [PMID: 31131352 DOI: 10.1002/ags3.12238]

15 **Mitsui T**, Niimi K, Yamashita H, Goto O, Aikou S, Hatao F, Wada I, Shimizu N, Fujishiro M, Koike K, Seto Y. Non-exposed endoscopic wall-inversion surgery as a novel partial gastrectomy technique. *Gastric Cancer* 2014; **17**: 594-599 [PMID: 23974429 DOI: 10.1007/s10120-013-0291-5]

16 **Eom BW**, Kim CG, Kook MC, Yoon HM, Ryu KW, Kim YW, Rho JY, Kim YI, Lee JY, Choi IJ. Feasibility of Non-Exposure Simple Suturing Endoscopic Full-Thickness Resection in Comparison with Laparoscopic Endoscopic Cooperative Surgery for Gastric Subepithelial Tumors: Results of Two Independent Prospective Trials. *Cancers (Basel)* 2021; **13** [PMID: 33924610 DOI: 10.3390/cancers13081858]

17 **Mahawongkajit P**, Chanswangphuvana P. Laparoscopy-assisted endoscopic full-thickness resection of upper gastrointestinal subepithelial tumors: A single-center early experience. *Mol Clin Oncol* 2020; **12**: 461-467 [PMID: 32257204 DOI: 10.3892/mco.2020.2011]

18 **Sugiyama T**, Ebi M, Ochiai T, Kurahashi S, Saito T, Onishi K, Yamamoto K, Inoue S, Adachi K, Yoshimine T, Yamaguchi Y, Tamura Y, Izawa S, Hijikata Y, Funaki Y, Ogasawara N, Sasaki M, Kasugai K. Gastric schwannoma with high accumulation on fluorodeoxyglucose-positron emission tomography resected by non-exposed endoscopic wall-inversion surgery. *Clin J Gastroenterol* 2020; **13**: 50-54 [PMID: 31270750 DOI: 10.1007/s12328-019-01014-5]

19 **Matsuda T**, Hiki N, Nunobe S, Aikou S, Hirasawa T, Yamamoto Y, Kumagai K, Ohashi M, Sano T, Yamaguchi T. Feasibility of laparoscopic and endoscopic cooperative surgery for gastric submucosal tumors (with video). *Gastrointest Endosc* 2016; **84**: 47-52 [PMID: 26684599 DOI: 10.1016/j.gie.2015.11.040]

20 **Shoji Y**, Takeuchi H, Goto O, Tokizawa K, Nakamura R, Takahashi T, Wada N, Kawakubo H, Yahagi N, Kitagawa Y. Optimal minimally invasive surgical procedure for gastric submucosal tumors. *Gastric Cancer* 2018; **21**: 508-515 [PMID: 28744619 DOI: 10.1007/s10120-017-0750-5]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 April 27; 14(4): 370-373

DOI: 10.4240/wjgs.v14.i4.370

ISSN 1948-9366 (online)

LETTER TO THE EDITOR

# Imaging of acute appendicitis: Advances

Sonay Aydın, Erdal Karavas, Düzgün Can Şenbil

**Specialty type:** Radiology, nuclear medicine and medical imaging

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Abd EL hafez A, Egypt; Wichmann D, Germany

**Received:** December 3, 2021
**Peer-review started:** December 3, 2021
**First decision:** January 30, 2022
**Revised:** February 2, 2022
**Accepted:** March 26, 2022
**Article in press:** March 26, 2022
**Published online:** April 27, 2022

**Sonay Aydın, Erdal Karavas, Düzgün Can Şenbil,** Department of Radiology, Erzincan Binali Yıldırım University Faculty of Medicine, Erzincan 24100, Turkey

**Corresponding author:** Düzgün Can Şenbil, MD, Academic Research, Doctor, Department of Radiology, Erzincan Binali Yıldırım University Faculty of Medicine, Başbağlar, Hacı Ali Akın Cd. No. 32 Erzincan 24100, Turkey. senbilcan@gmail.com

## Abstract

We read with interest the review by Teng *et al*, who summarized the current approach to the diagnosis and treatment of acute appendicitis (AA). Also, the article summarizes the clinical scoring systems very effectively. In one of the previous studies conducted by our research group, we showed that the use of the Alvarado score, ultrasound and C-reactive protein values in combination provides a safe confirmation or exclusion of the diagnosis of AA. Computed tomography is particularly sensitive in detecting periappendiceal abscess, peritonitis and gangrenous changes. Computed tomography is not a good diagnostic tool in pediatric patients because of the ionizing radiation it produces. Ultrasound is a valuable diagnostic tool to differentiate AA from lymphoid hyperplasia. Presence of fluid collection in the periappendiceal and lamina propria thickness less than 1 mm are the most effective parameters in differentiating appendicitis from lymphoid hyperplasia. Although AA is the most common cause of surgical acute abdomen, it remains an important diagnostic and clinical challenge. By combining clinical scoring systems, laboratory data and appropriate imaging methods, diagnostic accuracy and adherence to treatment can be increased. Lymphoid hyperplasia and perforated appendicitis present significant diagnostic challenges in children. Additional ultrasound findings are increasingly defined to differentiate AA from these conditions.

**Key Words:** Acute appendicitis; Inflammation; Acute abdomen; Perforation

**Core Tip:** Despite the fact that acute appendicitis is the most common cause of acute abdomen, it remains a diagnostic and clinical challenge. When the ultrasound, Alvarado scoring and C-reactive protein are used in conjunction to diagnose acute appendicitis, the diagnosis can be safely confirmed or ruled out. Computed tomography scans are extremely sensitive in detecting complications from acute appendicitis. Computed tomography scans are especially effective at detecting periappendix abscesses, peritonitis and gangrenous changes. Because of the ionizing radiation it emits, computed tomography is not a good diagnostic tool in pediatric patients. In pediatric patients, ultrasound should be the preferred method.

**Citation:** Aydın S, Karavas E, Şenbil DC. Imaging of acute appendicitis: Advances. *World J Gastrointest Surg* 2022; 14(4): 370-373
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i4/370.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i4.370

## TO THE EDITOR

We read with interest the review by Teng *et al*[1], who summarized the current approach to the diagnosis and treatment of acute appendicitis (AA). Also, the article summarizes the clinical scoring systems very effectively.

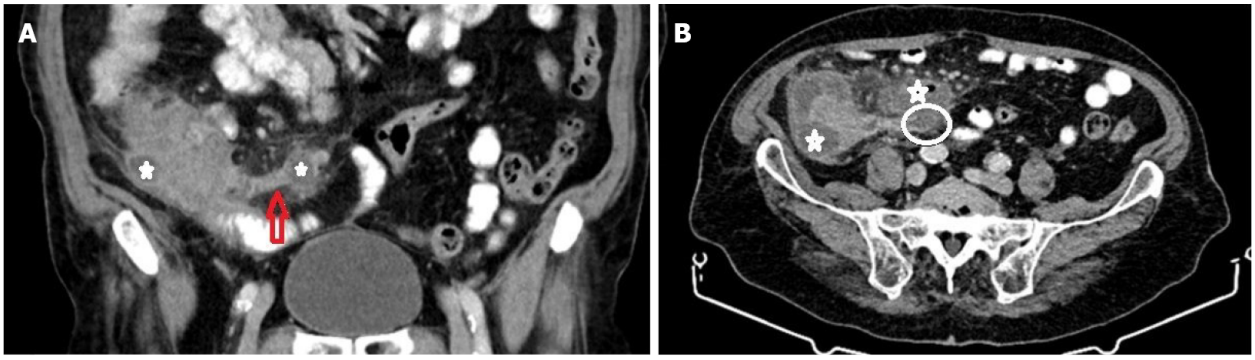
In one of the published studies of our research group, we have shown that using the Alvarado score, ultrasound (US) and C-reactive protein (CRP) levels in combination enables the confirmation or rejection of AA safely[2]. The Alvarado scoring system is one of the most commonly used methods[1]. Even though the scoring system contains series of laboratory parameters, it does not contain CRP levels. Rather than using the Alvarado system or US alone, combining these methods with CRP levels will increase diagnostic accuracy.

Teng *et al*[1] stated that computerized tomography scans have a well-established role in evaluating AA-related complications. Computed tomography is especially sensitive for detecting periappendiceal abscess, peritonitis and gangrenous changes[1] (Figure 1). Pediatric patients are more likely to develop perforated appendicitis. Imaging is critical in diagnosing perforated appendicitis; clinical differentiation can be challenging, especially in younger children. Computed tomography is not a good diagnostic tool in pediatric patients due to the ionizing radiation it produces. According to our results, US can also be used as an effective diagnostic tool for the detection of pediatric perforated appendicitis cases. The most valuable US parameters are the detection of loculated fluid in the periappendiceal area and fluid collection in all abdominal recesses. When these parameters are combined with CRP levels, diagnostic performance can be improved[3].

Teng *et al*[1] emphasized that AA occurs when the appendiceal orifice is obstructed (for example, by lymphoid hyperplasia or fecaliths), resulting in inflammation. We have demonstrated that, in addition to causing AA, lymphoid hyperplasia can serve as a significant mimicker of AA by forming an incompressible appendix larger than 6 mm in diameter, particularly in pediatric patients. US is a valuable diagnostic tool for differentiating AA from lymphoid hyperplasia. The presence of periappendiceal fluid collection and a lamina propria thickness of less than 1 mm are the most effective parameters for differentiating appendicitis from lymphoid hyperplasia[4] (Figure 2).

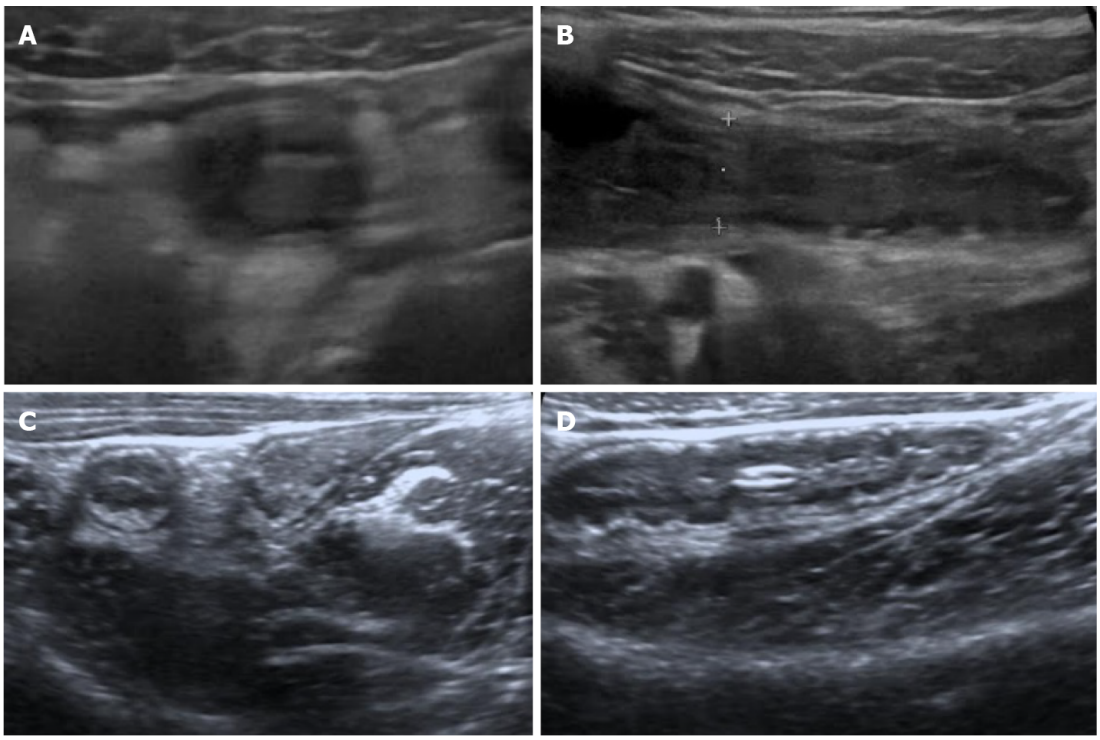
The portal vein can be affected from appendiceal inflammation, and thrombosis might occur[1]. In addition to complications, according to our data, portal vein hemodynamic changes can help to confirm AA diagnosis in children. In equivocal cases, detecting an increase in portal vein diameter and/or flow velocity may corroborate other clinical signs of AA[5].

To summarize, AA remains a significant diagnostic and clinical challenge despite being the most common cause of surgical acute abdomen. By combining clinical scoring systems, laboratory data and appropriate imaging methods, diagnostic accuracy and treatment adherence can be increased. Lymphoid hyperplasia and perforated appendicitis present significant diagnostic challenges in children. Additional US findings are increasingly being defined for the purpose of distinguishing AA from these entities.




**DOI:** 10.4240/wjgs.v14.i4.370 **Copyright** ©The Author(s) 2022.

**Figure 1 An 87-yr-old male.** Coronal (A) and axial (B) sections are shown. The appendix diameter has increased, and it appears inflamed (red arrow). The distal part of the appendix is perforated (white circle). Abscesses are seen in the periappendiceal and pericecal areas (white star).




**DOI:** 10.4240/wjgs.v14.i4.370 **Copyright** ©The Author(s) 2022.

**Figure 2 Acute appendicitis in a 12-yr-old boy.** A-B: Sonographic images taken axially (A) and longitudinally (B). The lamina propria is not discernible; C-D: For comparison, axial (C) and longitudinal (D) sonographic images of an 8-year-old girl with lymphoid hyperplasia. Note the prominent and thick lamina propria.

## FOOTNOTES

**Author contributions:** Aydın S put forward the concept; Şenbil DC was responsible for designing; Karavas E provided resources; Aydın S and Karavas E were responsible for supervision, did the literature search and reviewed the manuscript critically; Şenbil DC and Aydın S were responsible for materials and wrote the manuscript; All authors have read and approved the final manuscript.

**Conflict-of-interest statement:** The authors declare having no conflicts of interest.



**Country/Territory of origin:** Turkey

**ORCID number:** Sonay Aydın 0000-0002-3812-6333; Erdal Karavas 0000-0001-6649-3256; Düzgün Can Şenbil 0000-0003-0233-7371.

**S-Editor:** Wu YXJ
**L-Editor:** Filipodia
**P-Editor:** Wu YXJ

## REFERENCES

1 **Teng TZJ**, Thong XR, Lau KY, Balasubramaniam S, Shelat VG. Acute appendicitis-advances and controversies. *World J Gastrointest Surg* 2021; **13**: 1293-1314 [PMID: 34950421 DOI: 10.4240/wjgs.v13.i11.1293]
2 **Aydin S**, Fatihoglu E, Ramadan HS, Akhan B, Koseoglu EN. Alvarado score, ultrasound, and CRP: how to combine them for the most accurate acute appendicitis diagnosis. *Iranian J Radi* 2017; **14** [DOI: 10.5812/iranjradiol.38160]
3 **Aydin S**, Fatihoğlu E. Perforated appendicitis: A sonographic diagnostic challenge. *Ankara Eğitim ve Araştırma Hastanesi Tıp Dergisi* 2018; **51**: 110-115
4 **Aydin S**, Tek C, Ergun E, Kazci O, Kosar PN. Acute Appendicitis or Lymphoid Hyperplasia: How to Distinguish More Safely? *Can Assoc Radiol J* 2019; **70**: 354-360 [PMID: 31500858 DOI: 10.1016/j.carj.2018.09.006]
5 **Aydin S**, Ucan B. Pediatric acute appendicitis: Searching the diagnosis in portal vein. *Ultrasound* 2020; **28**: 174-179 [PMID: 32831890 DOI: 10.1177/1742271X20918001]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
**Telephone:** +1-925-3991568
**E-mail:** bpgoffice@wjgnet.com
**Help Desk:** https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 1948-9366 (online)

# World Journal of

# *Gastrointestinal Surgery*

*World J Gastrointest Surg* 2022 May 27; 14(5): 374-527

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 14 Number 5 May 27, 2022

*World Journal of Gastrointestinal Surgery*

**Monthly Volume 14 Number 5 May 27, 2022**

## Contents

*World Journal of Gastrointestinal Surgery*

**Monthly Volume 14 Number 5 May 27, 2022**

# Contents

## ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Chong-Chi Chiu, MD, Attending Doctor, Professor, Surgeon, Department of General Surgery, E-Da Cancer Hospital, Kaohsiung 82445, Taiwan. chiuchongchi@yahoo.com.tw

## AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJGS* mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

## INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJGS* as 2.582; IF without journal self cites: 2.564; 5-year IF: 3.378; Journal Citation Indicator: 0.53; Ranking: 97 among 212 journals in surgery; Quartile category: Q2; Ranking: 73 among 92 journals in gastroenterology and hepatology; and Quartile category: Q4.

## RESPONSIBLE EDITORS FOR THIS ISSUE



**NAME OF JOURNAL**
*World Journal of Gastrointestinal Surgery*

**ISSN**
ISSN 1948-9366 (online)

**LAUNCH DATE**
November 30, 2009

**FREQUENCY**
Monthly



**PUBLICATION DATE**
May 27, 2022



**INSTRUCTIONS TO AUTHORS**
https://www.wjgnet.com/bpg/gerinfo/204

**GUIDELINES FOR ETHICS DOCUMENTS**
https://www.wjgnet.com/bpg/GerInfo/287

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**
https://www.wjgnet.com/bpg/gerinfo/240

**PUBLICATION ETHICS**
https://www.wjgnet.com/bpg/GerInfo/288

**PUBLICATION MISCONDUCT**
https://www.wjgnet.com/bpg/gerinfo/208

**ARTICLE PROCESSING CHARGE**
https://www.wjgnet.com/bpg/gerinfo/242

**STEPS FOR SUBMITTING MANUSCRIPTS**
https://www.wjgnet.com/bpg/GerInfo/239

**ONLINE SUBMISSION**
https://www.f6publishing.com

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 May 27; 14(5): 374-382

DOI: 10.4240/wjgs.v14.i5.374

ISSN 1948-9366 (online)

*OPINION REVIEW*

# Comparison between recent sphincter-sparing procedures for complex anal fistulas-ligation of intersphincteric tract *vs* transanal opening of intersphincteric space

Pankaj Garg

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

**P-Reviewer:** Parellada CM, Guatemala; Yang BL, China

**Received:** December 29, 2021
**Peer-review started:** December 29, 2021
**First decision:** January 27, 2022
**Revised:** January 29, 2022
**Accepted:** April 27, 2022
**Article in press:** April 27, 2022
**Published online:** May 27, 2022

**Pankaj Garg,** Department of Colorectal Surgery, Garg Fistula Research Institute, Panchkula 134113, India

**Pankaj Garg,** Department of Colorectal Surgery, Indus International Hospital, Mohali 140507, India

**Corresponding author:** Pankaj Garg, MS, CEO, Chief Colorectal Surgeon, Department of Colorectal Surgery, Garg Fistula Research Institute, 1043, Sector 15, Panchkula 134113, India. drgargpankaj@gmail.com

## Abstract

Complex anal fistulas are difficult to treat. The main reasons for this are a higher recurrence rate and the risk of disrupting the continence mechanism because of sphincter involvement. Due to this, several sphincter-sparing procedures have been developed in the last two decades. Though moderately successful in simple fistulas (50%-75% healing rate), the healing rates in complex fistulas for most of these procedures has been dismal. Only two procedures, ligation of intersphincteric fistula tract and transanal opening of intersphincteric space have been shown to have good success rates in complex fistulas (60%-95%). Both of these procedures preserve continence while achieving high success rates. In this opinion review, I shall outline the history, compare the pros and cons, indications and contraindications and future application of both these procedures for the management of complex anal fistulas.

**Key Words:** Anal fistula; Fistulotomy; Incontinence; Ligation of intersphincteric fistula tract; Transanal opening of intersphincteric space; Recurrence

**Core Tip:** Ligation of intersphincteric fistula tract (LIFT) and transanal opening of intersphincteric space (TROPIS) are two of the more recent innovative procedures introduced in the last decade. Both of these procedures have been shown to be quite effective in complex anal fistulas. As both procedures are primarily sphincter-sparing, they do not lead to deterioration in continence. The advantages and disadvantages, indications and contraindications of LIFT and TROPIS have been discussed in this opinion viewpoint as well as the role both these procedures are likely to play in the future.

**Citation:** Garg P. Comparison between recent sphincter-sparing procedures for complex anal fistulas-ligation of intersphincteric tract *vs* transanal opening of intersphincteric space. *World J Gastrointest Surg* 2022; 14(5): 374-382
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i5/374.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i5.374

## INTRODUCTION

The management of complex anal fistulas is challenging[1]. This is because complex fistulas involve a significant part of the sphincter complex [internal anal sphincter (IAS), external anal sphincter (EAS) or both] and if adequate care is not taken, then the sphincters may be damaged leading to permanent incontinence[1,2]. Fistulotomy is the most common procedure performed for anal fistulas but fistulotomy is contraindicated in complex fistulas as the risk of sphincter injury is high[2]. Therefore, several new sphincter-sparing procedures have been developed over the last two decades like video-assisted anal fistula treatment (VAAFT)[3-7], anal fistula plug (AFP)[8,9], over the scope clip (OTSC)[10-12], fistula laser treatment (FiLac)[2], stem cells[13,14], fixcision[15], fibrin glue[16-18], ligation of intersphincteric fistula tract (LIFT)[19-25], Bio-LIFT[26] and transanal opening of intersphincteric space (TROPIS)[27-31].

The main feature of all of these newer procedures is that they are largely sphincter-preserving especially for the EAS. Though most of these procedures demonstrated a moderate success rate in simple fistulas (40%-75%), their success rate in complex fistulas was either not satisfactory or not studied. Only two of these procedures, LIFT[19,21,22,24,25] and TROPIS demonstrated encouraging results (60%-95%) in highly complex fistulas[27-30,32]. Though these two procedures (LIFT and TROPIS) are not very old, we now have enough evidence (published studies), including a few studies with long-term results on the basis of which preliminary comparison can be done between these two procedures.

## DEFINITIONS-PROCEDURE STEPS

### *LIFT*

A curvilinear incision is made in the intersphincteric groove on the perianal skin in the quadrant where the internal opening of the fistula is located. The plane between the two sphincters (IAS and EAS) is dissected and the fistula tract traversing through the intersphincteric space is identified and a loop is passed around it. The tract in the intersphincteric space is divided. The proximal end of the intersphincteric fistula tract (towards the IAS) is suture ligated with an absorbable suture. The distal end of the intersphincteric fistula tract (towards the EAS) is suture ligated or excised along with the tract in the ischioanal fossa. The dissected out intersphincteric plane may be left open to drain or loosely sutured.

### *TROPIS*

In this procedure, through the transanal route, an artery forceps is inserted into the fistula tract which is present in the intersphincteric plane through the internal opening. The mucosa and the internal sphincter over the artery forceps are incised and its edges are trimmed with electrocautery. Thus, the intersphincteric space is opened into the anal canal. This wound is left open to heal by secondary intention. The fistula tract lateral (external) to the EAS can be managed by any method convenient to the surgeon (excision or curettage with insertion of a drainage tube or laser ablation).

## HISTORY

Until 1958, anal fistulas were classified only as per their relationship to the anorectal ring without any

importance being attached to the intersphincteric space. Eisenhammer highlighted the importance of the intersphincteric space in pathogenesis and management of anal fistula for the first time in 1958[33]. After that, it was understood that intersphincteric abscesses could be drained into the anorectum through the transanal route thereby saving the EAS from iatrogenic injury. However, for several decades (till 2017), this concept of transanal drainage of intersphincteric sepsis was limited to high intersphincteric abscesses only[29].

In 1993, Matos *et al*[34], for the first time, dissected into the intersphincteric space through the intersphincteric groove. They excised the fistula tract in the intersphincteric space and then the defect in the IAS was oversewn with 2-0 polyglactin suture[34]. In a small cohort of 13 patients, they reported a success rate of 53.8% (7/13)[34]. However, the main credit of developing and popularizing this technique goes to Rojanasakul *et al*[25,35]. Instead of excising the fistula tract in the intersphincteric space, he ligated this tract[25,35]. This made the closure more secure, the procedure simpler and the success rate higher[35]. In the last decade, LIFT has made significant inroads into the armamentarium of fistula surgeons all across the globe. Success rates ranging from 42%[8] to more than 90%[23,24] have been reported (76% in recent reviews[22,36]), implying that proper execution of the procedure is one of the key determinants to achieving a high success rate[22].

In 2017, a new dimension was added to the importance of the intersphincteric space by Garg *et al*[29]. It was postulated that the fistula tract in the intersphincteric space, whenever present in any fistula, is sepsis between two sphincter muscles and is thus similar to an abscess in a closed space[2]. As any abscess is best treated by deroofing and healing by secondary intention, therefore, this intersphincteric 'abscess' (fistula tract in the intersphincteric space) should be treated by deroofing it into the anorectum through the transanal route. This is done by the TROPIS procedure. TROPIS is quite different from just drainage of high intersphincteric abscesses into the rectum. First, whereas the latter was only for pure high intersphincteric abscesses (which accounts for less than 10% of anorectal suppuration[37]), the TROPIS procedure is applicable in all fistulas including transsphincteric, suprasphincteric and supralevator fistulas as all fistulas have at least some intersphincteric component. Second, the intent in drainage of high intersphincteric abscesses was resolution of acute sepsis and the fistula was managed later in many cases. On the other hand, in TROPIS, the intent is curative in all fistula cases including even those presenting with acute abscess[29,37]. This happens because the fistula tract in the intersphincteric space is thoroughly cauterized and opened into the anal canal, the infected crypt glands are destroyed and the resulting wound is allowed to heal by secondary intention[37]. Though this takes 6-10 wk to heal completely but the chances of recurrences are reduced substantially[37]. It is known that in presence of infection, healing by secondary intention is better and more assured than healing by primary intention[29,37]. Therefore, TROPIS is the first procedure in complex fistulas in which the internal opening is allowed to heal by secondary intention. In simple fistulas, fistulotomy also follows the same principle and therefore results in high healing rates[37].

Thus, both these procedures, LIFT and TROPIS, are different because rather than primarily focusing on closure of the internal opening (as was done by other newer procedures), these two procedures lay equal, rather more, emphasis on the fistula tract in the intersphincteric space. This could be the reason for the much higher success rate of these procedures.

Malakorn *et al*[24] published their long-term experience with LIFT in 251 anal fistula patients and reported a primary healing rate of 87.65% at a median follow-up of 71 mo. Garg *et al*[37] published their long-term experience with TROPIS in 408 patients suffering from high complex fistulas and reported healing rates of 86% at a median follow-up of 30 mo. Both these procedures have also been shown to be effective in managing fistulas associated with acute abscess definitively in the first surgery (rather than draining the abscess first and then operating to treat fistula later)[23,29,37].

## PROS AND CONS

The main advantage of LIFT is that both sphincters, IAS and EAS, are completely preserved and therefore, the risk of incontinence is negligible[23,24]. Another main advantage is that the resultant wound is allowed to heal by primary intention due to which recovery is much faster (Table 1).

The disadvantages of LIFT are that it is technically demanding and it takes time and patience to master this procedure. Another disadvantage is that the tackling of infected crypt glands is less thorough in LIFT as compared to TROPIS. The healing in LIFT is by primary intention and as discussed above and in presence of infection, healing by secondary intention gives better long-term healing rates. Due to these reasons, the success rate of LIFT is perhaps less as compared to TROPIS. Recent meta-analysis has highlighted the healing rate of LIFT in 26 studies (1378 patients) to be 76.5%[22] while in the single largest study on LIFT, Malakorn *et al*[24] published healing rates of 87.65%. However, in both these, the sample consisted of simple as well as complex fistulas. There are only a few studies in which LIFT has been studied in exclusive high complex anal fistulas. A randomized controlled trial by Jayne *et al*[38] in 2020 reported a dismal success rate of 42% with LIFT in an exclusive cohort of complex fistulas.

On the other hand, the advantages of TROPIS are that it is technically simpler than LIFT. While performing the LIFT procedure, it is not uncommon to enter the submucosal space while dissecting the

**Table 1 Comparison between ligation of intersphincteric fistula tract and transanal opening of intersphincteric space procedures**

| | LIFT | TROPIS |
|---|---|---|
| Fistula tract in intersphincteric space | Ligated | Deroofed into anal canal |
| Healing of wound | Primary intention | Secondary intention |
| Tackling of infected crypt glands | Done | Much better |
| Technically | Difficult | Simpler |
| Indications | Not possible/ very difficult to perform in: Pure intersphincteric fistulas; Fistulas with more intersphincteric component like horseshoe fistulas; Fistulas in which intersphincteric component is high up like supralevator fistulas, suprasphincteric fistulas | Effective in all complex fistulas |
| Preferred over the other (LIFT or TROPIS) | Complex high fistula with minimal fistula component in the intersphincteric space (Figure 1); Patients having simple low fistula but they are not keen for fistulotomy | Horseshoe fistulas with extensive intersphincteric component (Figure 2); Recurrent fistulas especially fistulas recurring after undergoing LIFT; High transsphincteric (involving upper one-third of EAS); Suprasphincteric fistula (Figure 3) |
| Healing in postoperative period | Faster | Slower |
| Internal sphincter | Preserved | Partially incised; Study in a large number of patients with long-term follow-up have demonstrated that if patients did regular Kegel exercises in the postoperative period, then there was no significant deterioration in continence. |

LIFT: Ligation of intersphincteric fistula tract; TROPIS: Transanal opening of intersphincteric space.

intersphincteric space. In this scenario, continuation of the LIFT procedure becomes difficult. Occurrence of this digression does not make any difference to the TROPIS procedure as both the submucosal and intersphincteric spaces have to be laid open into the anal canal. Therefore, TROPIS is easy to learn and reproduce. In the LIFT procedure, a useful trick to avoid entering the submucosal space is to dissect the fistula in the intersphincteric space along the medial edge of the external sphincter.

In TROPIS procedure, the infected crypt glands are thoroughly destroyed as the fistula tract in the intersphincteric space is laid open and the resultant opened intersphincteric space is completely cauterized with electrocautery. The complete removal of infected crypt glands also happens in the LIFT procedure but the difference is that healing in LIFT occurs by primary intention whereas in TROPIS, the healing of the wound occurs by secondary intention. In the presence of infection, the healing by secondary intention is preferred and this could be the reason for high healing rates (80%-93%) by TROPIS in complex fistulas[27-29,37]. In the single largest study of TROPIS, 408 patients suffering from high complex fistulas (all fistulas involving > 1/3 of EAS), the reported healing rate was 86% at a median follow-up of 30 mo[37]. The data of 408 patients in this study[37] included 325 patients reported in an earlier study[29]. The study had several strong points. Apart from a large cohort with a fairly long follow-up, pre-operative MRI was done in all the patients and all 408 patients were documented to be high (involving > 1/3 of EAS) on clinical as well as on MRI assessment[37]. Additionally, the clinical fistula healing in the postoperative period was also documented on postoperative MRI assessment in the majority of cases[37]. So, from the evidence available so far, the healing rate of TROPIS seems better than LIFT in high complex fistulas. But, an important point to consider is that LIFT has been performed, studied and published from far more centers across the globe than the TROPIS procedure. Therefore, TROPIS would be considered highly successful in high complex fistulas only when its high success rate is replicated in many more centers in different regions of the world. For translation into practical guidelines, comparative prospective studies of LIFT and TROPIS in complex fistulas still need to be done.

The main disadvantage of TROPIS is that the intra-anal wound heals by secondary intention and the time taken for complete wound healing is relatively longer. Another disadvantage of TROPIS is that IAS is partially incised while laying open the fistula tract in the intersphincteric space. Though it is known that EAS is more important for continence mechanism than IAS[34], yet division of IAS can also lead to continence disturbances especially urgency and flatus incontinence[39]. But, studies of TROPIS in a large cohort of exclusive complex fistulas highlighted no significant deterioration in continence on long-term follow-up[29,37]. The reason for this could be that the patients were advised to do pelvic floor exercises (Kegel exercises) meticulously in the postoperative period[29,37]. These exercises perhaps compensated for the decrease in resting anal pressure (as IAS is primarily responsible for maintaining resting anal pressure)[34].

In a recent study (not published, under submission), the efficacy of Kegel exercises (KE) in improving incontinence was evaluated in 102 complex anal fistula patients in whom TROPIS procedure was performed. There were 65 recurrent fistulas, 92 had multiple tracts, 42 had associated abscess, 46 had horseshoe fistula and 34 were supralevator fistulas. All were MRI-documented high fistulas (> 1/3 EAS involved). The incontinence was evaluated objectively by Vaizey's incontinence scores [a score of 0 (minimum score) implies no continence problem while score of 24 (maximum score) implies total incontinence][40]. The scoring was done initially in the immediate postoperative period before commencement of KE (pre-KE group) and then on long-term follow-up at 18 mo after surgery (post-KE group). The incontinence scores in both groups were compared to evaluate the efficacy of KE. Overall continence disturbance occurred in 31% patients (pre-KE group) [urge and gas incontinence accounting for the majority of cases (28.3%)] but after doing regular KE, continence disturbance disappeared completely in 18 % and improved in 13 % (of 31% patients with continence disturbance in pre-KE group). The mean incontinence scores in the pre-KE group were 1.19 ± 1.96 (in 31 patients, solid = 0, liquid = 7, gas = 8, urge = 24) and in the post-KE group were 0.26 ± 0.77 (in 13 patients, solid = 0, liquid = 2, gas = 3, urge = 10) ($P$ = 0.00001, $t$-test). Division of the IAS led to mainly urge incontinence and all continence disturbance due to partial division of IAS by TROPIS improved significantly with regular Kegel exercises. Thus, the negative effect of partial division of IAS by TROPIS can be countered by regular KE in postoperative period for one year.

The IAS is primarily responsible for maintaining resting anal pressures. Division of the IAS leads to a decrease in resting anal pressure. Normally, the anal canal is free of fecal matter and only when the IAS relaxes during the act of defecation, the feces enter the anal canal. The human mind is tuned to associate the presence of fecal matter in the anal canal with impending passage of feces. Therefore, in patients with a divided IAS and decreased resting anal pressure, feces when present in the lower rectum passes unrestricted into the anal canal giving the feeling that 'feces are about to pass out of the anus' (urge incontinence). That's why the urge incontinence was seen in significant numbers of patients after the TROPIS procedure but it improved substantially with Kegel exercises[37].

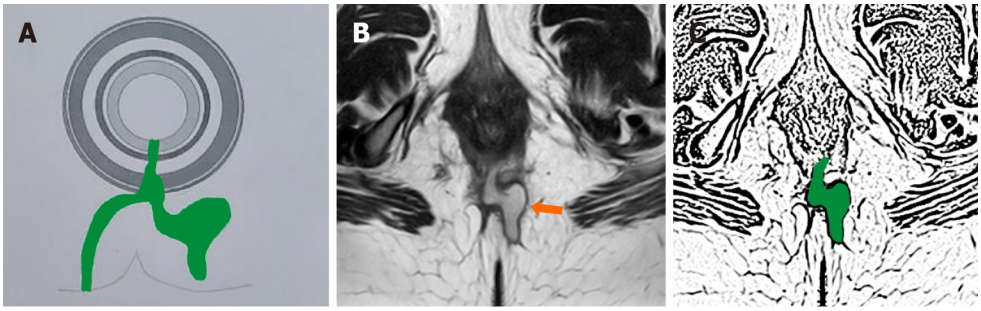
## INDICATIONS AND CONTRAINDICATIONS

The LIFT procedure can be performed in all simple as well as most complex fistulas (Figure 1). LIFT would be difficult to perform in fistulas with a greater intersphincteric component like horseshoe fistulas (Figure 2), fistulas in which the intersphincteric component is high up (like suprasphincteric fistulas (Figure 3), supralevator fistulas, high transsphincteric fistulas involving the upper-third of the EAS) as the procedure would be technically difficult to perform in these fistulas and pure intersphincteric fistulas (Table 1)[22]. The results of LIFT are lower in recurrent fistulas as the postoperative fibrosis and scarring obscure the anatomic planes making the surgery more challenging [22]. In horseshoe fistulas, the curved anatomic location of the tract renders complete eradication of fistula pathology more challenging[22].

TROPIS can be performed in all complex fistulas including high transsphincteric fistulas. Additionally, TROPIS can also be conveniently performed in fistulas in which LIFT is difficult to perform (fistulas with a high intersphincteric component-supralevator fistulas, suprasphincteric fistulas, high transsphincteric fistulas, fistulas with a greater intersphincteric component-horseshoe fistulas, recurrent fistulas and pure intersphincteric fistulas)[29,37] (Table 1).

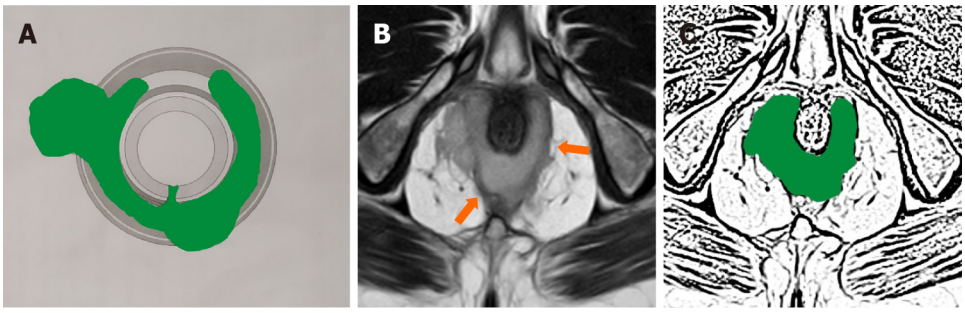
## PRESENT AND FUTURE SCENARIO

Both LIFT and TROPIS have added immense value to the management of complex anal fistulas. Both procedures have shown moderate to high success rates in complex fistulas without negatively impacting continence. This makes these procedures stand out from all other newer procedures developed in last two decades. LIFT is a 14 year old procedure and more evidence is available whereas TROPIS is only 5 years and the evidence is just emerging. In my opinion, both these procedures are conceptually sound and are coupled with good available evidence. It is likely that these two procedures are going to stay and become useful for the treatment of complex anal fistulas. These procedures complement each other and together they could become an important tool in the armamentarium of fistula surgeons. In complex high fistula in which the fistula component in the intersphincteric space is minimal, LIFT would be a better choice than TROPIS (Figure 1). Similarly, in a simple fistula, if the patient is not keen to undergo fistulotomy, then LIFT would be a better choice. In horseshoe fistulas with an extensive intersphincteric component (Figure 2), recurrent fistulas especially fistulas recurring after undergoing LIFT procedure, high transsphincteric (involving upper one-third of EAS) and suprasphincteric fistulas (Figure 3), TROPIS would be a better choice. Comparative studies comparing LIFT and TROPIS, preferably randomized, would provide vital insight into the efficacy of these procedures and the future role each procedure would likely have in the surgical practice of complex fistulas.



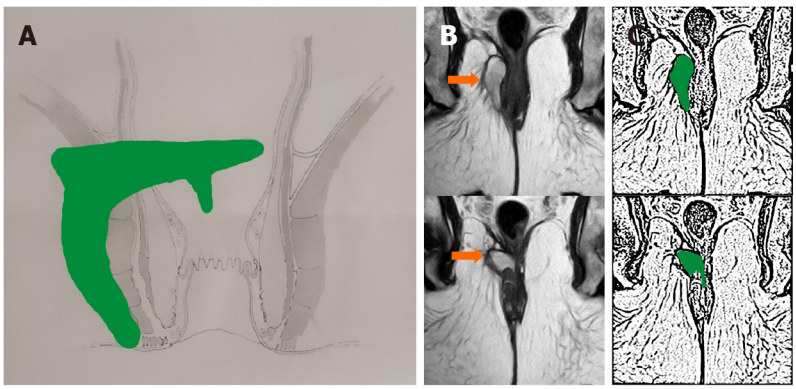

**DOI:** 10.4240/wjgs.v14.i5.374 **Copyright** ©The Author(s) 2022.

**Figure 1 A 43-year-old female patient with recurrent high transsphincteric posterior anal fistula with multiple branches.** The intersphincteric component of fistula is a single linear tract at 6 o'clock (posterior) and the rest of all the fistula tracts are outside the external sphincter. This fistula is better managed by ligation of intersphincteric fistula tract procedure. A: Axial section-schematic diagram; B: T2-weighted magnetic resonance imaging axial section (orange arrow pointing the fistula tract); C: Sketch of B (fistula tract being shown in green color).




**DOI:** 10.4240/wjgs.v14.i5.374 **Copyright** ©The Author(s) 2022.

**Figure 2 A 47-year-old male patient with high posterior intersphincteric anal fistula with abscess.** This fistula is difficult to manage by ligation of intersphincteric fistula tract and is better managed by transanal opening of intersphincteric space procedure. A: Axial section-schematic diagram; B: T2-weighted magnetic resonance imaging axial section (orange arrows pointing the fistula tract); C: Sketch of B (fistula tract being shown in green color).




**DOI:** 10.4240/wjgs.v14.i5.374 **Copyright** ©The Author(s) 2022.

**Figure 3 A 39-year-old male patient with right sided suprasphincteric anal fistula with abscess.** This fistula is difficult to manage by ligation of intersphincteric fistula tract and is better managed by transanal opening of intersphincteric space procedure. A: Coronal section-schematic diagram; B: T2-weighted magnetic resonance imaging coronal section (orange arrows pointing the fistula tract); C: Sketch of B (fistula tract being shown in green color).

It would be incorrect to conclude without discussing the third procedure which has been shown to be effective in complex anal fistulas, fistulectomy or fistulotomy with primary sphincter repair (FPR)[11,41-44]. In this procedure, the fistula tract is excised/ cored out (fistulectomy) or laid open (fistulotomy) and then the sphincter complex (IAS and EAS) is repaired primarily (sutured together) with the healing occurring by primary intention[11,41-44]. Long-term studies have shown that a high success rate (85%-95%) can be achieved with FPR in complex fistulas without having any negative effect on continence. However, the main disadvantage of this procedure is that it is technically quite demanding, the prospect of cutting a major part of anal sphincters is frightening to many patients and it is not recommended for fistulas involving the upper one-third of the EAS (especially suprasphincteric fistulas which involve

almost 100% of the EAS)[11,41-44].

## CONCLUSION

To conclude, both LIFT and TROPIS are new useful continence-preserving procedures to treat complex anal fistulas with high success rates. In complex anal fistulas, newer sphincter-saving procedures (VAAFT, AFP, OTSC, FiLac, stem cells and fixcision) can also be carried out if the surgeon is more well-versed with these as they are safe procedures. However, if recurrence or repeated failures occur, then one of these three procedures-LIFT, TROPIS or FPR-should be performed depending on the fistula and the expertise of the surgeon in these procedures.

## ACKNOWLEDGEMENTS

I wholeheartedly thank Prof Sushil Dawka for English language editing.

## FOOTNOTES

**Author contributions:** Garg P conceived and designed the study, collected and analyzed the data, revised the data, granted final approval and submitted the manuscript (guarantor of the review).

**Conflict-of-interest statement:** There is no conflict of interest.



**Country/Territory of origin:** India

**ORCID number:** Pankaj Garg 0000-0002-0800-3578.

**Corresponding Author's Membership in Professional Societies:** American Society of Colon Rectum Surgeons; Society of American of Gastrointestinal Endoscopic Surgeons; Endoscopic and Laparoscopic Surgeons of Asia; Association of Surgeons of India.

**S-Editor:** Zhang H
**L-Editor:** Filipodia CL
**P-Editor:** Zhang H

## REFERENCES

1 **Zhang Y**, Li F, Zhao T, Cao F, Zheng Y, Li A. Treatment of Complex Anal Fistula by Video-Assisted Anal Fistula Treatment Combined with Anal Fistula Plug: A Single-Center Study. *Surg Innov* 2021; **28**: 688-694 [PMID: 33568017 DOI: 10.1177/1553350621992924]
2 **Garg P**, Sodhi SS, Garg N. Management of Complex Cryptoglandular Anal Fistula: Challenges and Solutions. *Clin Exp Gastroenterol* 2020; **13**: 555-567 [PMID: 33204136 DOI: 10.2147/CEG.S198796]
3 **Zhang Y**, Li F, Zhao T, Cao F, Zheng Y, Li A. Video-assisted anal fistula treatment combined with anal fistula plug for treatment of horseshoe anal fistula. *J Int Med Res* 2021; **49**: 300060520980525 [PMID: 33435765 DOI: 10.1177/0300060520980525]
4 **Zelić M**, Karlović D, Kršul D, Bačić Đ, Warusavitarne J. Video-Assisted Anal Fistula Treatment for Treatment of Complex Cryptoglandular Anal Fistulas with 2 Years Follow-Up Period: Our Experience. *J Laparoendosc Adv Surg Tech A* 2020; **30**: 1329-1333 [PMID: 32412822 DOI: 10.1089/lap.2020.0231]
5 **Emile SH**, Elfeki H, Shalaby M, Sakr A. A Systematic review and meta-analysis of the efficacy and safety of video-assisted anal fistula treatment (VAAFT). *Surg Endosc* 2018; **32**: 2084-2093 [PMID: 29052068 DOI: 10.1007/s00464-017-5905-2]
6 **Zarin M**, Khan MI, Ahmad M, Ibrahim M, Khan MA. VAAFT: Video Assisted Anal Fistula Treatment; Bringing revolution in Fistula treatment. *Pak J Med Sci* 2015; **31**: 1233-1235 [PMID: 26649020 DOI: 10.12669/pjms.315.6836]
7 **Selvarajan A**. Video-Assisted Anal Fistula Treatment (VAAFT): Johor Bahru's Humble Beginnings. *Int J Intg Med Sci* 2015; **2**: 175-177 [DOI: 10.16965/ijims.2015.125]
8 **Jayne DG**, Scholefield J, Tolan D, Gray R, Senapati A, Hulme CT, Sutton AJ, Handley K, Hewitt CA, Kaur M, Magill L;

FIAT Trial Collaborative Group. A Multicenter Randomized Controlled Trial Comparing Safety, Efficacy, and Cost-effectiveness of the Surgisis Anal Fistula Plug Versus Surgeon's Preference for Transsphincteric Fistula-in-Ano: The FIAT Trial. *Ann Surg* 2021; **273**: 433-441 [PMID: 32516229 DOI: 10.1097/SLA.0000000000003981]

9 **Ji L**, Zhang Y, Xu L, Wei J, Weng L, Jiang J. Advances in the Treatment of Anal Fistula: A Mini-Review of Recent Five-Year Clinical Studies. *Front Surg* 2020; **7**: 586891 [PMID: 33644110 DOI: 10.3389/fsurg.2020.586891]

10 **Grossberg SJ**, Harran N, Bebington B, Lutrin DL. Use of the OVESCO OTSC® Proctology Clip for closure of fistula-in-ano at Wits Donald Gordon Medical Centre - a single centre experience. *S Afr J Surg* 2020; **58**: 74-77 [PMID: 32644310]

11 **Mascagni D**, Pironi D, Grimaldi G, Romani AM, La Torre G, Eberspacher C, Palma R, Sorrenti S, Pontone S. OTSC® Proctology vs. fistulectomy and primary sphincter reconstruction as a treatment for low trans-sphincteric anal fistula in a randomized controlled pilot trial. *Minerva Chir* 2019; **74**: 1-6 [PMID: 29397638 DOI: 10.23736/S0026-4733.18.07617-4]

12 **Marinello F**, Kraft M, Ridaura N, Vallribera F, Espín E. Treatment of Fistula-in-ano With OTSC® Proctology Clip Device: Short-term Results. *Cir Esp (Engl Ed)* 2018; **96**: 369-374 [PMID: 29525123 DOI: 10.1016/j.ciresp.2018.02.003]

13 **Garcia-Arranz M**, Garcia-Olmo D, Herreros MD, Gracia-Solana J, Guadalajara H, de la Portilla F, Baixauli J, Garcia-Garcia J, Ramirez JM, Sanchez-Guijo F, Prosper F; FISPAC Collaborative Group. Autologous adipose-derived stem cells for the treatment of complex cryptoglandular perianal fistula: A randomized clinical trial with long-term follow-up. *Stem Cells Transl Med* 2020; **9**: 295-301 [PMID: 31886629 DOI: 10.1002/sctm.19-0271]

14 **Cheng F**, Huang Z, Li Z. Efficacy and Safety of Mesenchymal Stem Cells in Treatment of Complex Perianal Fistulas: A Meta-Analysis. *Stem Cells Int* 2020; **2020**: 8816737 [PMID: 33299423 DOI: 10.1155/2020/8816737]

15 **Kasiri MM**, Riss S, Stift A, Binder AD, Kogovšek U, Huth M, Kronberger IE. Optimized fistulectomy using the novel FiXcision® device: a technical feasibility study and evaluation of short term healing rates. *Tech Coloproctol* 2019; **23**: 579-582 [PMID: 31270652 DOI: 10.1007/s10151-019-02025-7]

16 **Vitton V**, Gasmi M, Barthet M, Desjeux A, Orsoni P, Grimaud JC. Long-term healing of Crohn's anal fistulas with fibrin glue injection. *Aliment Pharmacol Ther* 2005; **21**: 1453-1457 [PMID: 15948812 DOI: 10.1111/j.1365-2036.2005.02456.x]

17 **Gisbertz SS**, Sosef MN, Festen S, Gerhards MF. Treatment of fistulas in ano with fibrin glue. *Dig Surg* 2005; **22**: 91-94 [PMID: 15849469 DOI: 10.1159/000085299]

18 **Tinay OE**, El-Bakry AA. Treatment of chronic fistula-in-ano using commercial fibrin glue. *Saudi Med J* 2003; **24**: 1116-1117 [PMID: 14578981]

19 **Placer Galán C**, Aguirre I, Pastor T, Etxart A, Enriquez Navascués JM. LIFT procedure for posterior fistula-in-ano. Are outcomes good enough? *Cir Esp (Engl Ed)* 2021; **99**: 183-189 [PMID: 33303194 DOI: 10.1016/j.ciresp.2020.08.009]

20 **Meima-van Praag EM**, van Rijn KL, Monraats MA, Buskens CJ, Stoker J. Magnetic resonance imaging after ligation of the intersphincteric fistula tract for high perianal fistulas in Crohn's disease: a retrospective cohort study. *Colorectal Dis* 2021; **23**: 169-177 [PMID: 32767809 DOI: 10.1111/codi.15296]

21 **Madbouly KM**, Emile SH, Issa YA, Omar W. Ligation of intersphincteric fistula tract (LIFT) with or without injection of platelet-rich plasma (PRP) in management of high trans-sphincteric fistula-in-ano: Short-term outcomes of a prospective, randomized trial. *Surgery* 2021; **170**: 61-66 [PMID: 33536119 DOI: 10.1016/j.surg.2020.12.025]

22 **Emile SH**, Khan SM, Adejumo A, Koroye O. Ligation of intersphincteric fistula tract (LIFT) in treatment of anal fistula: An updated systematic review, meta-analysis, and meta-regression of the predictors of failure. *Surgery* 2020; **167**: 484-492 [PMID: 31648932 DOI: 10.1016/j.surg.2019.09.012]

23 **Rojanasakul A**, Booning N, Huimin L, Pongpirul K, Sahakitrungruang C. Intersphincteric Exploration With Ligation of Intersphincteric Fistula Tract or Attempted Closure of Internal Opening for Acute Anorectal Abscesses. *Dis Colon Rectum* 2021; **64**: 438-445 [PMID: 33394781 DOI: 10.1097/DCR.0000000000001867]

24 **Malakorn S**, Sammour T, Khomvilai S, Chowchankit I, Gunarasa S, Kanjanasilp P, Thiptanakij C, Rojanasakul A. Ligation of Intersphincteric Fistula Tract for Fistula in Ano: Lessons Learned From a Decade of Experience. *Dis Colon Rectum* 2017; **60**: 1065-1070 [PMID: 28891850 DOI: 10.1097/DCR.0000000000000880]

25 **Rojanasakul A**, Pattanaarun J, Sahakitrungruang C, Tantiphlachiva K. Total anal sphincter saving technique for fistula-in-ano; the ligation of intersphincteric fistula tract. *J Med Assoc Thai* 2007; **90**: 581-586 [PMID: 17427539]

26 **Lau YC**, Brown KGM, Cheong J, Byrne C, Lee PJ. LIFT and BioLIFT: a 10-Year Single-Centre Experience of Treating Complex Fistula-In-Ano With Ligation of Intersphincteric Fistula Tract Procedure With or Without Bio-prosthetic Reinforcement (BioLIFT). *J Gastrointest Surg* 2020; **24**: 671-676 [PMID: 31240556 DOI: 10.1007/s11605-019-04305-x]

27 **Li YB**, Chen JH, Wang MD, Fu J, Zhou BC, Li DG, Zeng HQ, Pang LM. Transanal Opening of Intersphincteric Space for Fistula-in-Ano. *Am Surg* 2021; 3134821989048 [PMID: 33517706 DOI: 10.1177/0003134821989048]

28 **Huang B**, Wang X, Zhou D, Chen S, Li B, Wang Y, Tai J. Treating highly complex anal fistula with a new method of combined intraoperative endoanal ultrasonography (IOEAUS) and transanal opening of intersphincteric space (TROPIS). *Wideochir Inne Tech Maloinwazyjne* 2021; **16**: 697-703 [PMID: 34950264 DOI: 10.5114/wiitm.2021.104368]

29 **Garg P**, Kaur B, Menon GR. Transanal opening of the intersphincteric space: a novel sphincter-sparing procedure to treat 325 high complex anal fistulas with long-term follow-up. *Colorectal Dis* 2021; **23**: 1213-1224 [PMID: 33529491 DOI: 10.1111/codi.15555]

30 **Włodarczyk M**, Włodarczyk J, Sobolewska-Włodarczyk A, Trzciński R, Dziki Ł, Fichna J. Current concepts in the pathogenesis of cryptoglandular perianal fistula. *J Int Med Res* 2021; **49**: 300060520986669 [PMID: 33595349 DOI: 10.1177/0300060520986669]

31 **Yan J**, Ma L. Clinical Effect of Tunnel-Like Fistulectomy Plus Draining Seton Combined with Incision of Internal Opening of Anal Fistula (TFSIA) in the Treatment of High Trans-Sphincteric Anal Fistula. *Med Sci Monit* 2020; **26**: e918228 [PMID: 31929499 DOI: 10.12659/MSM.918228]

32 **Mei Z**, Wang Q, Zhang Y, Liu P, Ge M, Du P, Yang W, He Y. Risk Factors for Recurrence after anal fistula surgery: A meta-analysis. *Int J Surg* 2019; **69**: 153-164 [PMID: 31400504 DOI: 10.1016/j.ijsu.2019.08.003]

33 **Eisenhammer S**. A new approach to the anorectal fistulous abscess based on the high intermuscular lesion. *Surg Gynecol Obstet* 1958; **106**: 595-599 [PMID: 13556476]

34 **Matos D**, Lunniss PJ, Phillips RK. Total sphincter conservation in high fistula in ano: results of a new approach. *Br J Surg*

1993; **80**: 802-804 [PMID: 8330181 DOI: 10.1002/bjs.1800800651]
35 **Rojanasakul A**. LIFT procedure: a simplified technique for fistula-in-ano. *Tech Coloproctol* 2009; **13**: 237-240 [PMID: 19636496 DOI: 10.1007/s10151-009-0522-2]
36 **Hong KD**, Kang S, Kalaskar S, Wexner SD. Ligation of intersphincteric fistula tract (LIFT) to treat anal fistula: systematic review and meta-analysis. *Tech Coloproctol* 2014; **18**: 685-691 [PMID: 24957361 DOI: 10.1007/s10151-014-1183-3]
37 **Garg P**, Kaur B, Goyal A, Yagnik VD, Dawka S, Menon GR. Lessons learned from an audit of 1250 anal fistula patients operated at a single center: A retrospective review. *World J Gastrointest Surg* 2021; **13**: 340-354 [PMID: 33968301 DOI: 10.4240/wjgs.v13.i4.340]
38 **Jayne DG**, Scholefield J, Tolan D, Gray R, Edlin R, Hulme CT, Sutton AJ, Handley K, Hewitt CA, Kaur M, Magill L. Anal fistula plug versus surgeon's preference for surgery for trans-sphincteric anal fistula: the FIAT RCT. *Health Technol Assess* 2019; **23**: 1-76 [PMID: 31113531 DOI: 10.3310/hta23210]
39 **Sainio P**. A manometric study of anorectal function after surgery for anal fistula, with special reference to incontinence. *Acta Chir Scand* 1985; **151**: 695-700 [PMID: 4096174]
40 **Vaizey CJ**, Carapeti E, Cahill JA, Kamm MA. Prospective comparison of faecal incontinence grading systems. *Gut* 1999; **44**: 77-80 [PMID: 9862829 DOI: 10.1136/gut.44.1.77]
41 **De Hous N**, Van den Broeck T, de Gheldere C. Fistulectomy and primary sphincteroplasty (FIPS) to prevent keyhole deformity in simple anal fistula: a single-center retrospective cohort study. *Acta Chir Belg* 2021; **121**: 308-313 [PMID: 32253992 DOI: 10.1080/00015458.2020.1753151]
42 **Seyfried S**, Bussen D, Joos A, Galata C, Weiss C, Herold A. Fistulectomy with primary sphincter reconstruction. *Int J Colorectal Dis* 2018; **33**: 911-918 [PMID: 29651553 DOI: 10.1007/s00384-018-3042-6]
43 **Arroyo A**, Pérez-Legaz J, Moya P, Armañanzas L, Lacueva J, Pérez-Vicente F, Candela F, Calpena R. Fistulotomy and sphincter reconstruction in the treatment of complex fistula-in-ano: long-term clinical and manometric results. *Ann Surg* 2012; **255**: 935-939 [PMID: 22504192 DOI: 10.1097/SLA.0b013e31824e9112]
44 **Perez F**, Arroyo A, Serrano P, Sánchez A, Candela F, Perez MT, Calpena R. Randomized clinical and manometric study of advancement flap versus fistulotomy with sphincter reconstruction in the management of complex fistula-in-ano. *Am J Surg* 2006; **192**: 34-40 [PMID: 16769272 DOI: 10.1016/j.amjsurg.2006.01.028]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 May 27; 14(5): 383-396

DOI: 10.4240/wjgs.v14.i5.383

ISSN 1948-9366 (online)

*REVIEW*

# Recent advances in diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms

Meng Dai, Christina S Mullins, Lili Lu, Guido Alsfasser, Michael Linnebacher

**Specialty type:** Oncology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

**P-Reviewer:** Hou XH, China; Pelaez-Luna M, Mexico

**Received:** November 10, 2021
**Peer-review started:** November 10, 2021
**First decision:** January 9, 2022
**Revised:** January 17, 2022
**Accepted:** April 29, 2022
**Article in press:** April 29, 2022
**Published online:** May 27, 2022

**Meng Dai, Christina S Mullins, Lili Lu, Michael Linnebacher,** Clinic of General Surgery, Molecular Oncology and Immunotherapy, Rostock University Medical Center, 18057 Rostock, Germany

**Guido Alsfasser,** Clinic of General Surgery, Rostock University Medical Center, 18057 Rostock, Germany

**Corresponding author:** Michael Linnebacher, PhD, Academic Fellow, Research Fellow, Research Scientist, Senior Researcher, Senior Scientist, Clinic of General Surgery, Molecular Oncology and Immunotherapy, Rostock University Medical Center, Schillingallee 35, Rostock 18057, Mecklenburg-Vorpommern, Germany. michael.linnebacher@med.uni-rostock.de

## Abstract

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are a rare group of tumors originating from neuroendocrine cells of the digestive system. Their incidence has increased over the last decades. The specific pathogenetic mechanisms underlying GEP-NEN development have not been completely revealed. Unfunctional GEP-NENs are usually asymptomatic; some grow slowly and thus impede early diagnosis, which ultimately results in a high rate of misdiagnosis. Therefore, many GEP-NEN patients present with later staged tumors. Motivated hereby, research attention for diagnosis and treatment for GEP-NENs increased in recent years. The result of which is great progress in clinical diagnosis and treatment. According to the most recent clinical guidelines, improved grading standards can accurately define poorly differentiated grade 3 neuroendocrine tumors and neuroendocrine carcinomas (NECs), which are subclassified into large and small cell NECs. Combining different functional imaging methods facilitates precise diagnosis. The expression of somatostatin receptors helps to predict prognosis. Genetic analyses of mutations affecting death domain associated protein (*DAXX*), multiple endocrine neoplasia type 1 (*MEN 1*), alpha thalassemia/intellectual disability syndrome X-linked (*ATRX*), retinoblastoma transcriptional corepressor 1 (*RB 1*), and mothers against decapentaplegic homolog 4 (*SMAD 4*) help distinguishing grade 3 NENs from poorly differentiated NECs. The aim of this review is to summarize the latest research progress on diagnosis and treatment of GEP-NENs.

**Key Words:** GEP-NENs; Functional imaging; Peptide receptor radionuclide therapy; Targeting agents; Immune checkpoint inhibitors; Genetic mutations

**Core Tip:** Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are a group of heterogeneous tumors arising from neuroendocrine cells of the digestive system. Researchers have achieved great improvements in diagnosis and treatment. This includes improved grading, identification of specific genetic mutations, functional imaging, and broad application of peptide receptor radionuclide therapy. Here, we systematically summarized the latest progress in diagnosis and treatment of GEP-NENs, thereby providing guidance for clinicians active in this field.

**Citation:** Dai M, Mullins CS, Lu L, Alsfasser G, Linnebacher M. Recent advances in diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms. *World J Gastrointest Surg* 2022; 14(5): 383-396
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i5/383.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i5.383

## INTRODUCTION

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) originate from neuroendocrine cells of the pancreas or the gastrointestinal tract. They represent the second most common cancer of the digestive system (Figure 1)[1]. The Surveillance, Epidemiology, and End Results (commonly known as SEER) 18 registry (2000-2012) revealed an increased incidence of GEP-NENs in the United States to 3.56/100000 inhabitants in the year 2012[2]. In European countries, the incidence also increased and was reported to be in the range of 1.33 to 2.33/100000 inhabitants[3,4]. Improvements in the detection methods have been identified as the most probable explanation for the increased incidence of GEP-NENs over the last decades[5]. These neoplasms are classified into well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). Moreover, depending on the hormone and amine secretion activity, GEP-NENs can be classified into functional and nonfunctional neoplasms[1,6]. Functional GEP-NENs produce hormones and amines, which cause specific clinical manifestations, such as hypoglycemia, refractory gastric ulcer, flushing, diarrhea, *etc*. However, immunohistochemical hormone staining is not sufficient for diagnosis[7].

Due to the clinical manifestations, functional GEP-NENs can frequently be diagnosed in early stages, what translates into a relatively good prognosis. In contrast, non-functional GEP-NENs are asymptomatic until distant metastases or mass effect cause late symptoms, such as intestinal obstruction [8]. The 2019 World Health Organization (WHO) classification of GEP-NENs consisted of the following categories: Grade 1, Grade 2, Grade 3, and NEC. This grading is based on the mitotic rate and/or the Ki-67 proliferation index, as listed in Table 1 below. The mitotic rate is determined by an immunohistochemistry method, in which 50 fields of 0.2 $mm^2$ are counted. The Ki-67 proliferation index value is determined by counting more than 500 cells in the regions of highest labelling using scanning magnification. The NEN grade is assigned by the proliferation index of the two, which places the neoplasm in the higher-grade according to the classification. Mixed NENs consist of both neuroendocrine and non-neuroendocrine components and are poorly differentiated, and the neuroendocrine component has proliferation indexes in the same range as other NECs. This conceptual category however allows for respect of the fact that one or both components can also be well differentiated; if feasible, every component should be graded separately[9,10]. Surgery is still the mainstay of curative treatment for localized GEP-NENs[11]. Methods of clinical diagnosis and treatment have been continuously updated because of ongoing research and study activities. This review aims at systemically summarizing the latest research advances on diagnosis and treatment of GEP-NENs.

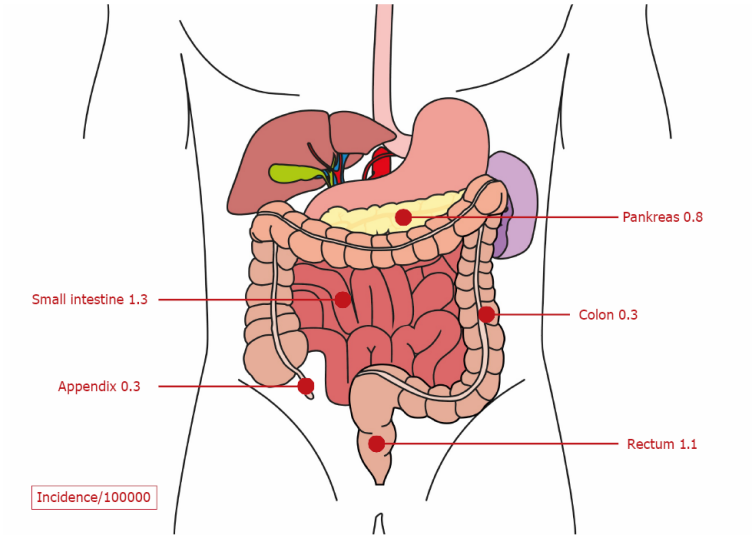
## CLINICAL PRESENTATION

GEP-NENs present as very heterogeneous, both because of different organs of origin and because of different biological behavior; consequently, clinical symptoms are various. Especially functional GEP-NENs, which secrete specific hormones, cause characteristic clinical syndromes[12]. Insulinomas produce excessive amounts of insulin, thereby causing hypoglycemia. Excessive secretion of gastrin from functional gastrinomas often results in refectory and recurrent peptic ulcerations. Glucagonoma patients regularly present with recent diabetic mellitus as well as migratory necrolytic erythema caused by extremely high glucagon levels, whereas somatostatinoma patients will present with hyperglycemia and steatorrhea. Contrary to that, non-functional GEP-NENs do not cause specific clinical symptoms, and they are often only diagnosed during routine physical examinations[13].

**Table 1 The 5th classification system of World Health Organization for gastroenteropancreatic neuroendocrine neoplasms (2019)[10]**

| Classification | Differentiation status | Ki-67 index | Mitotic rate |
|---|---|---|---|
| Grade 1, NET | Well differentiated | < 3% | < 2 |
| Grade 2, NET | Well differentiated | 3% to 20% | 2 to 20 |
| Grade 3, NET | Well differentiated | > 20% | > 20 |
| Small cell type, NEC | Poorly differentiated | > 20% | > 20 |
| Large cell type, NEC | Poorly differentiated | > 20% | > 20 |
| Mixed NEN | Well or poorlydifferentiated | Variable | Variable |

NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma; NEN: Neuroendocrine neoplasm.




**DOI:** 10.4240/wjgs.v14.i5.383 

**Figure 1 Incidence in gastroenteropancreatic organs.**

## DIAGNOSIS OF GEP-NENS

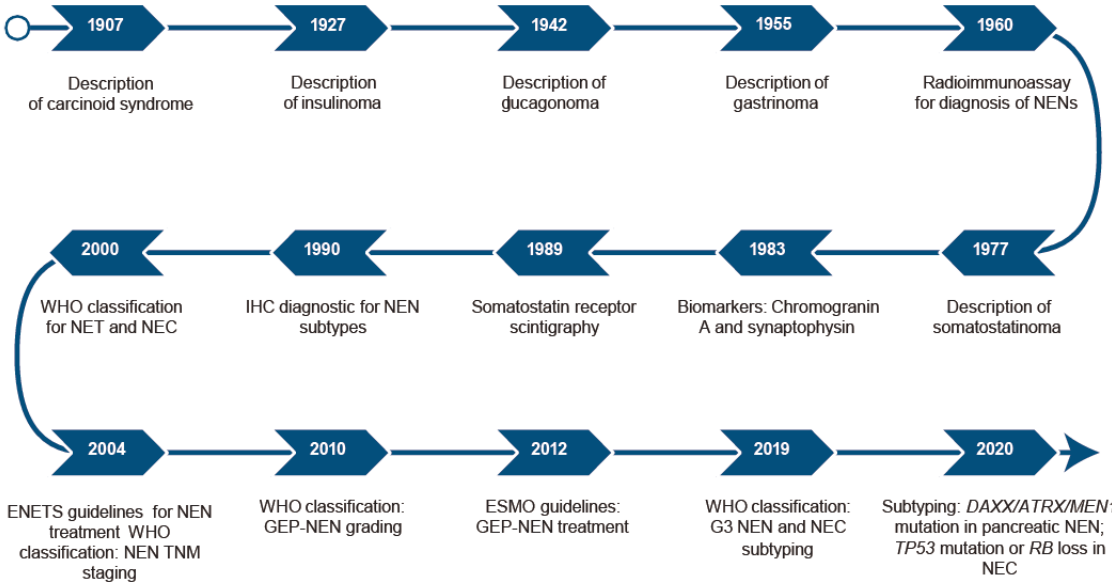
Diagnostic improvements over time are shown in Figure 2.

### *Biomarkers for diagnosis of NENs*

**Chromogranin-A:** Chromogranin-A (CgA) is a member of the chromogranin glycoprotein family and is physiologically secreted by neurons and neuroendocrine cells[14]. In clinical diagnosis, CgA is established as a universal routine diagnostic biomarker of neuroendocrine neoplasms. Sensitivity of CgA assays varies between 32% and 92%, depending on the NET type, secretory status, and tumor burden. The specificity can approach 100% if other diseases affecting serum CgA levels, such as kidney insufficiency and chronic atrophic gastritis, can be excluded[15].

**Serotonin:** Serotonin is assessed by measuring its degradation product, 5hydroxyindoleacetic acid (5-HIAA), in 24-h urine of patients with carcinoid symptoms[16]. A meta-analysis demonstrated that 5-HIAA can be a predictive biomarker for 1-year mortality rate of NEN patients[17]. However, since specific nutritious substances (such as eggplants, bananas, tomatoes, *etc*) and medications (such as nicotine, ephedrine, diazepam, *etc*) can affect 5-HIAA measurement, patients need to be guided to omit these substances.

**Gastrin:** Gastrinomas can result in elevation of serum gastrin levels. With excessive secretion of gastrin, patients will suffer from refractory peptic ulcers. Therefore, serum levels of gastrin are routinely measured in patients suspected to have gastrinomas. Criteria for diagnosis of Zollinger-Ellison syndrome as a result of gastrinomas are: At least 10-fold elevated serum gastrin levels and a gastric pH below 2.1. However, proton pump inhibitors (PPIs) can elevate serum gastrin levels. Patients receiving PPIs need to wean this medication for at least 1 wk before gastrin measurement[18].




| Year | Events |
|---|---|
| 1907 | Carcinoid syndrome described by Oberndorfer[94] |
| 1927 | Insulinoma described by Wilder[95] |
| 1942 | Glucagonoma reported by Becker[96] |
| 1955 | Gastrinoma reported by Robert Zollinger and Edvin Ellison[97] |
| 1960 | Radioimmunoassays for diagnosis of NENs by Rosalyn and Solomon[98] |
| 1977 | Somatostatinoma described by Ganda[99] |
| 1983 | Biomarkers: chromogranin A and synaptophysin[100] |
| 1989 | Somatostatin receptor scintigraphy introduced by Eric Krenning[101] |
| 1990 | IHC for diagnosing subtype of NENs[102] |
| 2000 | WHO classification for NET and NEC[103] |
| 2004 | ENETS guidelines for NETs; WHO classification TNM stage for NETs[104] |
| 2010 | WHO classification grading for GEP-NENs[105] |
| 2012 | ESMO guidelines for GEP-NENs[106] |
| 2019 | WHO classification for (re) definition of G3 NEN and G3 NEC[9] |
| 2020 | ESMO recommendation: DAXX/ATRX/MEN1 mutation in pancreatic NEN; p53 mutation or RB loss in NEC[66] |



**Figure 2 Milestones in the diagnosis of neuroendocrine neoplasms[94-106].** ENETS: European Neuroendocrine Tumor Society; ESMO: European Society for Medical Oncology; GEP-NEN: Gastroenteropancreatic neuroendocrine neoplasm; IHC: Immunohistochemistry; NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma; NEN: Neuroendocrine neoplasm; TNM: Tumor, Node, Metastasis; WHO: World Health Organization.

**Insulin:** Insulin is measured for diagnosis of insulinomas after a 72-h gastric fasting. If, during fasting-induced hypoglycemia, serum insulin levels reach more than 3 mcIU/mL, serum pro-insulin levels rise above 5 pmol/L, and Cpeptide concentrations are at least 0.6 ng/mL, an insulinoma is a probable diagnosis; especially in patients with concurrent pancreatic mass[19].

**Glucagon:** Glucagon is measured in the blood of patients suspected to suffer from glucagonomas and meeting the following criteria: Recently diagnosed with diabetes mellitus, migratory necrolytic erythema, and a positive imaging confirmation of a gastroenteropancreatic mass[20].

In summary, although these serum molecular tests are in standard use for GEP-NEN differential diagnosis, a consensus conference of multinational experts repeated that a single biomarker to diagnose efficaciously and predict prognosis for patients with GEP-NENs would be beneficial[7].

### *Imaging for diagnosis of GEP-NENs*

**Computed tomography and magnetic resonance imaging:** Computed tomography and magnetic resonance imaging are conventional techniques used to determine localization and to evaluate neoplasm burden of GEP-NENs. Multiphase computed tomography (CT) or magnetic resonance imaging (MRI) scans are recommended to diagnose distant metastatic lesions[21,22], because GEP-NENs are highly vascularized and thus show the same resolution as the liver in conventional CT scanning. They can, however, be detected by either of these advanced imaging techniques. Similarly, contrast CT chest scanning is recommended for the evaluation of lung metastases. Small peritoneal, liver, and lymphatic metastases < 1 cm cannot be detected by CT analyses[23].

**Functional imaging:** Nowadays, functional somatostatin receptor (SSR) imaging is widely used in clinical diagnosis of NENs. Beside localizing tumors and selecting SSR-positive patients for specific

therapies, it can be used to evaluate therapeutic responses[24]. Five subtypes of SSRs (SSR1 to SSR5) have been identified, and their molecular mechanisms of regulation and signaling have been elucidated [25]. The most prominent SSR subtype in GEP-NENs is SSR2, followed by SSR1 and SSR5; SSR3 and SSR4 are less frequently expressed[26]. Moreover, SSR2 and SSR5 are usually expressed in insulinomas [27].

The $^{68}$Ga-DOTA somatostatin analogues (SSA) imaging system consists of $^{68}$Ga-DOTA-Tyr3-octreotide ($^{68}$Ga-DOTA-TOC), $^{68}$Ga-DOTA-Nal3-octreotide ($^{68}$Ga-DOTA-NOC), and $^{68}$Ga-DOTA-Tyr3-octreotate ($^{68}$Ga-DOTA-TATE). These different imaging agents display distinct affinities to variable SSRs. Compared to $^{111}$In-pentetreotide functional imaging, $^{68}$Ga-DOTA-SSA imaging has been shown to improve diagnosis and staging for NENs[28] and has become the imaging method of choice. $^{68}$Ga-DOTA-TOC shows a higher affinity to SSR-2, $^{68}$Ga-DOTA-NOC towards SSR-2, SSR-3, and SSR-5, whereas $^{68}$Ga-DOTA-TATE towards SSR-2 and SSR-5[29]. Clinicians are supposed to select appropriate imaging agents for specific NENs. $^{18}$Fluorodeoxyglucose ($^{18}$FDG), a tracer for glucose metabolism, can indirectly assess metabolic activity of GEP-NENs. The ability of tumor cells to take up glucose is positively correlated with the tumor growth rate[30], which is in turn related to aggressiveness. Combining $^{18}$FDG-PET/CT with $^{18}$Ga-DOTA-TATE imaging is another functional imaging method for NENs[31]. Even for GEP-NENs with low or negative SSR expression, positive $^{18}$FDG PET/CT imaging denotes worse prognosis[32]. For the detection of tumor site and activity, the combination of SSR imaging and $^{18}$FDG imaging has proven to be complementary[33,34].

### *Endoscopy, ultrasonography, and endoscopic ultrasonography*

Endoscopy, ultrasonography, and endoscopic ultrasonography are also recommended for the diagnosis and treatment of GEP-NENs. For early-stage and smaller GEP-NENs, endoscopic resection should be taken into consideration when lymphatic metastases have been excluded by endoscopic ultrasonography (US) or imaging[35]. Endoscopic resection should be reserved for GEP-NENs with a diameter < 1 cm, superficial position, and low grading[35]. US can serve as the initial diagnostic approach for liver metastases. Moreover, it can guide the biopsy needle to collect tissues for histopathological assessment. Endoscopic US is currently the most sensitive diagnostic approach for pancreatic NENs and allows biopsy collection at the same time[36], whereas intraoperative US can detect tumors in liver and pancreas, otherwise not detected by imaging methods[37].

### *Histopathological examination*

Histopathological examination is the gold standard for GEP-NEN diagnosis; both from biopsies and resected tissues. Hematoxylin and eosin staining is used to determine cytological and histomorphological indices, and immunohistochemical staining of CgA and synaptophysin are mandatory for differential diagnosis in pathological reports[38]. Immunohistochemical Ki-67 index determination and mitotic counts per mm$^2$ are the basis of grade classification for GEP-NENs (see Table 1). According to the latest National Comprehensive Cancer Network (NCCN) guidelines, histological classification, the resection margin status, Tumor, Node, Metastasis (commonly known as TNM) stage, and the presence of vascular invasion are also mandatory in pathological reports, because these factors are significantly associated with patient prognosis[39].

### *Somatic mutations*

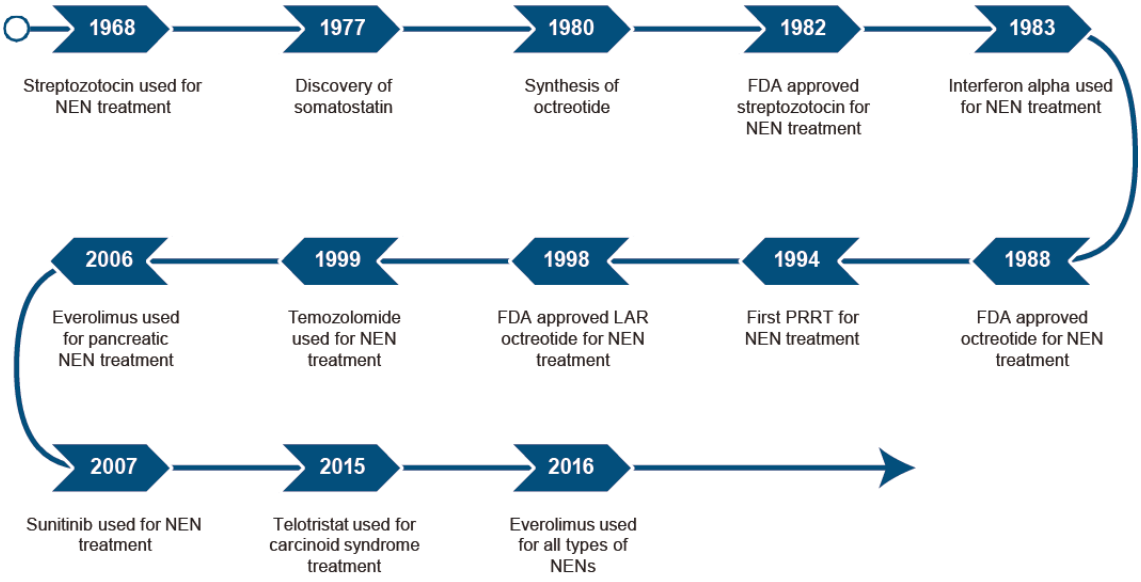
For WHO grade 3 NENs, somatic mutations in the genes death domain associated protein (*DAXX*), multiple endocrine neoplasia type 1 (*MEN1*), and alpha thalassemia/intellectual disability syndrome X-linked (*ATRX*) are most frequent. Whereas, in NECs, mutations affect the genes retinoblastoma transcriptional corepressor 1 (*RB1*), mothers against decapentaplegic homolog 4 (*SMAD4*), and tumor protein p53 (*TP53*)[40,41]. This difference in the occurrence of somatic mutations can be exploited to discriminate GEP-NECs from WHO grade 3 GEP-NENs in challenging cases[42]. In addition, NECs of the small intestine often show mutations in the cyclin-dependent kinase inhibitor 1B (*CDKN1B*)[43], and lack of *CDKN1B* gene expression has been described as a negative prognostic factor in GEP-NENs[6,44]. Insulinoma-associated protein 1 (*INSM1*) has proven to be a specific and sensitive biomarker for diagnosing NECs[45,46].

## TREATMENT APPROACHES FOR GEP-NENS

An overview of treatment developments is shown in Figure 3.

### *Surgery*

Surgical resection remains the sole curative form of therapy for patients with GEP-NENs[47]. Patients with local or locoregional GEP-NENs should be recommended for curative resection of the primary and the locoregional lymph nodes[48]. For patients with asymptomatic pancreatic NENs < 2 cm, a cautious surveillance with yearly imaging is recommended[49]. Patients with pancreatic NENs > 2 cm should




| Year | Events |
|---|---|
| 1968 | Streptozotocin for NETs by Murray-Lyon[107] |
| 1977 | Discovery of somatostatin by Roger Guillemin and Andrew Schally[108] |
| 1980 | Synthesis of octreotide by Bauer[109] |
| 1982 | US FDA approved streptozotocin for NENs |
| 1983 | Interferon alpha[110] |
| 1988 | FDA approved octreotide |
| 1994 | First PRRT treatment[111] |
| 1998 | FDA approved long-acting release (LAR) octreotide |
| 1999 | Temozolomide for NENs[112] |
| 2006 | Everolimus for pancreatic NENs[113] |
| 2007 | Sunitinib for NENs[114] |
| 2015 | Telotristat for carcinoid syndrome[93] |
| 2016 | Everolimus for all types of NENs |

**DOI:** 10.4240/wjgs.v14.i5.383 

**Figure 3 Milestones in the treatment of neuroendocrine neoplasms[107-114].** US FDA: United States Food and Drug Administration; NEN: Neuroendocrine neoplasm; LAR: Long-acting repeatable; PRRT: Peptide receptor radionuclide therapy.

receive pancreatectomy with regional lymphadenectomy[50]. Localized small intestinal NENs are resected radically, including removal of mesenteric lymph nodes[51]. This can also reduce the risk of associated comorbidities, such as intestinal obstruction. A clinical study including 581 patients operated on with metastatic NENs demonstrated that the median overall survival (OS) was 110.4 mo for curative resection. In comparison, resections resulting merely in debulking (OS: 89.2 mo) or performed in a palliative situation (OS: 50.0 mo) had significantly shorter OS rates ($P < 0.001$). Patients receiving cytoreductive surgery survived, in median, 89.2 mo, whereas when all metastatic lesions could be removed, the longest median survival of 112.5 mo could be reached ($P < 0.001$)[52]. Another clinical retrospective analysis of grade 3 GEP-NENs reported a 2-year OS rate after radical surgery of 64.5%, a 2-year progression-free survival (PFS) rate of 44.9%, and a median PFS of 14 mo[53]. Therefore, the 2021 NCCN guidelines[6] recommended that, for small (< 2 cm) and low-grade NENs, surgery or close monitoring should be individualized. For large (> 2 cm) and higher-graded NENs, resection with negative margins and removal of regional lymph nodes should be conducted. Cytoreductive or debulking resection for distant metastases is recommended when more than 90% of the lesions can be removed safely, especially if patients present with serious hormonal symptoms[54,55].

### *Systemic therapies*

**Somatostatin:** Somatostatin is a general endocrine "off-switch" due to its not only endocrine but also, exocrine, autocrine, and paracrine inhibitory effects. In the digestive system, somatostatin can inhibit bowel movements, decrease the blood flow of mesenteric vessels, inhibit gastrointestinal absorption as well as gallbladder contraction, and suppress hormone secretion[56]. The half-life of somatostatin is only 3 min, thus preventing its pharmacological use. Hence, SSAs with longer half-lives were developed to treat patients with GEP-NENs[57]. SSAs can control hormonal symptoms induced by GEP-NENs[58] by binding to SSRs, thereby preventing the activation. Currently, the most commonly used SSAs for GEP-NENs are octreotide and lanreotide. In the placebo-controlled, double-blind, prospective, and randomized study on the "effect of octreotide long-acting repeatable (LAR) in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors (PROMID)" clinical trial, it was

demonstrated that octreotide significantly delayed tumor progression time (LAR 14.3 mo *vs* placebo 6 mo)[59]. The controlled study of lanreotide anti-proliferative response in NEN (CLARINET) trial confirmed that lanreotide was associated with significantly higher 2-year PFS rates in patients with metastatic enteropancreatic NEN (65.1% in the lanreotide group *vs* 33.0% in the placebo group)[60]. In a phase III trial, pasireotide, a second generation SSA[61], was compared to octreotide. It prolonged the median PFS from 6.8 mo in the octreotide LAR control group to 11.8 mo in the pasireotide LAR group [62]. The guidelines of the European Neuroendocrine Tumor Society (ENETS) and the NCCN guidelines recommended SSAs as first-line therapeutic agents for GEP-NENs. For patients receiving LAR SSAs, cholecystectomy is recommended in case of cholecystitis and gallstones[63].

**Interferon-α:** Interferon-α (IFNα) has been used to inhibit hormone secretion and proliferation in NENs in the past decades[64]. The phase III clinical study of the Southwest Oncology Group compared octreotide LAR plus IFNα with octreotide LAR plus bevacizumab. Antitumor effectiveness was similar with median PFS of 15.4 mo and 16.6 mo, respectively[65]. When other available therapeutic options failed, IFNα could thus be taken into cautious consideration as a rescue antiproliferative therapy[66].

### *Molecular targeted agents*

**Mammalian target of rapamycin inhibitors:** When the phosphatase and tension homolog protein is phosphorylated, a negative feedback regulation *via* phosphatidylinositide 3-kinase (PI3K) is normally activated, which inhibits cell proliferation and promotes cell apoptosis. However, the reduction of phosphatase and tension homolog messenger RNA expression stimulates activation of the PI3K-AKT-mammalian target of rapamycin (mTOR) pathway and can trigger tumor formation[67]. The key role of this signaling pathway in GEP-NEN development inspired mechanistic research with the aim to develop drugs targeting PI3K-Akt-mTOR[68,69]. Phase III clinical studies of RAD001 application for patients with advanced NEN (RADIANT)-3 and -4, lead to the approval of everolimus. This targeted inhibitor of mTOR with the capacity to delay NEN progression attained approval for treatment of GEP-NENs[70,71]. Both ENETS and NCCN guidelines recommend everolimus as a second or third-line drug for advanced GEP-NENs. In patients with insulinomas, everolimus showed the positive side-effect of stabilizing glycemic levels[72]. However, low expression of SSR2 in patients with insulinomas results in poor response to SSAs[73]. Even worse, SSA treatment of patients with insulinomas can exacerbate hypoglycemia due to an inhibition of glucagon[56,74]. Therefore, everolimus should be prioritized for patients with insulinomas.

**Vascular endothelial growth factor receptors inhibitors:** Sunitinib, a broadly acting tyrosine kinase inhibitor targeting vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptors, has been affirmed to defer progression of pancreatic NENs in a phase III clinical trial[75]. Sunitinib was thus included for treatment of advanced pancreatic NENs in the ENETS and NCCN guidelines. However, there is a lack of clinical data for the effects of sunitinib on gastroenteric NENs. The Grupo Espanol de Tumores Neuroendocrinos (GETNE 1509) phase II trial has proven that lenvatinib, another VEGFR inhibitor, achieved an overall response rate of 29.9% (44.2% in pancreatic and 16.4% in gastrointestinal NENs), a median response duration of 21.5 mo (19.9 mo in pancreatic and 33.9 mo in gastrointestinal NENs), a median PFS of 15.7 mo (15.6 mo and 15.7 mo respectively), and a median OS of 32 mo in the pancreatic NEN group. The median OS was not reached in the gastrointestinal NEN group. The phase III trial of surufatinib, a novel VEGFR inhibitor, in advanced extrapancreatic and pancreatic neuroendocrine tumors (SANET-ep and SANET-p) showed a meaningful improvement of PFS to 9.2 mo and 10.8 mo in the surufatinib groups *vs* 3.8 mo and 3.7 mo in the placebo groups for patients with advanced, progressive, well differentiated, extrapancreatic NENs, and advanced pancreatic NENs[76], respectively.

### *Immune checkpoint inhibitors*

Immune checkpoint inhibitors, which target for example programmed death protein-1 (PD-1), its receptor programmed death-ligand 1 (PD-L1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), showed promising antitumor efficacy in various tumor types[77]. In a phase IB study of the anti-PD-1 antibody pembrolizumab in advanced solid tumors (KEYNOTE-028), pembrolizumab monotherapy proved antitumor efficacy in patients with PD-L1-positive carcinoid and pancreatic NENs with high stable disease rates of 60% and 88%, respectively; however, only a disappointing objective response rate (ORR) of 12% and 6.3%, respectively[78]. In a subsequent phase II (KEYNOTE-158) study, pembrolizumab monotherapy had an ORR of only 3.7%, a median PFS of 4.1 mo and a median OS of 24.2 mo in patients with previously treated advanced well-differentiated NENs[79]. Pembrolizumab is also proposed for patients with tumor progression after previous treatment, tumors with high tumor mutational burden and no adequate alternative treatment regimens[80,81]. A phase II clinical trial of dual anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) inhibition in patients with nonpancreatic NENs reported an auspicious ORR of 44% (18 of 32 patients) with high-grade NENs. This trial demonstrated that dual immunotherapy preferentially plays a role in grade 3 NENs[82]. A similar phase II study (CA209-538) also verified the significant efficacy of combination immunotherapy with ipilimumab and nivolumab in high-grade NEN patients (the median PFS of 4.8 mo and the OS of 14.8

mo in all the patients with NENs)[83].

### *Peptide receptor radionuclide therapy*

Peptide receptor radionuclide therapy is actually a kind of systemic and targeted radiotherapy in one [84]. SSAs are structured with a radioisotope [such as Yttrium-90 ($^{90}$Y) and Lutetium-177 ($^{177}$Lu)] *via* a chelating agent. The emitted radiation kills the cancer cells that express SSRs on the tumor cells' surface [85]. $^{177}$Lu-DOTA-TATE was approved by the European Medicines Agency for the treatment of patients with GEP-NENs in 2017 and a year later by the American Food and Drug Administration[86,87]. In a comprehensive meta-analysis of 1920 patients with unresectable metastatic NENs receiving $^{177}$Lu-DOTATATE therapy from 18 studies, the ORR was between 29.1% and 30.6%, and the disease control rate was 74.1% to 81.1%[88].

### *Chemotherapies*

For G1 and G2 pancreatic NENs, SSAs are recommended as first-line therapeutic regimen. When ineffective, however, both NCCN and ENETS guidelines recommend temozolomide combined with capecitabine or streptozotocin-based therapies. To date, there is no recommendation for systematic chemotherapy for G1 and G2 gastroenteric NENs from NCCN and ENETS. Similarly, no standard chemotherapeutic regimens are currently recommended for G3 NETs. The NORDIC NEC study demonstrated that NEC patients with Ki-67 < 55% were less sensitive to platinum-based chemotherapy than those with Ki-67 ≥ 55% (response rate: 15% *vs* 42%, respectively), yet survival times were better for patients with Ki-67 < 55% (14 mo *vs* 10 mo, respectively)[89]. Thus, ENETS and NCCN guidelines do not suggest platinum- but temozolomide-based chemotherapies for patients with Ki-67 < 65%. For grade 3 NEN patients with Ki-67 < 55%, temozolomide-based chemotherapies are recommended; whereas, patients with Ki-67 ≥ 55% should receive platinum-based regimens, such as cisplatin or carboplatin, both in combination with etoposide[90]. These regimens are also recommended for GEP-NEC patients in the 2021 NCCN guideline as first-line chemotherapy.

### *Related agents for controlling clinical manifestations*

PPIs can control hypersecretion of gastric acid in patients with gastrinomas. However, related studies have proven that PPIs can lead to hypomagnesemia and vitamin B12 deficiency in patients with long-term use[91], suggesting a cautious use paired with regular control of magnesium and vitamin B12 levels.

Tryptophan hydroxylase is the rate-limiting enzyme for the conversion of tryptophan to serotonin. The tryptophan hydroxylase inhibitor telotristat can reduce the serotonin production. It is thus used in clinical practice to treat patients with refractory diarrhea resulting from a carcinoid syndrome[92] and it has been validated to normalize bowel movements and urinary levels of 5-HIAA[93].

## CONCLUSION

In summary, the pathogenesis of GEP-NENs is still largely unclear. Multiple classification systems and treatment schedules have been accurately (re)defined thanks to the efforts of GEP-NEN experts. Because of the great improvement of detection technologies, an increasing number of suspicious patients can be diagnosed with GEP-NENs already at an early stage. Novel treatment approaches, including small molecule inhibitors, SSAs, and peptide receptor radionuclide therapy targeting GEP-NENs, have evolved remarkably. However, prospective research still needs to be conducted to confirm their efficacy. Also, many controversies concerning the therapy regimens for specific GEP-NENs of different types remain. Beside identifying and developing novel molecular targeted drugs, the rational combination of targeted, chemo-, and immunotherapy seems to be the future research direction in the field of GEP-NEN therapy.

## ACKNOWLEDGEMENTS

All authors appreciate the excellent help from Burmeister J for the figure designs.

## FOOTNOTES

**Author contributions:** Dai M and Linnebacher M analyzed the literature and wrote the manuscript; Alsfasser G, Lu L and Mullins CS critically reviewed the manuscript; Mullins CS edited the language as a native speaker.

**Supported by** China Scholarship Council, No. 202108080085 to (Dai M) and No. 201908080127 to (Lu LL).

**Conflict-of-interest statement:** None to be declared.



**Country/Territory of origin:** Germany

**ORCID number:** Meng Dai 0000-0001-5919-7512; Christina S Mullins 0000-0003-2296-2027; Lili Lu 0000-0001-6638-624X; Guido Alsfasser 0000-0002-2637-8947; Michael Linnebacher 0000-0001-8054-1402.

**Corresponding Author's Membership in Professional Societies:** European Association for Cancer Research, No. EACR30750.

**S-Editor:** Wu YXJ
**L-Editor:** Filipodia
**P-Editor:** Wu YXJ

## REFERENCES

1 **Cives M**, Strosberg JR. Gastroenteropancreatic Neuroendocrine Tumors. *CA Cancer J Clin* 2018; **68**: 471-487 [PMID: 30295930 DOI: 10.3322/caac.21493]
2 **Dasari A**, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T, Yao JC. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol* 2017; **3**: 1335-1342 [PMID: 28448665 DOI: 10.1001/jamaoncol.2017.0589]
3 **Zhang H**, Li R, Cao Y, Gu Y, Lin C, Liu X, Lv K, He X, Fang H, Jin K, Fei Y, Chen Y, Wang J, Liu H, Li H, Zhang H, He H, Zhang W. Poor Clinical Outcomes and Immunoevasive Contexture in Intratumoral IL-10-Producing Macrophages Enriched Gastric Cancer Patients. *Ann Surg* 2022; **275**: 626-635 [PMID: 28448665 DOI: 10.1097/sla.0000000000004037]
4 **Huguet I**, Grossman AB, O'Toole D. Changes in the Epidemiology of Neuroendocrine Tumours. *Neuroendocrinology* 2017; **104**: 105-111 [PMID: 26505990 DOI: 10.1159/000441897]
5 **Genus TSE**, Bouvier C, Wong KF, Srirajaskanthan R, Rous BA, Talbot DC, Valle JW, Khan M, Pearce N, Elshafie M, Reed NS, Morgan E, Deas A, White C, Huws D, Ramage J. Impact of neuroendocrine morphology on cancer outcomes and stage at diagnosis: a UK nationwide cohort study 2013-2015. *Br J Cancer* 2019; **121**: 966-972 [PMID: 31649320 DOI: 10.1038/s41416-019-0606-3]
6 **Shah MH**, Goldner WS, Benson AB, Bergsland E, Blaszkowsky LS, Brock P, Chan J, Das S, Dickson PV, Fanta P, Giordano T, Halfdanarson TR, Halperin D, He J, Heaney A, Heslin MJ, Kandeel F, Kardan A, Khan SA, Kuvshinoff BW, Lieu C, Miller K, Pillarisetty VG, Reidy D, Salgado SA, Shaheen S, Soares HP, Soulen MC, Strosberg JR, Sussman CR, Trikalinos NA, Uboha NA, Vijayvergia N, Wong T, Lynn B, Hochstetler C. Neuroendocrine and Adrenal Tumors, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2021; **19**: 839-868 [PMID: 34340212 DOI: 10.6004/jnccn.2021.0032]
7 **Oberg K**, Modlin IM, De Herder W, Pavel M, Klimstra D, Frilling A, Metz DC, Heaney A, Kwekkeboom D, Strosberg J, Meyer T, Moss SF, Washington K, Wolin E, Liu E, Goldenring J. Consensus on biomarkers for neuroendocrine tumour disease. *Lancet Oncol* 2015; **16**: e435-e446 [PMID: 26370353 DOI: 10.1016/S1470-2045(15)00186-2]
8 **Gorelik M**, Ahmad M, Grossman D, Grossman M, Cooperman AM. Nonfunctioning Incidental Pancreatic Neuroendocrine Tumors: Who, When, and How to Treat? *Surg Clin North Am* 2018; **98**: 157-167 [PMID: 29191272 DOI: 10.1016/j.suc.2017.09.014]
9 **Nagtegaal ID**, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, Washington KM, Carneiro F, Cree IA; WHO Classification of Tumours Editorial Board. The 2019 WHO classification of tumours of the digestive system. *Histopathology* 2020; **76**: 182-188 [PMID: 31433515 DOI: 10.1111/his.13975]
10 **Assarzadegan N**, Montgomery E. What is New in the 2019 World Health Organization (WHO) Classification of Tumors of the Digestive System: Review of Selected Updates on Neuroendocrine Neoplasms, Appendiceal Tumors, and Molecular Testing. *Arch Pathol Lab Med* 2021; **145**: 664-677 [PMID: 32233993 DOI: 10.5858/arpa.2019-0665-RA]
11 **Strosberg JR**, Cheema A, Weber JM, Ghayouri M, Han G, Hodul PJ, Kvols LK. Relapse-free survival in patients with nonmetastatic, surgically resected pancreatic neuroendocrine tumors: an analysis of the AJCC and ENETS staging classifications. *Ann Surg* 2012; **256**: 321-325 [PMID: 22415420 DOI: 10.1097/SLA.0b013e31824e6108]
12 **Fottner C**, Ferrata M, Weber MM. Hormone secreting gastro-entero-pancreatic neuroendocrine neoplasias (GEP-NEN): When to consider, how to diagnose? *Rev Endocr Metab Disord* 2017; **18**: 393-410 [PMID: 29256148 DOI: 10.1007/s11154-017-9438-8]
13 **Bonds M**, Rocha FG. Neuroendocrine Tumors of the Pancreatobiliary and Gastrointestinal Tracts. *Surg Clin North Am* 2020; **100**: 635-648 [PMID: 32402306 DOI: 10.1016/j.suc.2020.02.010]
14 **Kanakis G**, Kaltsas G. Biochemical markers for gastroenteropancreatic neuroendocrine tumours (GEP-NETs). *Best Pract Res Clin Gastroenterol* 2012; **26**: 791-802 [PMID: 23582919 DOI: 10.1016/j.bpg.2012.12.006]
15 **Marotta V**, Zatelli MC, Sciammarella C, Ambrosio MR, Bondanelli M, Colao A, Faggiano A. Chromogranin A as

circulating marker for diagnosis and management of neuroendocrine neoplasms: more flaws than fame. *Endocr Relat Cancer* 2018; **25**: R11-R29 [PMID: 29066503 DOI: 10.1530/ERC-17-0269]

16 **Oberg K**, Couvelard A, Delle Fave G, Gross D, Grossman A, Jensen RT, Pape UF, Perren A, Rindi G, Ruszniewski P, Scoazec JY, Welin S, Wiedenmann B, Ferone D; Antibes Consensus Conference participants. ENETS Consensus Guidelines for Standard of Care in Neuroendocrine Tumours: Biochemical Markers. *Neuroendocrinology* 2017; **105**: 201-211 [PMID: 28391265 DOI: 10.1159/000472254]

17 **Joish VN**, Shah S, Tierce JC, Patel D, McKee C, Lapuerta P, Zacks J. Serotonin levels and 1-year mortality in patients with neuroendocrine tumors: a systematic review and meta-analysis. *Future Oncol* 2019; **15**: 1397-1406 [PMID: 30734573 DOI: 10.2217/fon-2018-0960]

18 **Osefo N**, Ito T, Jensen RT. Gastric acid hypersecretory states: recent insights and advances. *Curr Gastroenterol Rep* 2009; **11**: 433-441 [PMID: 19903418 DOI: 10.1007/s11894-009-0067-6]

19 **Cryer PE**, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, Service FJ; Endocrine Society. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2009; **94**: 709-728 [PMID: 19088155 DOI: 10.1210/jc.2008-1410]

20 **Sandru F**, Carsote M, Albu SE, Valea A, Petca A, Dumitrascu MC. Glucagonoma: From skin lesions to the neuroendocrine component (Review). *Exp Ther Med* 2020; **20**: 3389-3393 [PMID: 32905095 DOI: 10.3892/etm.2020.8966]

21 **Kaltsas G**, Rockall A, Papadogias D, Reznek R, Grossman AB. Recent advances in radiological and radionuclide imaging and therapy of neuroendocrine tumours. *Eur J Endocrinol* 2004; **151**: 15-27 [PMID: 15248818 DOI: 10.1530/eje.0.1510015]

22 **Cwikła JB**, Buscombe JR, Caplin ME, Watkinson AF, Walecki J, Gorczyca-Wiśniewska E, Hilson AJ. Diagnostic imaging of carcinoid metastases to the abdomen and pelvis. *Med Sci Monit* 2004; **10** Suppl 3: 9-16 [PMID: 16538192]

23 **Norlen O**, Montan H, Hellman P, Stalberg P, Sundin A. Preoperative $^{68}$Ga-DOTA-Somatostatin Analog-PET/CT Hybrid Imaging Increases Detection Rate of Intra-abdominal Small Intestinal Neuroendocrine Tumor Lesions. *World J Surg* 2018; **42**: 498-505 [PMID: 5762814 DOI: 10.1007/s00268-017-4364-1]

24 **Hope TA**, Bergsland EK, Bozkurt MF, Graham M, Heaney AP, Herrmann K, Howe JR, Kulke MH, Kunz PL, Mailman J, May L, Metz DC, Millo C, O'Dorisio S, Reidy-Lagunes DL, Soulen MC, Strosberg JR. Appropriate Use Criteria for Somatostatin Receptor PET Imaging in Neuroendocrine Tumors. *J Nucl Med* 2018; **59**: 66-74 [PMID: 29025982 DOI: 10.2967/jnumed.117.202275]

25 **Reubi JC**, Schonbrunn A. Illuminating somatostatin analog action at neuroendocrine tumor receptors. *Trends Pharmacol Sci* 2013; **34**: 676-688 [PMID: 24183675 DOI: 10.1016/j.tips.2013.10.001]

26 **Reubi JC**, Waser B. Concomitant expression of several peptide receptors in neuroendocrine tumours: molecular basis for *in vivo* multireceptor tumour targeting. *Eur J Nucl Med Mol Imaging* 2003; **30**: 781-793 [PMID: 12707737 DOI: 10.1007/s00259-003-1184-3]

27 **Bertherat J**, Tenenbaum F, Perlemoine K, Videau C, Alberini JL, Richard B, Dousset B, Bertagna X, Epelbaum J. Somatostatin receptors 2 and 5 are the major somatostatin receptors in insulinomas: an *in vivo* and *in vitro* study. *J Clin Endocrinol Metab* 2003; **88**: 5353-5360 [PMID: 14602773 DOI: 10.1210/jc.2002-021895]

28 **Deppen SA**, Blume J, Bobbey AJ, Shah C, Graham MM, Lee P, Delbeke D, Walker RC. 68Ga-DOTATATE Compared with 111In-DTPA-Octreotide and Conventional Imaging for Pulmonary and Gastroenteropancreatic Neuroendocrine Tumors: A Systematic Review and Meta-Analysis. *J Nucl Med* 2016; **57**: 872-878 [PMID: 26769864 DOI: 10.2967/jnumed.115.165803]

29 **Virgolini I**, Gabriel M, Kroiss A, von Guggenberg E, Prommegger R, Warwitz B, Nilica B, Roig LG, Rodrigues M, Uprimny C. Current knowledge on the sensitivity of the (68)Ga-somatostatin receptor positron emission tomography and the SUVmax reference range for management of pancreatic neuroendocrine tumours. *Eur J Nucl Med Mol Imaging* 2016; **43**: 2072-2083 [PMID: 27174220 DOI: 10.1007/s00259-016-3395-4]

30 **Hofman MS**, Hicks RJ. Changing paradigms with molecular imaging of neuroendocrine tumors. *Discov Med* 2012; **14**: 71-81 [PMID: 22846204]

31 **Sorbye H**, Kong G, Grozinsky-Glasberg S. PRRT in high-grade gastroenteropancreatic neuroendocrine neoplasms (WHO G3). *Endocr Relat Cancer* 2020; **27**: R67-R77 [PMID: 31846429 DOI: 10.1530/ERC-19-0400]

32 **Binderup T**, Knigge U, Loft A, Federspiel B, Kjaer A. 18F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors. *Clin Cancer Res* 2010; **16**: 978-985 [PMID: 20103666 DOI: 10.1158/1078-0432.CCR-09-1759]

33 **Has Simsek D**, Kuyumcu S, Turkmen C, Sanlı Y, Aykan F, Unal S, Adalet I. Can complementary 68Ga-DOTATATE and 18F-FDG PET/CT establish the missing link between histopathology and therapeutic approach in gastroenteropancreatic neuroendocrine tumors? *J Nucl Med* 2014; **55**: 1811-1817 [PMID: 25315243 DOI: 10.2967/jnumed.114.142224]

34 **Naswa N**, Sharma P, Gupta SK, Karunanithi S, Reddy RM, Patnecha M, Lata S, Kumar R, Malhotra A, Bal C. Dual tracer functional imaging of gastroenteropancreatic neuroendocrine tumors using 68Ga-DOTA-NOC PET-CT and 18F-FDG PET-CT: competitive or complimentary? *Clin Nucl Med* 2014; **39**: e27-e34 [PMID: 24217539 DOI: 10.1097/RLU.0b013e31827a216b]

35 **Saund MS**, Al Natour RH, Sharma AM, Huang Q, Boosalis VA, Gold JS. Tumor size and depth predict rate of lymph node metastasis and utilization of lymph node sampling in surgically managed gastric carcinoids. *Ann Surg Oncol* 2011; **18**: 2826-2832 [PMID: 21455598 DOI: 10.1245/s10434-011-1652-0]

36 **Anderson MA**, Carpenter S, Thompson NW, Nostrant TT, Elta GH, Scheiman JM. Endoscopic ultrasound is highly accurate and directs management in patients with neuroendocrine tumors of the pancreas. *Am J Gastroenterol* 2000; **95**: 2271-2277 [PMID: 11007228 DOI: 10.1111/j.1572-0241.2000.02480.x]

37 **Sundin A**, Arnold R, Baudin E, Cwikla JB, Eriksson B, Fanti S, Fazio N, Giammarile F, Hicks RJ, Kjaer A, Krenning E, Kwekkeboom D, Lombard-Bohas C, O'Connor JM, O'Toole D, Rockall A, Wiedenmann B, Valle JW, Vullierme MP; Antibes Consensus Conference participants. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Radiological, Nuclear Medicine & Hybrid Imaging. *Neuroendocrinology* 2017; **105**: 212-244 [PMID: 28355596

DOI: 10.1159/000471879]

38 **Perren A**, Couvelard A, Scoazec JY, Costa F, Borbath I, Delle Fave G, Gorbounova V, Gross D, Grossma A, Jense RT, Kulke M, Oeberg K, Rindi G, Sorbye H, Welin S; Antibes Consensus Conference participants. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Pathology: Diagnosis and Prognostic Stratification. *Neuroendocrinology* 2017; **105**: 196-200 [PMID: 28190015 DOI: 10.1159/000457956]

39 **Klimstra DS**, Modlin IR, Adsay NV, Chetty R, Deshpande V, Gönen M, Jensen RT, Kidd M, Kulke MH, Lloyd RV, Moran C, Moss SF, Oberg K, O'Toole D, Rindi G, Robert ME, Suster S, Tang LH, Tzen CY, Washington MK, Wiedenmann B, Yao J. Pathology reporting of neuroendocrine tumors: application of the Delphic consensus process to the development of a minimum pathology data set. *Am J Surg Pathol* 2010; **34**: 300-313 [PMID: 20118772 DOI: 10.1097/PAS.0b013e3181ce1447]

40 **Tang LH**, Basturk O, Sue JJ, Klimstra DS. A Practical Approach to the Classification of WHO Grade 3 (G3) Well-differentiated Neuroendocrine Tumor (WD-NET) and Poorly Differentiated Neuroendocrine Carcinoma (PD-NEC) of the Pancreas. *Am J Surg Pathol* 2016; **40**: 1192-1202 [PMID: 27259015 DOI: 10.1097/PAS.0000000000000662]

41 **Konukiewitz B**, Schlitter AM, Jesinghaus M, Pfister D, Steiger K, Segler A, Agaimy A, Sipos B, Zamboni G, Weichert W, Esposito I, Pfarr N, Klöppel G. Somatostatin receptor expression related to TP53 and RB1 alterations in pancreatic and extrapancreatic neuroendocrine neoplasms with a Ki67-index above 20. *Mod Pathol* 2017; **30**: 587-598 [PMID: 28059098 DOI: 10.1038/modpathol.2016.217]

42 **Singhi AD**, Klimstra DS. Well-differentiated pancreatic neuroendocrine tumours (PanNETs) and poorly differentiated pancreatic neuroendocrine carcinomas (PanNECs): concepts, issues and a practical diagnostic approach to high-grade (G3) cases. *Histopathology* 2018; **72**: 168-177 [PMID: 29239037 DOI: 10.1111/his.13408]

43 **Francis JM**, Kiezun A, Ramos AH, Serra S, Pedamallu CS, Qian ZR, Banck MS, Kanwar R, Kulkarni AA, Karpathakis A, Manzo V, Contractor T, Philips J, Nickerson E, Pho N, Hooshmand SM, Brais LK, Lawrence MS, Pugh T, McKenna A, Sivachenko A, Cibulskis K, Carter SL, Ojesina AI, Freeman S, Jones RT, Voet D, Saksena G, Auclair D, Onofrio R, Shefler E, Sougnez C, Grimsby J, Green L, Lennon N, Meyer T, Caplin M, Chung DC, Beutler AS, Ogino S, Thirlwell C, Shivdasani R, Asa SL, Harris CR, Getz G, Kulke M, Meyerson M. Somatic mutation of CDKN1B in small intestine neuroendocrine tumors. *Nat Genet* 2013; **45**: 1483-1486 [PMID: 24185511 DOI: 10.1038/ng.2821]

44 **Kim HS**, Lee HS, Nam KH, Choi J, Kim WH. p27 Loss Is Associated with Poor Prognosis in Gastroenteropancreatic Neuroendocrine Tumors. *Cancer Res Treat* 2014; **46**: 383-392 [PMID: 25036575 DOI: 10.4143/crt.2013.102]

45 **Kim D**, Viswanathan K, Goyal A, Rao R. Insulinoma-associated protein 1 (INSM1) is a robust marker for identifying and grading pancreatic neuroendocrine tumors. *Cancer Cytopathol* 2020; **128**: 269-277 [PMID: 31977134 DOI: 10.1002/cncy.22242]

46 **Halfdanarson TR**, Strosberg JR, Tang L, Bellizzi AM, Bergsland EK, O'Dorisio TM, Halperin DM, Fishbein L, Eads J, Hope TA, Singh S, Salem R, Metz DC, Naraev BG, Reidy-Lagunes DL, Howe JR, Pommier RF, Menda Y, Chan JA. The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Pancreatic Neuroendocrine Tumors. *Pancreas* 2020; **49**: 863-881 [PMID: 32675783 DOI: 10.1097/MPA.0000000000001597]

47 **Woltering EA**, Voros BA, Beyer DT, Wang YZ, Thiagarajan R, Ryan P, Wright A, Ramirez RA, Ricks MJ, Boudreaux JP. Aggressive Surgical Approach to the Management of Neuroendocrine Tumors: A Report of 1,000 Surgical Cytoreductions by a Single Institution. *J Am Coll Surg* 2017; **224**: 434-447 [PMID: 28088602 DOI: 10.1016/j.jamcollsurg.2016.12.032]

48 **Coriat R**, Walter T, Terris B, Couvelard A, Ruszniewski P. Gastroenteropancreatic Well-Differentiated Grade 3 Neuroendocrine Tumors: Review and Position Statement. *Oncologist* 2016; **21**: 1191-1199 [PMID: 27401895 DOI: 10.1634/theoncologist.2015-0476]

49 **Partelli S**, Cirocchi R, Crippa S, Cardinali L, Fendrich V, Bartsch DK, Falconi M. Systematic review of active surveillance *vs* surgical management of asymptomatic small non-functioning pancreatic neuroendocrine neoplasms. *Br J Surg* 2017; **104**: 34-41 [PMID: 27706803 DOI: 10.1002/bjs.10312]

50 **Partelli S**, Gaujoux S, Boninsegna L, Cherif R, Crippa S, Couvelard A, Scarpa A, Ruszniewski P, Sauvanet A, Falconi M. Pattern and clinical predictors of lymph node involvement in nonfunctioning pancreatic neuroendocrine tumors (NF-PanNETs). *JAMA Surg* 2013; **148**: 932-939 [PMID: 23986355 DOI: 10.1001/jamasurg.2013.3376]

51 **Lardière-Deguelte S**, de Mestier L, Appéré F, Vullierme MP, Zappa M, Hoeffel C, Noaves M, Brixi H, Hentic O, Ruszniewski P, Cadiot G, Panis Y, Kianmanesh R. Toward a Preoperative Classification of Lymph Node Metastases in Patients with Small Intestinal Neuroendocrine Tumors in the Era of Intestinal-Sparing Surgery. *Neuroendocrinology* 2016; **103**: 552-559 [PMID: 26445315 DOI: 10.1159/000441423]

52 **Chakedis J**, Beal EW, Lopez-Aguiar AG, Poultsides G, Makris E, Rocha FG, Kanji Z, Weber S, Fisher A, Fields R. 343 - Surgery Provides Long-Term Survival in Patients with Metastatic Neuroendocrine Tumors Undergoing Resection for Non-Hormonal Symptoms. Journal of Gastrointestinal Surgery 2018; 23 [DOI: 10.1007/s11605-018-3986-4]

53 **Merola E**, Rinke A, Partelli S, Gress TM, Andreasi V, Kollár A, Perren A, Christ E, Panzuto F, Pascher A, Jann H, Arsenic R, Cremer B, Kaemmerer D, Kump P, Lipp RW, Agaimy A, Wiedenmann B, Falconi M, Pavel ME. Surgery with Radical Intent: Is There an Indication for G3 Neuroendocrine Neoplasms? *Ann Surg Oncol* 2020; **27**: 1348-1355 [PMID: 31720931 DOI: 10.1245/s10434-019-08049-5]

54 **Daskalakis K**, Karakatsanis A, Hessman O, Stuart HC, Welin S, Tiensuu Janson E, Öberg K, Hellman P, Norlén O, Stålberg P. Association of a Prophylactic Surgical Approach to Stage IV Small Intestinal Neuroendocrine Tumors With Survival. *JAMA Oncol* 2018; **4**: 183-189 [PMID: 29049611 DOI: 10.1001/jamaoncol.2017.3326]

55 **Partelli S**, Cirocchi R, Rancoita PMV, Muffatti F, Andreasi V, Crippa S, Tamburrino D, Falconi M. A Systematic review and meta-analysis on the role of palliative primary resection for pancreatic neuroendocrine neoplasm with liver metastases. *HPB (Oxford)* 2018; **20**: 197-203 [PMID: 29196022 DOI: 10.1016/j.hpb.2017.10.014]

56 **Cives M**, Strosberg J. The expanding role of somatostatin analogs in gastroenteropancreatic and lung neuroendocrine tumors. *Drugs* 2015; **75**: 847-858 [PMID: 25911185 DOI: 10.1007/s40265-015-0397-7]

57 **Stueven AK**, Kayser A, Wetz C, Amthauer H, Wree A, Tacke F, Wiedenmann B, Roderburg C, Jann H. Somatostatin

Analogues in the Treatment of Neuroendocrine Tumors: Past, Present and Future. *Int J Mol Sci* 2019; **20** [PMID: 31234481 DOI: 10.3390/ijms20123049]

58 **Baldelli R**, Barnabei A, Rizza L, Isidori AM, Rota F, Di Giacinto P, Paoloni A, Torino F, Corsello SM, Lenzi A, Appetecchia M. Somatostatin analogs therapy in gastroenteropancreatic neuroendocrine tumors: current aspects and new perspectives. *Front Endocrinol (Lausanne)* 2014; **5**: 7 [PMID: 24570674 DOI: 10.3389/fendo.2014.00007]

59 **Rinke A**, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, Mayer C, Aminossadati B, Pape UF, Bläker M, Harder J, Arnold C, Gress T, Arnold R; PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol* 2009; **27**: 4656-4663 [PMID: 19704057 DOI: 10.1200/JCO.2009.22.8510]

60 **Caplin ME**, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, Cadiot G, Wolin EM, Capdevila J, Wall L, Rindi G, Langley A, Martinez S, Blumberg J, Ruszniewski P; CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med* 2014; **371**: 224-233 [PMID: 25014687 DOI: 10.1056/NEJMoa1316158]

61 **Gomes-Porras M**, Cárdenas-Salas J, Álvarez-Escolá C. Somatostatin Analogs in Clinical Practice: a Review. *Int J Mol Sci* 2020; **21** [PMID: 32121432 DOI: 10.3390/ijms21051682]

62 **Wolin EM**, Jarzab B, Eriksson B, Walter T, Toumpanakis C, Morse MA, Tomassetti P, Weber MM, Fogelman DR, Ramage J, Poon D, Gadbaw B, Li J, Pasieka JL, Mahamat A, Swahn F, Newell-Price J, Mansoor W, Öberg K. Phase III study of pasireotide long-acting release in patients with metastatic neuroendocrine tumors and carcinoid symptoms refractory to available somatostatin analogues. *Drug Des Devel Ther* 2015; **9**: 5075-5086 [PMID: 26366058 DOI: 10.2147/DDDT.S84177]

63 **Oberg K**, Kvols L, Caplin M, Delle Fave G, de Herder W, Rindi G, Ruszniewski P, Woltering EA, Wiedenmann B. Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. *Ann Oncol* 2004; **15**: 966-973 [PMID: 15151956 DOI: 10.1093/annonc/mdh216]

64 **Rinke A**, Krug S. Neuroendocrine tumours - Medical therapy: Biological. *Best Pract Res Clin Endocrinol Metab* 2016; **30**: 79-91 [PMID: 26971845 DOI: 10.1016/j.beem.2015.09.004]

65 **Yao JC**, Guthrie KA, Moran C, Strosberg JR, Kulke MH, Chan JA, LoConte N, McWilliams RR, Wolin EM, Mattar B, McDonough S, Chen H, Blanke CD, Hochster HS. Phase III Prospective Randomized Comparison Trial of Depot Octreotide Plus Interferon Alfa-2b Versus Depot Octreotide Plus Bevacizumab in Patients With Advanced Carcinoid Tumors: SWOG S0518. *J Clin Oncol* 2017; **35**: 1695-1703 [PMID: 28384065 DOI: 10.1200/JCO.2016.70.4072]

66 **Pavel M**, Öberg K, Falconi M, Krenning EP, Sundin A, Perren A, Berruti A; ESMO Guidelines Committee. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2020; **31**: 844-860 [PMID: 32272208 DOI: 10.1016/j.annonc.2020.03.304]

67 **Capozzi M**, VON Arx C, DE Divitiis C, Ottaiano A, Tatangelo F, Romano GM, Tafuto S; (On behalf of ENETS Center of Excellence Multidisciplinary Group for Neuroendocrine Tumors in Naples, Italy). Antiangiogenic Therapy in Pancreatic Neuroendocrine Tumors. *Anticancer Res* 2016; **36**: 5025-5030 [PMID: 27798861 DOI: 10.21873/anticanres.11071]

68 **Wolin EM**. PI3K/Akt/mTOR pathway inhibitors in the therapy of pancreatic neuroendocrine tumors. *Cancer Lett* 2013; **335**: 1-8 [PMID: 23419523 DOI: 10.1016/j.canlet.2013.02.016]

69 **Aristizabal Prada ET**, Auernhammer CJ. Targeted therapy of gastroenteropancreatic neuroendocrine tumours: preclinical strategies and future targets. *Endocr Connect* 2018; **7**: R1-R25 [PMID: 29146887 DOI: 10.1530/EC-17-0286]

70 **Yao JC**, Pavel M, Lombard-Bohas C, Van Cutsem E, Voi M, Brandt U, He W, Chen D, Capdevila J, de Vries EGE, Tomassetti P, Hobday T, Pommier R, Öberg K. Everolimus for the Treatment of Advanced Pancreatic Neuroendocrine Tumors: Overall Survival and Circulating Biomarkers From the Randomized, Phase III RADIANT-3 Study. *J Clin Oncol* 2016; **34**: 3906-3913 [PMID: 27621394 DOI: 10.1200/JCO.2016.68.0702]

71 **Yao JC**, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, Tomasek J, Raderer M, Lahner H, Voi M, Pacaud LB, Rouyrre N, Sachs C, Valle JW, Fave GD, Van Cutsem E, Tesselaar M, Shimada Y, Oh DY, Strosberg J, Kulke MH, Pavel ME; RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet* 2016; **387**: 968-977 [PMID: 26703889 DOI: 10.1016/S0140-6736(15)00817-X]

72 **Agata**, Matej, Hanna, Bujwid, Jakub, Wroński. Glycemic control in patients with insulinoma. Hormones (Athens, Greece) 2016 [DOI: 10.14310/horm.2002.1706]

73 **Usukura M**, Yoneda T, Oda N, Yamamoto Y, Takata H, Hasatani K, Takeda Y. Medical treatment of benign insulinoma using octreotide LAR: a case report. *Endocr J* 2007; **54**: 95-101 [PMID: 17124362 DOI: 10.1507/endocrj.k05-157]

74 **Healy ML**, Dawson SJ, Murray RM, Zalcberg J, Jefford M. Severe hypoglycaemia after long-acting octreotide in a patient with an unrecognized malignant insulinoma. *Intern Med J* 2007; **37**: 406-409 [PMID: 17535385 DOI: 10.1111/j.1445-5994.2007.01371.x]

75 **Faivre S**, Niccoli P, Castellano D, Valle JW, Hammel P, Raoul JL, Vinik A, Van Cutsem E, Bang YJ, Lee SH, Borbath I, Lombard-Bohas C, Metrakos P, Smith D, Chen JS, Ruszniewski P, Seitz JF, Patyna S, Lu DR, Ishak KJ, Raymond E. Sunitinib in pancreatic neuroendocrine tumors: updated progression-free survival and final overall survival from a phase III randomized study. *Ann Oncol* 2017; **28**: 339-343 [PMID: 27836885 DOI: 10.1093/annonc/mdw561]

76 **Xu J**, Shen L, Bai C, Wang W, Li J, Yu X, Li Z, Li E, Yuan X, Chi Y, Yin Y, Lou W, Xu N, Bai Y, Zhang T, Xiu D, Wang X, Yuan Y, Chen J, Qin S, Jia R, Lu M, Cheng Y, Zhou Z, He J, Su W. Surufatinib in advanced pancreatic neuroendocrine tumours (SANET-p): a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2020; **21**: 1489-1499 [PMID: 32966810 DOI: 10.1016/S1470-2045(20)30493-9]

77 **Bagchi S**, Yuan R, Engleman EG. Immune Checkpoint Inhibitors for the Treatment of Cancer: Clinical Impact and Mechanisms of Response and Resistance. *Annu Rev Pathol* 2021; **16**: 223-249 [PMID: 33197221 DOI: 10.1146/annurev-pathol-042020-042741]

78 **Mehnert JM**, Bergsland E, O'Neil BH, Santoro A, Schellens JHM, Cohen RB, Doi T, Ott PA, Pishvaian MJ, Puzanov I, Aung KL, Hsu C, Le Tourneau C, Hollebecque A, Élez E, Tamura K, Gould M, Yang P, Stein K, Piha-Paul SA. Pembrolizumab for the treatment of programmed death-ligand 1-positive advanced carcinoid or pancreatic neuroendocrine tumors: Results from the KEYNOTE-028 study. *Cancer* 2020; **126**: 3021-3030 [PMID: 32320048 DOI: 10.1002/cncr.32883]

79 **Strosberg J**, Mizuno N, Doi T, Grande E, Delord JP, Shapira-Frommer R, Bergsland E, Shah M, Fakih M, Takahashi S, Piha-Paul SA, O'Neil B, Thomas S, Lolkema MP, Chen M, Ibrahim N, Norwood K, Hadoux J. Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Neuroendocrine Tumors: Results From the Phase II KEYNOTE-158 Study. *Clin Cancer Res* 2020; **26**: 2124-2130 [PMID: 31980466 DOI: 10.1158/1078-0432.CCR-19-3014]

80 **Marabelle A**, Fakih M, Lopez J, Shah M, Shapira-Frommer R, Nakagawa K, Chung HC, Kindler HL, Lopez-Martin JA, Miller WH Jr, Italiano A, Kao S, Piha-Paul SA, Delord JP, McWilliams RR, Fabrizio DA, Aurora-Garg D, Xu L, Jin F, Norwood K, Bang YJ. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol* 2020; **21**: 1353-1365 [PMID: 32919526 DOI: 10.1016/S1470-2045(20)30445-9]

81 **Merino DM**, McShane LM, Fabrizio D, Funari V, Chen SJ, White JR, Wenz P, Baden J, Barrett JC, Chaudhary R, Chen L, Chen WS, Cheng JH, Cyanam D, Dickey JS, Gupta V, Hellmann M, Helman E, Li Y, Maas J, Papin A, Patidar R, Quinn KJ, Rizvi N, Tae H, Ward C, Xie M, Zehir A, Zhao C, Dietel M, Stenzinger A, Stewart M, Allen J; TMB Harmonization Consortium. Establishing guidelines to harmonize tumor mutational burden (TMB): in silico assessment of variation in TMB quantification across diagnostic platforms: phase I of the Friends of Cancer Research TMB Harmonization Project. *J Immunother Cancer* 2020; **8** [PMID: 32217756 DOI: 10.1136/jitc-2019-000147]

82 **Patel SP**, Othus M, Chae YK, Giles FJ, Hansel DE, Singh PP, Fontaine A, Shah MH, Kasi A, Baghdadi TA, Matrana M, Gatalica Z, Korn WM, Hayward J, McLeod C, Chen HX, Sharon E, Mayerson E, Ryan CW, Plets M, Blanke CD, Kurzrock R. A Phase II Basket Trial of Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART SWOG 1609) in Patients with Nonpancreatic Neuroendocrine Tumors. *Clin Cancer Res* 2020; **26**: 2290-2296 [PMID: 31969335 DOI: 10.1158/1078-0432.CCR-19-3356]

83 **Klein O**, Kee D, Markman B, Michael M, Underhill C, Carlino MS, Jackett L, Lum C, Scott C, Nagrial A, Behren A, So JY, Palmer J, Cebon J. Immunotherapy of Ipilimumab and Nivolumab in Patients with Advanced Neuroendocrine Tumors: A Subgroup Analysis of the CA209-538 Clinical Trial for Rare Cancers. *Clin Cancer Res* 2020; **26**: 4454-4459 [PMID: 32532787 DOI: 10.1158/1078-0432.CCR-20-0621]

84 **Kwekkeboom DJ**, Krenning EP. Peptide Receptor Radionuclide Therapy in the Treatment of Neuroendocrine Tumors. *Hematol Oncol Clin North Am* 2016; **30**: 179-191 [PMID: 26614376 DOI: 10.1016/j.hoc.2015.09.009]

85 **Cives M**, Strosberg J. Radionuclide Therapy for Neuroendocrine Tumors. *Curr Oncol Rep* 2017; **19**: 9 [PMID: 28220446 DOI: 10.1007/s11912-017-0567-8]

86 **Camus B**, Cottereau AS, Palmieri LJ, Dermine S, Tenenbaum F, Brezault C, Coriat R. Indications of Peptide Receptor Radionuclide Therapy (PRRT) in Gastroenteropancreatic and Pulmonary Neuroendocrine Tumors: An Updated Review. *J Clin Med* 2021; **10** [PMID: 33803817 DOI: 10.3390/jcm10061267]

87 **Salner AL**, Blankenship B, Dunnack H, Niemann C, Bertsch H. Lutetium Lu-177 Dotatate Flare Reaction. *Adv Radiat Oncol* 2021; **6**: 100623 [PMID: 33490736 DOI: 10.1016/j.adro.2020.11.008]

88 **Saravana-Bawan B**, Bajwa A, Paterson J, McEwan AJB, McMullen TPW. Efficacy of 177Lu Peptide Receptor Radionuclide Therapy for the Treatment of Neuroendocrine Tumors: A Meta-analysis. *Clin Nucl Med* 2019; **44**: 719-727 [PMID: 31205149 DOI: 10.1097/RLU.0000000000002646]

89 **Sorbye H**, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, Dueland S, Hofsli E, Guren MG, Ohrling K, Birkemeyer E, Thiis-Evensen E, Biagini M, Gronbaek H, Soveri LM, Olsen IH, Federspiel B, Assmus J, Janson ET, Knigge U. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol* 2013; **24**: 152-160 [PMID: 22967994 DOI: 10.1093/annonc/mds276]

90 **Sorbye H**, Baudin E, Perren A. The Problem of High-Grade Gastroenteropancreatic Neuroendocrine Neoplasms: Well-Differentiated Neuroendocrine Tumors, Neuroendocrine Carcinomas, and Beyond. *Endocrinol Metab Clin North Am* 2018; **47**: 683-698 [PMID: 30098724 DOI: 10.1016/j.ecl.2018.05.001]

91 **Corleto VD**, Festa S, Di Giulio E, Annibale B. Proton pump inhibitor therapy and potential long-term harm. *Curr Opin Endocrinol Diabetes Obes* 2014; **21**: 3-8 [PMID: 24310148 DOI: 10.1097/MED.0000000000000031]

92 **Pavel M**, Gross DJ, Benavent M, Perros P, Srirajaskanthan R, Warner RRP, Kulke MH, Anthony LB, Kunz PL, Hörsch D, Weickert MO, Lapuerta P, Jiang W, Kassler-Taub K, Wason S, Fleming R, Fleming D, Garcia-Carbonero R. Telotristat ethyl in carcinoid syndrome: safety and efficacy in the TELECAST phase 3 trial. *Endocr Relat Cancer* 2018; **25**: 309-322 [PMID: 29330194 DOI: 10.1530/ERC-17-0455]

93 **Kulke MH**, Hörsch D, Caplin ME, Anthony LB, Bergsland E, Öberg K, Welin S, Warner RR, Lombard-Bohas C, Kunz PL, Grande E, Valle JW, Fleming D, Lapuerta P, Banks P, Jackson S, Zambrowicz B, Sands AT, Pavel M. Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome. *J Clin Oncol* 2017; **35**: 14-23 [PMID: 27918724 DOI: 10.1200/JCO.2016.69.2780]

94 **Oberndorfer S**. Karzinoide Tumoren des Dunndarms. *Frankfurt Z Path* 1907; **1**: 426-432 [DOI: 10.1159/000190091]

95 **Wilder RM**, Allan FN, Power MH, Robertson HE. Carcinoma of the islands of the pancreas: hyperinsulinism and hypoglycemia. *J Am Med Dir Assoc* 1927; **89**: 348-355 [DOI: 10.1001/jama.1927.02690050014007]

96 **Becker ER**. THE IOWA ACADEMY OF SCIENCE. *Science* 1942; **95**: 651-652 [PMID: 17819586 DOI: 10.1126/science.95.2478.651]

97 **Zollinger RM**, Ellison EH. Primary peptic ulcerations of the jejunum associated with islet cell tumors of the pancreas. *Ann Surg* 1955; **142**: 709-23; discussion, 724 [PMID: 13259432]

98 **Bloom SR**, Bryant MG, Polak JM. Proceedings: Distribution of gut hormones. *Gut* 1975; **16**: 821 [PMID: 812779]

99 **Ganda OP**, Weir GC, Soeldner JS, Legg MA, Chick WL, Patel YC, Ebeid AM, Gabbay KH, Reichlin S. "Somatostatinoma": a somatostatin-containing tumor of the endocrine pancreas. *N Engl J Med* 1977; **296**: 963-967

[PMID: 321960 DOI: 10.1056/NEJM197704282961703]
100 **Lloyd RV**, Wilson BS. Specific endocrine tissue marker defined by a monoclonal antibody. *Science* 1983; **222**: 628-630 [PMID: 6635661 DOI: 10.1126/science.6635661]
101 **Krenning EP**, Kwekkeboom DJ, Bakker WH, Breeman WA, Kooij PP, Oei HY, van Hagen M, Postema PT, de Jong M, Reubi JC, et al. Somatostatin receptor scintigraphy with [111In-DTPA-D-Phe1]- and [123I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. *Eur J Nucl Med* 1993; **20**: 716-731 [DOI: 10.1007/bf00181765]
102 **Solcia E**, Rindi G, Capella C. Histochemistry in pathology. Edinburgh, London, New York: Churchill-Livingstone 1990: 397-409 [DOI: 10.1016/s0344-0338(82)80057-5]
103 **Evans EB**, Eggers GW. World Health Organization International Histological Classification of Tumours: Histological Typing of Endocrine Tumours: Second Edition. *Clinical Endocrinology* 2000; **53**: 259-259 [DOI: 10.1046/j.1365-2265.2000.01073.x]
104 **Delellis RA**, Lloyd RV, Heitz PU. World Health Organization Classification Classification of Tumours: Pathology and Genetics of Tumours of Endocrine Organs. 2004 [DOI: 10.1016/j.urology.2004.09.048]
105 **Bosman FT**, Carneiro F, Hruban RH, Theise ND. WHO classification of tumours of the digestive system. *International Agency for Research on Cancer* 2010
106 **Oberg K**, Akerström G, Rindi G, Jelic S; ESMO Guidelines Working Group. Neuroendocrine gastroenteropancreatic tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; **21** Suppl 5: v223-v227 [PMID: 20555086 DOI: 10.1093/annonc/mdq192]
107 **Murray-Lyon IM**, Eddleston AL, Williams R, Brown M, Hogbin BM, Bennett A, Edwards JC, Taylor KW. Treatment of multiple-hormone-producing malignant islet-cell tumour with streptozotocin. *Lancet* 1968; **2**: 895-898 [PMID: 4176152 DOI: 10.1016/s0140-6736(68)91058-1]
108 **Reichlin S**. Somatostatin. *N Engl J Med* 1983; **309**: 1495-1501 [PMID: 6139753 DOI: 10.1056/nejm198312153092406]
109 **Bauer W**, Briner U, Doepfner W, Haller R, Huguenin R, Marbach P, Petcher TJ, Pless. SMS 201-995: a very potent and selective octapeptide analogue of somatostatin with prolonged action. *Life Sci* 1982; **31**: 1133-1140 [PMID: 6128648 DOI: 10.1016/0024-3205(82)90087-x]
110 **Oberg K**, Funa K, Alm G. Effects of leukocyte interferon on clinical symptoms and hormone levels in patients with mid-gut carcinoid tumors and carcinoid syndrome. *N Engl J Med* 1983; **309**: 129-133 [PMID: 6191217 DOI: 10.1056/NEJM198307213090301]
111 **Krenning EP**, Kooij PP, Bakker WH, Breeman WA, Postema PT, Kwekkeboom DJ, Oei HY, de Jong M, Visser TJ, Reijs AE, et al. Radiotherapy with a radiolabeled somatostatin analogue, [111In-DTPA-D-Phe1]-octreotide. A case history. *Ann N Y Acad Sci* 1994; **733**: 496-506 [DOI: 10.1111/j.1749-6632.1994.tb17300.x]
112 **Ekeblad S**, Sundin A, Janson ET, Welin S, Granberg D, Kindmark H, Dunder K, Kozlovacki G, Orlefors H, Sigurd M, Oberg K, Eriksson B, Skogseid B. Temozolomide as monotherapy is effective in treatment of advanced malignant neuroendocrine tumors. *Clin Cancer Res* 2007; **13**: 2986-2991 [PMID: 17505000 DOI: 10.1158/1078-0432.CCR-06-2053]
113 **Yao JC**, Phan AT, Chang DZ, Wolff RA, Hess K, Gupta S, Jacobs C, Mares JE, Landgraf AN, Rashid A, Meric-Bernstam F. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study. *J Clin Oncol* 2008; **26**: 4311-4318 [PMID: 18779618 DOI: 10.1200/JCO.2008.16.7858]
114 **Raymond E**, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, Valle J, Metrakos P, Smith D, Vinik A, Chen JS, Hörsch D, Hammel P, Wiedenmann B, Van Cutsem E, Patyna S, Lu DR, Blanckmeister C, Chao R, Ruszniewski P. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011; **364**: 501-513 [PMID: 21306237 DOI: 10.1056/NEJMoa1003825]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 May 27; 14(5): 397-408

DOI: 10.4240/wjgs.v14.i5.397

ISSN 1948-9366 (online)

*MINIREVIEWS*

# Role of surgical treatments in high-grade or advanced gastroenteropancreatic neuroendocrine neoplasms

Qing-Yang Que, Lin-Cheng Zhang, Jia-Qi Bao, Sun-Bin Ling, Xiao Xu

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Chiu CC, Taiwan; Kapritsou M, Greece; Rossi RE, Italy

**Received:** October 25, 2021
**Peer-review started:** October 25, 2021
**First decision:** December 27, 2021
**Revised:** January 19, 2022
**Accepted:** April 9, 2022
**Article in press:** April 9, 2022
**Published online:** May 27, 2022

**Qing-Yang Que, Lin-Cheng Zhang, Jia-Qi Bao, Sun-Bin Ling, Xiao Xu,** Key Laboratory of Integrated Oncology and Intelligent Medicine of Zhejiang Province, Hangzhou 310006, Zhejiang Province, China

**Qing-Yang Que, Lin-Cheng Zhang, Jia-Qi Bao, Sun-Bin Ling, Xiao Xu,** Zhejiang University Cancer Center, Hangzhou 310006, Zhejiang Province, China

**Qing-Yang Que, Lin-Cheng Zhang, Jia-Qi Bao, Sun-Bin Ling, Xiao Xu,** NHC Key Laboratory of Combined Multi-organ Transplantation, Hangzhou 310006, Zhejiang Province, China

**Qing-Yang Que, Lin-Cheng Zhang, Jia-Qi Bao, Sun-Bin Ling, Xiao Xu,** Department of Hepatobiliary and Pancreatic Surgery, Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou 310006, Zhejiang Province, China

**Xiao Xu,** Institute of Organ Transplantation, Zhejiang University, Hangzhou 310003, Zhejiang Province, China

**Corresponding author:** Xiao Xu, FACS, MD, PhD, Academic Fellow, Chief Doctor, Professor, Key Laboratory of Integrated Oncology and Intelligent Medicine of Zhejiang Province, No. 261 Huansha Road, Hangzhou 310006, Zhejiang Province, China. zjxu@zju.edu.cn

## Abstract

Over the last 40 years, the incidence and prevalence of gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) have continued to increase. Compared to other epithelial neoplasms in the same organ, GEP-NENs exhibit indolent biological behavior, resulting in more chances to undergo surgery. However, the role of surgery in high-grade or advanced GEP-NENs is still controversial. Surgery is associated with survival improvement of well-differentiated high-grade GEP-NENs, whereas poorly differentiated GEP-NENs that may benefit from resection require careful selection based on Ki67 and other tissue biomarkers. Additionally, surgery also plays an important role in locally advanced and metastatic disease. For locally advanced GEP-NENs, isolated major vascular involvement is no longer an absolute contraindication. In the setting of metastatic GEP-NENs, radical intended surgery is recommended for patients with low-grade and resectable metastases. For unresectable metastatic disease, a variety of surgical approaches, including cytoreduction of liver metastasis, liver transplantation, and surgery after neoadjuvant treatment, show survival benefits. Primary tumor resection in GEP-NENs with unresectable metastatic disease is associated with symptom control, prolonged survival, and improved sensitivity

toward systemic therapies. Although there is no established neoadjuvant or adjuvant strategy, increasing attention has been given to this emerging research area. Some studies have reported that neoadjuvant therapy effectively reduces tumor burden, improves the effectiveness of subsequent surgery, and decreases surgical complications.

**Key Words:** Gastroenteropancreatic neuroendocrine neoplasms; Neuroendocrine carcinomas; Surgery; Hepatic debulking; Liver transplant; Transplant oncology



**Core Tip:** Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) encompass a heterogeneous group of tumors with unique indolent biological behavior. The role of surgery in high-grade or advanced GEP-NENs is still controversial. There are several highlights of this review. First, we address the surgical benefits of selected high-grade GEP-NENs and summarize the tumor biological markers correlated with a prognosis. Second, we review various surgical strategies, including curative resection, debulking, resection after neoadjuvant therapy for metastatic GEP-NENs, and the latest clinical evidence. Finally, liver transplantation presents a curative therapeutic option for GEP-NEN patients with liver metastasis. We summarize the new findings and propose directions for future development.

**Citation:** Que QY, Zhang LC, Bao JQ, Ling SB, Xu X. Role of surgical treatments in high-grade or advanced gastroenteropancreatic neuroendocrine neoplasms. *World J Gastrointest Surg* 2022; 14(5): 397-408
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i5/397.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i5.397

## INTRODUCTION

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are rare lesions arising from neuroendocrine cells scattered throughout the body. Although GEP-NENs are still regarded as uncommon neoplasms, both their incidence and prevalence have continued to increase over the last 40 years[1,2]. As GEP-NENs are morphologically and biologically heterogeneous[3,4], the World Health Organization has classified them into three grades based on the proliferation index (Ki67) and differentiation level[5]. G3 NENs, showing a Ki67 value (> 20%) and/or mitotic index (> 20 mitoses/10 high-power field), are further subdivided into two subgroups as follows: Well-differentiated neuroendocrine tumors (G3 NET) and poorly differentiated neuroendocrine carcinomas (G3 NEC) (Table 1)[6]. The incidence of liver metastasis (LM) in GEP-NENs is high, and the median overall survival (OS) for patients with metastatic GEP-NENs is 2-4 years[7].

Given the associated high risk of developing distant metastases, the role of surgery in the treatment regimen for high-grade GEP-NEN (hgGEP-NEN) remains controversial. Since treatment strategies for hgGEP-NEN have generally been extrapolated from the findings for small-cell lung cancer[8,9], surgery is not included in the primary therapeutic regimen[10,11]. Given the differences in prognoses and therapeutic responses between pulmonary and digestive neuroendocrine carcinomas, it is necessary to evaluate the role of surgery in GEP-NENs. Moreover, surgery is generally considered nonbeneficial for patients with metastatic diseases. However, as a large proportion of GEP-NEN patients exhibit relatively indolent biology, some studies also report the survival benefits of surgery[12,13]. Therefore, the purpose of this review is to summarize and discuss surgical management strategies for high-grade or advanced GEP-NENs.

## SURGERY FOR LOCALIZED HGGEP-NEN

Platinum-based chemotherapy is considered the standard treatment for hgGEP-NEN, whereas the role of surgery has not been fully assessed. In this setting, Merola *et al*[14] investigated survival outcomes in 60 patients with localized hgGEP-NEN who underwent radical surgical procedures. The 2-year OS rate was 64.5%, and the 2-year recurrence-free survival (RFS) rate was 44.9%[14]. Moreover, in a Nordic multicenter retrospective cohort study, the median OS in 201-G3 GEP-NEN patients upon surgical resection was 32 mo[15]. In a large retrospective study consisting of 1517 G3 GEP-NEC patients, surgery was significantly associated with improved OS [hazard ratio (HR): 0.41][16]. Despite the lack of high-quality long-term prospective trials, there is sufficient evidence to suggest that careful patient selection for surgical resection can increase clinical benefits in G3 GEP-NENs. Many factors can predict the

**Table 1 Classification for gastroenteropancreatic neuroendocrine neoplasms by World Health Organization**

| Terminology | Differentiation | Grade | Ki67 index, % | Mitotic count, 2 mm$^2$ |
|---|---|---|---|---|
| NET, G1 | Well differentiated | Low | < 3 | < 2 |
| NET, G2 | Well differentiated | Intermediate | 3–20 | 2–20 |
| NET, G3 | Well differentiated | High | > 20 | > 20 |
| NEC, G3 | Poorly differentiated | High | > 20 | > 20 |

NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma.

prognosis of GEP-NENs and may aid in the selection of suitable patients for surgery; among them, differentiation and the Ki67 value are the two most important prognostic factors[17-19].

Since hgGEP-NENs are highly heterogeneous, comprising both G3 NETs and G3 NECs, G3 NENs cannot be considered a single entity[20]. In contrast to well-differentiated NENs, G3 NEC is highly aggressive and metastasizes early, resulting in a poor prognosis[4]. Tumor differentiation is associated with surgical prognosis. In a retrospective study consisting of 67 patients, including 21 with pancreatic G3 NETs and 46 with pancreatic G3 NECs, those with G3 NETs were found to benefit from surgical resection, unlike those with G3 NENs who did not show any significant improvements[21]. Consistently, Merola *et al*[14] drew a similar conclusion from their study involving 60 hgGEP-NEN patients [14]. The OS of patients with G3 NET was significantly better than that in G3 NEC patients; G3 NEC was a marker of a poor prognosis (NEC G3 *vs* NET G3: HR 4.24, $P = 0.05$). However, in another study, no significant difference was observed in postsurgical survival between G3 NETs and G3 NECs in patients with pancreatic hgGEP-NENs[22]. In a large-scale retrospective study consisting of 2245 patients with GEP NECs, the median survival after surgery was 31 mo ($n = 1549$) *vs* 9 mo after nonoperative therapy ( $n = 696$, $P < 0.001$)[23]. The 5-year OS rates were 39% and 10%, respectively. Abdel-Rahman *et al*[16] performed propensity score matching between 233 G3 GEP NEC patients who did not undergo surgery and 233 G3 GEP NEC surgical patients. They reported that radical surgery was significantly associated with improved survival ($P < 0.001$)[16]. GEP G3 NECs were further distinguished based on poorly differentiated histology and undifferentiated histology; poorly differentiated histology was significantly associated with improved OS compared with undifferentiated histology (HR: 0.83), which could explain the discrepancy in the results of the abovementioned studies. Additionally, heterogeneity within hgGEP-NENs could lead to differences in surgical outcomes, which may be observed in a small sample size. Moreover, the heterogeneity is not only derived from hgGEP-NENs themselves but also the difficulty associated with the morphological diagnoses by pathologists[9,24]. A high percentage of inconclusive diagnoses have been reported (61%), which may be attributed to limited pathological resources, a lack of well-defined histological criteria, and the complexity underlying GEP-NEN origins [25].

The Ki67 value is easier to examine and provides a more objective basis for evaluation. Ki67 can reflect the heterogeneity of hgGEP-NENs and predict responsiveness to treatment[4,26]. Sorbye *et al*[27] evaluated 305 hgGEP-NEN cases and obtained a cutoff value (55% Ki67) by ROC analysis[27]. Patients with Ki67 < 55% showed a better OS than those with Ki67 ≥ 55% but a lower response rate to platinum-based chemotherapy. Differences in treatment responses were also observed for surgical resection. Merola *et al*[14] reported that the median OS for Ki67 ≤ 55% was not achieved *vs* 26 mo in patients with Ki67 > 55% after surgery[14]. Similarly, in a study from Tokyo, 63 hgGEP-NEN patients who underwent surgical resections between 2005 and 2018 were reviewed[28]. Patients were divided into low-Ki67 (Ki67 < 52%) and high-Ki67 (Ki67 ≥ 52%) groups according to the median Ki67 value (52%). In the low Ki67 group, the median survival times were 82.7, 16.3, and 27.7 mo for patients in the R0/1, R2, and chemotherapy groups, respectively. Surgery ($P = 0.013$, HR = 0.46) and low Ki67 ($P = 0.007$, HR = 0.43) were independent prognostic factors related to improved OS.

Recently, the National Comprehensive Cancer Network guidelines have recommended hgGEP-NENs with Ki67 < 55%, slow growth, and positivity for somatostatin receptor as the criteria for surgery, although caution for heterogeneity remains[29]. In addition to the Ki67 value, other tissue biomarkers are also correlated with differentiation, including the neuroendocrine markers synaptophysin, chromogranin-A (CgA), death domain-associated protein (DAXX), p53, and Rb1. At present, a conclusive decision for the prognostic value remains lacking for all these biomarkers. Therefore, there is a need for large, long-term studies using GEP-NEN cohorts and assessing the effects of tissue and blood biomarkers.

## SURGERY FOR LOCALLY ADVANCED GEP-NEN

Recently, experts from the European Neuroendocrine Tumor Society acknowledged that the surgical strategy for locally advanced pancreatic NENs (pNENs) is an important unanswered query[30]. Birnbaum *et al*[13] evaluated 43 cases of advanced pNENs and 91 cases of isolated pNENs[13]. In the advanced pNEN group, the median survival time for 16 patients who underwent resections of adjacent organs was 90 mo, and the 5-year OS (84%) was not significantly different from that in the isolated pNEN group ($P$ = 0.175), which indicated that nonmetastatic locally advanced pNENs showed a favorable prognosis after surgery. A case series study reviewed 99 locally advanced pNEN patients who underwent surgical resection between 2003 and 2018, including 84 G1/G2, 1 G3, and 14 'tumor grade not available' patients[31]. The 5-year disease-free survival (DFS) was 61%, and the 5-year OS was 91%. Although there was no control group in this study, the excellent prognosis suggested that surgery could be beneficial in patients with locally advanced pNEN. In another study, 25% of patients showed major vascular involvement on preoperative imaging; however, only 17% required resection and reconstruction. Similar to previous studies, major vascular invasion implicated by preoperative imaging might not be fully consistent with intraoperative situations, as the tumors were only abutting or distorting the vein rather than invading in most cases[32,33]. Even though 17% of patients underwent venous resection/reconstruction, none of them died postoperatively. Based on these impressive results, the latest guidelines from the North American Neuroendocrine Tumor Society (NANETS) also recommend that isolated major vascular involvement should not be an absolute contraindication to surgery for patients with advanced pNEN[34]. However, it should be noted that these conclusions were drawn for advanced pNEN only. The outcomes for patients with different primary tumor sites may vary correspondingly. Future studies should examine the role of surgery in GEP-NENs for different primary tumor sites.

Retrospective studies suggest that neoadjuvant peptide receptor radionuclide therapy (PRRT) can effectively reduce the tumor burden and improve surgical safety[35,36]. Parghane *et al*[36] evaluated 57 patients with locally advanced GEP-NENs who had received PRRT[36]. They found that 48 (84%) patients exhibited symptomatic responses, and 15 patients were eligible for resection according to the National Comprehensive Cancer Network criteria for pancreatic ductal adenocarcinoma. Although long-term survival following surgery has not been reported, regression of primary tumors following PRRT was observed, and no hematological or renal side effects were encountered. Therefore, neoadjuvant PRRT may be a potential therapeutic option for locally advanced GEP-NETs.

## SURGERY FOR METASTATIC GEP-NEN

Metastasis is the main feature of GEP-NENs, and its most common location is the liver. The incidence of LM is 40%-95%[37-39], which varies based on the origin of primary NEN, with extremely low rates in gastric, appendiceal, and rectal NENs, an incidence rate of 28%-78% in pNENs, and 67%-91% in small intestinal NENs. LM represents a major risk factor for cancer-related death in GEP-NENs, and the only potentially curative option is surgery. However, strategies for surgery and selection of the appropriate patients remain controversial.

### *Surgery for primary GEP-NEN*

According to NANETS guidelines, primary tumor resection (PTR) is recommended for small bowel NEN in unresectable disease, but for pNEN in unresectable disease, there is no consensus[34,40]. Possible benefits for PTR include the reduction of tumor burden, which controls functional symptoms or prevents obstructive complications, and improvement in survival by decreasing the likelihood of distant metastasis and increasing sensitivity toward systemic therapies. A substantial number of studies based on the Surveillance, Epidemiology, and End Results database have demonstrated that PTR is significantly associated with prolonged survival in metastatic GEP-NEN patients[41-43]. Zheng *et al*[42] evaluated a large cohort of 1547 GEP-NEN cases with unresectable LM, including 897 cases with PTR and 650 nonresection patients, using the Surveillance, Epidemiology, and End Results database[42]. They found that the 5-year OS rate for PTR patients was 57% *vs* 15.4% in those who did not undergo PTR; a significant difference in median OS between the groups was observed (not reached *vs* 14 mo, $P$ < 0.001). When the two groups were further stratified into four groups according to their primary tumor locations (gastric, small intestinal, colorectal, and pancreatic NENs), the 5-year OS rates were significantly prolonged in all groups compared with non-PTR patients. However, some differences were observed among the groups, as PTR groups patients were younger, had many small tumors, and presented well-differentiated and a few poorly differentiated neoplasms. All these factors were significantly associated with survival in both the univariate and multivariate analyses.

Another large study evaluating PTR in a total of 854 IV stage GEP-NEN cases with unresectable or resectable LM from the California Cancer Registry showed similar results[44]. To reduce selection bias, Hüttner *et al*[43] used propensity matching to 442 stage IV pNEN patients who did not receive surgery for metastasis[43]. After propensity score adjustment, significant differences in 5-year OS rates were

found between the two groups (52.5% of the PTR group *vs* 20.6% of the non-PTR group). Daskalakis *et al* [45] performed a similar study with 363 asymptomatic stage IV SBNEN cases, including 161 patients undergoing PTR[45]. After propensity matching, no substantial differences were found in the median OS and cancer-specific survival between the surgical and nonsurgical groups. This study suggested that surgery for asymptomatic patients is a topic of further discussion. The survival benefits in the overall GEP-NEN cases may arise from the survival improvement in functional GEP-NENs. Some studies have shown that systemic agents can effectively improve the prognosis of GEP-NENs[46,47]. The use of systemic agents as an adjuvant treatment cannot be controlled in retrospective studies, which leads to an inevitable bias. A lower tumor burden further increases the responsiveness of GEP-NENs to PRRT[7, 48]. A retrospective study reviewed 889 GEP-NEN cases; among them, 483 patients who underwent PTR before PRRT and 403 patients who did not undergo PTR before PRRT[49]. In this study, 56 of the 617 patients showed G3 tumors (based on the available grading data). In the prior PTR group, the median OS was 134 mo, and the 5-year OS rate was 70.8%, while in the nonresected group, the median OS was 67 mo, and the 5-year OS rate was 41.7% ($P < 0.001$). Additionally, in patients with pNENs or SBNENs, accounting for 70% of the total patients, these remarkable differences were detected.

Taken together, although several retrospective studies have reported a potential benefit of PTR in metastatic GEP-NENs, the selection bias may be inadvertent. Some factors may aid in the identification and distinction of GEP-NENs from PTR, including functional metastatic GEP-NENs, young age, a small tumor size, and well-differentiated tumor characteristics. The excellent clinical benefits of postoperative PRRT have been previously reported. Based on these encouraging results, a large-scale multicenter prospective study is warranted to confirm and obtain further novel definitive prognostic factors.

### *Surgery for liver metastasis*

Current guidelines propose that G1/G2 NEN LM patients without extrahepatic disease should undergo surgical interventions, while for those with G3 NET LM, resection is not recommended[34,50], as the prognoses and survival outcomes in G3 NEN LM are suboptimal (median OS range: 4.6-29 mo)[51-54]. However, several studies in G3 GEP-NEN patients with resectable LMs have yielded encouraging results in recent years. Galleberg *et al*[55] reviewed the central Nordic GEP-NEC database and reported an OS and RFS in 32 G3 NEN LM cases (8 NETs and 24 NECs) after resection/radiofrequency ablation of 35.9 mo and 8.4 mo, respectively[55]. Ki67 < 55% along with adjuvant chemotherapy were independent significant prognostic factors for favorable outcomes. Consistently, in a retrospective study of a stage IV G3 GEP-NEN cohort, Merola *et al*[56] analyzed 15 patients who underwent radical resection (R0/R1); among them, 7 had G3 NETs, 6 had G3 NECs, and 2 had MiNENs[56]. The median OS was 59 mo, and the median RFS was 8 mo. Unfortunately, there were no comparison groups in these two trials. A direct comparison of different results from the literature is unreliable, especially due to the heterogeneity in G3 GEP-NENs as discussed above, varying range of metastases, and selection biases. However, these findings suggest that highly advanced G3 GEP-NEN cases might benefit from radical resection procedures. Thus far, the lack of studies and small sample sizes limit the identification of subgroups suitable for surgical interventions.

As NEN LMs are seldom isolated or few and most cannot be removed completely, debulking, also referred to as "cytoreductive resection" or "R2 resection", is used to treat unresectable NEN LMs. Several retrospective studies have suggested that cytoreduction of NEN LMs improves both symptoms and survival[57,58]. Forty years ago, Foster *et al*[59,60] reported good symptom control in 44 cases with at least 95% surgical cytoreduction[59,60]. Likewise, three subsequent studies from the Mayo Clinic reported that at least 90% hepatic cytoreduction provides effective symptomatic palliation and prolongs survival[61,62] However, 90% as the debulking threshold was not carefully calculated using an algorithm but was chosen with the intent to select a suitable threshold, which may result in a loss of potential operative and curative opportunities for numerous patients.

Additionally, the development of new adjuvant therapies (such as the availability of somatostatin analog) may further enhance the efficacy of cytoreduction and expand the beneficiary population. Recently, studies have attempted to propose a lower threshold, and some have demonstrated that cytoreduction > 70% provides survival benefits. Maxwell *et al*[63] estimated the threshold level by dividing 28 pNEN LM cases and 80 SB NEN LM cases into < 50%, ≥ 50%, ≥ 70%, and ≥ 90% categories [63]. The 5-year PFS of all patients was 30.2%, and the 5-year OS was 76.1%. Patients with cytoreduction ≥ 70% showed better OS and PFS than those with cytoreduction < 50%. In this study, only 38.9% of patients showed debulking ≥ 90%, while 63.9% of patients exhibited cytoreduction with a lower threshold of > 70%.

Scott *et al*[64] reviewed 188 NEN LM patients who underwent cytoreductive procedures and stratified them into three groups according to the number of treated metastases (1-5, 6-10, and > 10)[64]. The median OS was 89 mo, and the PFS was 23 mo; there were no significant differences in OS or PFS among the three groups. In both univariate and multivariate analyses, age, grade, Ki67 index, percent liver replacement, and debulking > 70% were significantly associated with OS. When the study population was grouped by percent cytoreduction, the debulking > 70% group showed an improved OS compared with the debulking < 70% group (median 134.3 mo *vs* 37.6 mo, $P < 0.01$); debulking > 90% was not significantly associated with a better outcome compared to the 70%-90% or < 90% groups. This study provided further evidence for adopting a debulking threshold > 70% and indicated that NEN LM

patients who underwent cytoreduction for > 10 lesions had acceptable OS. Moreover, the grade was associated with a poor OS and PFS, with HRs of 2.12 for the G2 (97 cases) and 11.69 for the G3 (15 cases) groups. The 23-mo median OS and absence of 5-year OS of G3 did not improve after debulking, unlike previously reported results[65]. However, whether G3 GEP-NEN LM patients may benefit from cytoreduction remains difficult to address based on the current data, and evidence of heterogeneity between primary tumors and LMs is scarce. NANETS recommends that G2 primary or LM is not a contraindication for hepatic cytoreduction[34].

Neoadjuvant therapy may convert unresectable GEP-NEN LMs to resectable forms, reduce the difficulty of surgery, and decrease postoperative complications. To date, various systemic treatments demonstrated their efficacy in controlling tumor progression and reducing tumor burden[66,67]. However, whether neoadjuvant treatments can improve the surgical prognoses in GEP-NEN LM remains unclear. Murase *et al*[68] analyzed 106 pNEN cases with LM or locally advanced tumors[68]. All patients received sunitinib, among which 31 underwent surgery after sunitinib treatment. The median OS was not achieved in the surgical group *vs* 36.7 mo in the nonsurgical group. Poor predictive factors included the absence of surgical resection (HR: 13.1, $P = 0.001$), poor differentiation, and bilateral liver metastases. Thus, surgery after sunitinib treatment could improve OS for distant metastases or in locally advanced pNEN.

### *Liver transplantation for hepatic metastases*

Compared with debulking, liver transplantation (LT) offers a long-term curative solution to expand the conventional margin in surgical oncology and LT for LMs, an important component of transplant oncology. The world-renowned LT expert Makowka *et al*[69] and Mazzaferro *et al*[70] proposed the Milan NEN criteria in 1995 (Table 2)[69,70]. In their recent report, Mazzaferro *et al*[71] prospectively analyzed 280 GEP-NEN LM cases during a 15-year follow-up[71]. Ultimately, 88 unresectable GEP-NEN LM patients who met the predetermined criteria were included, 42 of whom underwent LT. The 5- and 10-year OS rates for LT patients were 97.2% and 88.8%, respectively, *vs* 50.9% and 22.4% in the non-LT group, with eligibility according to Milan-NEN criteria ($n = 46$). Moreover, the researchers estimated that the 5- and 10-year survival benefits associated with LT were 12.79 mo and 48.62 mo, respectively, which suggested that the survival benefits increased over time. However, there was an inherent selection bias between the LT and non-LT groups, including a more advanced T-stage and older patients with less locoregional treatments included in the non-LT group. Considering the shortage of donated organs, it is necessary to weight carefully the benefits against the risks.

Kim *et al*[72] performed a systematic review of GEP-NEN LM patients who underwent LT and reported that the 5-year DFS rate ranged from 20% to 32%, which was worse than that of hepatocellular carcinoma (HCC) patients who underwent LT[72]. Due to these high rates of recurrence, Sposito *et al*[73] focused on the postrecurrence survival of GEP-NEN LT patients and observed excellent long-term survival (5-year survival rate of 76.5%, 10-year survival rate of 45.5%)[73]. In conclusion, despite the high recurrence rate, GEP-NEN LT patients still have promising long-term outcomes, which may be attributable to the indolent biological behaviors of GEP-NENs.

For resectable GEP-NEN LM patients who are consistent with the Milan criteria, surgical resection may still be the first option. Ruzzenente *et al*[74] investigated the long-term survival of a multi-institutional cohort of GEP-NEN LM patients undergoing surgical resection and found that 28 of 238 patients met Milan criteria with a 5-year OS of 83%, which was comparable to that reported in GEP-NEN LM patients undergoing LT within Milan criteria[74].

Similar to findings for LT in HCC, patients conforming to the Milan criteria show excellent prognoses from LT; however, this does not imply that the Milan criteria cover all patients who may potentially benefit from LT[75,76]. In a retrospective study, 15 NEN LMs who were up to 64 years of age with 12 of the 15 exceeding 50% hepatic involvement were included; the 5-year OS rate was 90%[77]. Downstaging in HCC has been extensively discussed[75], while in GEP-NEN LMs, high-quality studies are lacking.

Taken together, the survival benefits for resectable GEP-NEN LMs are limited, but for unresectable GEP-NEN LM patients who meet the Milan-NEN criteria, LT is recommended. Several outstanding questions remain to be addressed, including the following: (1) Can the Milan-NEN criteria be safely expanded, and what is the exact threshold? (2) What are the appropriate prognostic factors of GEP-NEN LMs? and (3) How can neoadjuvant be used as downstaging/bridging therapy before LT?

## NEOADJUVANT PRRT FOR GEP-NEN

Recently, neoadjuvant therapy has become a critical treatment for various tumors, which may potentially reduce the tumor load, increase the likelihood that patients undergo surgical resection, enhance the safety of surgery, monitor the tumor response, and guide subsequent treatment based on the response to neoadjuvant therapy. Neoadjuvant therapy for NENs primarily includes chemotherapy small molecule drugs and PRRT. At present, the effectiveness of chemotherapy for NENs is not clear [78]. However, neoadjuvant PRRT, particularly $^{90}$Y-DOTATATE and $^{177}$Lu-DOTATATE, has been used in NENs with good prospects. In a randomized phase III trial (NETTER-1 Clinical Trial), PRRT for well-

**Table 2 Milan neuroendocrine neoplasms criteria**

| | Milan selection criteria of GEP-NEN LM |
|---|---|
| 1 | Low grade NEN |
| 2 | Portal drainage of the primary tumor with complete resection of extrahepatic disease |
| 3 | Liver involvement < 50% |
| 4 | Duration of stable disease over 6 mo |
| 5 | Age < 60 yr (relative criteria) |

GEP-NEN: Gastroenteropancreatic neuroendocrine neoplasms; LM: Liver metastasis.

differentiated, metastatic GEP-NEN effectively reduced the tumor burden, suppressed tumor progression, and prolonged survival[79]. In a study reported by van Vliet *et al*[35], PRRT was used as neoadjuvant therapy in 29 borderline or unresectable nonfuctional pNEN[35]. Thirty-one percent of these patients underwent successful surgery and achieved a better median PFS than those who were not resected (69 mo *vs* 49 mo). In addition to PTR, neoadjuvant PRRT has been evaluated in unresectable NEN LMs and successfully aids downstaging[80]. Several clinical studies are currently underway, including a phase II trial aimed at assessing the safety and efficacy of neoadjuvant PRRT for resectable pNENs with a high recurrence risk (NCT04385992), indicating that neoadjuvant PRRT for GEP-NEN is a promising field.

## CONCLUSION

In conclusion, surgery plays a crucial role in the management of GEP-NENs and comprises curative resection, debulking, resection after neoadjuvant therapy, and LT for LMs. Compared with epithelial neoplasms of the same organs, GEP-NENs exhibit indolent biology and better outcomes, which increases the possibility of surgery for patients with hgGEP-NENs or advanced GEP-NENs. HgGEP-NEN is correlated with a poor prognosis. However, its heterogeneity is the major feature, and after careful selection for tumor biology, hgGEP-NENs with low Ki67 show greater benefits from resection. In metastatic GEP-NENs, radical surgery represents a favorable outcome but is limited to only a few patients. For unresectable LMs, cytoreduction improves the prognoses of patients, and the threshold for cytoreduction is reduced from 90% to 70%. LT for hgGEP-NEN LMs shows therapeutic advantages, but several problems need to be addressed. Additionally, neoadjuvant and adjuvant therapies have been investigated in the setting of advanced GEP-NENs, which may further control tumor recurrence. However, in cases of low prevalence and incidence, most of the evidence comes from retrospective studies that include less than 100 cases, and the administration of systemic therapy is not well controlled. The heterogeneity in GEP-NENs further influences the accuracy of the conclusions. Therefore, further multicenter collaborative prospective studies are needed to assess the effects of surgery and determine the prognostic factors.

## FOOTNOTES

**Author contributions:** Que QY, Ling SB, and Xu X formulated the research goals and aims; Que QY, Bao JQ, Zhang LC, Ling SB, and Xu X performed the research; Que QY, Bao JQ, and Zhang LC wrote the manuscript; All authors have read and approve the final manuscript.

**Supported by** State Key Program of National Natural Science Foundation of China, No. 81930016; Zhejiang Provincial Natural Science Foundation of China, No. LY21H160026.

**Conflict-of-interest statement:** No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.



**Country/Territory of origin:** China

**ORCID number:** Qing-Yang Que 0000-0002-0687-8661; Lin-Cheng Zhang 0000-0001-6989-1399; Jia-Qi Bao 0000-0001-5726-5534; Sun-Bin Ling 0000-0003-0846-5489; Xiao Xu 0000-0002-2761-2811.

**S-Editor:** Fan JR
**L-Editor:** Filipodia
**P-Editor:** Fan JR

## REFERENCES

1 **Xu Z**, Wang L, Dai S, Chen M, Li F, Sun J, Luo F. Epidemiologic Trends of and Factors Associated With Overall Survival for Patients With Gastroenteropancreatic Neuroendocrine Tumors in the United States. *JAMA Netw Open* 2021; **4**: e2124750 [PMID: 34554237 DOI: 10.1001/jamanetworkopen.2021.24750]

2 **Dasari A**, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T, Yao JC. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol* 2017; **3**: 1335-1342 [PMID: 28448665 DOI: 10.1001/jamaoncol.2017.0589]

3 **Tang LH**, Untch BR, Reidy DL, O'Reilly E, Dhall D, Jih L, Basturk O, Allen PJ, Klimstra DS. Well-Differentiated Neuroendocrine Tumors with a Morphologically Apparent High-Grade Component: A Pathway Distinct from Poorly Differentiated Neuroendocrine Carcinomas. *Clin Cancer Res* 2016; **22**: 1011-1017 [PMID: 26482044 DOI: 10.1158/1078-0432.CCR-15-0548]

4 **Heetfeld M**, Chougnet CN, Olsen IH, Rinke A, Borbath I, Crespo G, Barriuso J, Pavel M, O'Toole D, Walter T; other Knowledge Network members. Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer* 2015; **22**: 657-664 [PMID: 26113608 DOI: 10.1530/ERC-15-0119]

5 **Lloyd RV**, Osamura RY, Klöppel G, Rosai J. WHO Classification of Tumours of Endocrine Organs. [cited 10 October 2021]. Available from: https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-Endocrine-Organs-2017

6 **WHO Classification of Tumours Editorial Board**. Digestive System Tumours. [cited 10 October 2021]. Available from: https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Digestive-System-Tumours-2019

7 **Kwekkeboom DJ**, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, Feelders RA, van Aken MO, Krenning EP. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. *J Clin Oncol* 2008; **26**: 2124-2130 [PMID: 18445841 DOI: 10.1200/JCO.2007.15.2553]

8 **Yao JC**, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008; **26**: 3063-3072 [PMID: 18565894 DOI: 10.1200/JCO.2007.15.4377]

9 **Basturk O**, Yang Z, Tang LH, Hruban RH, Adsay V, McCall CM, Krasinskas AM, Jang KT, Frankel WL, Balci S, Sigel C, Klimstra DS. The high-grade (WHO G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogenous and includes both well differentiated and poorly differentiated neoplasms. *Am J Surg Pathol* 2015; **39**: 683-690 [PMID: 25723112 DOI: 10.1097/PAS.0000000000000408]

10 **Ettinger DS**, Wood DE, Aggarwal C, Aisner DL, Akerley W, Bauman JR, Bharat A, Bruno DS, Chang JY, Chirieac LR, D'Amico TA, Dilling TJ, Dobelbower M, Gettinger S, Govindan R, Gubens MA, Hennon M, Horn L, Lackner RP, Lanuti M, Leal TA, Lin J, Loo BW Jr, Martins RG, Otterson GA, Patel SP, Reckamp KL, Riely GJ, Schild SE, Shapiro TA, Stevenson J, Swanson SJ, Tauer KW, Yang SC, Gregory K; OCN, Hughes M. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 1.2020. *J Natl Compr Canc Netw* 2019; **17**: 1464-1472 [PMID: 31805526 DOI: 10.6004/jnccn.2019.0059]

11 **Andreasi V**, Muffatti F, Guarneri G, Falconi M, Partelli S. Surgical Principles in the Management of Pancreatic Neuroendocrine Neoplasms. *Curr Treat Options Oncol* 2020; **21**: 48 [PMID: 32350693 DOI: 10.1007/s11864-020-00736-w]

12 **Kleine M**, Schrem H, Vondran FW, Krech T, Klempnauer J, Bektas H. Extended surgery for advanced pancreatic endocrine tumours. *Br J Surg* 2012; **99**: 88-94 [PMID: 22135173 DOI: 10.1002/bjs.7681]

13 **Birnbaum DJ**, Turrini O, Vigano L, Russolillo N, Autret A, Moutardier V, Capussotti L, Le Treut YP, Delpero JR, Hardwigsen J. Surgical management of advanced pancreatic neuroendocrine tumors: short-term and long-term results from an international multi-institutional study. *Ann Surg Oncol* 2015; **22**: 1000-1007 [PMID: 25190116 DOI: 10.1245/s10434-014-4016-8]

14 **Merola E**, Rinke A, Partelli S, Gress TM, Andreasi V, Kollár A, Perren A, Christ E, Panzuto F, Pascher A, Jann H, Arsenic R, Cremer B, Kaemmerer D, Kump P, Lipp RW, Agaimy A, Wiedenmann B, Falconi M, Pavel ME. Surgery with Radical Intent: Is There an Indication for G3 Neuroendocrine Neoplasms? *Ann Surg Oncol* 2020; **27**: 1348-1355 [PMID: 31720931 DOI: 10.1245/s10434-019-08049-5]

15 **Pommergaard HC**, Nielsen K, Sorbye H, Federspiel B, Tabaksblat EM, Vestermark LW, Janson ET, Hansen CP, Ladekarl M, Garresori H, Hjortland GO, Sundlöv A, Galleberg R, Knigge P, Kjaer A, Langer SW, Knigge U. Surgery of the primary tumour in 201 patients with high-grade gastroenteropancreatic neuroendocrine and mixed neuroendocrine-non-neuroendocrine neoplasms. *J Neuroendocrinol* 2021; **33**: e12967 [PMID: 33769624 DOI: 10.1111/jne.12967]

16 **Abdel-Rahman O**, Rahbari N, Reissfelder C, Oweira H. Outcomes of non-metastatic poorly differentiated gastroenteropancreatic neuroendocrine neoplasms treated with surgery: a real-world population-based study. *Int J Colorectal Dis* 2021; **36**: 941-947 [PMID: 33145607 DOI: 10.1007/s00384-020-03793-7]

17 **Mosquera C**, Koutlas NJ, Fitzgerald TL. Localized high-grade gastroenteropancreatic neuroendocrine tumors: Defining prognostic and therapeutic factors for a disease of increasing clinical significance. *Eur J Surg Oncol* 2016; **42**: 1471-1477 [PMID: 27528467 DOI: 10.1016/j.ejso.2016.07.137]

18 **Rinke A**, Auernhammer CJ, Bodei L, Kidd M, Krug S, Lawlor R, Marinoni I, Perren A, Scarpa A, Sorbye H, Pavel ME, Weber MM, Modlin I, Gress TM. Treatment of advanced gastroenteropancreatic neuroendocrine neoplasia, are we on the way to personalised medicine? *Gut* 2021; **70**: 1768-1781 [PMID: 33692095 DOI: 10.1136/gutjnl-2020-321300]

19 **Kidd M**, Modlin I, Öberg K. Towards a new classification of gastroenteropancreatic neuroendocrine neoplasms. *Nat Rev Clin Oncol* 2016; **13**: 691-705 [PMID: 27273044 DOI: 10.1038/nrclinonc.2016.85]

20 **Fazio N**, Milione M. Heterogeneity of grade 3 gastroenteropancreatic neuroendocrine carcinomas: New insights and treatment implications. *Cancer Treat Rev* 2016; **50**: 61-67 [PMID: 27636009 DOI: 10.1016/j.ctrv.2016.08.006]

21 **Yoshida T**, Hijioka S, Hosoda W, Ueno M, Furukawa M, Kobayashi N, Ikeda M, Ito T, Kodama Y, Morizane C, Notohara K, Taguchi H, Kitano M, Yane K, Tsuchiya Y, Komoto I, Tanaka H, Tsuji A, Hashigo S, Mine T, Kanno A, Murohisa G, Miyabe K, Takagi T, Matayoshi N, Sakaguchi M, Ishii H, Kojima Y, Matsuo K, Yoshitomi H, Nakamori S, Yanagimoto H, Yatabe Y, Furuse J, Mizuno N. Surgery for Pancreatic Neuroendocrine Tumor G3 and Carcinoma G3 Should be Considered Separately. *Ann Surg Oncol* 2019; **26**: 1385-1393 [PMID: 30863939 DOI: 10.1245/s10434-019-07252-8]

22 **Worth PJ**, Leal J, Ding Q, Trickey A, Dua MM, Chatzizacharias N, Soonawalla Z, Athanasopoulos P, Toumpanakis C, Hansen P, Parks RW, Connor S, Parker K, Koea J, Srinavasa S, Ielpo B, Vicente Lopez E, Lawrence B, Visser BC; International Pancreatic Neuroendocrine Tumor Study Group. Pancreatic grade 3 neuroendocrine tumors behave similarly to neuroendocrine carcinomas following resection: a multi-center, international appraisal of the WHO 2010 and WHO 2017 staging schema for pancreatic neuroendocrine lesions. *HPB (Oxford)* 2020; **22**: 1359-1367 [PMID: 32081540 DOI: 10.1016/j.hpb.2019.12.014]

23 **Thornblade LW**, Warner SG, Melstrom L, Ituarte PHG, Chang S, Li D, Fong Y, Singh G. Does surgery provide a survival advantage in non-disseminated poorly differentiated gastroenteropancreatic neuroendocrine neoplasms? *Surgery* 2021; **169**: 1417-1423 [PMID: 33637345 DOI: 10.1016/j.surg.2021.01.026]

24 **Sorbye H**, Strosberg J, Baudin E, Klimstra DS, Yao JC. Gastroenteropancreatic high-grade neuroendocrine carcinoma. *Cancer* 2014; **120**: 2814-2823 [PMID: 24771552 DOI: 10.1002/cncr.28721]

25 **Tang LH**, Basturk O, Sue JJ, Klimstra DS. A Practical Approach to the Classification of WHO Grade 3 (G3) Well-differentiated Neuroendocrine Tumor (WD-NET) and Poorly Differentiated Neuroendocrine Carcinoma (PD-NEC) of the Pancreas. *Am J Surg Pathol* 2016; **40**: 1192-1202 [PMID: 27259015 DOI: 10.1097/PAS.0000000000000662]

26 **Vélayoudom-Céphise FL**, Duvillard P, Foucan L, Hadoux J, Chougnet CN, Leboulleux S, Malka D, Guigay J, Goere D, Debaere T, Caramella C, Schlumberger M, Planchard D, Elias D, Ducreux M, Scoazec JY, Baudin E. Are G3 ENETS neuroendocrine neoplasms heterogeneous? *Endocr Relat Cancer* 2013; **20**: 649-657 [PMID: 23845449 DOI: 10.1530/ERC-13-0027]

27 **Sorbye H**, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, Dueland S, Hofsli E, Guren MG, Ohrling K, Birkemeyer E, Thiis-Evensen E, Biagini M, Gronbaek H, Soveri LM, Olsen IH, Federspiel B, Assmus J, Janson ET, Knigge U. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol* 2013; **24**: 152-160 [PMID: 22967994 DOI: 10.1093/annonc/mds276]

28 **Asano D**, Kudo A, Akahoshi K, Maekawa A, Murase Y, Ogawa K, Ono H, Ban D, Tanaka S, Tanabe M. Curative Surgery and Ki-67 Value Rather than Tumor Differentiation Predict the Survival of Patients with High-grade Neuroendocrine Neoplasms. *Ann Surg* 2020 [PMID: 32941267 DOI: 10.1097/SLA.0000000000004495]

29 **Shah MH**, Goldner WS, Benson AB, Bergsland E, Blaszkowsky LS, Brock P, Chan J, Das S, Dickson PV, Fanta P, Giordano T, Halfdanarson TR, Halperin D, He J, Heaney A, Heslin MJ, Kandeel F, Kardan A, Khan SA, Kuvshinoff BW, Lieu C, Miller K, Pillarisetty VG, Reidy D, Salgado SA, Shaheen S, Soares HP, Soulen MC, Strosberg JR, Sussman CR, Trikalinos NA, Uboha NA, Vijayvergia N, Wong T, Lynn B, Hochstetler C. Neuroendocrine and Adrenal Tumors, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2021; **19**: 839-868 [PMID: 34340212 DOI: 10.6004/jnccn.2021.0032]

30 **Jensen RT**, Bodei L, Capdevila J, Couvelard A, Falconi M, Glasberg S, Kloppel G, Lamberts S, Peeters M, Rindi G, Rinke A, Rothmund M, Sundin A, Welin S, Fazio N; The ENETS 2016 Munich Advisory Board Participants; ENETS 2016 Munich Advisory Board Participants. Unmet Needs in Functional and Nonfunctional Pancreatic Neuroendocrine Neoplasms. *Neuroendocrinology* 2019; **108**: 26-36 [PMID: 30282083 DOI: 10.1159/000494258]

31 **Titan AL**, Norton JA, Fisher AT, Foster DS, Harris EJ, Worhunsky DJ, Worth PJ, Dua MM, Visser BC, Poultsides GA, Longaker MT, Jensen RT. Evaluation of Outcomes Following Surgery for Locally Advanced Pancreatic Neuroendocrine Tumors. *JAMA Netw Open* 2020; **3**: e2024318 [PMID: 33146734 DOI: 10.1001/jamanetworkopen.2020.24318]

32 **Prakash L**, Lee JE, Yao J, Bhosale P, Balachandran A, Wang H, Fleming JB, Katz MH. Role and Operative Technique of Portal Venous Tumor Thrombectomy in Patients with Pancreatic Neuroendocrine Tumors. *J Gastrointest Surg* 2015; **19**: 2011-2018 [PMID: 26282850 DOI: 10.1007/s11605-015-2914-0]

33 **Glebova NO**, Hicks CW, Piazza KM, Abularrage CJ, Cameron AM, Schulick RD, Wolfgang CL, Black JH 3rd. Technical risk factors for portal vein reconstruction thrombosis in pancreatic resection. *J Vasc Surg* 2015; **62**: 424-433 [PMID: 25953018 DOI: 10.1016/j.jvs.2015.01.061]

34 **Howe JR**, Merchant NB, Conrad C, Keutgen XM, Hallet J, Drebin JA, Minter RM, Lairmore TC, Tseng JF, Zeh HJ, Libutti SK, Singh G, Lee JE, Hope TA, Kim MK, Menda Y, Halfdanarson TR, Chan JA, Pommier RF. The North American Neuroendocrine Tumor Society Consensus Paper on the Surgical Management of Pancreatic Neuroendocrine Tumors. *Pancreas* 2020; **49**: 1-33 [PMID: 31856076 DOI: 10.1097/MPA.0000000000001454]

35 **van Vliet EI**, van Eijck CH, de Krijger RR, Nieveen van Dijkum EJ, Teunissen JJ, Kam BL, de Herder WW, Feelders RA, Bonsing BA, Brabander T, Krenning EP, Kwekkeboom DJ. Neoadjuvant Treatment of Nonfunctioning Pancreatic Neuroendocrine Tumors with [177Lu-DOTA0,Tyr3]Octreotate. *J Nucl Med* 2015; **56**: 1647-1653 [PMID: 26272813 DOI: 10.2967/jnumed.115.158899]

36 **Parghane RV**, Bhandare M, Chaudhari V, Ostwal V, Ramaswamy A, Talole S, Shrikhande SV, Basu S. Surgical Feasibility, Determinants, and Overall Efficacy of Neoadjuvant $^{177}$Lu-DOTATATE PRRT for Locally Advanced Unresectable Gastroenteropancreatic Neuroendocrine Tumors. *J Nucl Med* 2021; **62**: 1558-1563 [PMID: 33637590 DOI: 10.2967/jnumed.120.258772]

37 **Riihimäki M**, Hemminki A, Sundquist K, Sundquist J, Hemminki K. The epidemiology of metastases in neuroendocrine tumors. *Int J Cancer* 2016; **139**: 2679-2686 [PMID: 27553864 DOI: 10.1002/ijc.30400]

38 **Frilling A**, Clift AK. Surgical Approaches to the Management of Neuroendocrine Liver Metastases. *Endocrinol Metab Clin North Am* 2018; **47**: 627-643 [PMID: 30098720 DOI: 10.1016/j.ecl.2018.04.001]

39 **Cai W**, Tan Y, Ge W, Ding K, Hu H. Pattern and risk factors for distant metastases in gastrointestinal neuroendocrine neoplasms: a population-based study. *Cancer Med* 2018; **7**: 2699-2709 [PMID: 29733523 DOI: 10.1002/cam4.1507]

40 **Howe JR**, Cardona K, Fraker DL, Kebebew E, Untch BR, Wang YZ, Law CH, Liu EH, Kim MK, Menda Y, Morse BG, Bergsland EK, Strosberg JR, Nakakura EK, Pommier RF. The Surgical Management of Small Bowel Neuroendocrine Tumors: Consensus Guidelines of the North American Neuroendocrine Tumor Society. *Pancreas* 2017; **46**: 715-731 [PMID: 28609357 DOI: 10.1097/MPA.0000000000000846]

41 **Feng T**, Lv W, Yuan M, Shi Z, Zhong H, Ling S. Surgical resection of the primary tumor leads to prolonged survival in metastatic pancreatic neuroendocrine carcinoma. *World J Surg Oncol* 2019; **17**: 54 [PMID: 30898132 DOI: 10.1186/s12957-019-1597-5]

42 **Zheng M**, Li Y, Li T, Zhang L, Zhou L. Resection of the primary tumor improves survival in patients with gastro-entero-pancreatic neuroendocrine neoplasms with liver metastases: A SEER-based analysis. *Cancer Med* 2019; **8**: 5128-5136 [PMID: 31328428 DOI: 10.1002/cam4.2431]

43 **Hüttner FJ**, Schneider L, Tarantino I, Warschkow R, Schmied BM, Hackert T, Diener MK, Büchler MW, Ulrich A. Palliative resection of the primary tumor in 442 metastasized neuroendocrine tumors of the pancreas: a population-based, propensity score-matched survival analysis. *Langenbecks Arch Surg* 2015; **400**: 715-723 [PMID: 26198970 DOI: 10.1007/s00423-015-1323-x]

44 **Lewis A**, Raoof M, Ituarte PHG, Williams J, Melstrom L, Li D, Lee B, Singh G. Resection of the Primary Gastrointestinal Neuroendocrine Tumor Improves Survival With or Without Liver Treatment. *Ann Surg* 2019; **270**: 1131-1137 [PMID: 29746336 DOI: 10.1097/SLA.0000000000002809]

45 **Daskalakis K**, Karakatsanis A, Hessman O, Stuart HC, Welin S, Tiensuu Janson E, Öberg K, Hellman P, Norlén O, Stålberg P. Association of a Prophylactic Surgical Approach to Stage IV Small Intestinal Neuroendocrine Tumors With Survival. *JAMA Oncol* 2018; **4**: 183-189 [PMID: 29049611 DOI: 10.1001/jamaoncol.2017.3326]

46 **Yao JC**, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, Tomasek J, Raderer M, Lahner H, Voi M, Pacaud LB, Rouyrre N, Sachs C, Valle JW, Fave GD, Van Cutsem E, Tesselaar M, Shimada Y, Oh DY, Strosberg J, Kulke MH, Pavel ME; RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet* 2016; **387**: 968-977 [PMID: 26703889 DOI: 10.1016/S0140-6736(15)00817-X]

47 **Strosberg J**, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, Mittra E, Kunz PL, Kulke MH, Jacene H, Bushnell D, O'Dorisio TM, Baum RP, Kulkarni HR, Caplin M, Lebtahi R, Hobday T, Delpassand E, Van Cutsem E, Benson A, Srirajaskanthan R, Pavel M, Mora J, Berlin J, Grande E, Reed N, Seregni E, Öberg K, Lopera Sierra M, Santoro P, Thevenet T, Erion JL, Ruszniewski P, Kwekkeboom D, Krenning E; NETTER-1 Trial Investigators. Phase 3 Trial of $^{177}$Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med* 2017; **376**: 125-135 [PMID: 28076709 DOI: 10.1056/NEJMoa1607427]

48 **Kwekkeboom DJ**, Teunissen JJ, Bakker WH, Kooij PP, de Herder WW, Feelders RA, van Eijck CH, Esser JP, Kam BL, Krenning EP. Radiolabeled somatostatin analog [177Lu-DOTA0,Tyr3]octreotate in patients with endocrine gastroenteropancreatic tumors. *J Clin Oncol* 2005; **23**: 2754-2762 [PMID: 15837990 DOI: 10.1200/JCO.2005.08.066]

49 **Kaemmerer D**, Twrznik M, Kulkarni HR, Hörsch D, Sehner S, Baum RP, Hommann M; Center for Neuroendocrine Tumors, Bad Berka – ENETS Center of Excellence. Prior Resection of the Primary Tumor Prolongs Survival After Peptide Receptor Radionuclide Therapy of Advanced Neuroendocrine Neoplasms. *Ann Surg* 2021; **274**: e45-e53 [PMID: 33030849 DOI: 10.1097/SLA.0000000000003237]

50 **Partelli S**, Bartsch DK, Capdevila J, Chen J, Knigge U, Niederle B, Nieveen van Dijkum EJM, Pape UF, Pascher A, Ramage J, Reed N, Ruszniewski P, Scoazec JY, Toumpanakis C, Kianmanesh R, Falconi M; Antibes Consensus Conference participants. ENETS Consensus Guidelines for Standard of Care in Neuroendocrine Tumours: Surgery for Small Intestinal and Pancreatic Neuroendocrine Tumours. *Neuroendocrinology* 2017; **105**: 255-265 [PMID: 28237989 DOI: 10.1159/000464292]

51 **Yamaguchi T**, Machida N, Morizane C, Kasuga A, Takahashi H, Sudo K, Nishina T, Tobimatsu K, Ishido K, Furuse J, Boku N, Okusaka T. Multicenter retrospective analysis of systemic chemotherapy for advanced neuroendocrine carcinoma of the digestive system. *Cancer Sci* 2014; **105**: 1176-1181 [PMID: 24975505 DOI: 10.1111/cas.12473]

52 **Rogowski W**, Wachuła E, Gorzelak A, Lebiedzińska A, Sulżyc-Bielicka V, Iżycka-Świeszewska E, Żołnierek J, Kos-Kudła B. Capecitabine and temozolomide combination for treatment of high-grade, well-differentiated neuroendocrine tumour and poorly-differentiated neuroendocrine carcinoma - retrospective analysis. *Endokrynol Pol* 2019; **70**: 313-317 [PMID: 30843182 DOI: 10.5603/EP.a2019.0010]

53 **Panzuto F**, Rinzivillo M, Spada F, Antonuzzo L, Ibrahim T, Campana D, Fazio N, Delle Fave G. Everolimus in Pancreatic Neuroendocrine Carcinomas G3. *Pancreas* 2017; **46**: 302-305 [PMID: 28099254 DOI: 10.1097/MPA.0000000000000762]

54 **Carlsen EA**, Fazio N, Granberg D, Grozinsky-Glasberg S, Ahmadzadehfar H, Grana CM, Zandee WT, Cwikla J, Walter MA, Oturai PS, Rinke A, Weaver A, Frilling A, Gritti S, Arveschoug AK, Meirovitz A, Knigge U, Sorbye H. Peptide receptor radionuclide therapy in gastroenteropancreatic NEN G3: a multicenter cohort study. *Endocr Relat Cancer* 2019; **26**: 227-239 [PMID: 30540557 DOI: 10.1530/ERC-18-0424]

55 **Galleberg RB**, Knigge U, Tiensuu Janson E, Vestermark LW, Haugvik SP, Ladekarl M, Langer SW, Grønbæk H, Österlund P, Hjortland GO, Assmus J, Tang L, Perren A, Sorbye H. Results after surgical treatment of liver metastases in patients with high-grade gastroenteropancreatic neuroendocrine carcinomas. *Eur J Surg Oncol* 2017; **43**: 1682-1689 [PMID: 28522174 DOI: 10.1016/j.ejso.2017.04.010]

56 **Merola E**, Falconi M, Rinke A, Staettner S, Krendl F, Partelli S, Andreasi V, Gress TM, Pascher A, Arsenic R, Doglioni C, Kaemmerer D, Wiedenmann B, Pavel ME. Radical intended surgery for highly selected stage IV neuroendocrine neoplasms

G3. *Am J Surg* 2020; **220**: 284-289 [PMID: 32209239 DOI: 10.1016/j.amjsurg.2020.03.009]
57 **Ejaz A**, Reames BN, Maithel S, Poultsides GA, Bauer TW, Fields RC, Weiss MJ, Marques HP, Aldrighetti L, Pawlik TM. Cytoreductive debulking surgery among patients with neuroendocrine liver metastasis: a multi-institutional analysis. *HPB (Oxford)* 2018; **20**: 277-284 [PMID: 28964630 DOI: 10.1016/j.hpb.2017.08.039]
58 **Chakedis J**, Beal EW, Lopez-Aguiar AG, Poultsides G, Makris E, Rocha FG, Kanji Z, Weber S, Fisher A, Fields R, Krasnick BA, Idrees K, Marincola-Smith P, Cho C, Beems M, Pawlik TM, Maithel SK, Schmidt CR, Dillhoff M. Surgery Provides Long-Term Survival in Patients with Metastatic Neuroendocrine Tumors Undergoing Resection for Non-Hormonal Symptoms. *J Gastrointest Surg* 2019; **23**: 122-134 [PMID: 30334178 DOI: 10.1007/s11605-018-3986-4]
59 **Foster JH**, Lundy J. Liver Metastases. *Curr Probl Surg* 1981; **18**: 157-202 [PMID: 7016459 DOI: 10.1016/s0011-3840(81)80009-3]
60 **Foster JH**, Berman MM. Solid liver tumors. *Major Probl Clin Surg* 1977; **22**: 1-342 [PMID: 839860]
61 **Que FG**, Nagorney DM, Batts KP, Linz LJ, Kvols LK. Hepatic resection for metastatic neuroendocrine carcinomas. *Am J Surg* 1995; **169**: 36-42; discussion 42 [PMID: 7817996 DOI: 10.1016/s0002-9610(99)80107-x]
62 **Sarmiento JM**, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, Que FG. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. *J Am Coll Surg* 2003; **197**: 29-37 [PMID: 12831921 DOI: 10.1016/S1072-7515(03)00230-8]
63 **Maxwell JE**, Sherman SK, O'Dorisio TM, Bellizzi AM, Howe JR. Liver-directed surgery of neuroendocrine metastases: What is the optimal strategy? *Surgery* 2016; **159**: 320-333 [PMID: 26454679 DOI: 10.1016/j.surg.2015.05.040]
64 **Scott AT**, Breheny PJ, Keck KJ, Bellizzi AM, Dillon JS, O'Dorisio TM, Howe JR. Effective cytoreduction can be achieved in patients with numerous neuroendocrine tumor liver metastases (NETLMs). *Surgery* 2019; **165**: 166-175 [PMID: 30343949 DOI: 10.1016/j.surg.2018.04.070]
65 **Richards-Taylor S**, Ewings SM, Jaynes E, Tilley C, Ellis SG, Armstrong T, Pearce N, Cave J. The assessment of Ki-67 as a prognostic marker in neuroendocrine tumours: a systematic review and meta-analysis. *J Clin Pathol* 2016; **69**: 612-618 [PMID: 26680267 DOI: 10.1136/jclinpath-2015-203340]
66 **Mizuno Y**, Kudo A, Akashi T, Akahoshi K, Ogura T, Ogawa K, Ono H, Mitsunori Y, Ban D, Tanaka S, Tateishi U, Tanabe M. Sunitinib shrinks NET-G3 pancreatic neuroendocrine neoplasms. *J Cancer Res Clin Oncol* 2018; **144**: 1155-1163 [PMID: 29602973 DOI: 10.1007/s00432-018-2636-2]
67 **van der Zwan WA**, Bodei L, Mueller-Brand J, de Herder WW, Kvols LK, Kwekkeboom DJ. GEPNETs update: Radionuclide therapy in neuroendocrine tumors. *Eur J Endocrinol* 2015; **172**: R1-R8 [PMID: 25117465 DOI: 10.1530/EJE-14-0488]
68 **Murase Y**, Kudo A, Akahoshi K, Maekawa A, Ishikawa Y, Ueda H, Ogawa K, Ono H, Tanaka S, Tanabe M. Surgery after sunitinib administration to improve survival of patients with advanced pancreatic neuroendocrine neoplasms. *Ann Gastroenterol Surg* 2021; **5**: 692-700 [PMID: 34585054 DOI: 10.1002/ags3.12458]
69 **Makowka L**, Tzakis AG, Mazzaferro V, Teperman L, Demetris AJ, Iwatsuki S, Starzl TE. Transplantation of the liver for metastatic endocrine tumors of the intestine and pancreas. *Surg Gynecol Obstet* 1989; **168**: 107-111 [PMID: 2536198]
70 **Mazzaferro V**, Pulvirenti A, Coppa J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? *J Hepatol* 2007; **47**: 460-466 [PMID: 17697723 DOI: 10.1016/j.jhep.2007.07.004]
71 **Mazzaferro V**, Sposito C, Coppa J, Miceli R, Bhoori S, Bongini M, Camerini T, Milione M, Regalia E, Spreafico C, Gangeri L, Buzzoni R, de Braud FG, De Feo T, Mariani L. The Long-Term Benefit of Liver Transplantation for Hepatic Metastases From Neuroendocrine Tumors. *Am J Transplant* 2016; **16**: 2892-2902 [PMID: 27134017 DOI: 10.1111/ajt.13831]
72 **Kim J**, Zimmerman MA, Hong JC. Liver transplantation in the treatment of unresectable hepatic metastasis from neuroendocrine tumors. *J Gastrointest Oncol* 2020; **11**: 601-608 [PMID: 32655939 DOI: 10.21037/jgo.2019.11.03]
73 **Sposito C**, Rossi RE, Monteleone M, Coppa J, Bongini M, Milione M, Bhoori S, Mazzaferro V. Postrecurrence Survival After Liver Transplantation for Liver Metastases From Neuroendocrine Tumors. *Transplantation* 2021; **105**: 2579-2586 [PMID: 33908381 DOI: 10.1097/TP.0000000000003802]
74 **Ruzzenente A**, Bagante F, Bertuzzo F, Aldrighetti L, Campagnaro T, Ercolani G, Conci S, Giuliante F, Dore A, Ferrero A, Torzilli G, Grazi GL, Ratti F, Cucchetti A, De Rose AM, Russolillo N, Cimino M, Perri P, Guglielmi A, Iacono C. Liver Resection for Neuroendocrine Tumor Liver Metastases Within Milan Criteria for Liver Transplantation. *J Gastrointest Surg* 2019; **23**: 93-100 [PMID: 30242647 DOI: 10.1007/s11605-018-3973-9]
75 **Jiang G**, Ling S, Zhan Q, Zhuang L, Xu X. Downstaging treatment for patients with hepatocelluar carcinoma before transplantation. *Transplant Rev (Orlando)* 2021; **35**: 100606 [PMID: 33636480 DOI: 10.1016/j.trre.2021.100606]
76 **Xu X**, Lu D, Ling Q, Wei X, Wu J, Zhou L, Yan S, Wu L, Geng L, Ke Q, Gao F, Tu Z, Wang W, Zhang M, Shen Y, Xie H, Jiang W, Wang H, Zheng S. Liver transplantation for hepatocellular carcinoma beyond the Milan criteria. *Gut* 2016; **65**: 1035-1041 [PMID: 25804634 DOI: 10.1136/gutjnl-2014-308513]
77 **Olausson M**, Friman S, Herlenius G, Cahlin C, Nilsson O, Jansson S, Wängberg B, Ahlman H. Orthotopic liver or multivisceral transplantation as treatment of metastatic neuroendocrine tumors. *Liver Transpl* 2007; **13**: 327-333 [PMID: 17318853 DOI: 10.1002/Lt.21056]
78 **Xie H**, Liu J, Yadav S, Keutgen XM, Hobday TJ, Strosberg JR, Halfdanarson TR. The Role of Perioperative Systemic Therapy in Localized Pancreatic Neuroendocrine Neoplasms. *Neuroendocrinology* 2020; **110**: 234-245 [PMID: 31121586 DOI: 10.1159/000501126]
79 **Strosberg JR**, Caplin ME, Kunz PL, Ruszniewski PB, Bodei L, Hendifar A, Mittra E, Wolin EM, Yao JC, Pavel ME, Grande E, Van Cutsem E, Seregni E, Duarte H, Gericke G, Bartalotta A, Mariani MF, Demange A, Mutevelic S, Krenning EP; NETTER-1 investigators. $^{177}$Lu-Dotatate plus long-acting octreotide *vs* highdose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. *Lancet Oncol* 2021; **22**: 1752-1763 [PMID: 34793718 DOI: 10.1016/S1470-2045(21)00572-6]
80 **Chiapponi C**, Lürssen N, Cremer B, Wahba R, Drebber U, Faust M, Schmidt M, Stippel DL. Peptide receptor radionuclide therapy as a two-step strategy for initially unresectable liver disease from neuroendocrine tumors: a single-center

experience. *Endocrine* 2020; **70**: 187-193 [PMID: 32419082 DOI: 10.1007/s12020-020-02341-1]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 May 27; 14(5): 409-418

DOI: 10.4240/wjgs.v14.i5.409

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

# Laparoscopic *vs* open liver re-resection for cirrhotic patients with post-hepatectomy hepatocellular carcinoma recurrence: A comparative study

Kai-Chi Cheng, Kit-Man Ho

**Specialty type:** Surgery

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Gupta T, India; Mazzarella G, Italy

**Received:** December 30, 2021
**Peer-review started:** December 30, 2021
**First decision:** March 10, 2022
**Revised:** March 12, 2022
**Accepted:** April 26, 2022
**Article in press:** April 26, 2022
**Published online:** May 27, 2022

**Kai-Chi Cheng, Kit-Man Ho,** Department of Surgery, Kwong Wah Hospital, Hong Kong 999077, China

**Corresponding author:** Kai-Chi Cheng, FRCS (Ed), Doctor, Department of Surgery, Kwong Wah Hospital, No. 25 Waterloo Road, Kowloon, Hong Kong 999077, China.
thomascheng@hotmail.com

## Abstract

***BACKGROUND***

Repeated liver resection is an effective treatment for recurrent hepatocellular carcinoma (HCC). However, few studies have compared the outcome of laparoscopic repeat hepatectomy (LRH) and open repeat hepatectomy (ORH) for recurrent HCC, and few of those have included cirrhotic patients.

***AIM***

To compare short-term and long-term outcomes of cirrhotic patients with LRH and ORH for recurrent HCC.

***METHODS***

We retrospectively analysed the clinical records retrieved from a prospectively collected database of all patients who underwent hepatectomy for post-hepatectomy recurrent HCC at our institute between May 2006 and June 2021. Cases of recurrent HCCs larger than 7 cm were excluded. Patient demographics, operative details, perioperative outcomes, pathologic details, disease-free survival (DFS), and overall survival (OS) data of LRH and ORH were compared.

***RESULTS***

Data from 29 patients with LRH and 22 with ORH were compared. The LRH group showed significantly better outcomes for blood loss (median 300 mL *vs* 750 mL, $P = 0.013$) and length of hospital stay (median 5 d *vs* 7 d, $P = 0.003$). The 1-, 3- and 5-year OS rates in the LRH group were 100.0%, 60.0% and 30.0%, respectively; the corresponding rates in the ORH group were 81.8%, 36.4% and 18.2% ($P = 0.336$). The 1-, 3- and 5-year DFS rates in the LRH group were 68.2%, 27.3% and 4.5%, respectively; the corresponding rates in the ORH group were 31.3%, 6.3% and 6.3% ($P = 0.055$). There were no significant differences in overall and DFS between the two groups.

*CONCLUSION*
Laparoscopic re-resection should be considered for patients presenting with recurrent HCC less than or equal to 7 cm after previous hepatectomy.

**Key Words:** Hepatocellular carcinoma; Recurrence; Repeat hepatectomy; Laparoscopic hepatectomy; Outcome; Overall survival; Disease-free survival



**Core Tip:** Laparoscopic liver re-resection for recurrent hepatocellular carcinoma had similar oncological outcomes compared with open surgery, even in patients with cirrhosis. Laparoscopic re-resection should be considered for all patients suitable for liver re-resection for recurrent hepatocellular carcinoma.

**Citation:** Cheng KC, Ho KM. Laparoscopic *vs* open liver re-resection for cirrhotic patients with post-hepatectomy hepatocellular carcinoma recurrence: A comparative study. *World J Gastrointest Surg* 2022; 14(5): 409-418
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i5/409.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i5.409

## INTRODUCTION

Hepatocellular carcinoma (HCC) can be cured by liver resection[1]. Although, the oncological outcome of liver resection is frequently jeopardized by tumour recurrence, with a reported 5-year recurrence rate of 50%-70%[2-4], and intrahepatic recurrence accounts for approximately 80% of postoperative recurrences[2]. Repeated liver resection has been demonstrated to be an effective treatment for recurrent HCC, and has low morbidity and mortality[5-7]. However, owing to multiple liver metastases, reduced liver function, and poor general health, less than 30% of patients with recurrences can undergo recurrent resection[8].

Laparoscopic liver resection (LLR) has emerged as a valuable treatment option for HCC during the last decade. LLR has a shorter operative time, less blood loss, shorter hospital stay, and lower overall morbidity than open liver resection, along with comparable disease-free and overall survival (OS)[9-15]. However, because of the development of adhesions, altered anatomy, the establishment of collateral circulation, reduced liver function, and loss of liver parenchyma following the prior surgery, laparoscopic repeat hepatectomy (LRH) is technically more complex than primary resection. Patients with HCC are likely to suffer from liver cirrhosis and portal hypertension resulting from underlying hepatitis B or C infection, and intraoperative haemorrhage and haemostasis associated with abnormal primary haemostasis are a challenge even for surgeons experienced in LLR[16,17]. Furthermore, these patients are more likely to develop postoperative complications like pleural effusion, chest infection, ascites, portal vein thrombosis, kidney failure and liver failure after hepatectomy[18,19].

Few retrospective studies have compared the outcome of LRH and open repeat hepatectomy (ORH) for recurrent HCC, and few of those have included cirrhotic patients[20-29]. This study aimed to compare the short-term and long-term outcomes of cirrhotic patients with post-hepatectomy HCC recurrence and undergoing LRH or ORH.

## MATERIALS AND METHODS

This study was approved by the Hong Kong Hospital Authority Research Ethics Committee (Kowloon Central/Kowloon East; Ref. KC/KE-21-0278/ER-4). The clinical records of all patients undergoing hepatectomy for post-hepatectomy recurrent HCC at our institute from May 2006 to June 2021 were retrieved and retrospectively analyzed from a prospectively collected database. Patients with radiological features typical of recurrent HCC of less than or equal to 7 cm in size on contrast-enhanced computed tomography or magnetic resonance imaging were included. All patients received the same perioperative care and evaluation protocols. Functional liver reserve for major hepatectomy was assessed by indocyanine green retention at 15 min and computed tomography liver volumetry. The criteria for LLR and open hepatectomy were previously described[30]. The same team of hepatobiliary surgeons performed all the operations. Liver resection was described using the Brisbane 2000 terminology[31].

Patient demographics and preoperative characteristics included in the analysis were the date and extent of the previous operation, date of recurrence, liver function tests, and serum alpha-fetoprotein

(AFP) levels. Operative details, including the operative time, extent of liver resection, operative approach, volume of blood loss, and blood transfusion requirements, were collected. Short-term outcomes included operative factors (operative time, use of Pringle manoeuvre, blood loss, blood transfusion, and conversion) and postoperative factors (length of hospital stay, resection margin, and complications). Long-term outcomes included OS and disease-free survival (DFS). Major hepatectomy was defined as resection of three or more Couinaud liver segments. Cirrhosis was diagnosed by histology findings. Perioperative outcomes included 30-d mortality and Clavien-Dindo complications [32]. International Study Group of Liver Surgery criteria were used to define post-hepatectomy liver failure and bile leakage[33,34]. The number of tumors, the size of the largest tumor nodule, and the resection margin were all derived from the specimens' histological information. The presence of tumor cells within 1 mm of the transection line was classified as a positive resection margin.

Blood tests for liver function, AFP, chest X-ray, and abdominal computed tomography scan with contrast, or ultrasonography of the liver if contrast injection was contraindicated, were all part of the patient's follow-up routine. Patients were checked every three months for the first two years after surgery and then every six months after that. If a patient missed an appointment, they were actively contacted for follow-up. Recurrence was reported as the date of radiological recurrence. A multidisciplinary team of surgeons, radiologists, and oncologists chose subsequent treatments, such as re-resection, microwave or radiofrequency ablation (RFA), transarterial chemo-embolisation, or systemic therapy.

### Surgical procedures

All hepatectomies, except for lesions near important vascular structures, aimed to achieve a gross resection margin of 1 cm, and intraoperative ultrasonography was performed. A right subcostal incision with an upper midline extension was used for open liver re-resections. Hepatic parenchymal transection was performed with a Cavitron Ultrasonic Surgical Aspirator (Olympus, Tokyo, Japan). Haemostasis was achieved by electrocautery or suture. For laparoscopic procedures, patients were placed in a Lloyd-Davies position (right side up for posterosuperior lesions). The chief surgeon stood between the patient's legs and two assistants stood at the patient's left side. The open Hasson technique was used to introduce the first trocar and pneumoperitoneum was established at a pressure of 12 mmHg. Depending on the tumor site, four working ports were inserted with direct vision after introducing the flexible laparoscope. Harmonic Scalpel (Ethicon, Somerville, NJ, United States) was used to accomplish adhesiolysis. The procedure was then followed by intraoperative ultrasonography. For major or segmental liver resections, the extrahepatic Glissonian method was used to control hepatic inflow, liver parenchymal transection was accomplished with Harmonic Scalpel, and haemostasis was achieved by bipolar diathermy, clips, or sutures. Resected specimens were placed in plastic bags and removed using a Pfannenstiel incision or the extension of one of the ports. In both laparoscopic and open surgery, the Pringle manoeuvre was used selectively in cases with excessive bleeding, and drains were placed only when indicated. Intraoperative RFA was occasionally used for small lesions deep within the liver parenchyma and was carried out using a Cooltip RFA system (Medtronic, Minneapolis, MN, United States) by either the surgeon or interventional radiologist.

### Statistical analysis

Statistical analysis was performed with SPSS version 26 (IBM Corp., Armonk, NY, United States). Mann-Whitney *U* test was used to compare differences between the values of quantitative variables and Pearson chi-squared or Fisher's exact test was used to compare categorical variables. Survival analysis was analysed by the Kaplan-Meier method and differences were compared using the log-rank test. Statistical significance was set at $P \leq 0.05$.

## RESULTS

During the study period, 52 patients had liver resection for recurrent HCC following an initial curative liver resection at our center. There were no missing data. One patient with a 7.5-cm diameter tumour and ORH was excluded, and the remaining 29 patients with LRH and 22 patients with ORH were included. Of the 29 LRH patients, 18 had one previous liver resection and 11 had two or more (Table 1). The demographic and clinicopathological characteristics are shown in Table 2. Between-group differences in baseline characteristics, including age, sex, cirrhosis, hepatitis B carrier status, liver function, AFP level, tumour size, number, and location, type of resection, and concurrent ablation, were not significant. Preoperative bilirubin was higher in the LRH (median 17 mmol/L) than in the ORH (13 mmol/L) group ($P = 0.007$). The median tumour size was 1.75 cm in the LRH group and 2.75 cm in the ORH group. There was one hepatitis C patient in the ORH group and none in the LRH group.

Operative outcomes are shown in Table 3. Blood loss (median 300 mL *vs* 750 mL, $P = 0.013$) and length of hospital stay (median 5 d *vs* 7 d, $P = 0.003$) were significantly better in the LRH group. One patient in the ORH group who underwent right anterior sectionectomy died within 30 d after the operation because of chest infection, sepsis, and multiorgan failure. All other complications were successfully treated by conservative measures or interventional radiological drainage. There were six

**Table 1 Details of hepatectomy in previous liver resection**

| Previous liver resection | LRH, *n* = 29 | ORH, *n* = 22 | *P* value |
|---|---|---|---|
| Approach | | | 0.395 |
| Laparoscopic | 14 (48.3) | 8 (36.4) | |
| Open | 15 (51.7) | 14 (63.6) | |
| Type of resection | | | 0.224 |
| Major | 24 (82.8) | 15 (68.2) | |
| Minor | 5 (17.2) | 7 (31.8) | |
| Tumour location, segment | | | 0.780 |
| II, III, IV, V, VI | 16 (55.2) | 13 (59.1) | |
| VII, VIII | 13 (44.8) | 9 (40.9) | |
| Number of previous hepatectomy | | | 0.478 |
| 1 | 17 (58.6) | 16 (72.7) | |
| 2 | 9 (31.0) | 5 (22.7) | |
| 3 | 2 (6.9) | 0 (0.0) | |
| 4 | 0 (0.0) | 1 (4.5) | |
| 5 | 1 (3.4) | 0 (0.0) | |
| Microscopic lymphovascular invasion | | | 1.000 |
| No | 20 (69.0) | 15 (68.2) | |
| Yes | 4 (13.8) | 4 (18.2) | |
| Not assessed | 5 (17.2) | 3 (13.6) | |

Values are *n* (%). LRH: Laparoscopic repeat hepatectomy; ORH: Open repeat hepatectomy.

conversions from laparoscopic to open surgery. Three were owed to insecure margins, two due to dense adhesions from previous open surgery, and one due to profuse bleeding from the hepatic vein.

Median follow-up was 54 mo (interquartile range 28-85 mo). No patients were lost to follow-up. OS and DFS are shown in Figure 1. The 1-, 3- and 5-year OS rates were 100.0%, 60.0% and 30.0% in the LRH group and 81.8%, 36.4% and 18.2% in the ORH group, respectively. Except for the single case of 30-d postoperative mortality mentioned above, all patients died of malignant cachexia. The 1-, 3- and 5-year DFS were 68.2%, 27.3% and 4.5% in the LRH group and 31.3%, 6.3% and 6.3% in the ORH group, respectively. Differences in overall ($P$ = 0.336) and DFS ($P$ = 0.055) between the two groups were not significant.

## DISCUSSION

Although the benefits of LLR over open liver resection in terms of improved short-term postoperative outcomes and equivalent oncological outcomes are well established[9-15], the importance of LLR in recurrent HCC has yet to be determined. The short-term benefits of LRH were established in this trial, including decreased blood loss, a shorter hospital stay, and oncological results were comparable to ORH.

The presence of abdominal adhesions makes re-resection more challenging. Menzies and Ellis[35] observed that 93% of patients with past laparotomy had intra-abdominal adhesions in a prospective analysis, and their findings were corroborated in an autopsy investigation by Weibel *et al*[36], who detected adhesions in 67% of cases with prior abdominal surgery. For surgeons doing laparoscopic liver resection, dense or highly vascularized adhesions, particularly those around the hepatic hilum or major vessels, remain a significant challenge. However, optical magnification during laparoscopic re-resection increases the precision of dissection, and the pneumoperitoneum tightens the adhesion bands, making the dissection and adhesiolysis easier. LLR may also decrease the formation of adhesions and injury to the liver parenchyma, collateral arteries, and surrounding structures, allowing for further resections[37, 38]. In this retrospective study, although adhesion scoring was not documented, the conversion rate was higher than reported in our previously reported series of primary LLR patients (20% *vs* 10%)[15,30].

**Table 2 Patient and tumour characteristics**

| Characteristic | LRH, *n* = 29 | ORH, *n* = 22 | *P* value |
|---|---|---|---|
| Age | 64 (57.5-67.5) | 65.5 (59.75-69.25) | 0.607 |
| Sex | | | 0.688 |
| Male | 25 (86.2) | 20 (90.9) | |
| Female | 4 (13.8) | 2 (9.1) | |
| Cirrhosis on histology | 19 (65.5) | 13 (59.1) | 0.638 |
| HBsAg-positive | 27 (93.1) | 20 (90.9) | 1.000 |
| Albumin in g/L | 39 (36-41) | 36 (34-40) | 0.109 |
| Total bilirubin in μmol/L | 17 (13-20) | 13 (10-16) | 0.007 |
| International normalized ratio | 1.1 (1.05-1.20) | 1.085 (1.055-1.148) | 0.587 |
| Platelet count as × $10^9$/L | 123 (99-173) | 161.5 (115.25-201.00) | 0.092 |
| Alpha-fetoprotein in IU/mL | 11 (4.25-288.00) | 17 (4.0-174.5) | 0.814 |
| Type of resection | | | 0.055 |
| Sub-segmentectomy | 19 (65.5) | 8 (36.4) | |
| Segmentectomy | 5 (17.2) | 2 (9.1) | |
| Left lateral sectionectomy | 2 (6.9) | 1 (4.5) | |
| Right bisegmentectomy | 1 (3.4) | 4 (18.2) | |
| Left hepatectomy +/− extended | 1 (3.4) | 1 (4.5) | |
| Right hepatectomy +/− extended | 1 (3.4) | 5 (22.7) | |
| Central bisectionectomy | 0 (0.0) | 1 (4.5) | |
| Intraoperative ablation | 1 (3.4) | 2 (9.1) | 0.571 |
| Tumour size in cm | | | 0.054 |
| < 1 | 2 (6.9) | 1 (4.5) | |
| ≥ 1-2 | 15 (51.7) | 7 (31.8) | |
| ≥ 2-3 | 5 (17.2) | 3 (13.6) | |
| ≥ 3-4 | 5 (17.2) | 2 (9.1) | |
| ≥ 4-5 | 1 (3.4) | 8 (36.4) | |
| ≥ 5 | 1 (3.4) | 1 (4.5) | |
| Number of tumours | | | 0.295 |
| Single | 25 (86.2) | 16 (72.7) | |
| Multiple | 4 (13.8) | 6 (27.3) | |
| Tumour location, segment | | | 0.491 |
| I | 2 (6.9) | 0 (0.0) | |
| II, III, IV, V, VI | 14 (48.3) | 9 (40.9) | |
| VII, VIII | 13 (44.8) | 13 (59.1) | |

Values are *n* (%) or median (interquartile range). HBsAg: Hepatitis B surface antigen; LRH: Laparoscopic repeat hepatectomy; ORH: Open repeat hepatectomy. Right bisegmentectomy: Right anterior sectionectomy or right posterior sectionectomy; Left hepatectomy +/− extended: Left hepatectomy or extended left hepatectomy; Right hepatectomy +/− extended: Right hepatectomy or extended right hepatectomy.

Two of the conversions to open surgery were because of adhesions related to previous open surgery. The conversions illustrate the impact of adhesions on liver resection.

In this series, 62.7% of the patients had a histological diagnosis of cirrhosis, and more than 90% were hepatitis B carriers. Even for cirrhotic patients with recurrent HCC, LRH was safe and feasible, and it had a superior short-term outcome than ORH. Over a decade ago, Belli *et al*[39] suggested that laparo-

**Table 3 Operative outcomes**

| Outcome | LRH, *n* = 29 | ORH, *n* = 22 | *P* value |
|---|---|---|---|
| Operative time in min | 250 (177.5-320.5) | 300.5 (223.00-378.75) | 0.224 |
| Pringle manoeuvre used | 2 (6.9) | 3 (13.6) | 0.641 |
| Blood loss in mL | 300 (200-700) | 750 (300-1450) | 0.013 |
| Blood transfusion | 6 (20.7) | 8 (36.4) | 0.214 |
| Conversion | 6 (20.7) | | |
| Hospital stay in d | 5 (4-7) | 7 (5.75-11.50) | 0.003 |
| Resection margin in mm | 7.25 (5.00-13.25) | 4.25 (1.00-8.25) | 0.073 |
| Positive margin | 2 (7.1) | 2 (9.1) | 0.801 |
| Complications | 3 (10.3) | 6 (27.3) | 0.150 |
| Chest infection | 0 | 1 | |
| Pleural effusion | 1 | 3 | |
| Arrhythmia | 2 | 0 | |
| Bile leak | 0 | 2 | |
| Liver failure | 0 | 0 | |
| UTI | 0 | 1 | |
| Intra-abdominal infection | 1 | 1 | |
| Clavien-Dindo severity of complications | | | |
| IIIa | 1 (1.1) | 5 (22.7) | 0.073 |
| IIIb | 0 | 0 | |
| IV | 0 | 0 | |
| V | 0 (0.0) | 1 (4.5) | 0.431 |

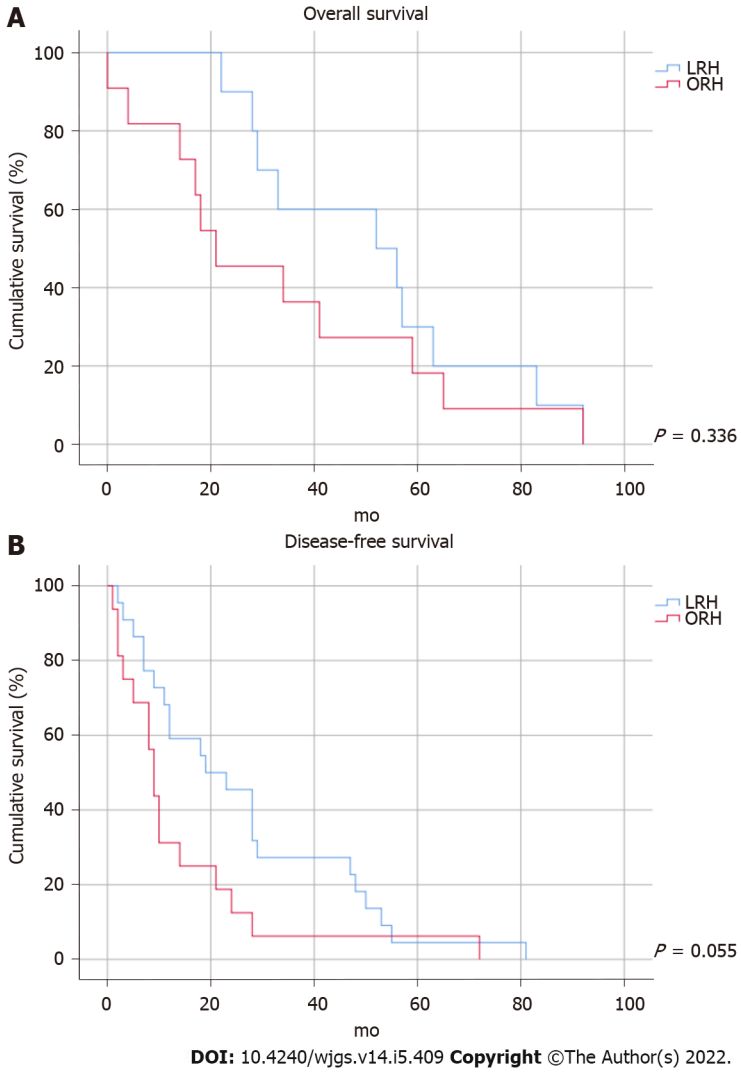
Values are *n* (%) or median (interquartile range). LRH: Laparoscopic repeat hepatectomy; ORH: Open repeat hepatectomy; UTI: Urinary tract infection.

scopic liver re-resection was only indicated for HCC in patients with well-compensated Child-Pugh class A chronic liver disease without signs of severe portal hypertension, a single exophytic or subcapsular HCC located in the left (segments II, III, or IVb) or right (segments V or VI) liver and a maximum size of 4 cm to 5 cm. Increased experience and advances in technology have extended the indications for laparoscopic hepatectomy. After a previous hepatectomy, intrahepatic recurrence in the liver remnant might benefit from LRH with less blood loss and a shorter hospital stay.

RFA has been recommended as an alternative to repeat liver resection for recurrent HCC. A recent meta-analysis by Liu *et al*[40] found that 1-, 3- and 5-year OS and 1-year DFS rates following repeated liver resection for recurrent HCC were similar to those achieved by RFA in patients who satisfied the Milan criteria (*i.e.* maximal diameter of a single tumour ≤ 5 cm, or ≤ 3 tumours ≤ 3 cm each). Repeated liver resection was superior to RFA in 3- and 5-year DFS, but if the tumour size for RFA was not limited, 3- and 5-year OS and 1-, 3- and 5-year DFS were better with repeated liver resection than with RFA. RFA should therefore be reserved for patients with small deep-seated tumors that meet the Milan criteria, and liver re-resection should be the first-line treatment for subcapsular or massive tumors.

There were a few study limitations. First, it was a retrospective analysis, and there were missing data on the adhesion scores after the first hepatectomy. Second, only 51 patients had repeated hepatectomy during the study period. The small sample size was prone to type 2 errors. Third, we conducted only univariate analysis, which is subject to confounding factors. For confounder control, Cox regression or propensity score matching should be considered. However, our sample size was too small for such an analysis. Fourth, we included patients with hepatectomies between 2006 and 2021. Surgical instruments and techniques have improved throughout time, despite the fact that all of the operations were performed by the same group of devoted hepatobiliary surgeons.

Larger studies, or even randomized controlled trials, are needed to further understand the role of LRH in the treatment of recurrent HCC. Documentation of the adhesion score upon repeated hepatectomy would allow an analysis of the benefits of laparoscopic surgery on the formation of adhesions.




**DOI:** 10.4240/wjgs.v14.i5.409 

**Figure 1 Kaplan-Meier curve.** A: Kaplan-Meier curve comparing overall survival of laparoscopic repeat hepatectomy and open repeat hepatectomy; B: Kaplan-Meier curve comparing disease-free survival of laparoscopic repeat hepatectomy and open repeat hepatectomy. LRH: Laparoscopic repeat hepatectomy; ORH: Open repeat hepatectomy.

## CONCLUSION

Laparoscopic liver re-resection for recurrent HCC was associated with less blood loss and shorter hospital stays than open surgery, even in patients with cirrhosis. According to the long-term assessment, overall and DFS was similar between the two groups. Laparoscopic re-resection should be considered for patients who have undergone previous hepatectomy and present with recurrent HCC of less than or equal to 7 cm in size. Regardless, more extensive prospective trials are required to guide the optimal treatment choice for patients with recurrent HCC.

## ARTICLE HIGHLIGHTS

### *Research background*

Recurrent hepatocellular carcinoma can be effectively treated with repeated liver resection (HCC). For recurrent HCC, few studies have compared the outcomes of laparoscopic repeat hepatectomy (LRH) with open repeat hepatectomy (ORH), and even fewer have included cirrhotic patients.

### *Research motivation*

Currently, there is a lack of evidence of the effectiveness of LRH for the treatment of recurrent HCC in cirrhotic patients.

### *Research objectives*

This study aimed to compare the short-term and long-term outcomes for cirrhotic patients with LRH and ORH for recurrent HCC. The study was intended to provide insights on performing LRH for cirrhotic patients with recurrent HCC.

### *Research methods*

A prospectively collected database identified all patients undergoing repeat hepatectomy for recurrent HCC between May 2006 and June 2021. Recurrent HCC with tumours > 7 cm were excluded. Patient demographics, operative details, perioperative outcomes, pathologic details, disease-free survival (DFS) and overall survival (OS) associated with LRH and ORH were compared.

### *Research results*

Cirrhosis was histologically diagnosed in 62.7% of our patients and more than 90% were hepatitis B carriers. Blood loss (median 300 mL *vs* 200 mL, $P = 0.013$) and length of hospital stay (median 5 d *vs* 7 d, $P = 0.003$) were significantly better in the LRH group. There were no significant differences in the 1-, 3- and 5-year OS and DFS rates between the LRH and ORH groups.

### *Research conclusions*

Even in patients with cirrhosis, laparoscopic liver resection for recurrent HCC was associated with decreased blood loss, a shorter hospital stay, and equivalent overall and DFS to open surgery.

### *Research perspectives*

Laparoscopic re-resection should be considered for patients with recurrent HCC of less than or equal to 7 cm in size that develop subsequent to a previous hepatectomy. However, larger studies or randomised controlled trials should be conducted to confirm the advantages of LRH for the management of recurrent HCC.


## FOOTNOTES


**Author contributions:** Cheng KC designed the research study, performed the research, analyzed the data and drafted the manuscript; Ho KM wrote and revised the manuscript; All authors have read and approve the final manuscript.

**Institutional review board statement:** The protocol was approved by The Hong Kong Hospital Authority Research Ethics Committee (Kowloon Central/Kowloon East) (Ref: KC/KC-21-0278/ER-4) following the applicable laws and regulations (including Hong Kong laws), hospital authority policy, professional code of conduct, International Council for Harmonisation, Good Clinical Practice, and the Declaration of Helsinki.

**Informed consent statement:** Written consent was not required as this was a retrospective study, and no data were collected prospectively.

**Conflict-of-interest statement:** The authors declare that they have no conflicting interests.

**Data sharing statement:** The datasets generated during and/or analysed during the current study are not publicly available due to the potential that individual privacy could be compromised, but they are available in an anonymized form from the corresponding author upon reasonable request.

**STROBE statement:** The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.





**Country/Territory of origin:** China



**ORCID number:** Kai-Chi Cheng 0000-0002-6440-7825; Kit-Man Ho 0000-0003-3929-4854.



**S-Editor:** Zhang H
**L-Editor:** A
**P-Editor:** Zhang H

## REFERENCES


1 **Takayama T**, Makuuchi M, Hirohashi S, Sakamoto M, Yamamoto J, Shimada K, Kosuge T, Okada S, Takayasu K, Yamasaki S. Early hepatocellular carcinoma as an entity with a high rate of surgical cure. *Hepatology* 1998; **28**: 1241-1246 [PMID: 9794907 DOI: 10.1002/hep.510280511]

2 **Poon RT**, Fan ST, Lo CM, Liu CL, Ng IO, Wong J. Long-term prognosis after resection of hepatocellular carcinoma associated with hepatitis B-related cirrhosis. *J Clin Oncol* 2000; **18**: 1094-1101 [PMID: 10694562 DOI: 10.1200/JCO.2000.18.5.1094]

3 **Grazi GL**, Ercolani G, Pierangeli F, Del Gaudio M, Cescon M, Cavallari A, Mazziotti A. Improved results of liver resection for hepatocellular carcinoma on cirrhosis give the procedure added value. *Ann Surg* 2001; **234**: 71-78 [PMID: 11420485 DOI: 10.1097/00000658-200107000-00011]

4 **Ercolani G**, Grazi GL, Ravaioli M, Del Gaudio M, Gardini A, Cescon M, Varotti G, Cetta F, Cavallari A. Liver resection for hepatocellular carcinoma on cirrhosis: univariate and multivariate analysis of risk factors for intrahepatic recurrence. *Ann Surg* 2003; **237**: 536-543 [PMID: 12677151 DOI: 10.1097/01.SLA.0000059988.22416.F2]

5 **Chan AC**, Poon RT, Cheung TT, Chok KS, Chan SC, Fan ST, Lo CM. Survival analysis of re-resection versus radiofrequency ablation for intrahepatic recurrence after hepatectomy for hepatocellular carcinoma. *World J Surg* 2012; **36**: 151-156 [PMID: 22030561 DOI: 10.1007/s00268-011-1323-0]

6 **Nakajima Y**, Ko S, Kanamura T, Nagao M, Kanehiro H, Hisanaga M, Aomatsu Y, Ikeda N, Nakano H. Repeat liver resection for hepatocellular carcinoma. *J Am Coll Surg* 2001; **192**: 339-344 [PMID: 11245376 DOI: 10.1016/s1072-7515(00)00789-4]

7 **Minagawa M**, Makuuchi M, Takayama T, Kokudo N. Selection criteria for repeat hepatectomy in patients with recurrent hepatocellular carcinoma. *Ann Surg* 2003; **238**: 703-710 [PMID: 14578733 DOI: 10.1097/01.sla.0000094549.11754.e6]

8 **Sugimachi K**, Maehara S, Tanaka S, Shimada M, Sugimachi K. Repeat hepatectomy is the most useful treatment for recurrent hepatocellular carcinoma. *J Hepatobiliary Pancreat Surg* 2001; **8**: 410-416 [PMID: 11702249 DOI: 10.1007/s005340100002]

9 **Cheung TT**, Dai WC, Tsang SH, Chan AC, Chok KS, Chan SC, Lo CM. Pure Laparoscopic Hepatectomy Versus Open Hepatectomy for Hepatocellular Carcinoma in 110 Patients With Liver Cirrhosis: A Propensity Analysis at a Single Center. *Ann Surg* 2016; **264**: 612-620 [PMID: 27433917 DOI: 10.1097/SLA.0000000000001848]

10 **Memeo R**, de'Angelis N, Compagnon P, Salloum C, Cherqui D, Laurent A, Azoulay D. Laparoscopic vs. open liver resection for hepatocellular carcinoma of cirrhotic liver: a case-control study. *World J Surg* 2014; **38**: 2919-2926 [PMID: 24912628 DOI: 10.1007/s00268-014-2659-z]

11 **Takahara T**, Wakabayashi G, Beppu T, Aihara A, Hasegawa K, Gotohda N, Hatano E, Tanahashi Y, Mizuguchi T, Kamiyama T, Ikeda T, Tanaka S, Taniai N, Baba H, Tanabe M, Kokudo N, Konishi M, Uemoto S, Sugioka A, Hirata K, Taketomi A, Maehara Y, Kubo S, Uchida E, Miyata H, Nakamura M, Kaneko H, Yamaue H, Miyazaki M, Takada T. Long-term and perioperative outcomes of laparoscopic versus open liver resection for hepatocellular carcinoma with propensity score matching: a multi-institutional Japanese study. *J Hepatobiliary Pancreat Sci* 2015; **22**: 721-727 [PMID: 26096910 DOI: 10.1002/jhbp.276]

12 **Xiang L**, Li J, Chen J, Wang X, Guo P, Fan Y, Zheng S. Prospective cohort study of laparoscopic and open hepatectomy for hepatocellular carcinoma. *Br J Surg* 2016; **103**: 1895-1901 [PMID: 27716899 DOI: 10.1002/bjs.10294]

13 **Sposito C**, Battiston C, Facciorusso A, Mazzola M, Muscarà C, Scotti M, Romito R, Mariani L, Mazzaferro V. Propensity score analysis of outcomes following laparoscopic or open liver resection for hepatocellular carcinoma. *Br J Surg* 2016; **103**: 871-880 [PMID: 27029597 DOI: 10.1002/bjs.10137]

14 **Komatsu S**, Brustia R, Goumard C, Perdigao F, Soubrane O, Scatton O. Laparoscopic versus open major hepatectomy for hepatocellular carcinoma: a matched pair analysis. *Surg Endosc* 2016; **30**: 1965-1974 [PMID: 26194255 DOI: 10.1007/s00464-015-4422-4]

15 **Ho KM**, Cheng KC, Chan FK, Yeung YP. Laparoscopic hepatectomy versus open hepatectomy for hepatocellular carcinoma: A propensity case-matched analysis of the long-term survival. *Ann Hepatobiliary Pancreat Surg* 2021; **25**: 1-7 [PMID: 33649248 DOI: 10.14701/ahbps.2021.25.1.1]

16 **Violi F**, Leo R, Vezza E, Basili S, Cordova C, Balsano F. Bleeding time in patients with cirrhosis: relation with degree of liver failure and clotting abnormalities. C.A.L.C. Group. Coagulation Abnormalities in Cirrhosis Study Group. *J Hepatol* 1994; **20**: 531-536 [PMID: 8051393 DOI: 10.1016/s0168-8278(05)80501-x]

17 **Garcia-Tsao G**, Sanyal AJ, Grace ND, Carey W; Practice Guidelines Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007; **46**: 922-938 [PMID: 17879356 DOI: 10.1002/hep.21907]

18 **Farges O**, Malassagne B, Flejou JF, Balzan S, Sauvanet A, Belghiti J. Risk of major liver resection in patients with underlying chronic liver disease: a reappraisal. *Ann Surg* 1999; **229**: 210-215 [PMID: 10024102 DOI: 10.1097/00000658-199902000-00008]

19 **Kanazawa A**, Tsukamoto T, Shimizu S, Kodai S, Yamazoe S, Yamamoto S, Kubo S. Impact of laparoscopic liver resection for hepatocellular carcinoma with F4-liver cirrhosis. *Surg Endosc* 2013; **27**: 2592-2597 [PMID: 23392977 DOI: 10.1007/s00464-013-2795-9]

20 **Kanazawa A**, Tsukamoto T, Shimizu S, Kodai S, Yamamoto S, Yamazoe S, Ohira G, Nakajima T. Laparoscopic liver resection for treating recurrent hepatocellular carcinoma. *J Hepatobiliary Pancreat Sci* 2013; **20**: 512-517 [PMID: 23404252 DOI: 10.1007/s00534-012-0592-9]

21 **Chan AC**, Poon RT, Chok KS, Cheung TT, Chan SC, Lo CM. Feasibility of laparoscopic re-resection for patients with recurrent hepatocellular carcinoma. *World J Surg* 2014; **38**: 1141-1146 [PMID: 24305932 DOI: 10.1007/s00268-013-2380-3]

22 **Liu K**, Chen Y, Wu X, Huang Z, Lin Z, Jiang J, Tan W, Zhang L. Laparoscopic liver re-resection is feasible for patients with posthepatectomy hepatocellular carcinoma recurrence: a propensity score matching study. *Surg Endosc* 2017; **31**:

4790-4798 [PMID: 28389803 DOI: 10.1007/s00464-017-5556-3]
23 **Hallet J**, Sa Cunha A, Cherqui D, Gayet B, Goéré D, Bachellier P, Laurent A, Fuks D, Navarro F, Pessaux P; French Colorectal Liver Metastases Working Group, Association Française de Chirurgie. Laparoscopic Compared to Open Repeat Hepatectomy for Colorectal Liver Metastases: a Multi-institutional Propensity-Matched Analysis of Short- and Long-Term Outcomes. *World J Surg* 2017; **41**: 3189-3198 [PMID: 28717911 DOI: 10.1007/s00268-017-4119-z]
24 **Noda T**, Eguchi H, Wada H, Iwagami Y, Yamada D, Asaoka T, Gotoh K, Kawamoto K, Takeda Y, Tanemura M, Umeshita K, Doki Y, Mori M. Short-term surgical outcomes of minimally invasive repeat hepatectomy for recurrent liver cancer. *Surg Endosc* 2018; **32**: 46-52 [PMID: 28639044 DOI: 10.1007/s00464-017-5632-8]
25 **Ome Y**, Hashida K, Yokota M, Nagahisa Y, Yamaguchi K, Okabe M, Kawamoto K. The feasibility and efficacy of pure laparoscopic repeat hepatectomy. *Surg Endosc* 2018; **32**: 3474-3479 [PMID: 29344784 DOI: 10.1007/s00464-018-6066-7]
26 **Goh BKP**, Syn N, Teo JY, Guo YX, Lee SY, Cheow PC, Chow PKH, Ooi LLPJ, Chung AYF, Chan CY. Perioperative Outcomes of Laparoscopic Repeat Liver Resection for Recurrent HCC: Comparison with Open Repeat Liver Resection for Recurrent HCC and Laparoscopic Resection for Primary HCC. *World J Surg* 2019; **43**: 878-885 [PMID: 30361747 DOI: 10.1007/s00268-018-4828-y]
27 **Inoue Y**, Fujii K, Ishii M, Kagota S, Tomioka A, Hamamoto H, Osumi W, Tsuchimoto Y, Terasawa T, Ogura T, Masubuchi S, Yamamoto M, Imoto A, Asai A, Komeda K, Fukunishi S, Hirokawa F, Goto M, Tanaka K, Okuda J, Higuchi K, Uchiyama K. Laparoscopic Repeat Hepatic Resection for the Management of Liver Tumors. *J Gastrointest Surg* 2019; **23**: 2314-2321 [PMID: 31313147 DOI: 10.1007/s11605-019-04276-z]
28 **van der Poel MJ**, Barkhatov L, Fuks D, Berardi G, Cipriani F, Aljaiuossi A, Lainas P, Dagher I, D'Hondt M, Rotellar F, Besselink MG, Aldrighetti L, Troisi RI, Gayet B, Edwin B, Abu Hilal M. Multicentre propensity score-matched study of laparoscopic versus open repeat liver resection for colorectal liver metastases. *Br J Surg* 2019; **106**: 783-789 [PMID: 30706451 DOI: 10.1002/bjs.11096]
29 **Onoe T**, Yamaguchi M, Irei T, Ishiyama K, Sudo T, Hadano N, Kojima M, Kubota H, Ide R, Tazawa H, Shimizu W, Suzuki T, Shimizu Y, Hinoi T, Tashiro H. Feasibility and efficacy of repeat laparoscopic liver resection for recurrent hepatocellular carcinoma. *Surg Endosc* 2020; **34**: 4574-4581 [PMID: 31853630 DOI: 10.1007/s00464-019-07246-3]
30 **Chan FK**, Cheng KC, Yeung YP. Laparoscopic liver resection: lessons learnt after 100 cases. *Hong Kong Med J* 2014; **20**: 386-392 [PMID: 24722724 DOI: 10.12809/hkmj134066]
31 **Pang YY**. The Brisbane 2000 terminology of liver anatomy and resections. HPB 2000; 2:333-39. *HPB (Oxford)* 2002; **4**: 99 [PMID: 18332933 DOI: 10.1080/136518202760378489]
32 **Dindo D**, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205-213 [PMID: 15273542 DOI: 10.1097/01.sla.0000133083.54934.ae]
33 **Rahbari NN**, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, Koch M, Makuuchi M, Dematteo RP, Christophi C, Banting S, Usatoff V, Nagino M, Maddern G, Hugh TJ, Vauthey JN, Greig P, Rees M, Yokoyama Y, Fan ST, Nimura Y, Figueras J, Capussotti L, Büchler MW, Weitz J. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery* 2011; **149**: 713-724 [PMID: 21236455 DOI: 10.1016/j.surg.2010.10.001]
34 **Koch M**, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L, Fan ST, Yokoyama Y, Crawford M, Makuuchi M, Christophi C, Banting S, Brooke-Smith M, Usatoff V, Nagino M, Maddern G, Hugh TJ, Vauthey JN, Greig P, Rees M, Nimura Y, Figueras J, DeMatteo RP, Büchler MW, Weitz J. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. *Surgery* 2011; **149**: 680-688 [PMID: 21316725 DOI: 10.1016/j.surg.2010.12.002]
35 **Menzies D**, Ellis H. Intestinal obstruction from adhesions--how big is the problem? *Ann R Coll Surg Engl* 1990; **72**: 60-63 [PMID: 2301905]
36 **Weibel MA**, Majno G. Peritoneal adhesions and their relation to abdominal surgery. A postmortem study. *Am J Surg* 1973; **126**: 345-353 [PMID: 4580750 DOI: 10.1016/s0002-9610(73)80123-0]
37 **Gutt CN**, Oniu T, Schemmer P, Mehrabi A, Büchler MW. Fewer adhesions induced by laparoscopic surgery? *Surg Endosc* 2004; **18**: 898-906 [PMID: 15108105 DOI: 10.1007/s00464-003-9233-3]
38 **Machairas N**, Papaconstantinou D, Stamopoulos P, Prodromidou A, Garoufalia Z, Spartalis E, Kostakis ID, Sotiropoulos GC. The Emerging Role of Laparoscopic Liver Resection in the Treatment of Recurrent Hepatocellular Carcinoma: A Systematic Review. *Anticancer Res* 2018; **38**: 3181-3186 [PMID: 29715160 DOI: 10.21873/anticanres.12582]
39 **Belli G**, Cioffi L, Fantini C, D'Agostino A, Russo G, Limongelli P, Belli A. Laparoscopic redo surgery for recurrent hepatocellular carcinoma in cirrhotic patients: feasibility, safety, and results. *Surg Endosc* 2009; **23**: 1807-1811 [PMID: 19277781 DOI: 10.1007/s00464-009-0344-3]
40 **Liu J**, Zhao J, Gu HAO, Zhu Z. Repeat hepatic resection VS radiofrequency ablation for the treatment of recurrent hepatocellular carcinoma: an updated meta-analysis. *Minim Invasive Ther Allied Technol* 2022; **31**: 332-341 [PMID: 33143517 DOI: 10.1080/13645706.2020.1839775]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 May 27; 14(5): 419-428

DOI: 10.4240/wjgs.v14.i5.419

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

# Effect of overtime pancreaticoduodenectomy on the short-term prognosis of patients

Jin-Zhu Zhang, Shu Li, Wei-Hua Zhu, Xi-Sheng Leng, Da-Fang Zhang

**Specialty type:** Surgery

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** de Souza HSP, Brazil; Shah OJ, India

**Received:** December 26, 2021
**Peer-review started:** December 26, 2021
**First decision:** March 10, 2022
**Revised:** March 23, 2022
**Accepted:** April 21, 2022
**Article in press:** April 21, 2022
**Published online:** May 27, 2022

**Jin-Zhu Zhang, Shu Li, Wei-Hua Zhu, Xi-Sheng Leng, Da-Fang Zhang,** Department of Hepatobiliary Surgery, Peking University People's Hospital, Beijing 100044, China

**Corresponding author:** Da-Fang Zhang, MD, PhD, Assistant Professor, Assistant Statistician, Department of Hepatobiliary Surgery, Peking University People's Hospital, No. 11 Xizhimen South Street, Xicheng District, Beijing 100044, China. byronzdf@sina.com

## Abstract

### *BACKGROUND*

Due to the large number of operations, surgeons sometimes need to work overtime or even stay up late to perform pancreaticoduodenectomy. Fatigue and sleep deprivation can result in an increased error rate at work. There have been numerous studies about the effect of overtime surgery on the prognosis of patients. However, the effect of overtime work for pancreaticoduodenectomy on the prognosis of patients is unclear. This study explores the impact of overtime work for pancreaticoduodenectomy on the prognosis of patients.

### *AIM*

To explore the impact of overtime work for pancreaticoduodenectomy on the short-term prognosis of patients.

### *METHODS*

This was a single-center, retrospective cohort study. The patients who underwent pancreaticoduodenectomy between January 2017 and December 2019 were included. Patients were stratified by operative start time into the control group (surgery that started between 8:00 and 16:49) and the overtime group (surgery that started between 17:00 and 22:00) and compared intraoperative and postoperative parameters. The following parameters were compared between the overtime group and the control group: Operative time, blood loss, number of lymph nodes removed, duration of treatment in the Intensive Care Unit (ICU), and incidence of complications.

### *RESULTS*

From January 2017 to December 2019, a total of 239 patients underwent pancreaticoduodenectomy in the Department of Hepatobiliary Surgery of our institution. Four patients were excluded from this study due to lack of clinical data. A total of 235 patients were included, with 177 in the control group and 58 in the overtime group. There was no difference between the two groups in operative time, blood

loss, number of lymph nodes removed, ICU length of stay, hospital length of stay, mortality during hospitalization. Compared with the control group, the overtime group had a higher incidence of pancreatic fistula (32.8% *vs* 15.8%, $P < 0.05$). Multivariate analysis showed that overtime work, higher Body Mass Index were independent risk factors for pancreatic fistula ($P < 0.05$).

*CONCLUSION*
Overtime work for pancreaticoduodenectomy increases the incidence of pancreatic fistula. The effect of overtime surgery on the long-term prognosis of patients' needs to be further studied.

**Key Words:** Pancreaticoduodenectomy; Fatigue; Surgery; Pancreatic fistula; General surgery; Overtime surgery



**Core Tip:** The effect of overtime work for pancreaticoduodenectomy on the prognosis of patients is unclear. We explore the impact of overtime work for pancreaticoduodenectomy on the prognosis of patients. A total of 235 patients were included, with 177 in the control group and 58 in the overtime group. Overtime work for pancreaticoduodenectomy increases the incidence of pancreatic fistula. The effect of overtime surgery on the long-term prognosis of patients' needs to be further studied.

**Citation:** Zhang JZ, Li S, Zhu WH, Leng XS, Zhang DF. Effect of overtime pancreaticoduodenectomy on the short-term prognosis of patients. *World J Gastrointest Surg* 2022; 14(5): 419-428
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i5/419.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i5.419

## INTRODUCTION

Due to the large number of operations, surgeons sometimes need to work overtime to perform elective surgery. When this occurs, surgeons performing the operation are faced with fatigue or even sleep deprivation. Fatigue and sleep deprivation affect cognitive function, leading to an increased error rate at work[1-3]. There have been numerous studies about the effect of overtime surgery on the prognosis of patients. However, the impact of surgery on patients due to surgeon fatigue and sleep deprivation is still controversial. Halvachizadeh *et al*[4] observed higher complication and mortality rates for after-hour orthopedic trauma surgery. Boscà *et al*[5] suggest that the prognosis of patients undergoing liver transplantation by fatigued surgeons is not poor. Brunschot *et al*[6] reported that nighttime kidney transplantation is associated with less pure technical graft failure.

Pancreaticoduodenectomy is widely used to treat pancreatic cancer, bile duct carcinoma, duodenal carcinoma, and ampullary carcinoma[7]. The operation is complicated[8], and usually lasts more than 5 h. Postoperative complications such as pancreatic fistula, delayed gastric emptying, abdominal infection, and postoperative hemorrhage are prone to occur[9]. Extensive literature has clarified the risk factors related to complications after pancreaticoduodenectomy[10,11]. At present, there is no report on the effect of pancreaticoduodenectomy over time on the prognosis of patients. Therefore, the study explores the impact of overtime work for pancreaticoduodenectomy on the prognosis of patients.

## MATERIALS AND METHODS

### *Study design and population*

Approval of the Ethics Committee of the Peking University People's Hospital was obtained. Patients who underwent pancreaticoduodenectomy at the Department of Hepatobiliary Surgery, Peking University People's Hospital from January 2017 to December 2019 were reviewed. Patients with missing clinical data were excluded. All patients were scheduled to undergo elective surgery. The center stipulates that the working hours of surgeons are 8:00-17:00 from Monday to Friday. The definition of overtime surgery in this study is that the surgeon starts the operation after 17:00. So Patients were stratified by operative start time into the control group (surgery that started between 8:00 and 16:49) and the overtime group (surgery that started between 17:00 and 22:00). Since the off-hours in our institution begin at 17:00, five o'clock was set as the cutoff point. The operating room did not accept new elective surgery after 22:00.

**Table 1 Preoperative clinical characteristic of all patients**

| Characteristic | Total (*n* = 235) |
|---|---|
| Age (median, range), yr | 64 (range 14-89) |
| Sex, *n* (%) | |
| Male | 153 (65.1) |
| Female | 82 (34.9) |
| Preoperative comorbidities, *n* (%) | |
| Diabetes | 46 (19.6) |
| Hypertension | 98 (37.4) |
| Coronary heart disease | 19 (8.1) |
| Hepatobiliary and pancreatic diseases | 46 (19.6) |
| Location of the lesions, *n* (%) | |
| Pancrea | 95 (40.4) |
| Bile duct | 81 (34.6) |
| Duodenum | 59 (25.1) |

The following parameters were included as possible confounders: patient age, sex, body mass index (BMI), American Society of Anesthesiologists grade, preoperative comorbidities, preoperative total bilirubin, site of lesion, surgeon, technique of reconstruction, and techinique of pancreaticojejunostomy. The following parameters were compared between the overtime group and the control group: operative time, blood loss, number of lymph nodes removed, duration of treatment in the Intensive Care Unit (ICU), incidence of complications and number of hospital death.

### Surgery and surgeons

A total of 6 surgeons performed pancreaticoduodenectomy at the institution. All surgeons had more than 10 years of experience in performing pancreaticoduodenectomy. Each surgeon performed operations two days a week. Karolinska Sleepiness Scale (KSS)[12] was used to assess surgeon sleepiness. The surgeons involved in this study self-assessed their level of sleepiness for each surgery, and expressed with KSS.

Pancreaticoduodenectomy was used to treat pancreatic cancer, cholangiocarcinoma, duodenal cancer, ampullary cancer, and a small number of benign diseases. All pancreaticoduodenectomy were performed by laparotomy. Roux-en-y or child surgery was used to reconstruct the digestive tract, and pancreaticojejunostomy was performed by duct-mucosa or invagination.

### Definition of postoperative pancreatic fistula and delayed gastric emptying

A clinically relevant postoperative pancreatic fistula is defined as a drain output of any measurable volume of fluid with an amylase level > 3 times the upper limit of institutional normal serum amylase activity[13]. Delayed gastric emptying was defined as the patient not removing the gastric tube or needing to have the tube reinserted for more than 3 d after the operation[14]. Delayed gastric emptying can be classified as grade A (3-7 d), B (8-14 d), and C (more than 14 d) according to the duration of retention of the gastric tube. In this study, only grades B and C of delayed gastric emptying were included in the postoperative complication analysis.

### Statistical analysis

Continuous variables were tested with the Shapiro-Wilk test to determine whether they were normally distributed. Continuous variables that were proven to have a normal distribution are reported as the mean and standard deviation. Otherwise, continuous variables are reported by medians. Categorical variables are reported as frequencies or percentages. Continuous, normally distributed variables were compared with the t-test and non-normally distributed variables were compared with the Mann-Whitney test. The chi-square test was used to compare categorical variables. Reverse stepwise multivariable logistic regression was performed to assess the effects of the potential covariates on outcome. Variables with p-values less than 0.2 in univariate logistic regression models will be included in the multivariable logistic regression analysis. *P* values less than 0.05 were considered significant. Data were analyzed in Statistical Package for the Social Sciences version 21.0 (SPSS 21.0). The study was reviewed by our expert Biostatistic Da-Fang Zhang.

**Table 2 Patient characteristics and operative parameters**

| | Control group (*n* = 177) | Overtime group (*n* = 58) | *P* value |
|---|---|---|---|
| Age (yr) | 63 (14-89) | 64 (29-84) | 0.987 |
| Sex | | | 0.694 |
| Male | 114 (64.4%) | 39 (67.2%) | |
| Female | 63 (35.6%) | 19 (32.8%) | |
| BMI (kg/m$^2$) | 22.7 (14.8-36.8) | 22.9 ± 2.79 | 0.922 |
| ASA classification | | | 0.227 |
| I | 14 (7.9%) | 3 (5.2%) | |
| II | 130 (73.4%) | 49 (84.5%) | |
| III | 33 (18.6%) | 6 (10.3%) | |
| History of hepatobiliary and pancreatic disease | 32 (18.1%) | 14 (24.1%) | 0.313 |
| Diabetes | 33 (18.6%) | 13 (22.4%) | 0.53 |
| Hypertension | 67 (37.9%) | 21 (36.2%) | 0.822 |
| Coronary artery disease | 14 (7.9%) | 5 (8.6%) | 0.863 |
| Cerebrovascular disease | 16 (9.0%) | 2 (3.4%) | 0.165 |
| Preoperative total bilirubin | 85.8 (5.4-793.5) | 93.8 (5.3-610.2) | 0.566 |
| Primary site | | | 0.644 |
| Pancreas | 74 (41.8%) | 21 (36.2%) | |
| Bile duct | 61 (34.5%) | 20 (34.5%) | |
| Duodenum | 42 (23.7%) | 17 (29.3%) | |
| Surgeon | | | 0.085 |
| A | 21 (11.9%) | 5 (8.6%) | |
| B | 30 (16.9%) | 17 (29.3%) | |
| C | 32 (18.1%) | 13 (22.4%) | |
| D | 17 (9.6%) | 6 (10.3%) | |
| E | 34 (19.2%) | 3 (5.2%) | |
| F | 43 (24.3%) | 14 (24.1%) | |
| Technique of reconstruction | | | 0.233 |
| Roux-en-Y | 94 (53.1%) | 36 (62.1%) | |
| Child surgery | 83 (46.9%) | 22 (37.9%) | |
| Pancreaticojejunostomy technique | | | 0.686 |
| Duct-to-mucosa | 53 (29.9%) | 19 (32.8%) | |
| Invagination | 124 (70.1%) | 39 (67.2%) | |
| Operative time (min) | 413 (260-796) | 421.1 ± 83.4 | 0.757 |
| Blood loss (mL) | 600 (100-4700) | 700 (150-2800) | 0.185 |
| Number of lymph nodes removed | 9 (0-62) | 10 (1-45) | 0.994 |

BMI: Body mass index.

## RESULTS

### *Preoperative clinical characteristic*

From January 2017 to December 2019, a total of 239 patients underwent pancreaticoduodenectomy in the Department of Hepatobiliary Surgery of our institution. Four patients were excluded from this

**Table 3 Intraoperative and postoperative clinical characteristic of all patients**

| Characteristic | Total (*n* = 235) |
|---|---|
| Operating time (median, range), min | 416 (260-796) |
| Blood loss volume (median, range), mL | 600 (100-4700) |
| Number of lymph nodes removed (median, range) | 10 (0-62) |
| ICU length of stay (median, range), h | 16 (0-518) |
| Hospital length of stay (median, range), d | 19 (7-160) |
| Postoperative complications, *n* (%) | |
| Pancreatic fistula | 47 (20.0) |
| Delayed gastric emptying (B/C) | 39 (16.6) |
| Gastrointestinal bleeding | 25 (10.6) |
| Abdominal infection | 14 (3.0) |
| Pneumonia | 6 (2.6) |
| Arrhythmia | 6 (2.6) |
| Thromboembolism | 2 (0.9) |
| Respiratory failure | 1 (0.4) |
| Gastrointestinal bleeding | 1 (0.4) |
| Death during hospitalization, *n* (%) | |
| Gastrointestinal bleeding | 2 (0.9) |
| Pancreatic fistula | 4 (1.7) |
| Abdominal infection | 1 (0.4) |
| Pneumonia | 3 (1.3) |

ICU: Intensive Care Unit.

**Table 4 Postoperative factors and complications**

| | Control group (*n* = 177) | Overtime group (*n* = 58) | *P* value |
|---|---|---|---|
| Operative time (min) | 413 (260-796) | 421.1 ± 83.4 | 0.757 |
| Blood loss (mL) | 600 (100-4700) | 700 (150-2800) | 0.185 |
| Number of lymph nodes removed | 9 (0-62) | 10 (1-45) | 0.994 |
| Duration of treatment in ICU after surgery | 17 (0-325) | 14 (0-518) | 0.511 |
| Duration of postoperative hospitalization | 20 (7-160) | 18 (7-61) | 0.181 |
| Postoperative pancreatic fistula | 28 (15.8%) | 19 (32.8%) | 0.005 |
| Delayed gastric emptying (B/C) | 30 (16.9%) | 9 (15.5%) | 0.799 |
| Gastrointestinal bleeding | 17 (9.6%) | 8 (13.8%) | 0.369 |
| Abdominal infection | 12 (6.8%) | 2 (3.4%) | 0.352 |
| Pneumonia | 3 (1.7%) | 3 (5.2%) | 0.162 |
| Arrhythmia | 6 (3.4%) | 0 | 0.341 |
| Thromboembolism | 2 (1.1%) | 0 | 1.000 |
| Respiratory failure | 1 (0.6%) | 0 | 1.000 |
| Hemothorax | 1 (0.6%) | 0 | 1.000 |
| Hospital death | 7 (4.0%) | 3 (5.2%) | 0.690 |

ICU: Intensive Care Unit.

study due to lack of clinical data. A total of 235 patients were included in this study. A total of 177 (75.3%) patients underwent surgery before 16:59. In addition, 58 (24.7%) patients underwent surgery after 17:00. The median age of the patients was 64 (range 14-89) years. There were 153 (65.1%) males and 82 (34.9%) females. The preoperative clinical characteristic of all patients were shown in Table 1. There was no significant difference in any baseline characteristic between the two groups of patients (Table 2).

### Outcome

The intraoperative and postoperative clinical characteristic of all patients were shown in Table 3. Ten patients (4.3%) died during postoperative hospitalization. Of the ten patients who died, 2 died of gastrointestinal bleeding, 4 died of pancreatic fistula, 3 died of pneumonia, and 1 died of abdominal infection. Compared with the control group, the overtime group had a higher incidence of pancreatic fistula (32.8% *vs* 15.8%, $P = 0.005$). There was no difference between the two groups in operative time, blood loss, number of lymph nodes removed, ICU length of stay, hospital length of stay, mortality during hospitalization or complications except pancreatic fistula (Table 4).

### Univariate and multivariate logistic regression analysis of the risk factors for pancreatic fistula

To identify the prognostic factors of pancreatic fistula, we performed univariate and multivariate logistic regression analyses. In the multivariate logistic regression, parameters that significantly increased the risk of pancreatic fistula were high BMI and overtime surgery (Tables 5 and 6).

### KSS of surgeons during overtime and non-overtime operations

The average values of KSS in the control group and overtime group were 1.95 ± 0.6 and 6.4 ± 1.0, respectively. The statistical analysis demonstrates differences between groups regarding KSS ($P < 0.001$), with increased mean KSS in overtime group (Table 7).

## DISCUSSION

Due to the large demand for surgery, surgeons often need to work overtime or even stay up late to complete a surgery. In a state of fatigue and sleep deprivation, surgeons may make more mistakes during the operation, which may result in a worse prognosis for the patient after surgery. McCormick *et al*[15] reported that residents' fatigue levels were predicted to increase the risk of medical error by 22% compared with well-rested historical control subjects. Taffinder *et al*[16] found that surgeons who were sleep deprived made 20% more mistakes in laparoscopic procedures and had an increase in operating time of 14%. Because of pancreaticoduodenectomy is complicated operation with long operation time, its requirements for the surgeon's physical and mental stamina are higher. Although a large number of studies on pancreaticoduodenectomy have been reported. To the best of our knowledge, our study is the first to explore the relationship between the overtime surgery and the short-term prognosis of pancreaticoduodenectomy. All surgeons at our center perceive a decrease in alertness during overtime surgery. Therefore, the KSS of the overtime group were higher than control group. This means that surgeons tend to be fatigued when they work overtime.

There was no significant difference in the preoperative and intraoperative results of patients between the overtime group and the control group. However, the postoperative results showed that the overtime group had a higher incidence of pancreatic fistula. In the multivariate regression analysis, operation time was still the influencing factor on pancreatic fistula. The incidence of pancreatic fistula in the night shift group was approximately twice that in the day shift group (32.8% *vs* 15.8%). In addition, elevated BMI was risk factors for pancreatic fistula. Relevant studies have confirmed that high BMI is a risk factor for pancreatic fistula[17,18]. High BMI causes abdominal fat to increase, which in turn leads to increased difficulty in surgery, thereby increasing the incidence of pancreatic fistula.

Pancreatico-enteric anastomosis in pancreaticoduodenectomy places stricter requirements on the operation of the surgeon. Due to more than 8 h of work during the day, the surgeon is physically and mentally exhausted, which may lead to a decline in surgical proficiency. Therefore, overtime surgery may cause a significant increase in the incidence of pancreatic fistula. This study confirmed that overtime pancreaticoduodenectomy increased the incidence of postoperative pancreatic fistula in patients. According to previous literature[19-21], about 16.3%-23.9% of patients who underwent pancreaticoduodenectomy developed pancreatic fistula after surgery. The result was consistent with the report in our center. Postoperative pancreatic fistula can prolong the patients' hospital stay, increase the patient's medical expenses, and even lead to the patient's death. So avoiding pancreatic fistula as much as possible is crucial for surgeons.

**Table 5 *P* values, odds ratios, and selected 95%CI for pancreatic fistula from univariate logistic regression models**

| Parameter | *P* value | Odds ratio | 95%CI |
|---|---|---|---|
| Age (yr) | 0.474 | 1.011 | 0.981-1.042 |
| Male | 0.068 | 1.986 | 0.951-4.149 |
| BMI (kg/m$^2$) | 0.036 | 1.113 | 1.007-1.229 |
| ASA classification | | | |
| I | 0.723 | 0.733 | 0.132-4.066 |
| II | 0.373 | 1.532 | 0.599-3.920 |
| III | | Reference | |
| History of hepatobiliary and pancreatic disease | 0.368 | 0.669 | 0.278-1.607 |
| Diabetes | 0.368 | 0.669 | 0.278-1.607 |
| Hypertension | 0.071 | 1.813 | 0.950-3.460 |
| Coronary artery disease | 0.905 | 1.073 | 0.339-3.396 |
| Cerebrovascular disease | 0.714 | 0.786 | 0.218-2.837 |
| Preoperative total bilirubin | 0.324 | 1.001 | 0.999-1.003 |
| Primary site | | | |
| Pancreas | 0.581 | 0.777 | 0.317-1.905 |
| Bile duct | 0.087 | 2.063 | 0.899-4.735 |
| Duodenum | Reference | | |
| Surgeon | | | |
| A | 0.44 | 1.482 | 0.545-4.030 |
| B | 0.55 | 0.757 | 0.303-1.888 |
| C | 0.308 | 0.605 | 0.231-1.589 |
| D | 0.053 | 0.127 | 0.016-1.028 |
| E | 0.076 | 0.339 | 0.103-1.119 |
| F | | Reference | |
| Overtime case | 0.006 | 2.592 | 1.312-5.122 |
| Reconstruction technique | | | |
| Roux-en-Y | | Reference | |
| Child surgery | 0.743 | 1.113 | 0.586-2.114 |
| Pancreaticojejunostomy technique | | | |
| Duct-to-mucosa | 0.572 | 1.217 | 0.617-2.4 |
| Invagination | | Reference | |

BMI: Body mass index.

The institution stipulates that surgeons cannot start new elective operations after ten o'clock in the evening. However, clinicians need to complete a large number of surgical tasks on their own surgery days. To extend working hours, surgeons will schedule short-term operations such as cholecystectomy to be completed during the day and long-term operations such as pancreaticoduodenectomy to be performed near ten o'clock in the evening. Therefore, a large number of pancreaticoduodenectomies are performed after hours in our institution. Working overtime to perform pancreaticoduodenectomy reduces the safety of the operation and increases the incidence of postoperative pancreatic fistula. In addition, overtime work has an adverse effect on doctors' health. Studies have confirmed that overtime work will lead to an increase in the incidence of cardiovascular diseases[22,23].

The government and hospital administrators may need to take measures to change the situation where surgeons frequently work overtime or even stay up late for surgery. At the government level, investment in medical care should be increased to alleviate the shortage of medical resources. In

**Table 6 *P* values, odds ratios, and selected 95%CI for pancreatic fistula from multivariate logistic regression models**

| Parameter | *P* value | Odds ratio | 95%CI |
|---|---|---|---|
| BMI (kg/m$^2$) | 0.034 | 1.12 | 1.008-1.243 |
| Primary site | | | |
| Pancreas | 0.773 | 0.873 | 0.346-2.201 |
| Bile duct | 0.062 | 2.273 | 0.960-5.380 |
| Duodenum | | Reference | |
| Overtime case | 0.004 | 2.803 | 1.382-5.685 |

BMI: Body mass index.

**Table 7 Karolinska Sleepiness Scale of surgeons during overtime and non-overtime operations**

| | Control group | Overtime group | *P* value |
|---|---|---|---|
| KSS | 1.95 ± 0.6 | 6.4 ± 1.0 | 0 |

KSS: Karolinska Sleepiness Scale.

addition, the government can legislate to limit the working hours of medical staff. At the hospital level, the clinical workload of surgeons should be appropriately reduced to ensure medical safety. Surgeons should try to avoid working overtime to perform pancreaticoduodenectomy. For patients undergoing overtime pancreaticoduodenectomy, surgeons should pay close attention to the amylase content of the patient's drainage fluid to find potential postoperative pancreatic fistulas in a timely manner.

There are still some limitations in this study. The subgroup analysis considering different diagnosis (not only location of lesions), and also different types of surgeries, and the different surgical teams, might render the final analysis difficult to interpret (due to small numbers considering the subgroups). Therefore, the results of this study should be interpreted with caution. Also, this study was a single-center retrospective cohort study, and only six surgeons performed pancreaticoduodenectomy. The conclusions of this study may not be convincing enough to extend to all institutions. Finally, this study did not analyze the long-term prognosis of patients, such as progression-free survival, and overall survival. More research is needed in the future.

## CONCLUSION

Overtime pancreaticoduodenectomy may increase the incidence of postoperative pancreatic fistula. The government and hospital administrators may need to take measures to change the situation where surgeons frequently work overtime or even stay up late for surgery.

## ARTICLE HIGHLIGHTS

### *Research background*

Fatigue and sleep deprivation can result in an increased error rate at work. The effect of overtime work for pancreaticoduodenectomy on the prognosis of patients is unclear.

### *Research motivation*

Overtime surgery may result in an increased incidence of intraoperative errors. This study is intended to be further clarified.

### *Research objectives*

To explore the impact of overtime work for pancreaticoduodenectomy on the short-term prognosis of patients.

### *Research methods*

Patients were stratified by operative start time into the control group (surgery that started between 8:00 and 16:49) and the overtime group (surgery that started between 17:00 and 22:00) and compared intraoperative and postoperative parameters.

### *Research results*

The overtime group had a higher incidence of pancreatic fistula than control group (32.8% *vs* 15.8%, $P < 0.05$).

### *Research conclusions*

The overtime group had a higher incidence of pancreatic fistula.

### *Research perspectives*

This study did not analyze the long-term prognosis of patients, such as progression-free survival, and overall survival. More research is needed in the future.

## FOOTNOTES

**Author contributions:** Zhang JZ designed the study, acquired and analyzed the data, and wrote the paper; Li S acquired and analyzed the data, and revised the paper; Zhu WH acquired and analyzed the data, and revised the paper; Leng XS revised the paper; Zhang DF designed the study, revised the paper, and supervised the study.

**Supported by** Peking University People's Hospital Scientific Research Development Funds, No. RDY2017-28.

**Institutional review board statement:** The study was reviewed and approved by the Peking University People's Hospital Institutional Review Board (Approval No. 2021PHB050-001).

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** No conflict-of-interest to declare.

**Data sharing statement:** No additional data are available.

**STROBE statement:** The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.



**Country/Territory of origin:** China

**ORCID number:** Jin-Zhu Zhang 0000-0001-6979-0539; Shu Li 0000-0002-0080-3562; Wei-Hua Zhu 0000-0002-4293-881X; Xi-Sheng Leng 0000-0001-5184-1035; Da-Fang Zhang 0000-0002-4613-806X.

**S-Editor:** Zhang H
**L-Editor:** A
**P-Editor:** Zhang H

## REFERENCES

1 **Harrison Y**, Horne JA. One night of sleep loss impairs innovative thinking and flexible decision making. *Organ Behav Hum Decis Process* 1999; **78**: 128-145 [PMID: 10329298 DOI: 10.1006/obhd.1999.2827]
2 **Mu Q**, Mishory A, Johnson KA, Nahas Z, Kozel FA, Yamanaka K, Bohning DE, George MS. Decreased brain activation during a working memory task at rested baseline is associated with vulnerability to sleep deprivation. *Sleep* 2005; **28**: 433-446 [PMID: 16171288 DOI: 10.1093/sleep/28.4.433]
3 **Folkard S**, Lombardi DA. Modeling the impact of the components of long work hours on injuries and "accidents". *Am J Ind Med* 2006; **49**: 953-963 [PMID: 16570251 DOI: 10.1002/ajim.20307]
4 **Halvachizadeh S**, Teuber H, Cinelli P, Allemann F, Pape HC, Neuhaus V. Does the time of day in orthopedic trauma surgery affect mortality and complication rates? *Patient Saf Surg* 2019; **13**: 8 [PMID: 30766615 DOI:

10.1186/s13037-019-0186-4]
5 **Boscà A**, Montalvá EM, Maupoey J, Argüelles B, Navío A, Calatayud D, Camacho A, García-Eliz M, López-Andújar R. Does Surgeon Fatigue Influence the Results of Liver Transplantation? *Transplant Proc* 2019; **51**: 67-70 [PMID: 30611547 DOI: 10.1016/j.transproceed.2018.03.139]
6 **Brunschot DM**, Hoitsma AJ, van der Jagt MF, d'Ancona FC, Donders RA, van Laarhoven CJ, Hilbrands LB, Warlé MC. Nighttime kidney transplantation is associated with less pure technical graft failure. *World J Urol* 2016; **34**: 955-961 [PMID: 26369548 DOI: 10.1007/s00345-015-1679-0]
7 **McEvoy SH**, Lavelle LP, Hoare SM, O'Neill AC, Awan FN, Malone DE, Ryan ER, McCann JW, Heffernan EJ. Pancreaticoduodenectomy: expected post-operative anatomy and complications. *Br J Radiol* 2014; **87**: 20140050 [PMID: 25026968 DOI: 10.1259/bjr.20140050]
8 **Warshaw AL**, Thayer SP. Pancreaticoduodenectomy. *J Gastrointest Surg* 2004; **8**: 733-741 [PMID: 15358336 DOI: 10.1016/j.gassur.2004.03.005]
9 **Cameron JL**, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. *Ann Surg* 2006; **244**: 10-15 [PMID: 16794383 DOI: 10.1097/01.sla.0000217673.04165.ea]
10 **Ramacciato G**, Mercantini P, Petrucciani N, Nigri GR, Kazemi A, Muroni M, Del Gaudio M, Balesh A, Cescon M, Cucchetti A, Ravaioli M. Risk factors of pancreatic fistula after pancreaticoduodenectomy: a collective review. *Am Surg* 2011; **77**: 257-269 [PMID: 21375833 DOI: 10.1177/000313481107700310]
11 **Hanna MM**, Gadde R, Allen CJ, Meizoso JP, Sleeman D, Livingstone AS, Merchant N, Yakoub D. Delayed gastric emptying after pancreaticoduodenectomy. *J Surg Res* 2016; **202**: 380-388 [PMID: 27229113 DOI: 10.1016/j.jss.2015.12.053]
12 **Laverde-López MC**, Escobar-Córdoba F, Eslava-Schmalbach J. Validation of the Colombian version of the Karolinska sleepiness scale. *Sleep Sci* 2022; **15**: 97-104 [PMID: 35273753 DOI: 10.5935/1984-0063.20220006]
13 **Bassi C**, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, Allen P, Andersson R, Asbun HJ, Besselink MG, Conlon K, Del Chiaro M, Falconi M, Fernandez-Cruz L, Fernandez-Del Castillo C, Fingerhut A, Friess H, Gouma DJ, Hackert T, Izbicki J, Lillemoe KD, Neoptolemos JP, Olah A, Schulick R, Shrikhande SV, Takada T, Takaori K, Traverso W, Vollmer CR, Wolfgang CL, Yeo CJ, Salvia R, Buchler M; International Study Group on Pancreatic Surgery (ISGPS). The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. *Surgery* 2017; **161**: 584-591 [PMID: 28040257 DOI: 10.1016/j.surg.2016.11.014]
14 **Wente MN**, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Traverso LW, Yeo CJ, Büchler MW. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2007; **142**: 761-768 [PMID: 17981197 DOI: 10.1016/j.surg.2007.05.005]
15 **McCormick F**, Kadzielski J, Landrigan CP, Evans B, Herndon JH, Rubash HE. Surgeon fatigue: a prospective analysis of the incidence, risk, and intervals of predicted fatigue-related impairment in residents. *Arch Surg* 2012; **147**: 430-435 [PMID: 22785637 DOI: 10.1001/archsurg.2012.84]
16 **Taffinder NJ**, McManus IC, Gul Y, Russell RC, Darzi A. Effect of sleep deprivation on surgeons' dexterity on laparoscopy simulator. *Lancet* 1998; **352**: 1191 [PMID: 9777838 DOI: 10.1016/s0140-6736(98)00034-8]
17 **You L**, Zhao W, Hong X, Ma L, Ren X, Shao Q, Du Y, Cong L, Zhao Y. The Effect of Body Mass Index on Surgical Outcomes in Patients Undergoing Pancreatic Resection: A Systematic Review and Meta-Analysis. *Pancreas* 2016; **45**: 796-805 [PMID: 27295531 DOI: 10.1097/MPA.0000000000000525]
18 **Peng YP**, Zhu XL, Yin LD, Zhu Y, Wei JS, Wu JL, Miao Y. Risk factors of postoperative pancreatic fistula in patients after distal pancreatectomy: a systematic review and meta-analysis. *Sci Rep* 2017; **7**: 185 [PMID: 28298641 DOI: 10.1038/s41598-017-00311-8]
19 **Yin J**, Zhu Q, Zhang K, Gao W, Wu J, Lu Z, Jiang K, Miao Y. Development and validation of risk prediction nomogram for pancreatic fistula and risk-stratified strategy for drainage management after pancreaticoduodenectomy. *Gland Surg* 2022; **11**: 42-55 [PMID: 35242668 DOI: 10.21037/gs-21-550]
20 **Miller BC**, Christein JD, Behrman SW, Drebin JA, Pratt WB, Callery MP, Vollmer CM Jr. A multi-institutional external validation of the fistula risk score for pancreatoduodenectomy. *J Gastrointest Surg* 2014; **18**: 172-79; discussion 179 [PMID: 24002771 DOI: 10.1007/s11605-013-2337-8]
21 **Molinari E**, Bassi C, Salvia R, Butturini G, Crippa S, Talamini G, Falconi M, Pederzoli P. Amylase value in drains after pancreatic resection as predictive factor of postoperative pancreatic fistula: results of a prospective study in 137 patients. *Ann Surg* 2007; **246**: 281-287 [PMID: 17667507 DOI: 10.1097/SLA.0b013e3180caa42f]
22 **Liu Y**, Tanaka H; Fukuoka Heart Study Group. Overtime work, insufficient sleep, and risk of non-fatal acute myocardial infarction in Japanese men. *Occup Environ Med* 2002; **59**: 447-451 [PMID: 12107292 DOI: 10.1136/oem.59.7.447]
23 **Kageyama T**, Nishikido N, Kobayashi T, Kurokawa Y, Kabuto M. Commuting, overtime, and cardiac autonomic activity in Tokyo. *Lancet* 1997; **350**: 639 [PMID: 9288053 DOI: 10.1016/s0140-6736(05)63328-4]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 May 27; 14(5): 429-441

DOI: 10.4240/wjgs.v14.i5.429

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

# Para-aortic lymph node involvement should not be a contraindication to resection of pancreatic ductal adenocarcinoma

Rupaly Pande, Shafiq Chughtai, Manish Ahuja, Rachel Brown, David C Bartlett, Bobby V Dasari, Ravi Marudanayagam, Darius Mirza, Keith Roberts, John Isaac, Robert P Sutcliffe, Nikolaos A Chatzizacharias

**Specialty type:** Surgery

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Jiang L, China; Kuo SH, Taiwan; Nguyen LT, Viet Nam

**Received:** December 21, 2021
**Peer-review started:** December 21, 2021
**First decision:** March 13, 2022
**Revised:** March 19, 2022
**Accepted:** April 21, 2022
**Article in press:** April 21, 2022
**Published online:** May 27, 2022

**Rupaly Pande, Shafiq Chughtai, Manish Ahuja, David C Bartlett, Bobby V Dasari, Ravi Marudanayagam, Darius Mirza, Keith Roberts, John Isaac, Robert P Sutcliffe, Nikolaos A Chatzizacharias,** Department of Hepato-Pancreato-Biliary and Liver Transplant Surgery, University Hospitals Birmingham NHS Foundation Trust, Birmingham B15 2GW, United Kingdom

**Rachel Brown,** Department of Pathology, University Hospitals Birmingham NHS Foundation Trust, Birmingham B15 2GW, United Kingdom

**Corresponding author:** Nikolaos A Chatzizacharias, FACS, FRCS, MD, PhD, Consultant Surgeon, Department of Hepato-Pancreato-Biliary and Liver Transplant Surgery, University Hospitals Birmingham NHS Foundation Trust, Mindelsohn Way, Birmingham B15 2GW, United Kingdom. chatzizacharias@gmail.com

## Abstract

### *BACKGROUND*

Para-aortic lymph nodes (PALN) are found in the aortocaval groove and they are staged as metastatic disease if involved by pancreatic ductal adenocarcinoma (PDAC). The data in the literature is conflicting with some studies having associated PALN involvement with poor prognosis, while others not sharing the same results. PALN resection is not included in the standard lymphadenectomy during pancreatic resections as per the International Study Group for Pancreatic Surgery and there is no consensus on the management of these cases.

### *AIM*

To investigate the prognostic significance of PALN metastases on the oncological outcomes after resection for PDAC.

### *METHODS*

This is a retrospective cohort study of data retrieved from a prospectively maintained database on consecutive patients undergoing pancreatectomies for PDAC where PALN was sampled between 2011 and 2020. Statistical comparison of the data between PALN+ and PALN- subgroups, survival analysis with the Kaplan-Meier method and risk analysis with univariable and multivariable time to event Cox regression analysis were performed, specifically assessing oncological outcomes such as median overall survival (OS) and disease-free survival

(DFS).

***RESULTS***

81 cases had PALN sampling and 17 (21%) were positive. Pathological N stage was significantly different between PALN+ and PALN- patients ($P$ = 0.005), while no difference was observed in any of the other characteristics. Preoperative imaging diagnosed PALN positivity in one case. OS and DFS were comparable between PALN+ and PALN- patients with lymph node positive disease (OS: 13.2 mo *vs* 18.8 mo, $P$ = 0.161; DFS: 13 mo *vs* 16.4 mo, $P$ = 0.179). No difference in OS or DFS was identified between PALN positive and negative patients when they received chemotherapy either in the neoadjuvant or in the adjuvant setting (OS: 23.4 mo *vs* 20.6 mo, $P$ = 0.192; DFS: 23.9 mo *vs* 20.5 mo, $P$ = 0.718). On the contrary, when patients did not receive chemotherapy, PALN disease had substantially shorter OS (5.5 mo *vs* 14.2 mo; $P$ = 0.015) and DFS (4.4 mo *vs* 9.8 mo; $P$ < 0.001). PALN involvement was not identified as an independent predictor for OS after multivariable analysis, while it was for DFS doubling the risk of recurrence.

***CONCLUSION***

PALN involvement does not affect OS when patients complete the indicated treatment pathway for PDAC, surgery and chemotherapy, and should not be considered as a contraindication to resection.

**Key Words:** Para-aortic lymph node; Pancreatectomy; Survival; Pancreatic adenocarcinoma; Chemotherapy; Lymph node sampling



**Core Tip:** Currently there is no consensus on the prognostic significance of para-aortic lymph node (PALN) involvement in pancreatic ductal adenocarcinoma (PDAC), which is staged as metastatic disease (M1). Our study has demonstrated that patients with PALN involvement have comparable oncological outcomes, overall survival (OS) and disease free survival, to ones without PALN disease, when the appropriate treatment pathway is competed (surgery and chemotherapy). Multivariable risk analysis did not identify PALN involvement as an independent predictor for OS, while it doubled the risk of disease recurrence. Our data support that PALN involvement should not be considered a contraindication to resection for PDAC.

**Citation:** Pande R, Chughtai S, Ahuja M, Brown R, Bartlett DC, Dasari BV, Marudanayagam R, Mirza D, Roberts K, Isaac J, Sutcliffe RP, Chatzizacharias NA. Para-aortic lymph node involvement should not be a contraindication to resection of pancreatic ductal adenocarcinoma. *World J Gastrointest Surg* 2022; 14(5): 429-441
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i5/429.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i5.429

## INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) presents as localised disease for only a small subset of patients for whom only 20% are eligible for resection[1] with 5-year survival of 6.8%[2]. Nodal status is amongst the most important prognostic indicators. Early lymph node involvement can be as common as 90% and may lead to tumour recurrence even after complete resection[3]. Survival difference has been demonstrated between N0 and lymph node positive disease within variances of lymph node ratio[4] and nodal stations[5] However, para-aortic lymph nodes found in the aortocaval groove (PALN, station Ln16b1) are distinct from regional lymph node stations and are staged as distant metastatic (M1) disease [6]. PALN metastases are found in 14%-18% of pancreatic head/uncinate PDAC at resection[7]. The exact significance and management of PALN is yet to be fully determined. Within the literature, various studies have alluded to PALN metastases being associated with poor prognosis, whereas others have failed to replicate this effect[8,9] and a meta-analysis[10] has only concluded the need for intra-operative assessment of PALN. A consensus statement from the International Study Group for Pancreatic Surgery (ISGPS) supported standard lymphadenectomy for pancreatic resections, as evidence do not support any benefit with an extended approach[11]. There was no recommendation to include PALN in standard lymphadenectomy, however it was acknowledged that PALN may be included in the resection plane based on individual practice. Currently, whether intra-operative assessment should be undertaken or whether there is sufficient evidence that resection should be abandoned depends on

surgeon or unit policy.

The aim of this study was to determine the prognostic significance of PALN metastases on the oncological outcomes after pancreatic resections for PDAC.

## MATERIALS AND METHODS

The study was conducted in line with STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines[12]. It was conducted at the University Hospitals of Birmingham, a tertiary specialist centre for the treatment of pancreatic cancer, after departmental approval. Staging of the tumours was based on the NCCN staging criteria[13]. The unit adopts a policy of fast-track[14] upfront surgery approach for resectable and borderline resectable PDAC with venous only involvement as supported by the United Kingdom National Institute for Care and Health Excellence[15], patients with borderline tumours with arterial involvement and locally advanced PDAC undergo neoadjuvant chemotherapy before resection is contemplated. All patients are referred for adjuvant chemotherapy after resection. In the early part of the study gemcitabine-based regimens were used both in the neoadjuvant and adjuvant setting. In the more recent years, modified FOLFIRINOX has been the preferred regimen, with gemcitabine-based regimens as back-up option depending on patients' status and tolerance. PALN were sampled from the infra-renal, aortacaval lymph nodes and more specifically from the level of the third part of the duodenum to the angle of the left renal vein (station 16). PALN sampling was performed at the discretion of the operating surgeon. Over the last 3 years of the study 3 surgeons sampled PALN routinely, accounting for 36% of the cases in the study. Pre-operative staging included a computer tomography (CT) with IV contrast of the thorax, abdomen and pelvis and endoscopic ultrasound (EUS) with fine needle aspiration when preoperative cytological diagnosis was required. Magnetic resonance imaging (MRI) liver and positron emission tomography/CT (PET/CT) were used selectively if there were concerns for metastatic disease based on the CT scan. The management of all cases was discussed and agreed in the hepatopancreaticobiliary multidisciplinary meeting. Follow-up of patients was determined from time of diagnosis until disease recurrence or death. The study cohort included all patients that had PALN sampling during pancreatic resection for PDAC between 2011 and 2020. Clinical, radiological and pathological data were obtained from the hospital's electronic records and the departmental prospectively maintained database. The American Joint Committee on Cancer 8$^{th}$ edition was used for tumor-node-metastasis (TNM) staging statistical analysis. Overall survival (OS) was defined as the time from diagnosis to death or last follow-up and disease free survival as the time from resection to diagnosis of disease recurrence.

The cohort characteristics are presented with standard descriptive statistical analysis. One way Anova, Chi-Square and Mann-Whitney *U* tests were used as appropriate to compare variables and outcomes between PALN positive and negative subgroups, with statistical significance set at $P < 0.05$. Exact statistics were used for all tests to account for small sample size. Survival analysis was performed with the Kaplan-Meier method and log rank test was used to compare survival curves. Univariable and multivariable time to event analyses were performed using the Cox proportional hazard model to determine risk factors for median OS and disease-free survival (DFS). Variables were subjected to a univariable analysis first and those with $P < 0.2$ were introduced into a multivariable model. Hazard ratios and associated 95% confidence intervals (CI) were calculated. A two-tailed $P$ value < 0.05 was considered statistically significant. All statistical analyses were performed using the software package SPSS Statistics for Windows (version 25.0; SPSS Inc., Chicago, IL, United States).

## RESULTS

During the study period there were 81 patients who underwent pancreatectomies for PDAC where PALN were sampled. PALN metastasis was identified in 17 (21%) cases. The median sampled LNs were 2 (range 1-7) and median positivity ratio 0.5 (range 0.14-1). Patient, tumour and post-operative parameters for the whole cohort, as well as for the PALN positive and negative subgroups, are displayed in Table 1. Pathology N stage (pN) was significantly different between patients with PALN positive and negative disease ($P = 0.005$). All patients with PALN metastases also had regional lymph node disease, with 82% having pN2 disease (in contrast to 45% of PALN negative patients). There was no difference observed in any of the other characteristics. PALN sampling did not cause any significant morbidity in terms of chyle leak or post-pancreatectomy haemorrhage.

### *Radiological detection of PALN*

Amongst patients with metastatic PALN on pathology, there was no modality of investigation which detected this during preoperative staging (CT 1/81, EUS 0/5 or PET 0/3).

**Table 1 Patient demographics, operative and pathological characteristics and outcomes**

| Factors | Total (*n* = 81) | PALN+ (*n* = 17) | PALN- (*n* = 64) | *P* value |
|---|---|---|---|---|
| Demographics | | | | |
| Age (median and range in years) | 69 (43-84) | 68.8 (61-72.3) | 69 (61-75) | 0.404 |
| Gender, male (%) | 38 (47) | 12 (71) | 33 (52) | 0.171 |
| BMI (kg/m$^2$) | 25.1 (22.0-27.8) | 26.2 (22.2-27.8) | 24.9 (21.9-27.7) | 0.413 |
| Non-smoker (%) | 13 (73) | 14 (82) | 46 (72) | 0.462 |
| Preoperative CA19-9 levels (KU/L) | 286 (2-36000) | 410 (14-2784) | 252 (2-36000) | 0.594 |
| Charlson comorbidity index | 4 (3-5) | 4 (3-5) | 4.5 (3-5) | 0.079 |
| Preoperative radiological stage *n* (%) | | | | |
| Resectable | 41 (51) | 8 (47) | 33 (52) | 0.601 |
| Borderline resectable | 31 (38) | 8(47) | 23 (36) | |
| Locally advanced | 9 (11) | 1 (6) | 8 (12) | |
| Operation, *n* (%) | | | | |
| Distal pancreatectomy | 1 (1) | 0 | 1 (1) | 0.681 |
| Total pancreatectomy | 14 (17) | 2 (12) | 12 (19) | |
| Pancreaticoduodenectomy | 66 (82) | 15 (88) | 51 (80) | |
| Vein resection | 33 (41) | 7 (41) | 26 (41) | 0.310 |
| Arterial resection | 3 (4) | 1 (6) | 2 (3) | 0.842 |
| Pathological staging, *n* (%) | | | | 1.000 |
| pT1 | 13 (16) | 3 (18) | 10 (16) | 0.951 |
| pT2 | 46 (57) | 9 (53) | 37 (58) | |
| pT3 | 21 (26) | 5 (29) | 16 (25) | |
| pT4 | 1 (1) | 0 | 1 (1) | |
| pN0 | 14 (79) | 0 | 14 (22) | 0.005 |
| pN1 | 24 (30) | 3 (18) | 21 (33) | |
| pN2 | 43 (53) | 14 (82) | 29 (45) | |
| Resection margin, *n* (%) | | | | |
| Negative | 39 (48) | 6 (35) | 33 (52) | 0.282 |
| Positive | 42 (52) | 11 (65) | 31 (48) | |
| Perineural invasion | 66 (83) | 15 (88) | 51 (80) | 0.722 |
| Perivascular invasion | 59 (73) | 13 (77) | 46 (72) | 1.000 |
| Chemotherapy, *n* (%) | 55 (74) | 12 (71) | 43 (67) | 0.746 |
| Neoadjuvant therapy | 13 (16) | 2 (12) | 11 (17) | 0.726 |
| Adjuvant chemotherapy | 49 (66) | 12 (71) | 37 (58) | 0.553 |
| Post-operative complications, *n* (%) | | | | |
| Clavien Dindo category ≥ 3 | 10 (12) | 2 (11.8) | 8 (12.5) | 0.549 |
| Chyle leak | 1 (1) | 0 | 1 (1.56) | 0.835 |
| Perioperative haemorrhage | 2 (2) | 0 | 2 (3.13) | 0.712 |
| Comprehensive complication index | 0 (0-20.9) | 0 (0-20.9) | 0 (0-20.9) | 0.083 |
| Hospital length of stay (median and range in days) | 9 (1-76) | 8 (5-30) | 10 (1-76) | 0.138 |

BMI: Body mass index; PALN: Para-aortic lymph nodes.

### OS

OS was better in PALN negative patients with a median of 20.6 mo compared to 13.2 mo in PALN positive patients ($P$ = 0.037) (Figure 1A). However, OS among patients with lymph node disease (pN1 and pN2) was comparable between PALN positive and negative cases (13.2 mo *vs* 18.8 mo, $P$ = 0.161) (Figure 1B).

Similarly, when patients were stratified based on receipt of chemotherapy, either in the neoadjuvant or the adjuvant setting, no difference in OS was observed between PALN positive and negative patients who had chemo-therapy (23.4 mo *vs* 20.6 mo, $P$ = 0.192). Interestingly OS of PALN positive patients was slightly longer by about 3 mo (Figure 1C). On the contrary, when patients did not receive chemotherapy, PALN metastatic disease had substantially shorter OS (5.5 mo *vs* 14.2 mo; $P$ = 0.015) (Figure 1D).

Univariable Cox regression analysis showed that pT, pN, presence of PALN metastases, resection margin status and receipt of chemotherapy were associated with OS (Table 2). Multivariable analysis identified pT, pN, margin status and receipt of chemotherapy as independent predictors of survival (Table 2). Of note PALN positivity was not identified as an independent prognostic factor for OS.

### Disease-free survival

Median DFS in the PALN positive group was 13 mo compared to 20.5 mo in the PALN negative one (Figure 2A). This approached but did not achieve statistical significance ($P$ = 0.093). However, among patients with lymph node disease (pN1 and pN2), DFS was comparable between PALN positive and negative cases (13 mo *vs* 16.4 mo, $P$ = 0.179) (Figure 2B).

When the patients were stratified based on receipt of chemotherapy, either in the neoadjuvant or the adjuvant setting, no difference in DFS was observed between PALN positive and negative patients that had chemotherapy (23.9 mo *vs* 20.5 mo, $P$ = 0.718). Interestingly DFS of PALN positive patients was slightly longer by about 3 mo (Figure 2C). When patients did not receive chemotherapy, PALN metastatic disease had substantially shorter DFS (4.4 mo *vs* 9.8 mo; $P$ < 0.001) (Figure 2D).

Univariable Cox regression analysis showed that pT, resection margin status and receipt of chemotherapy were associated with DFS. Age, pN, PALN metastases, perineural and perivascular invasion approached but did not achieve significance (Table 3). On multivariable analysis PALN positivity was identified as an independent predictor of DFS, doubling the risk of recurrence. Other predictors were age, pT, margin status, PNI and chemotherapy (Table 3).

## DISCUSSION

The prognostic significance of PALN positivity has long been an area of debate. The anatomic location of PALN in the aortocaval groove and away from the peri-pancreatic area has resulted in staging these as extra-regional lymph nodes and therefore metastatic disease on TNM if involved[16]. On the other hand, PALN (LN16b1) drain lymph nodes around groups 13 and 14[7,17,18] which are commonly involved in PDAC and therefore PALN could be considered the next lymph node station involved in cases of node positive disease. Furthermore, one theory that has been proposed to explain PALN acting similarly to nodal disease rather than metastatic is that LN16 involvement is due to local invasion through the fascia of Treitz[19] and this is why it is also associated with a high incidence of positive resection margins[9,19]. In this case, PALN excision may allow extensive mesopancreas dissection[20]. The published evidence on the significance of PALN positive disease and its impact in oncological outcomes is conflicting. A consensus statement from the ISGPS suggested that extended lymphadenectomy is not indicated in pancreatic resections[11]. The same group defined standard lymphadenectomy for pancreaticoduodenectomy to include lymph nodes in the hepatoduodenal ligament (stations 5, 6, 8a, 12b, 12c), pancreaticoduodenal groove (stations 13 and 17), right side of the superior mesenteric artery (stations 14a and 14b) and for distal pancreatectomy those along the splenic artery (station 11), along the inferior border of the pancreas (station 18) and in the splenic hilum (station 10), with station 9 to be included only in pancreatic body tumours. Resection of PALN (station 16) was not recommended based on the reported poor outcomes of patients with PALN positive disease. Nonetheless, it was acknowledged that PALN may be included in the resection plane based on individual practice. Some studies have stated no impact of PALN involvement on survival[7,19,21] with others suggested the opposite and even abandoning resection if this is identified intra-operatively upon sampling[8,22,23]. A confounding flaw in many studies is the comparison of survival between PALN+ and PALN-, where the latter group includes a subgroup of N0 patients with invariably better survival rates. A meta-analysis by Agalianos *et al*[9] made a pertinent comparison of PALN+ with pN1 PALN- patients, showing that survival rates at 1 and 2 years were significantly worse in PALN+ group. This was contested by Hempel *et al*[6] who showed that the OS of PALN+ and pN1 PALN- patients were not significantly different. In our study all PALN positive patients also had regional lymph node disease, whereas 22% of PALN negative patients were staged as pN0. No significant difference in OS and DFS was identified in regional lymph node positive (pN1 and pN2) PALN positive patients compared to PALN negative ones. Given that resection in the presence of nodal disease has been shown to prolong survival[24-28] there is

**Table 2 Risk analysis for overall survival**

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| | ***P* value** | **HR (CI)** | ***P* value** | **HR (CI)** |
| Age | 0.668 | 0.994 (0.966-1.022) | | |
| Sex | 0.359 | 0.756 (0.416-1.374) | | |
| Preoperative CA19-9 | 0.626 | 1.000 (1.000-1.000) | | |
| Pre-operative stage | 0.949 | 0.986 (0.641-1.517) | | |
| Resection type | 0.517 | 1.141 (0.765-1.702) | | |
| Venous resection | 0.659 | 1.146 (0.625-2.104) | | |
| Arterial resection | 0.327 | 2.045 (0.489-8.559) | | |
| pT | 0.001 | 2.148 (1.368-3.371) | 0.008 | |
| pT1 | | | 0.842 | 1.114 (0.385-3.226) |
| pT2 | | | 0.115 | 2.459 (0.803-7.536) |
| pT3 | | | 0.008 | 31.275 (2.491-392.605) |
| pN | 0.002 | 2.195 (1.337-3.604) | 0.004 | |
| pN1 | | | 0.329 | 2.332 (0.427-12.740) |
| pN2 | | | 0.016 | 7.564 (1.459-39.224) |
| PALN positivity | 0.041 | 1.970 (1.028-3.776) | | |
| Margin status | 0.007 | 2.331 (1.261-4.308) | 0.049 | 1.986 (1.003-3.932) |
| Perineural invasion | 0.212 | 1.691 (0.741-3.861) | | |
| Perivascular invasion | 0.464 | 1.278 (0.663-2.461) | | |
| Chemotherapy | 0.033 | 0.487 (0.251-0.944) | 0.002 | 0.283 (0.129-0.622) |

All parameters with $P < 0.200$ on univariable entered into multivariable model. HR: Hazard ratios; CI: Confidence intervals; PALN: Para-aortic lymph nodes.

no indication on this basis to abandon resection.

The appropriateness of PALN+ being termed M1 disease has also been challenged where long term survival after PALN+ resection has been achieved by various studies[6,29,30] including a multicentre study of 102 (12.4%) PALN+ which has shown survival of 2 years of PALN+ patients[20]. Our study covers a 10 year period during which the chemotherapy practice has changed from single agent gemcitabine to gemcitabine combined with capecitabine and more recently FOLFIRINOX. This along with the fact that approximately 30% of patients did not receive any systemic treatment can explain the OS of 20.6 mo in PALN negative and 13.2 mo in PALN positive patients. However, in patients who received chemotherapy, whether NAT or adjuvant chemotherapy, this disparity disappeared. Furthermore, on multivariable analysis PALN positivity was not an independent predictor for OS. Interestingly, OS was slightly longer in the PLAN positive patients after chemotherapy (23.4 mo *vs* 20.6 mo). This may reflect a treatment selection bias by the oncology teams as patients with more aggressive disease received more commonly chemotherapy in the adjuvant period (71% for PALN positive disease compared to 58% for PALN negative), even though this difference did not reach statistical significance. During the same time period, patients diagnosed with metastatic disease intra-operatively had a medial OS of 14.1 mo after palliative treatment (6.1 mo if they did not receive any palliative treatment), which is substantially less than the 23.4 mo OS recorded for PALN+ patients with chemotherapy.

Similarly, DFS was only worse in PALN positive patients if they did not receive any systemic treatment. However, in patients that had systemic treatment DFS was slightly longer in PALN positive patients (23.9 mo *vs* 20.5 mo). Similar to OS, this is most likely a reflection of oncological treatment selection bias. Furthermore, the fact that PALN positivity was identified on multivariable analysis as an independent predictor of DFS, doubling the risk for recurrence, is not an unexpected finding, as nodal disease is a well established prognostic factor for recurrence of PDAC.

The survival benefit of completion of the treatment pathway (surgery and chemotherapy) in patients with PDAC is well established and the sequence of chemotherapy is based on preoperative staging (neoadjuvant or adjuvant setting)[31,32]. With regards to PALN involvement, this is further supported by the results of this study as well as others on PALN disease[20,33,34]. Therefore, the comparable OS

**Table 3 Risk analysis for disease-free survival**

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| | *P* value | HR (CI) | *P* value | HR (CI) |
| Age | 0.129 | 0.979 (0.952-1.006) | 0.023 | 0.964 (0.933-0.995) |
| Sex | 0.881 | 0.955 (0.526-1.736) | | |
| Preoperative CA19-9 | 0.773 | 1.000 (1.000-1.000) | | |
| Preoperative stage | 0.943 | 1.016 (0.656-1.573) | | |
| Resection type | 0.215 | 1.272 (0.869-1.862) | | |
| Venous resection | 0.739 | 0.899 (0.481-1.681) | | |
| Arterial resection | 0.567 | 0.048 (0.000-1578.950) | | |
| pT | 0.002 | 2.102 (1.308-3.378) | 0.004 | |
| pT1 | | | 0.265 | 1.726 (0.661-4.509) |
| pT2 | | | 0.015 | 3.689 (1.287-10.576) |
| pT3 | | | 0.002 | 49.543 (4.018-610.815) |
| pN | 0.121 | 1.387 (0.917-2.097) | | |
| PALN positivity | 0.101 | 1.748 (0.896-3.410) | 0.045 | 2.287 (1.018-5.136) |
| Margin status | 0.032 | 1.927 (1.057-3.514) | 0.007 | 2.48 (1.275-4.822) |
| Perineural invasion | 0.103 | 2.084 (0.862-5.036) | 0.041 | 2.938 (1.045-8.255) |
| Perivascular invasion | 0.152 | 1.657 (0.830-3.308) | | |
| Chemotherapy | 0.047 | 0.509 (0.261-0.992) | 0.001 | 0.242 (0.105-0.559) |

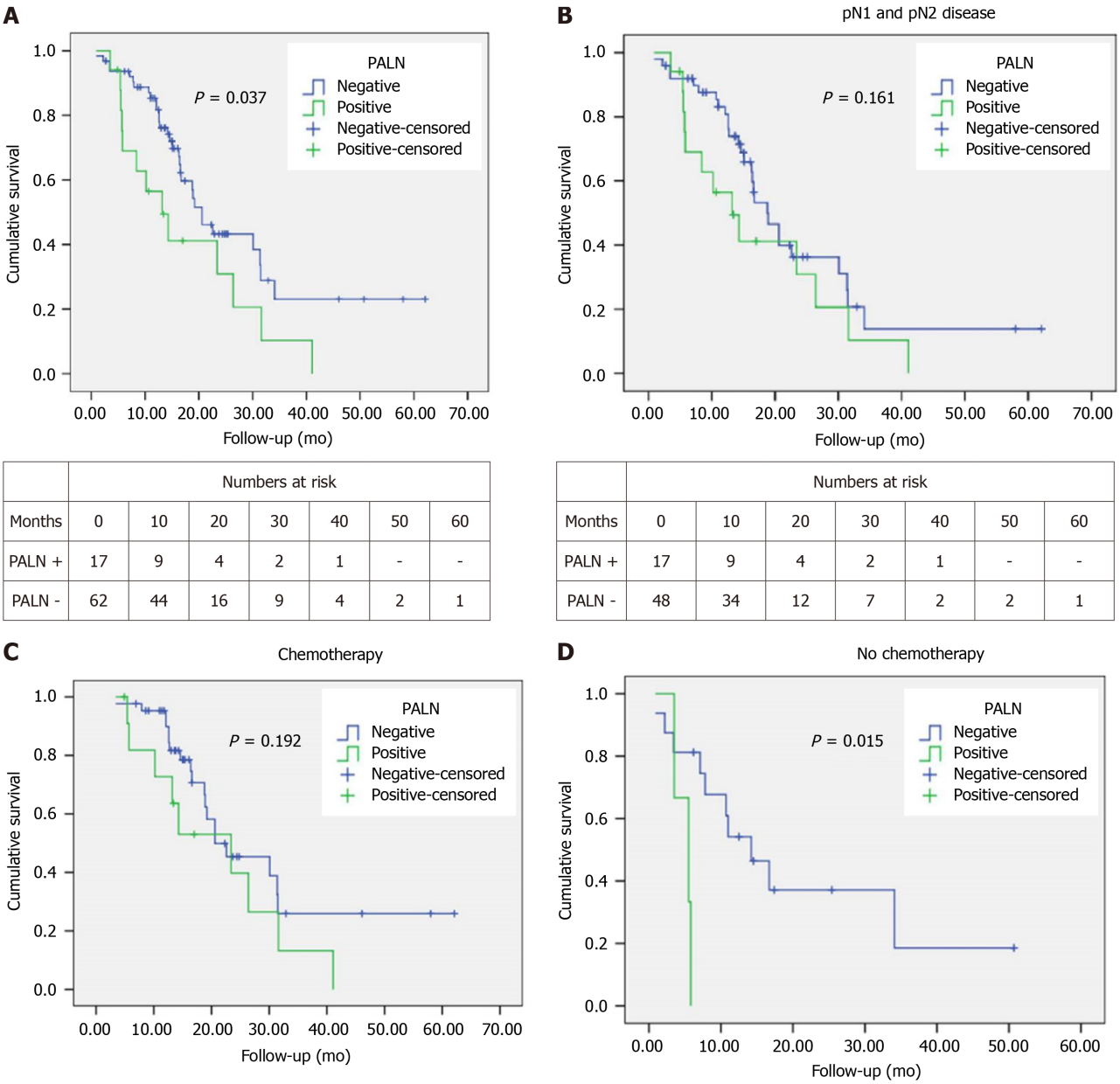
All parameters with $P < 0.200$ on univariable entered into multivariable model. HR: Hazard ratios; CI: Confidence intervals; PALN: Para-aortic lymph nodes.

and DFS after completion of the whole treatment, surgery and chemotherapy, suggest that PALN should not be considered as a contraindication for resection if identified intra-operatively. The substantially worse OS in patients who did not receive any chemotherapy, stresses the importance of considering PALN positive disease in preoperative staging as an indication for NAT. Pre-operative CA19-9 Levels have been associated with PALN+[20,23,35]. Nonetheless, preoperative staging investigations have a very low sensitivity for this in the current as well as other studies to provide the required confirmation. The sensitivity of CT and MRI has been suggested to be close to zero for PALN+[36] while $^{18}$F-flurodeoxyglucose positron emission tomography (FDG-PET) was shown to have sensitivity 37%-50%[37-39]. EUS is used for staging of nodal involvement with accuracy reaching around 65%[40,41] though one small study of 21 patients with PALN+ was shown to have 95% sensitivity[42]. In our study only one case of PALN metastasis was identified on preoperative staging scans, while operative excisional sampling upstaged the diagnosis in 21% of the cases without increasing the risk of perioperative complications.

The limitations of this study include its retrospective and single centre nature, as well as the selection bias associated with intra-operative PALN sampling. Additionally, as the study covers a 10 year period with changes in the preferred systemic treatment regimens for PDAC, systemic treatment selection time bias is inevitable. The small number of PALN positive patients precluded a subgroup analysis of types and duration of NAT or adjuvant chemotherapy. Despite these limitations, the study accurately reflects the practice around PALN over the previous decade and the results clearly add to the body of evidence advocating against considering PALN involvement in the absence of evidence of distant metastases as unresectable disease and against treating these patients with palliative intent.

## CONCLUSION

This study suggests that PALN sampling is safe and should be routinely performed during resection of PDAC for accurate staging, even in the absence of involvement in the pre-operative imaging. PALN involvement does not affect OS when patients complete the indicated treatment pathway (surgery and chemotherapy) and occult involvement identified intra-operatively should not be considered as a contraindication to resection. Future studies should focus on improving pre-operative diagnosis and on




| | Numbers at risk | | | | | | |
|---|---|---|---|---|---|---|---|
| Months | 0 | 10 | 20 | 30 | 40 | 50 | 60 |
| PALN + | 17 | 9 | 4 | 2 | 1 | - | - |
| PALN - | 62 | 44 | 16 | 9 | 4 | 2 | 1 |

| | Numbers at risk | | | | | | |
|---|---|---|---|---|---|---|---|
| Months | 0 | 10 | 20 | 30 | 40 | 50 | 60 |
| PALN + | 17 | 9 | 4 | 2 | 1 | - | - |
| PALN - | 48 | 34 | 12 | 7 | 2 | 2 | 1 |

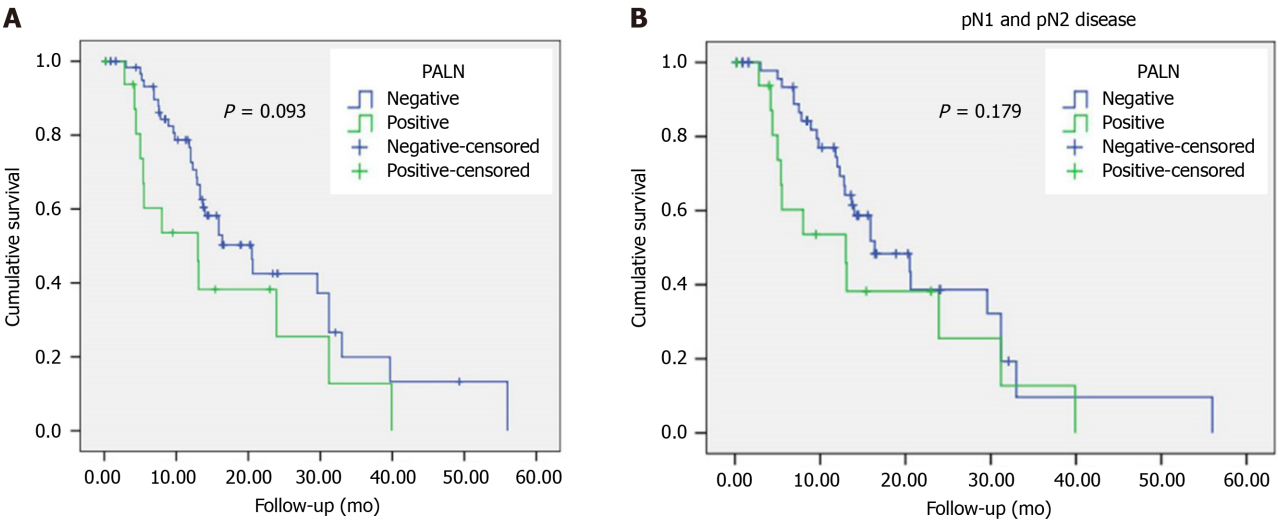
| | Numbers at risk | | | | | | |
|---|---|---|---|---|---|---|---|
| Months | 0 | 10 | 20 | 30 | 40 | 50 | 60 |
| PALN + | 12 | 8 | 4 | 2 | 1 | - | - |
| PALN - | 42 | 32 | 12 | 7 | 3 | 2 | 1 |

| | Numbers at risk | | | | | | |
|---|---|---|---|---|---|---|---|
| Months | 0 | 10 | 20 | 30 | 40 | 50 | |
| PALN + | - | - | - | - | - | - | |
| PALN - | 16 | 9 | 3 | 2 | 1 | 1 | |

| | Subgroups | Overall survival PALN+ | Overall survival PALN- | *P* value |
|---|---|---|---|---|
| A | Total cohort | 13.2 (6.531-19.869) | 20.6 (16.457-24.743) | 0.037 |
| B | Nodal disease | 13.2 (6.531-19.869) | 18.8 (14.869-22.731) | 0.161 |
| C | Chemotherapy | 23.400 (9.718-37.082) | 20.6 (9.918-31.282) | 0.192 |
| D | No chemotherapy | 5.50 (2.299-8.701) | 14.20 (7.714-20.686) | 0.015 |

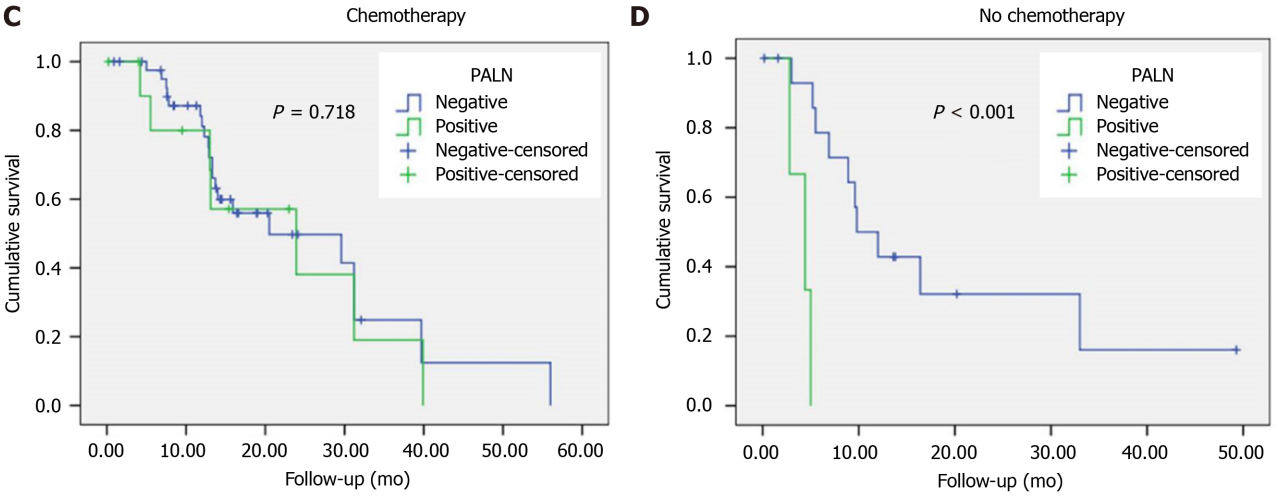
**DOI:** 10.4240/wjgs.v14.i5.429 

**Figure 1 Kaplan Meier curves comparing overall survival in patients with para-aortic lymph nodes(+) *vs* para-aortic lymph nodes(-).** A: Total cohort; B: Patients with positive nodal disease; C: Patients who received chemotherapy; D: Patients who did not receive chemo-therapy. PALN: Para-aortic lymph nodes.




| | Numbers at risk | | | | | |
|---|---|---|---|---|---|---|
| Months | 0 | 10 | 20 | 30 | 40 | 50 |
| PALN + | 16 | 7 | 4 | 2 | - | - |
| PALN - | 59 | 35 | 13 | 7 | 2 | 1 |

| | Numbers at risk | | | | | |
|---|---|---|---|---|---|---|
| Months | 0 | 10 | 20 | 30 | 40 | 50 |
| PALN + | 16 | 7 | 4 | 2 | - | - |
| PALN - | 46 | 27 | 10 | 5 | 1 | 1 |




| | Numbers at risk | | | | | |
|---|---|---|---|---|---|---|
| Months | 0 | 10 | 20 | 30 | 40 | 50 |
| PALN + | 11 | 7 | 4 | 2 | - | - |
| PALN - | 40 | 26 | 9 | 5 | 1 | 1 |

| | Numbers at risk | | | | | |
|---|---|---|---|---|---|---|
| Months | 0 | 10 | 20 | 30 | 40 | 50 |
| PALN + | - | - | - | - | - | - |
| PALN - | 15 | 6 | 3 | 2 | 1 | - |

| | Subgroup | Disease-free survival PALN+ | Disease free survival PALN- | *P* value |
|---|---|---|---|---|
| A | Total cohort | 13.0 (4.123-21.877) | 20.5 (14.135-26.865) | 0.093 |
| B | Nodal disease | 13.0 (4.123-21.877) | 16.4 (9.361-23.439) | 0.179 |
| C | Chemotherapy | 23.9 (2.782-45.018) | 20.5 (2.505-38.495) | 0.718 |
| D | No chemotherapy | 4.40 (1.839-6.961) | 9.80 (5.400-14.200) | < 0.001 |

**DOI:** 10.4240/wjgs.v14.i5.429 

**Figure 2 Kaplan Meier curves comparing disease-free survival in patients with para-aortic lymph nodes(+) *vs* para-aortic lymph nodes(-).** A: Total cohort b; B: Patients with positive nodal disease; C: Patients who received chemotherapy; D: Patients who did not receive chemotherapy. PALN: Para-aortic lymph nodes.

the value of NAT for these cases.

## ARTICLE HIGHLIGHTS

### *Research background*

Pancreatic ductal adenocarcinoma (PDAC) presents as localised disease for only a small subset of patients for whom only 20% are eligible for resection with 5-year survival of 6.8%. Nodal status is amongst the most important prognostic indicators. Para-aortic lymph nodes found in the aortocaval groove (PALN) are staged as distant metastatic (M1) disease and are found in 14%-18% of pancreatic head/uncinate PDAC at resection. Various studies have alluded to PALN metastases being associated with poor prognosis, whereas others have failed to replicate this effect and a meta-analysis has only concluded the need for intra-operative assessment of PALN. A consensus statement from the International Study Group for Pancreatic Surgery supported standard lymphadenectomy for pancreatic resections, which does not include PALN.

### *Research motivation*

Currently, whether intra-operative assessment of PALN should be undertaken or whether there is sufficient evidence that resection should be abandoned depends on surgeon or unit policy.

### *Research objectives*

The aim of this study was to determine the prognostic significance of PALN metastases on the oncological outcomes after pancreatic resections for PDAC.

### *Research methods*

This is a retrospective cohort study of data from a prospectively maintained database on consecutive patients undergoing pancreatectomies for PDAC where PALN was sampled between 2011 and 2020 in a tertiary specialist centre. The study was conducted in line with STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines. Staging of the tumours was based on the NCCN staging criteria. PALN were sampled from the infra-renal, aortacaval lymph nodes and more specifically from the level of the third part of the duodenum to the angle of the left renal vein (station 16). PALN sampling was performed at the discretion of the operating surgeon. Over the last 3 years of the study 3 surgeons sampled PALN routinely, accounting for 36% of the cases in the study. Follow-up of patients was determined from time of diagnosis until disease recurrence or death. OS was defined as the time from diagnosis to death or last follow-up and disease free survival as the time from resection to diagnosis of disease recurrence.

The cohort characteristics are presented with standard descriptive statistical analysis. One way Anova, Chi-Square and Mann-Whitney *U* tests were used as appropriate for statistical comparisons with statistical significance set at $P < 0.05$. Exact statistics were used for all tests to account for small sample size. Survival analysis was performed with the Kaplan-Meier method and log rank test was used to compare survival curves. Univariable and multivariable time to event analyses were performed using the Cox proportional hazard model to determine risk factors for median OS and disease-free survival (DFS). Variables were subjected to a univariable analysis first and those with $P < 0.2$ were introduced into a multivariable model. Hazard ratios and associated 95% confidence intervals were calculated. A two-tailed *P* value < 0.05 was considered statistically significant. All statistical analyses were performed using the software package SPSS Statistics for Windows (version 25.0; SPSS Inc., Chicago, IL, United States).

### *Research results*

81 cases had PALN sampling and 17 (21%) were positive. Pathological N stage was significantly different between PALN+ and PALN- patients ($P = 0.005$), while no difference was observed in any of the other characteristics. Preoperative imaging diagnosed PALN positivity in one case. OS and DFS were comparable between PALN+ and PALN- patients with lymph node positive disease (OS: 13.2 mo *vs* 18.8 mo, $P = 0.161$; DFS: 13 mo *vs* 16.4 mo, $P = 0.179$). No difference in OS or DFS was identified between PALN positive and negative patients when they received chemotherapy either in the neoadjuvant or in the adjuvant setting (OS: 23.4 mo *vs* 20.6 mo, $P = 0.192$; DFS: 23.9 mo *vs* 20.5 mo, $P = 0.718$). On the contrary, when patients did not receive chemotherapy, PALN disease had substantially shorter OS (5.5 mo *vs* 14.2 mo; $P = 0.015$) and DFS (4.4 mo *vs* 9.8 mo; $P < 0.001$). PALN involvement was not identified as an independent predictor for OS after multivariable analysis, while it was for DFS doubling the risk of recurrence.

### *Research conclusions*

This study suggests that PALN sampling is safe and should be routinely performed during resection of PDAC for accurate staging, even in the absence of involvement in the pre-operative imaging. PALN

involvement does not affect OS when patients complete the indicated treatment pathway (surgery and chemotherapy) and occult involvement identified intra-operatively should not be considered as a contraindication to resection.

### *Research perspectives*

Future studies should focus on improving pre-operative diagnosis and on the value of NAT for these cases.

## FOOTNOTES

**Author contributions:** Pande R, Chughtai S, Ahuja M, Brown R, Chatzizacharias NA developed this protocol/project, collected data and performed the research; Pande R, Chughtai S, Ahuja M, and Chatzizacharias NA contributed analytical tools; Pande R, Chughtai S, Ahuja M, Brown R, Chatzizacharias NA, Bartlett DC, Marudanayagam R, Mirza D, Isaac J, Sutcliffe RP, and Roberts KJ analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

**Institutional review board statement:** The study was reviewed and approved for publication by the Departmental Institutional Review Board.

**Informed consent statement:** As this was an anonymised retrospective cohort study over a period of 10 years, individual consent forms were not required based on the policy of Queen Elizabeth Hospital and the UK on ethics and research.

**Conflict-of-interest statement:** All the Authors have no conflict of interest related to the manuscript.

**Data sharing statement:** The original anonymous dataset is available upon request from the corresponding author.

**STROBE statement:** the authors have reviewed the STROBE statement-checklist of items. The written material was prepared concordant with the STROBE statement-check list of items.



**Country/Territory of origin:** United Kingdom

**ORCID number:** Rupaly Pande 0000-0003-2346-373X; Shafiq Chughtai 0000-0002-5726-6032; Manish Ahuja 0000-0001-9242-5038; Rachel Brown 0000-0001-5395-8456; David C Bartlett 0000-0001-8564-9420; Bobby V Dasari 0000-0003-2375-1141; Ravi Marudanayagam 0000-0002-0640-3535; Darius Mirza 0000-0002-7531-9089; Keith Roberts 0000-0003-1799-9829; John Isaac 0000-0002-7946-1277; Robert P Sutcliffe 000-0002-1881-7655; Nikolaos A Chatzizacharias 0000-0002-4864-189X.

**S-Editor:** Gong ZM
**L-Editor:** A
**P-Editor:** Gong ZM

## REFERENCES

1 **Hartwig W**, Werner J, Jäger D, Debus J, Büchler MW. Improvement of surgical results for pancreatic cancer. *Lancet Oncol* 2013; **14**: e476-e485 [PMID: 24079875 DOI: 10.1016/S1470-2045(13)70172-4]
2 **Allemani C**, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, Bonaventure A, Valkov M, Johnson CJ, Estève J, Ogunbiyi OJ, Azevedo E Silva G, Chen WQ, Eser S, Engholm G, Stiller CA, Monnereau A, Woods RR, Visser O, Lim GH, Aitken J, Weir HK, Coleman MP; CONCORD Working Group. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* 2018; **391**: 1023-1075 [PMID: 29395269 DOI: 10.1016/S0140-6736(17)33326-3]
3 **Slidell MB**, Chang DC, Cameron JL, Wolfgang C, Herman JM, Schulick RD, Choti MA, Pawlik TM. Impact of total lymph node count and lymph node ratio on staging and survival after pancreatectomy for pancreatic adenocarcinoma: a large, population-based analysis. *Ann Surg Oncol* 2008; **15**: 165-174 [PMID: 17896141 DOI: 10.1245/s10434-007-9587-1]
4 **Malleo G**, Maggino L, Capelli P, Gulino F, Segattini S, Scarpa A, Bassi C, Butturini G, Salvia R. Reappraisal of Nodal Staging and Study of Lymph Node Station Involvement in Pancreaticoduodenectomy with the Standard International Study Group of Pancreatic Surgery Definition of Lymphadenectomy for Cancer. *J Am Coll Surg* 2015; **221**: 367-79.e4 [PMID: 26081176 DOI: 10.1016/j.jamcollsurg.2015.02.019]

5 **Chun YS**, Pawlik TM, Vauthey JN. 8th Edition of the AJCC Cancer Staging Manual: Pancreas and Hepatobiliary Cancers. *Ann Surg Oncol* 2018; **25**: 845-847 [PMID: 28752469 DOI: 10.1245/s10434-017-6025-x]

6 **Hempel S**, Plodeck V, Mierke F, Distler M, Aust DE, Saeger HD, Weitz J, Welsch T. Para-aortic lymph node metastases in pancreatic cancer should not be considered a watershed for curative resection. *Sci Rep* 2017; **7**: 7688 [PMID: 28794500 DOI: 10.1038/s41598-017-08165-w]

7 **Kayahara M**, Nagakawa T, Ohta T, Kitagawa H, Ueno K, Tajima H, Elnemr A, Miwa K. Analysis of paraaortic lymph node involvement in pancreatic carcinoma: a significant indication for surgery? *Cancer* 1999; **85**: 583-590 [PMID: 10091731 DOI: 10.1002/(sici)1097-0142(19990201)85:3<583::aid-cncr8>3.0.co;2-j]

8 **Doi R**, Kami K, Ito D, Fujimoto K, Kawaguchi Y, Wada M, Kogire M, Hosotani R, Imamura M, Uemoto S. Prognostic implication of para-aortic lymph node metastasis in resectable pancreatic cancer. *World J Surg* 2007; **31**: 147-154 [PMID: 17171496 DOI: 10.1007/s00268-005-0730-5]

9 **Agalianos C**, Gouvas N, Papaparaskeva K, Dervenis C. Positive para-aortic lymph nodes following pancreatectomy for pancreatic cancer. Systematic review and meta-analysis of impact on short term survival and association with clinicopathologic features. *HPB (Oxford)* 2016; **18**: 633-641 [PMID: 27485057 DOI: 10.1016/j.hpb.2016.04.007]

10 **Paiella S**, Sandini M, Gianotti L, Butturini G, Salvia R, Bassi C. The prognostic impact of para-aortic lymph node metastasis in pancreatic cancer: A systematic review and meta-analysis. *Eur J Surg Oncol* 2016; **42**: 616-624 [PMID: 26916137 DOI: 10.1016/j.ejso.2016.02.003]

11 **Tol JA**, Gouma DJ, Bassi C, Dervenis C, Montorsi M, Adham M, Andrén-Sandberg A, Asbun HJ, Bockhorn M, Büchler MW, Conlon KC, Fernández-Cruz L, Fingerhut A, Friess H, Hartwig W, Izbicki JR, Lillemoe KD, Milicevic MN, Neoptolemos JP, Shrikhande SV, Vollmer CM, Yeo CJ, Charnley RM; International Study Group on Pancreatic Surgery. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). *Surgery* 2014; **156**: 591-600 [PMID: 25061003 DOI: 10.1016/j.surg.2014.06.016]

12 **von Elm E**, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453-1457 [PMID: 18064739 DOI: 10.1016/S0140-6736(07)61602-X]

13 **NCCN**. Cancer Network Clinical Practice Guidelines in Oncology: Pancreatic adenocarcinoma. Version 2.2021. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1455

14 **Roberts KJ**, Prasad P, Steele Y, Marcon F, Faulkner T, Cilliers H, Dasari B, Abradelo M, Marudanayagam R, Sutcliffe RP, Muiesan P, Mirza DF, Isaac J. A reduced time to surgery within a 'fast track' pathway for periampullary malignancy is associated with an increased rate of pancreatoduodenectomy. *HPB (Oxford)* 2017; **19**: 713-720 [PMID: 28566239 DOI: 10.1016/j.hpb.2017.04.011]

15 **NICE**. Pancreatic cancer in adults: diagnosis and ancreatic cancer in adults: diagnosis and management management NICE guideline. 2018. Available from: https://www.nice.org.uk/guidance/ng85/resources/pancreatic-cancer-in-adults-diagnosis-and-management-pdf-1837696373701

16 **Isaji S**, Murata Y, Kishiwada M. New Japanese Classification of Pancreatic Cancer. In: Neoptolemos J, Urrutia R, Abbruzzese J, Büchler M. (eds) Pancreatic Cancer. Springer, New York, 2018: 1021-1037 [DOI: 10.1007/978-1-4939-7193-0_84]

17 **Kayahara M**, Nagakawa T, Kobayashi H, Mori K, Nakano T, Kadoya N, Ohta T, Ueno K, Miyazaki I. Lymphatic flow in carcinoma of the head of the pancreas. *Cancer* 1992; **70**: 2061-2066 [PMID: 1327485 DOI: 10.1002/1097-0142(19921015)70:8<2061::aid-cncr2820700808>3.0.co;2-v]

18 **Ohta T**, Kitagawa H, Kayahara M, Kinami S, Ninomiya I, Fushida S, Fujimura T, Nishimura G, Shimizu K, Yi S, Miwa K. Sentinel lymph node navigation surgery for pancreatic head cancers. *Oncol Rep* 2003; **10**: 315-319 [PMID: 12579265]

19 **Connor S**, Bosonnet L, Ghaneh P, Alexakis N, Hartley M, Campbell F, Sutton R, Neoptolemos JP. Survival of patients with periampullary carcinoma is predicted by lymph node 8a but not by lymph node 16b1 status. *Br J Surg* 2004; **91**: 1592-1599 [PMID: 15515111 DOI: 10.1002/bjs.4761]

20 **Sho M**, Murakami Y, Motoi F, Satoi S, Matsumoto I, Kawai M, Honda G, Uemura K, Yanagimoto H, Kurata M, Fukumoto T, Akahori T, Kinoshita S, Nagai M, Nishiwada S, Unno M, Yamaue H, Nakajima Y. Postoperative prognosis of pancreatic cancer with para-aortic lymph node metastasis: a multicenter study on 822 patients. *J Gastroenterol* 2015; **50**: 694-702 [PMID: 25341657 DOI: 10.1007/s00535-014-1005-4]

21 **Yeo CJ**, Cameron JL, Lillemoe KD, Sohn TA, Campbell KA, Sauter PK, Coleman J, Abrams RA, Hruban RH. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. *Ann Surg* 2002; **236**: 355-66; discussion 366 [PMID: 12192322 DOI: 10.1097/00000658-200209000-00012]

22 **Schwarz L**, Lupinacci RM, Svrcek M, Lesurtel M, Bubenheim M, Vuarnesson H, Balladur P, Paye F. Para-aortic lymph node sampling in pancreatic head adenocarcinoma. *Br J Surg* 2014; **101**: 530-538 [PMID: 24633831 DOI: 10.1002/bjs.9444]

23 **Shimada K**, Sakamoto Y, Sano T, Kosuge T. The role of paraaortic lymph node involvement on early recurrence and survival after macroscopic curative resection with extended lymphadenectomy for pancreatic carcinoma. *J Am Coll Surg* 2006; **203**: 345-352 [PMID: 16931307 DOI: 10.1016/j.jamcollsurg.2006.05.289]

24 **Delcore R**, Rodriguez FJ, Forster J, Hermreck AS, Thomas JH. Significance of lymph node metastases in patients with pancreatic cancer undergoing curative resection. *Am J Surg* 1996; **172**: 463-8; discussion 468 [PMID: 8942545 DOI: 10.1016/S0002-9610(96)00237-1]

25 **van Geenen RC**, van Gulik TM, Offerhaus GJ, de Wit LT, Busch OR, Obertop H, Gouma DJ. Survival after pancreaticoduodenectomy for periampullary adenocarcinoma: an update. *Eur J Surg Oncol* 2001; **27**: 549-557 [PMID: 11520088 DOI: 10.1053/ejso.2001.1162]

26 **Neoptolemos JP**, Stocken DD, Dunn JA, Almond J, Beger HG, Pederzoli P, Bassi C, Dervenis C, Fernandez-Cruz L, Lacaine F, Buckels J, Deakin M, Adab FA, Sutton R, Imrie C, Ihse I, Tihanyi T, Olah A, Pedrazzoli S, Spooner D, Kerr DJ, Friess H, Büchler MW; European Study Group for Pancreatic Cancer. Influence of resection margins on survival for

patients with pancreatic cancer treated by adjuvant chemoradiation and/or chemotherapy in the ESPAC-1 randomized controlled trial. *Ann Surg* 2001; **234**: 758-768 [PMID: 11729382 DOI: 10.1097/00000658-200112000-00007]

27 **Sohn TA**, Yeo CJ, Cameron JL, Koniaris L, Kaushal S, Abrams RA, Sauter PK, Coleman J, Hruban RH, Lillemoe KD. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg* 2000; **4**: 567-579 [PMID: 11307091 DOI: 10.1016/s1091-255x(00)80105-5]

28 **Benassai G**, Mastrorilli M, Quarto G, Cappiello A, Giani U, Forestieri P, Mazzeo F. Factors influencing survival after resection for ductal adenocarcinoma of the head of the pancreas. *J Surg Oncol* 2000; **73**: 212-218 [PMID: 10797334 DOI: 10.1002/(sici)1096-9098(200004)73:4<212::aid-jso5>3.0.co;2-d]

29 **Masui T**, Kubota T, Aoki K, Nakanishi Y, Miyamoto T, Nagata J, Morino K, Fukugaki A, Takamura M, Sugimoto S, Onuma H, Tokuka A. Long-term survival after resection of pancreatic ductal adenocarcinoma with para-aortic lymph node metastasis: case report. *World J Surg Oncol* 2013; **11**: 195 [PMID: 23945441 DOI: 10.1186/1477-7819-11-195]

30 **Shrikhande SV**, Kleeff J, Reiser C, Weitz J, Hinz U, Esposito I, Schmidt J, Friess H, Büchler MW. Pancreatic resection for M1 pancreatic ductal adenocarcinoma. *Ann Surg Oncol* 2007; **14**: 118-127 [PMID: 17066229 DOI: 10.1245/s10434-006-9131-8]

31 **Neoptolemos JP**, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, Beger H, Fernandez-Cruz L, Dervenis C, Lacaine F, Falconi M, Pederzoli P, Pap A, Spooner D, Kerr DJ, Büchler MW; European Study Group for Pancreatic Cancer. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004; **350**: 1200-1210 [PMID: 15028824 DOI: 10.1056/NEJMoa032295]

32 **Versteijne E**, Vogel JA, Besselink MG, Busch ORC, Wilmink JW, Daams JG, van Eijck CHJ, Groot Koerkamp B, Rasch CRN, van Tienhoven G; Dutch Pancreatic Cancer Group. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. *Br J Surg* 2018; **105**: 946-958 [PMID: 29708592 DOI: 10.1002/bjs.10870]

33 **Sperti C**, Gruppo M, Blandamura S, Valmasoni M, Pozza G, Passuello N, Beltrame V, Moletta L. Para-aortic node involvement is not an independent predictor of survival after resection for pancreatic cancer. *World J Gastroenterol* 2017; **23**: 4399-4406 [PMID: 28706422 DOI: 10.3748/wjg.v23.i24.4399]

34 **Yamada S**, Nakao A, Fujii T, Sugimoto H, Kanazumi N, Nomoto S, Kodera Y, Takeda S. Pancreatic cancer with paraaortic lymph node metastasis: a contraindication for radical surgery? *Pancreas* 2009; **38**: e13-e17 [PMID: 18797422 DOI: 10.1097/MPA.0b013e3181889e2d]

35 **Gaedcke J**, Gunawan B, Grade M, Szöke R, Liersch T, Becker H, Ghadimi BM. The mesopancreas is the primary site for R1 resection in pancreatic head cancer: relevance for clinical trials. *Langenbecks Arch Surg* 2010; **395**: 451-458 [PMID: 19418067 DOI: 10.1007/s00423-009-0494-8]

36 **Imai H**, Doi R, Kanazawa H, Kamo N, Koizumi M, Masui T, Iwanaga Y, Kawaguchi Y, Takada Y, Isoda H, Uemoto S. Preoperative assessment of para-aortic lymph node metastasis in patients with pancreatic cancer. *Int J Clin Oncol* 2010; **15**: 294-300 [PMID: 20232101 DOI: 10.1007/s10147-010-0066-5]

37 **Asagi A**, Ohta K, Nasu J, Tanada M, Nadano S, Nishimura R, Teramoto N, Yamamoto K, Inoue T, Iguchi H. Utility of contrast-enhanced FDG-PET/CT in the clinical management of pancreatic cancer: impact on diagnosis, staging, evaluation of treatment response, and detection of recurrence. *Pancreas* 2013; **42**: 11-19 [PMID: 22699206 DOI: 10.1097/MPA.0b013e3182550d77]

38 **Kauhanen SP**, Komar G, Seppänen MP, Dean KI, Minn HR, Kajander SA, Rinta-Kiikka I, Alanen K, Borra RJ, Puolakkainen PA, Nuutila P, Ovaska JT. A prospective diagnostic accuracy study of 18F-fluorodeoxyglucose positron emission tomography/computed tomography, multidetector row computed tomography, and magnetic resonance imaging in primary diagnosis and staging of pancreatic cancer. *Ann Surg* 2009; **250**: 957-963 [PMID: 19687736 DOI: 10.1097/SLA.0b013e3181b2fafa]

39 **Maemura K**, Takao S, Shinchi H, Noma H, Mataki Y, Kurahara H, Jinnouchi S, Aikou T. Role of positron emission tomography in decisions on treatment strategies for pancreatic cancer. *J Hepatobiliary Pancreat Surg* 2006; **13**: 435-441 [PMID: 17013719 DOI: 10.1007/s00534-006-1102-8]

40 **Soriano A**, Castells A, Ayuso C, Ayuso JR, de Caralt MT, Ginès MA, Real MI, Gilabert R, Quintó L, Trilla A, Feu F, Montanyà X, Fernández-Cruz L, Navarro S. Preoperative staging and tumor resectability assessment of pancreatic cancer: prospective study comparing endoscopic ultrasonography, helical computed tomography, magnetic resonance imaging, and angiography. *Am J Gastroenterol* 2004; **99**: 492-501 [PMID: 15056091 DOI: 10.1111/j.1572-0241.2004.04087.x]

41 **Li JH**, He R, Li YM, Cao G, Ma QY, Yang WB. Endoscopic ultrasonography for tumor node staging and vascular invasion in pancreatic cancer: a meta-analysis. *Dig Surg* 2014; **31**: 297-305 [PMID: 25376486 DOI: 10.1159/000368089]

42 **Kurita A**, Kodama Y, Nakamoto Y, Isoda H, Minamiguchi S, Yoshimura K, Kuriyama K, Sawai Y, Uza N, Hatano E, Uemoto S, Togashi K, Haga H, Chiba T. Impact of EUS-FNA for preoperative para-aortic lymph node staging in patients with pancreatobiliary cancer. *Gastrointest Endosc* 2016; **84**: 467-475.e1 [PMID: 26970011 DOI: 10.1016/j.gie.2016.02.045]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 May 27; 14(5): 442-451

DOI: 10.4240/wjgs.v14.i5.442

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

# Prognostic factors for patients with mass-forming intrahepatic cholangiocarcinoma: A case series of 68 patients

Jian Feng, Bin Liang, Hang-Yu Zhang, Zhe Liu, Kai Jiang, Xiang-Qian Zhao

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): A
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Andersen JB, Denmark; Jusakul A, Thailand; Pandya S, United States

**Received:** October 11, 2021
**Peer-review started:** October 11, 2021
**First decision:** November 17, 2021
**Revised:** November 30, 2021
**Accepted:** April 20, 2022
**Article in press:** April 20, 2022
**Published online:** May 27, 2022

**Jian Feng,** Department of Hepatopancreatobiliary Surgery, Peking University Shougang Hospital, Beijing 100144, China

**Jian Feng, Bin Liang, Hang-Yu Zhang, Zhe Liu, Kai Jiang, Xiang-Qian Zhao,** Faculty of Hepato-Pancreato-Biliary Surgery, Institute of Hepatobiliary Surgery of Chinese PLA, Key Laboratory of Digital Hepatobiliary Surgery, Chinese PLA General Hospital, Beijing 100853, China

**Corresponding author:** Xiang-Qian Zhao, MD, PhD, Deputy Director, Director, Professor, Surgeon, Faculty of Hepato-Pancreato-Biliary Surgery, Institute of Hepatobiliary Surgery of Chinese PLA, Key Laboratory of Digital Hepatobiliary Surgery, Chinese PLA General Hospital, No. 28 Fuxing Road, Beijing 100853, China. zhaoxq8014@163.com

## Abstract

### *BACKGROUND*

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer in humans after hepatocellular carcinoma and a rare epithelial malignancy that results in a poor prognosis. According to the Liver Cancer Study Group of Japan classification, ICC can be divided into three types: Mass-forming (MF) type, periductal-infiltrating (PI) type, and intraductal-growth type. The MF type is the most common, accounting for 57.1-83.6% of ICCs. Nevertheless, little is known about the epidemiology and treatment of MF ICC.

### *AIM*

To examine the prognostic factors for patients with MF ICC.

### *METHODS*

We carried out a retrospective analysis of consecutive patients with MF ICC treated at the Faculty of Hepato-Pancreato-Biliary Surgery of Chinese PLA General Hospital between January 2008 and December 2018. According to the treatment received, the patients were divided into either a resection group or an exploration group.

### *RESULTS*

The pooled 1-, 3-, and 5-year survival rates in the 68 patients with MF ICC were 66.5%, 36.3%, and 9.3%, respectively. Univariate analysis revealed that surgical resection ($P < 0.001$), nodal metastasis ($P < 0.001$), tumor location ($P = 0.039$), vascular invasion ($P < 0.001$), ascites ($P < 0.001$), and differentiation ($P = 0.009$) were significantly associated with the prognosis and survival of MF ICC.

Multivariate analysis revealed that ascites (hazard ratio [HR] = 5.6, 95% confidence interval [CI]: 1.6-18.9, $P$ = 0.006) and vascular invasion (HR = 2.5, 95%CI: 1.0-6.1, $P$ = 0.045) were independent risk factors for MF ICC. The pooled 1-, 3-, and 5-year survival rates in the 19 patients of the exploration group were 5.3%, 5.3%, and 0, respectively. Among the 49 patients who underwent surgical resection, the pooled 1-, 3-, and 5-year survival rates were 93.5%, 49.7%, and 14.4%, respectively. Univariate and multivariate analyses revealed that vascular invasion (HR = 3.1, 95%CI: 1.2-8.5, $P$ = 0.024) and nodal metastasis (HR = 3.2, 95%CI: 1.4-7.6, $P$ = 0.008) were independent prognostic risk factors for surgical resection patients.

*CONCLUSION*

The prognosis of MF ICC patients is dismal, especially those with ascites or vascular invasion. Surgical resection is a key factor in improving overall survival in patients with MF ICC, and vascular invasion and lymph node metastasis affect the efficacy of surgical resection.

**Key Words:** Intrahepatic cholangiocarcinoma; Mass-forming; Treatment; Prognosis



**Core Tip:** This is a single-center, large-scale retrospective study on mass-forming intrahepatic cholangiocarcinoma (MF ICC) to examine the prognostic factors for MF ICC and improve the outcomes. The study found the patients with MF ICC with ascites and vascular invasion have a poor prognosis. Surgical resection is a key factor in improving overall survival in patients with MF ICC, and patients with vascular invasion and lymph node metastasis have poor surgical results.

**Citation:** Feng J, Liang B, Zhang HY, Liu Z, Jiang K, Zhao XQ. Prognostic factors for patients with mass-forming intrahepatic cholangiocarcinoma: A case series of 68 patients. *World J Gastrointest Surg* 2022; 14(5): 442-451
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i5/442.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i5.442

## INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) refers to a malignant tumor originating from the branching epithelial cells of the intrahepatic secondary bile duct and above, with a poor prognosis[1-2]. It has been reported that both the morbidity and mortality have gradually increased in recent years[1-4]. Surgical resection is currently the only potentially curative treatment for ICC[3-5], but the cure rates and survival of patients with ICC remain very low because of the high aggressiveness of the disease[6-7]. It has been reported that many factors influence the prognosis of surgical resection[8-11].

According to the Liver Cancer Study Group of Japan classification, ICC can be divided into three types: Mass-forming (MF) type, periductal-infiltrating (PI) type, and intraductal-growth (IG) type[11]. Among them, the MF type is the most common, accounting for 57.1-83.6% of ICCs[12-14].

Nevertheless, little is known about the epidemiology and treatment of MF ICC. Therefore, the aim of the present retrospective study was to analyze prognostic factors for patients with MF ICC.

## MATERIALS AND METHODS

### *Study design*

This was a retrospective analysis of consecutive patients with MF ICC treated at the Faculty of Hepato-Pancreato-Biliary Surgery of Chinese PLA General Hospital between January 2008 and December 2018. The study was approved by the Medical Ethics Committee of the Chinese PLA General Hospital.

### *Patients*

The inclusion criteria were: (1) ≥ 18 years of age; (2) Hospitalized patients; (3) Confirmed as MF ICC by histopathological examination; and (4) No prior history of any malignancy. The exclusion criteria were: (1) Incomplete data; (2) Metastasis; (3) Hilar cholangiocarcinoma; (4) Cystadenocarcinoma; (5) PI ICC; or (6) IG ICC. The patients were divided into either a resection group or an exploration group according to the received treatment.

### Treatments

All cases were discussed in tumor boards before any treatment. The indications for radical hepatectomy were: (1) No distant metastases preoperatively; (2) Preoperative imaging suggesting that the tumors could be completely resected, including eventual satellite lesions; (3) Child-Pugh grade A or B; and (4) Good cardiopulmonary function and no surgical or anesthetic contraindications.

The surgical principle was to achieve R0 resection. The pattern of hepatectomy was based on residual liver function, tumour size, and tumour-vessel relationship. Anatomic resection (AR) was the priority if feasible, while non-AR (NAR) was more frequently applied if the tumour was adjacent to major vascular structure. Surgical exploration was only performed in patients with extensive metastases in the liver, abdominal wall, and omentum. Lymph node dissection of the hepatoduodenal ligament was performed for patients with lymphadenectasis found by imaging or intraoperatively. Tumor and lymph node biopsies were performed in patients undergoing surgical exploration.

### Data collection

General data and results of auxiliary examinations were recorded, including carbohydrate antigen 19-9 (CA19-9), hepatitis B virus (HBV), glutamic pyruvic transaminase (ALT), glutamic oxaloacetic transaminase, alkaline phosphatase, gamma-glutamyltransferase, and total bilirubin tests.

### Follow-up

All patients were followed after surgery. Follow-up visits were performed once every 3 mo during the first year, once every 6 mo during the second and third years, and once a year later. Items checked during the follow-up visits included routine laboratory tests, tumor markers, chest roentgenogram, abdominal ultrasound, CT, and/or MRI examinations. The follow-up deadline was December 31, 2019, and the follow-up duration ranged from 1 to 82 mo, with a median duration of 13 mo.

### Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics ver. 21.0 (IBM Co, Armonk, NY, United States). Continuous data meeting a normal distribution are presented as the mean ± SD. Differences between the two groups were determined using independent sample *t* test. Continuous data not meeting a non-normal distribution are presented as the median (range). The non-parametric Mann-Whitney *U* test was used to determine the differences between the two groups. The chi-square test or the Fisher's exact test was used for categorical data. Univariate Cox proportional hazard regression model analysis was used for survival data. Variables with $P < 0.05$ in univariate analysis were included in the multivariate Cox proportional hazard regression model. Kaplan-Meier analysis was used to calculate the survival rate. Log-rank method was used for group-wise comparison. Two-sided *P* values < 0.05 were considered statistically significant.

## RESULTS

### Characteristics of the patients

Among the 68 patients, 50 were male and 18 female, ranging from 24 to 74 years with a median age of 54. There were 40 patients with tumors in the right lobe of the liver and 28 with tumors in the left lobe of the liver. The median tumor diameter was 7.0 cm (range, 2.2-14.0). Twenty-eight (41.2%) patients had elevated CA 19-9 levels, five of whom had CA 19-9 > 1000 U/mL. Sixteen and four had concomitant hepatitis B and C viral infections, respectively. Fourteen cases were accompanied with ascites. The characteristics were similar between the two groups, except that the exploration group had higher levels of ALT ($P = 0.031$), higher frequencies of ascites ($P < 0.001$), nodal metastasis ($P < 0.001$), and vascular invasion ($P < 0.001$), and the tumors were mostly located in the left lobe ($P < 0.001$) (Table 1).

### Survival

All patients were discharged successfully from the hospital. During follow-up, 48 patients died and 20 survived. Survival time ranged from 1 to 82 mo (median, 24 mo). The pooled 1-, 3-, and 5-year survival rates in the 68 patients with MF ICC were 66.5%, 36.3%, and 9.3%, respectively (Table 2). Univariate analysis revealed that surgical resection ($P < 0.001$), nodal metastasis ($P < 0.001$), tumor location ($P = 0.039$), vascular invasion ($P < 0.001$), ascites ($P < 0.001$), and differentiation ($P = 0.009$) were significantly associated with the prognosis and survival of MF ICC (Table 3). Multivariate analysis revealed that ascites (hazard ratio [HR] = 5.6, 95% confidence interval [CI]: 1.6-18.9, $P = 0.006$) and vascular invasion (HR = 2.5, 95%CI: 1.0-6.1, $P = 0.045$) were independent risk factors for MF ICC (Table 3).

### Subgroup analysis

The pooled 1-, 3-, and 5-year survival rates in the 19 patients of the exploration group were 5.3%, 5.3%, and 0, respectively. Correspondingly, the pooled 1-, 3-, and 5-year survival rates in the 49 patients of the surgical resection group were 93.5%, 49.7%, and 14.4%, respectively. The survival rates of the resection

**Table 1 Baseline characteristics of the patients**

| Variable | All (*n* = 68) | Surgery (*n* = 49) | Exploration (*n* = 19) | *P* value |
|---|---|---|---|---|
| Age (yr) | 54.3 ± 1.4 | 52.6 ± 1.7 | 58.6 ± 2.2 | 0.435 |
| Gender, Male | 50 (73.5%) | 34 (69.4%) | 16 (84.2%) | 0.924 |
| HBV infection | 16 (23.5%) | 13(26.5%) | 3 (15.8%) | 0.997 |
| HCV infection | 4 (5.9%) | 2 (4.1%) | 2 (10.5%) | 0.314 |
| Ascites | 14 (20.6%) | 1 (2.0%) | 13(68.4%) | < 0.001 |
| Tumor size(cm) | 6.9 ± 0.3 | 6.8 ± 0.4 | 7.63 ± 0.5 | 0.495 |
| ALT (IU/L)(median) | 1.8-92.1 (26) | 1.8-92.1 (24.9) | 23-76.3 (32.1) | 0.031 |
| AST (IU/L) (median) | 9.6-74.2 (29) | 9.6-74.2 (27.3) | 18.2-61.9 (31) | 0.142 |
| ALP (U/L) (median) | 13.4-280.5 (82.8) | 13.4-280.5 (81.4) | 45.3-109.9 (85.4) | 0.149 |
| GGT (U/L) (median) | 11-325.6 (42.4) | 11-325.6 (41.1) | 28.9-104.7 (45.8) | 0.512 |
| TBIL (mg/dL) (median) | 4.2-140.0 (18) | 4.2-140 (18.1) | 4.2-42.6 (17.8) | 0.707 |
| CA19-9 (U/mL) (median) | 21-2000 (34.5) | 21-1891 (36) | 22-2000 (30) | 0.104 |
| Differentiation | | | | 0.536 |
| Poor | 30 (44.1%) | 20 (40.8%) | 10 (40.052.6 | |
| Poor-moderate | 24 (35.3%) | 19 (38.8%) | 5 (26.3%) | |
| Moderate | 14 (20.6%) | 10 (20.4%) | 4 (21.1%) | |
| Nodal metastasis | 33 (48.5%) | 14 (28.6%) | 19 (100.0%) | < 0.001 |
| Tumor location | | | | < 0.001 |
| Left lobe | 28 (41.2%) | 11 (22.4%) | 17 (89.5%) | |
| Right lobe | 40 (58.8%) | 38 (77.6%) | 2 (10.5%) | |
| Vascular invasion | 31 (45.6%) | 13 (26.5%) | 19 (100.0%) | < 0.001 |

HBV: Hepatitis B virus; HCV: Hepatitis C virus; ALT: Glutamic pyruvic transaminase; AST: Glutamic oxaloacetic transaminase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyltransferase; TBIL: Total bilirubin; CA19-9: Carbohydrate antigen 19-9.

**Table 2 Overall survival of the patients with mass-forming intrahepatic cholangiocarcinoma**

| | All (*n* = 68) | Surgery (*n* = 49) | Exploration (*n* = 19) | *P* value |
|---|---|---|---|---|
| Follow-up (mo) | 1-82 | 3-82 | 1-57 | |
| Survival | | | | < 0.001 |
| 1 yr | 66.5% | 93.5% | 5.3% | |
| 3 yr | 36.3% | 49.7% | 5.3% | |
| 5 yr | 9.3% | 14.4% | 0.00% | |

group were significantly better than those of the exploration group ($P < 0.001$) (Figure 1). Table 4 presents the univariate and multivariate analyses of the factors associated with survival in the surgery group. Unlike the whole group of patients, univariate and multivariate analyses revealed that vascular invasion (HR = 3.1, 95%CI: 1.2-8.5, $P = 0.024$) and nodal metastasis (HR = 3.2, 95%CI: 1.4-7.6, $P = 0.008$) were independent prognostic risk factors for surgical resection patients.

## DISCUSSION

Little is known about the epidemiology and treatment of MF ICC. Therefore, this study aimed to examine the prognostic factors for patients with MF ICC. The results showed that the prognosis of MF ICC patients is dismal, especially those with ascites or vascular invasion. Resectable patients have a

**Table 3 Univariate and multivariate analyses of clinical and pathological factors for overall survival of 68 patients with mass-forming intrahepatic cholangiocarcinoma**

| Variable | Patients (*n*) | 1 yr (%) | 3 yr (%) | 5 yr (%) | *P* value | HR | 95%CI | *P* value |
|---|---|---|---|---|---|---|---|---|
| Age (yr) | | | | | 0.278 | | | |
| ≤ 54 | 35 | 71.8 | 39.8 | 13.5 | | | | |
| >54 | 33 | 61.4 | 32.7 | 6.1 | | | | |
| Gender | | | | | 0.292 | | | |
| Male | 50 | 62.2 | 34.2 | 9.7 | | | | |
| Female | 18 | 79.6 | 43.0 | 10.8 | | | | |
| HBV infection | | | | | 0.327 | | | |
| Yes | 16 | 74.0 | 24.7 | 0 | | | | |
| No | 52 | 64.0 | 40.0 | 13.3 | | | | |
| Ascites | | | | | < 0.001 | 5.553 | 1.628-18.941 | 0.006 |
| Present | 14 | 0 | 0 | 0 | | | | |
| Absent | 54 | 84.0 | 45.8 | 11.8 | | | | |
| Tumor size (cm) | | | | | 0.230 | | | |
| ≤ 7 | 41 | 64,3 | 49.0 | 10.1 | | | | |
| > 7 | 27 | 70.2 | 12.5 | 6.3 | | | | |
| CA 19-9 (IU/mL) | | | | | 0.881 | | | |
| ≤ 27 | 40 | 62.7 | 36.6 | 7.8 | | | | |
| > 27 | 28 | 72.3 | 34.8 | 15.5 | | | | |
| Differentiation | | | | | 0.009 | 0.769 | 0.466-1.270 | 0.305 |
| Poor | 30 | 56.4 | 21.7 | 0 | | | | |
| Poor-moderate | 24 | 78.5 | 62.4 | 12.8 | | | | |
| Moderate | 14 | 66.1 | 23.6 | 23.6 | | | | |
| Nodal metastasis | | | | | < 0.001 | 2.294 | 0.983-5.353 | 0.055 |
| Yes | 35 | 97.0 | 64.0 | 21.7 | | | | |
| No | 33 | 37.8 | 9.1 | 0 | | | | |
| Tumor location | | | | | 0.032 | 2.186 | 0.801-5.965 | 0.127 |
| Left lobe | 28 | 40.9 | 28.6 | 0 | | | | |
| Right lobe | 40 | 86.8 | 43.9 | 12.4 | | | | |
| Vascular invasion | | | | | < 0.001 | 2.501 | 1.020-6.131 | 0.045 |
| Yes | 31 | 35.5 | 9.7 | 0 | | | | |
| No | 37 | 97.1 | 66.3 | 22.2 | | | | |
| Group | | | | | < 0.001 | 1.619 | 0.351-7.469 | 0.537 |
| Resection | 49 | 93.5 | 49.7 | 14.4 | | | | |
| Exploration | 19 | 5.3 | 5.3 | 0 | | | | |

HBV: Hepatitis B virus; CA19-9: Carbohydrate antigen 19-9.

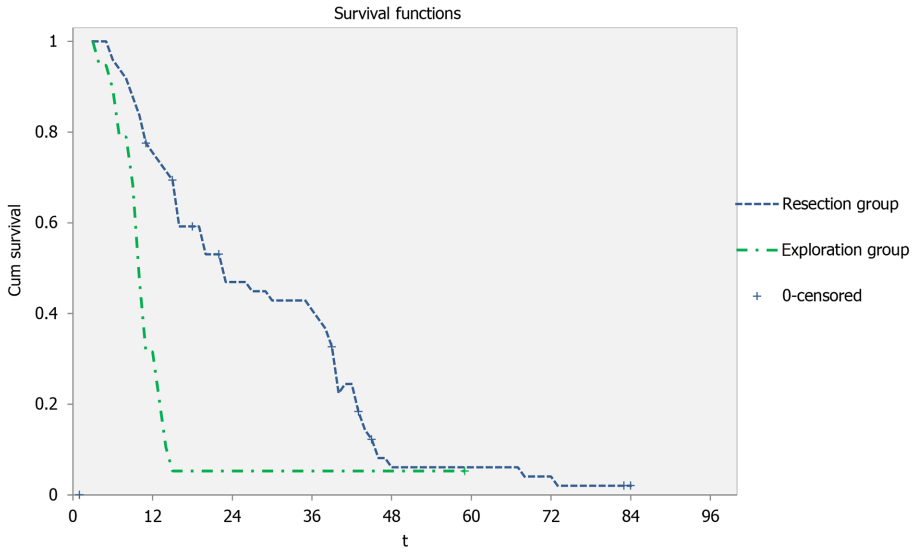
better prognosis, and vascular invasion and lymph node metastasis affected the efficacy of surgical resection. It is reported that the morbidity of ICC in males is 40-63.5%[14,16-18], and the age at diagnosis is mainly in the 6th decade of life, but ranges from 21 to 86 years[17-20]. Among the 68 cases in the current study, 50 were males, accounting for 73.5% of the patients, which was higher than that reported in the literature. The age of onset was 24-74 years with a median age of 54 years, which was consistent with literature reports but could still be a little younger than that in the literature. This discrepancy

**Table 4 Univariate and multivariate analyses of clinical and pathological factors for overall survival of patients in the surgery group**

| Variable | Patients (*n*) | 1 yr (%) | 3 yr (%) | 5 yr (%) | *P* value | HR | 95%CI | *P* value |
|---|---|---|---|---|---|---|---|---|
| Age (yr) | | | | | 0.633 | | | |
| ≤ 54 | 27 | 92.3 | 48.6 | 21.2 | | | | |
| > 54 | 22 | 95.0 | 50.7 | 9.5 | | | | |
| Gender | | | | | 0.441 | | | |
| Male | 34 | 90.9 | 48.2 | 18.1 | | | | |
| Female | 15 | 100.0 | 54.0 | 13.5 | | | | |
| HBV infection | | | | | 0.063 | | | |
| Yes | 13 | 92.3 | 30.8 | 0 | | | | |
| No | 36 | 94.0 | 57.1 | 22.5 | | | | |
| Ascites | | | | | 0.836 | | | |
| Present | 1 | 0 | 0 | 0 | | | | |
| Absent | 48 | 93.4 | 49.6 | 14.4 | | | | |
| Tumor size (cm) | | | | | 0.044 | 1.273 | 0.485-3.339 | 0.624 |
| ≤ 7 | 28 | 92.9 | 69.6 | 16.9 | | | | |
| > 7 | 21 | 94.1 | 33.6 | 8.4 | | | | |
| CA 19-9 (IU/mL) | | | | | 0.571 | | | |
| ≤ 27 | 26 | 96.0 | 53.9 | 12.9 | | | | |
| > 27 | 23 | 90.6 | 43.7 | 19.4 | | | | |
| Differentiation | | | | | 0.061 | | | |
| Poor | 20 | 89.7 | 34.5 | 0 | | | | |
| Poor-moderate | 19 | 94.7 | 73.9 | 23.9 | | | | |
| Moderate | 10 | 100.0 | 35.7 | 35.7 | | | | |
| Nodal metastasis | | | | | 0.001 | 3.221 | 1.364-7.610 | 0.008 |
| Yes | 35 | 97.0 | 64.0 | 21.7 | | | | |
| No | 14 | 85.7 | 11.9 | 0 | | | | |
| Tumor location | | | | | 0.545 | | | |
| Left lobe | 11 | 100.0 | 66.7 | 33.3 | | | | |
| Right lobe | 38 | 91.4 | 46.3 | 13.0 | | | | |
| Vascular invasion | | | | | < 0.001 | 3.148 | 1.160-8.544 | 0.024 |
| Yes | 12 | 83.3 | 16.7 | 0 | | | | |
| No | 37 | 97.1 | 66.3 | 22.2 | | | | |
| Pattern of liver resection | | | | | 0.773 | | | |
| AR resection | 23 | 96.0 | 50.6 | 11.4 | | | | |
| NAR resection | 25 | 95.5 | 51.7 | 9.7 | | | | |
| Resection margin(cm) | | | | | 0.361 | | | |
| ≤ 1 | 21 | 95.2 | 40.3 | 16.1 | | | | |
| > 1 | 27 | 96.0 | 57.3 | 14.6 | | | | |

CA19-9: Carbohydrate antigen 19-9.

could be due to a number of reasons including genetics, environment, and methods of detection.




**DOI:** 10.4240/wjgs.v14.i5.442 

**Figure 1 The resection group (blue line) *vs* the exploration group (green dashed line) (*P* < 0.001).**

Many previous studies showed that HBV and hepatitis C virus (HCV) infections were associated with the occurrence of ICC. It has been reported that the rate of HBV infection ranges from 3.9% to 28.8% in ICC patients, and the rate of HCV infection ranges from 0.6% to 16.5%[20-22]. In the present study, the infection rates of HBV and HCV were 23.5% and 5.9%, respectively, which were similar to those reported in the literature. Currently, the relationship between HBV and ICC prognosis is still controversial. Pan *et al*[23] reported that the 1- and 3-year overall survival rates of patients with HBV infection was higher than that of patients without (67.6% and 47.2% *vs* 43.8% and 18.4%, respectively). Ahn *et al*[24] reported that HBV infection itself was not regarded as an independent prognostic factor. Tao *et al*[25] described that 1-, 3-, and 5-year cumulative survival rates of HBsAg-positive ICC patients are significantly lower than those of HBV-negative ICC patients. The present study found that there was no significant difference in survival between patients with HBV infection and those without. Nevertheless, among the 68 patients, the 5-year survival was 0 in patients with HBV infection, while it was 13.3% in those without HBV infection. In the surgery group, the 5-year survival was 0 in patients with HBV infection, while it was 22.5% in patients without HBV infection. These rates raise the question of the impact of HBV infection on the survival of ICC patients and further study is needed to investigate this point.

Surgical resection is the most important factor for long-term survival of ICC patients. In this study, the 5-year survival rate was 14.4% for patients in the resection group, while it was 0% for patients in the exploration group. The surgical approach required tumor-free surgical margins, *i.e.*, R0 resection. The literature has reported that the R0 resection rate of ICC ranges from 24.1% to 92.8%[10,26], but the relationship between margins and survival is still controversial in patients with ICC. Bagante *et al*[13] deemed that patients with positive margins had a poor prognosis. Tang *et al*[16] reported that the prognosis in patients with margins > 1 cm was better than that of patients with margins ≤ 1 cm, while Bartsch *et al*[10] showed that the margin width was not related to prognosis. Other studies reported that no significant difference in survival was observed between patients with R0 resection and patients with R1 resection[7,27,28]. In the present study, the resection rate was 72.1% (49/68), and all resections were R0. Whether the margins were > 1 cm or not was not related to survival. Furthermore, there was no significant difference in 1-, 3-, and 5-year survival rates between AR and NAR resection (96.0%, 50.6%, and 11.4% *vs* 95.5%, 51.7%, and 9.7%, respectively). These results suggest that the objective is to achieve R0 no mater using AR or NAR resection. A number of studies have indicated that patients with positive lymph nodes have a poor prognosis[11,13,17,18]. Bagante *et al*[13] showed that the 5-year survival rate in patients with positive lymph nodes was 9.4%, while in patients with negative lymph nodes, it was 45.5%. In the present study, the 5-year survival rate in patients of the resection group and with positive lymph nodes was 0%, compared with 21.7%, in patients with negative lymph nodes. Lymph node metastasis could be an important prognostic factor for ICC. Nevertheless, there is still no definite conclusion as to whether resection of positive lymph nodes can extend survival or not[17,18,29,30].

Previous studies showed that vascular invasion was an important factor affecting the prognosis of ICC[27,31,32] . Our results revealed that the 3- and 5-year survival rates in the resection group with vascular invasion were 16.7% and 0%, respectively, compared with 66.3% and 22.2%, respectively, in patients without. The survival rate in patients without vascular invasion was higher than that of patients with vascular invasion. The multivariate analysis revealed that vascular invasion was an independent prognostic factor in patients with ICC.

In the present study, there was no significant difference in survival for left and right lobe tumors in the resection group. However, in the whole group of 68 patients, the resection rate of tumor in the right lobe was 95.0% (38/40), and that in the left lobe was 39.3% (11/28), indicating that the resection rate of tumors in the left lobe was low. Survival analysis also suggested that the survival rate was low for patients with tumors in the left lobe, which may be because tumors in the left lobe are more prone to metastasis through the ligament of the liver and stomach. In addition, we also noted that tumors in the left lobe could metastasize from the round ligament of the liver and sickle ligament of the liver to the abdominal wall. Nevertheless, further study is necessary for confirmation.

Data revealed that 25%-40% of the tumors with metastasis could not be dissected by surgical exploration for ICC patients whose tumors are considered to be removable before surgery. Therefore, laparoscopic examination should be performed before operation for patients with multicentric lesions, high CA19-9, suspected vascular infiltration, or peritoneal carcinomatosis[4]. In the present study, 19 patients (27.9%) underwent surgical exploration. Among the 40 cases with tumors in the right lobe of the liver, 5% ($n$ = 2) underwent surgical exploration, while 60.7% ($n$ = 17) underwent surgical exploration among the 28 patients with tumors in the left lobe of the liver, suggesting that the exploration rate was high for tumors in the left lobe of the liver. Among the 14 cases with preoperative ascites, there were 13 cases with abdominal metastasis and peritoneal metastasis. Therefore, we believe that routine laparoscopic exploration should be performed before operation for patients with tumors in the left lobe of the liver or with ascites in order to avoid meaningless laparotomy.

The present study is not without limitations. This was a retrospective, single-center study with a small sample size. In addition, it was limited to Chinese patients. Thus, the results should be validated using multicenter studies.

## CONCLUSION

The prognosis of MF ICC patients is dismal, especially those with ascites or vascular invasion. Surgical resection is a key factor in improving overall survival in patients with MF ICC, and vascular invasion and lymph node metastasis affect the efficacy of surgical resection.

## ARTICLE HIGHLIGHTS

### *Research background*

The mass-forming (MF) type is the most common intrahepatic cholangiocarcinoma (ICC), accounting for 57.1%-83.6% of ICCs. Nevertheless, little is known about the epidemiology and treatment of MF ICC.

### *Research motivation*

To improve the outcomes of ICC.

### *Research objectives*

To examine the prognostic factors for patients with MF ICC.

### *Research methods*

We carried out a retrospective analysis of consecutive patients with MF ICC. The patients were divided into either a resection group or an exploration group according to the treatment received.

### *Research results*

The pooled 1-, 3-, and 5-year survival rates in the 68 patients with MF ICC were 66.5%, 36.3%, and 9.3%, respectively. Univariate analysis revealed that surgical resection ($P$ < 0.001), nodal metastasis ($P$ < 0.001), tumor location ($P$ = 0.039), vascular invasion ($P$ < 0.001), ascites ($P$ < 0.001), and differentiation ($P$ = 0.009) were significantly associated with the prognosis and survival of MF ICC. Multivariate analysis revealed that ascites (hazard ratio [HR] = 5.6, 95% confidence interval [CI]: 1.6-18.9, $P$ = 0.006) and vascular invasion (HR = 2.5, 95%CI: 1.0-6.1, $P$ = 0.045) were independent risk factors for MF ICC. The pooled 1-, 3-, and 5-year survival rates in the 19 patients of the exploration group were 5.3%, 5.3%, and 0, respectively. Among the 49 patients who underwent surgical resection, the pooled 1-, 3-, and 5-year survival rates were 93.5%, 49.7%, and 14.4%, respectively. Univariate and multivariate analyses revealed that vascular invasion (HR = 3.1, 95%CI: 1.2-8.5, $P$ = 0.024) and nodal metastasis (HR = 3.2, 95%CI: 1.4-7.6, $P$ = 0.008) were independent prognostic risk factors for surgical resection patients.

### *Research conclusions*

The prognosis of MF ICC patients is dismal, especially those with ascites or vascular invasion. Surgical resection is a key factor in improving overall survival in patients with MF ICC, and vascular invasion

and lymph node metastasis affect the efficacy of surgical resection.

### *Research perspectives*

Surgical resection is a key factor in improving overall survival in patients with MF ICC, and vascular invasion and lymph node metastasis affect the efficacy of surgical resection.

## FOOTNOTES

**Author contributions:** Zhao XQ is the guarantor of integrity of the entire study, carried out the study design, defined the intellectual content, participated in the literature search, and reviewed the manuscript; Feng J and Liang B performed the research, wrote the first draft, and analyzed the data; Feng J and Liang B should be regarded as co-first authors; Zhang HY carried out the clinical studies and acquired the data; Liu Z and Jiang K carried out the clinical studies; all authors read and approved the final manuscript.

**Institutional review board statement:** The study was approved by the Medical Ethics Committee of the Chinese PLA General Hospital.

**Conflict-of-interest statement:** All authors have no competing interests to disclose.

**Data sharing statement:** Additional date are available.



**Country/Territory of origin:** China

**ORCID number:** Jian Feng 0000-0001-7804-5223; Bin Liang 0000-0003-2378-9924; Hang-Yu Zhang 0000-0001-9040-4073; Zhe Liu 0000-0003-2114-5201; Kai Jiang 0000-0002-5411-2724; Xiang-Qian Zhao 0000-0001-6793-1641.

**S-Editor:** Wang LL
**L-Editor:** Wang TQ
**P-Editor:** Wang LL

## REFERENCES

1 **Bridgewater J**, Galle PR, Khan SA, Llovet JM, Park JW, Patel T, Pawlik TM, Gores GJ. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol* 2014; **60**: 1268-1289 [PMID: 24681130 DOI: 10.1016/j.jhep.2014.01.021]
2 **Moeini A**, Sia D, Bardeesy N, Mazzaferro V, Llovet JM. Molecular Pathogenesis and Targeted Therapies for Intrahepatic Cholangiocarcinoma. *Clin Cancer Res* 2016; **22**: 291-300 [PMID: 26405193 DOI: 10.1158/1078-0432.CCR-14-3296]
3 **Ransome E**, Tong L, Espinosa J, Chou J, Somnay V, Munene G. Trends in surgery and disparities in receipt of surgery for intrahepatic cholangiocarcinoma in the US: 2005-2014. *J Gastrointest Oncol* 2019; **10**: 339-347 [DOI: 10.21037/jgo.2018.12.07]
4 **Weber SM**, Ribero D, O'Reilly EM, Kokudo N, Miyazaki M, Pawlik TM. Intrahepatic cholangiocarcinoma: expert consensus statement. *HPB (Oxford)* 2015; **17**: 669-680 [PMID: 26172134 DOI: 10.1111/hpb.12441]
5 **Cillo U**, Fondevila C, Donadon M, Gringeri E, Mocchegiani F, Schlitt HJ, Ijzermans JNM, Vivarelli M, Zieniewicz K, Olde Damink SWM, Groot Koerkamp B. Surgery for cholangiocarcinoma. *Liver Int* 2019; **39** Suppl 1: 143-155 [PMID: 30843343 DOI: 10.1111/Liv.14089]
6 **Bartsch F**, Hahn F, Müller L, Baumgart J, Hoppe-Lotichius M, Kloeckner R, Lang H. Relevance of suspicious lymph nodes in preoperative imaging for resectability, recurrence and survival of intrahepatic cholangiocarcinoma. *BMC Surg* 2020; **20**: 75 [PMID: 32295646 DOI: 10.1186/s12893-020-00730-x]
7 **Luvira V**, Eurboonyanun Ch, Bhudhisawasdi V, Pugkhem A, Pairojkul Ch, Luvira V, Sathitkarnmanee E, Somsap K, Kamsa-ard S. Patterns of Recurrence after Resection of Mass-Forming Type Intrahepatic Cholangiocarcinomas. *Asian Pac J Cancer Prev* 2016; **17**: 4735-4739 [PMID: 27893205 DOI: 10.22034/apjcp.2016.17.10.4735]
8 **Buettner S**, Galjart B, van Vugt JLA, Bagante F, Alexandrescu S, Marques HP, Lamelas J. Performance of prognostic scores and staging systems in predicting long-term survival outcomes after surgery for intrahepatic cholangiocarcinoma. *J Surg Oncol* 2017; **116**: 1085-1095 [DOI: 10.1002/jso.24759]
9 **Conci S**, Ruzzenente A, Viganò L, Ercolani G, Fontana A, Bagante F, Bertuzzo F, Dore A, Pinna AD, Torzilli G, Iacono C, Guglielmi A. Patterns of Distribution of Hepatic Nodules (Single, Satellites or Multifocal) in Intrahepatic Cholangiocarcinoma: Prognostic Impact After Surgery. *Ann Surg Oncol* 2018; **25**: 3719-3727 [PMID: 30088126 DOI: 10.1245/s10434-018-6669-1]
10 **Bartsch F**, Baumgart J, Hoppe-Lotichius M, Straub BK, Heinrich S, Lang H. Intrahepatic cholangiocarcinoma - influence

of resection margin and tumor distance to the liver capsule on survival. *BMC Surg* 2020; **20**: 61 [PMID: 32252724 DOI: 10.1186/s12893-020-00718-7]

11 **Ma CH**, Hwang DW, Song KB, Kim SC, Shin SH, Lee JH. Prognostic factors predicting survival rate over 10 years of patients with intrahepatic cholangiocarcinoma after hepatic resection. *Ann Surg Treat Res* 2020; **98**: 116-123 [PMID: 32158731 DOI: 10.4174/astr.2020.98.3.116]

12 **Uno M**, Shimada K, Yamamoto Y, Nara S, Esaki M, Sakamoto Y, Kosuge T, Ojima H. Periductal infiltrating type of intrahepatic cholangiocarcinoma: a rare macroscopic type without any apparent mass. *Surg Today* 2012; **42**: 1189-1194 [PMID: 22350300 DOI: 10.1007/s00595-012-0145-5]

13 **Bagante F**, Weiss M, Alexandrescu S, Marques HP, Aldrighetti L, Maithel SK, Pulitano C, Bauer TW, Shen F, Poultsides GA, Soubrane O, Martel G, Koerkamp BG, Guglielmi A, Itaru E, Pawlik TM. Long-term outcomes of patients with intraductal growth sub-type of intrahepatic cholangiocarcinoma. *HPB (Oxford)* 2018; **20**: 1189-1197 [PMID: 29958811 DOI: 10.1016/j.hpb.2018.05.017]

14 **Dover LL**, Jacob R, Wang TN, Richardson JH, Redden DT, Li P, DuBay DA. Improved Postoperative Survival for Intraductal-Growth Subtype of Intrahepatic Cholangiocarcinoma. *Am Surg* 2016; **82**: 1133-1139 [PMID: 28206944]

15 **Ohira M**, Yoshizumi T, Yugawa K, Kosai-Fujimoto Y, Inokuchi S, Motomura T, Mano Y, Toshima T, Itoh S, Harada N, Ikegami T, Soejima Y, Taketomi A, Mori M. Association of inflammatory biomarkers with long-term outcomes after curative surgery for mass-forming intrahepatic cholangiocarcinoma. *Surg Today* 2020; **50**: 379-388 [PMID: 31667580 DOI: 10.1007/s00595-019-01905-7]

16 **Tang H**, Lu W, Li B, Meng X, Dong J. Influence of surgical margins on overall survival after resection of intrahepatic cholangiocarcinoma: A meta-analysis. *Medicine (Baltimore)* 2016; **95**: e4621 [PMID: 27583880 DOI: 10.1097/MD.0000000000004621]

17 **Navarro JG**, Lee JH, Kang I, Rho SY, Choi GH, Han DH. Prognostic significance of and risk prediction model for lymph node metastasis in resectable intrahepatic cholangiocarcinoma: do all require lymph node dissection? *HPB (Oxford)* 2020; **8**: S1365 [DOI: 10.1016/j.hpb.2020.01.009]

18 **Asaoka T**, Kobayashi S, Hanaki T, Iwagami Y, Tomimaru Y, Akita H, et al Clinical significance of preoperative CA199 and lymph node metastasis in intrahepatic cholangiocarcinoma. *Surg Today* 2020 [DOI: 10.1007/s00595-020-01992-x]

19 **Li Y**, Wang H, Li D, Hu J, Zhou D, Li Q, Jiang X, Zhou H, Hu H. Occult hepatitis B virus infection in Chinese cryptogenic intrahepatic cholangiocarcinoma patient population. *J Clin Gastroenterol* 2014; **48**: 878-882 [PMID: 24356457 DOI: 10.1097/MCG.0000000000000058]

20 **De Rose AM**, Cucchetti A, Clemente G, Ardito F, Giovannini I, Ercolani G, Giuliante F, Pinna AD, Nuzzo G. Prognostic significance of tumor doubling time in mass-forming type cholangiocarcinoma. *J Gastrointest Surg* 2013; **17**: 739-747 [PMID: 23292461 DOI: 10.1007/s11605-012-2129-6]

21 **Reddy SK**, Hyder O, Marsh JW, Sotiropoulos GC, Paul A, Alexandrescu S, Marques H, Pulitano C, Barroso E, Aldrighetti L, Geller DA, Sempoux C, Herlea V, Popescu I, Anders R, Rubbia-Brandt L, Gigot JF, Mentha G, Pawlik TM. Prevalence of nonalcoholic steatohepatitis among patients with resectable intrahepatic cholangiocarcinoma. *J Gastrointest Surg* 2013; **17**: 748-755 [PMID: 23355033 DOI: 10.1007/s11605-013-2149-x]

22 **Wang JJ**, Li H, Li JX, Xu L, Wu H, Zeng Y. Preoperative gamma-glutamyltransferase to lymphocyte ratio predicts long-term outcomes in intrahepatic cholangiocarcinoma patients following hepatic resection. *World J Gastroenterol* 2020; **26**: 1501-1512 [PMID: 32308350 DOI: 10.3748/wjg.v26.i13.1501]

23 **Pan QX**, Su ZJ, Zhang JH, Wang CR, Ke SY. Glasgow Prognostic Score predicts prognosis of intrahepatic cholangiocarcinoma. *Mol Clin Oncol* 2017; **6**: 566-574 [PMID: 28413670 DOI: 10.3892/mco.2017.1166]

24 **Ahn CS**, Hwang S, Lee YJ, Kim KH, Moon DB, Ha TY, Song GW, Lee SG. Prognostic impact of hepatitis B virus infection in patients with intrahepatic cholangiocarcinoma. *ANZ J Surg* 2018; **88**: 212-217 [PMID: 27598539 DOI: 10.1111/ans.13753]

25 **Tao LY**, He XD, Xiu DR. Hepatitis B virus is associated with the clinical features and survival rate of patients with intrahepatic cholangiocarcinoma. *Clin Res Hepatol Gastroenterol* 2016; **40**: 682-687 [PMID: 27282820 DOI: 10.1016/j.clinre.2016.04.001]

26 **Li MX**, Bi XY, Li ZY, Huang Z, Han Y, Zhao JJ, Zhao H, Cai JQ. Impaction of surgical margin status on the survival outcome after surgical resection of intrahepatic cholangiocarcinoma: a systematic review and meta-analysis. *J Surg Res* 2016; **203**: 163-173 [PMID: 27338547 DOI: 10.1016/j.jss.2016.02.012]

27 **Kinoshita M**, Kanazawa A, Takemura S, Tanaka S, Kodai S, Shinkawa H, Shimizu S, Murata A, Nishio K, Hamano G, Ito T, Tsukamoto T, Kubo S. Indications for laparoscopic liver resection of mass-forming intrahepatic cholangiocarcinoma. *Asian J Endosc Surg* 2020; **13**: 46-58 [PMID: 30924307 DOI: 10.1111/ases.12703]

28 **Bektas H**, Yeyrek C, Kleine M, Vondran FW, Timrott K, Schweitzer N, Vogel A, Jäger MD, Schrem H, Klempnauer J, Kousoulas L. Surgical treatment for intrahepatic cholangiocarcinoma in Europe: a single center experience. *J Hepatobiliary Pancreat Sci* 2015; **22**: 131-137 [PMID: 25159731 DOI: 10.1002/jhbp.158]

29 **Morine Y**, Shimada M. The value of systematic lymph node dissection for intrahepatic cholangiocarcinoma from the viewpoint of liver lymphatics. *J Gastroenterol* 2015; **50**: 913-927 [PMID: 25833009 DOI: 10.1007/s00535-015-1071-2]

30 **Zhou R**, Lu D, Li W, Tan W, Zhu S, Chen X, Min J, Shang C, Chen Y. Is lymph node dissection necessary for resectable intrahepatic cholangiocarcinoma? *HPB (Oxford)* 2019; **21**: 784-792 [PMID: 30878490 DOI: 10.1016/j.hpb.2018.12.011]

31 **Chan KM**, Tsai CY, Yeh CN, Yeh TS, Lee WC, Jan YY, Chen MF. Characterization of intrahepatic cholangiocarcinoma after curative resection: outcome, prognostic factor, and recurrence. *BMC Gastroenterol* 2018; **18**: 180 [PMID: 30514231 DOI: 10.1186/s12876-018-0912-x]

32 **Lin ZY**, Liang ZX, Zhuang PL, Chen JW, Cao Y, Yan LX, Yun JP, Xie D, Cai MY. Intrahepatic cholangiocarcinoma prognostic determination using pre-operative serum C-reactive protein levels. *BMC Cancer* 2016; **16**: 792 [PMID: 27733196 DOI: 10.1186/s12885-016-2827-7]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 May 27; 14(5): 452-469

DOI: 10.4240/wjgs.v14.i5.452

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

# Short and long-term outcomes between laparoscopic and open total gastrectomy for advanced gastric cancer after neoadjuvant chemotherapy

Hao Cui, Ke-Cheng Zhang, Bo Cao, Huan Deng, Gui-Bin Liu, Li-Qiang Song, Rui-Yang Zhao, Yi Liu, Lin Chen, Bo Wei

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Nakano H, Japan; Otowa Y, Japan; Quartuccio N, Italy

**Received:** October 24, 2021
**Peer-review started:** October 24, 2021
**First decision:** December 27, 2021
**Revised:** January 17, 2022
**Accepted:** April 22, 2022
**Article in press:** April 22, 2022
**Published online:** May 27, 2022

**Hao Cui, Gui-Bin Liu, Li-Qiang Song,** School of Medicine, Nankai University, Tianjin 300071, China

**Ke-Cheng Zhang, Bo Cao, Huan Deng, Rui-Yang Zhao, Yi Liu, Lin Chen, Bo Wei,** Department of General Surgery and Institute of General Surgery, the First Medical Center, Chinese PLA General Hospital, Beijing 100853, China

**Bo Cao, Huan Deng, Rui-Yang Zhao,** Medical School, Chinese PLA General Hospital, Beijing 100853, China

**Corresponding author:** Bo Wei, MD, PhD, Chief Doctor, Professor, Staff Physician, Department of General Surgery and Institute of General Surgery, the First Medical Center, Chinese PLA General Hospital, No. 28 Fuxing Road, Haidian District, Beijing 100853, China.
18431143691@163.com

## Abstract

### *BACKGROUND*

Neoadjuvant chemotherapy (NACT) combined with surgery is regarded as an effective treatment for advanced gastric cancer (AGC). Laparoscopic surgery represents the mainstream of minimally invasive surgery. Currently, surgeons focus more on surgical safety and oncological outcomes of laparoscopic gastrectomy after NACT. Thus, we sought to evaluate short- and long-term outcomes between laparoscopic total gastrectomy (LTG) and open total gastrectomy (OTG) after NACT.

### *AIM*

To compare the short and long-term outcomes between LTG and OTG for AGC after NACT.

### *METHODS*

We retrospectively collected the clinicopathological data of 136 patients who accepted gastrectomy after NACT from June 2012 to June 2019, including 61 patients who underwent LTG and 75 who underwent OTG. Clinicopathological characteristics between the LTG and OTG groups showed no significant difference. SPSS 26.0, R software, and GraphPad PRISM 8.0 were used to perform

statistical analyses.

***RESULTS***

Of the 136 patients included, eight acquired pathological complete response, and the objective response rate was 47.8% (65/136). The LTG group had longer operation time ($P$ = 0.015), less blood loss ($P$ = 0.003), shorter days to first flatus ($P$ < 0.001), and shorter postoperative hospitalization days ($P$ < 0.001). LTG spent more surgical cost than OTG ($P$ < 0.001), while total hospitalized cost of LTG was less than OTG ($P$ < 0.001). 21 (28.0%) patients in the OTG group and 14 (23.0%) in the LTG group had 30-d postoperative complications, but there was no significant difference between the two groups ($P$ = 0.503). The 3-year overall survival (OS) rate was 60.6% and 64.6% in the LTG and OTG groups, respectively [hazard ratio (HR) = 0.859, 95% confidence interval (CI): 0.522-1.412, $P$ = 0.546], while the 3-year disease-free survival (DFS) rate was 54.5% and 51.8% in the LTG and OTG group, respectively (HR = 0.947, 95%CI: 0.582-1.539, $P$ = 0.823). Multivariate cox analysis showed that body mass index and pTNM stage were independent risk factors for OS while vascular invasion and pTNM stage were independent risk factors for DFS ($P$ < 0.05).

***CONCLUSION***

After NACT, LTG shows comparable 30-d postoperative morbidity as well as 3-year OS and DFS rate to OTG. We recommend that experienced surgeons select LTG other than OTG for proper AGC patients after NACT.

**Key Words:** Neoadjuvant chemotherapy; Gastric cancer; Laparoscope; Total gastrectomy; Morbidity; Survival



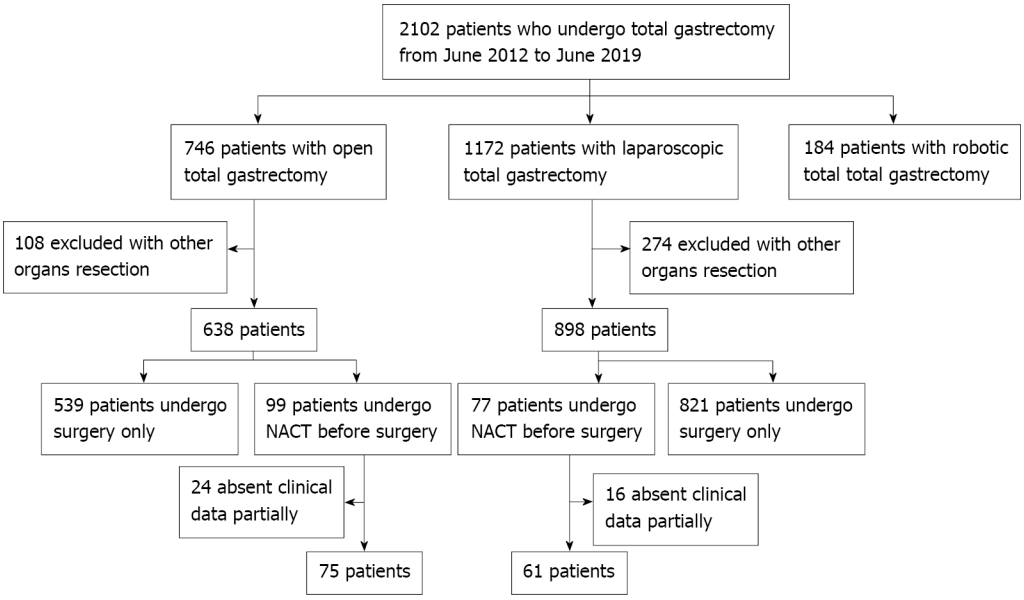
**Core Tip:** Neoadjuvant chemotherapy (NACT), defined as chemotherapy before surgery, is currently a hot research topic of perioperative therapy for advanced gastric cancer. In this study, we focused on the short- and long-term outcomes between laparoscopic total gastrectomy (LTG) and open total gastrectomy (OTG) after NACT. We found that the LTG group had longer operation time, less blood loss, shorter time to first flatus, and shorter postoperative hospitalization days. LTG showed comparable 30-d postoperative morbidity as well as 3-year overall survival and disease-free survival rate to OTG. Based on our results, we recommend that experienced surgeons select LTG for proper patients after NACT.

**Citation:** Cui H, Zhang KC, Cao B, Deng H, Liu GB, Song LQ, Zhao RY, Liu Y, Chen L, Wei B. Short and long-term outcomes between laparoscopic and open total gastrectomy for advanced gastric cancer after neoadjuvant chemotherapy. *World J Gastrointest Surg* 2022; 14(5): 452-469
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i5/452.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i5.452

## INTRODUCTION

Gastric cancer (GC) is the fifth most prevalent malignant tumor and its tumor-related death ranks fourth according to the updated database of GLOBOCAN in 2020[1]. In China, it is the second most lethal tumor[2]. Perioperative integrated therapy is gradually taken into account in the treatment of GC. Neoadjuvant chemotherapy (NACT), as a crucial part of integrated therapy, is currently a hot research topic. Unlike postoperative chemotherapy, NACT puts chemotherapy prior to surgery, which brings advantages as follows: (1) More possibility of reducing tumor stages and increasing R0 resection rate[3]; (2) Better tolerance to chemotherapy before surgery; (3) Identical surgical safety compared with surgery-first therapy[4,5]; (4) High complete rate of total chemotherapy; and (5) Potential survival benefit relative to other interventional treatments. After MAGIC study[6] first proved the surgical safety and long-term survival benefit of perioperative chemotherapy, more prospective randomized clinical trials like FLOT4[7], RESOLVE[8], and RESONANCE[9] sprung up and acquired the initial conclusion that NACT showed superiority in terms of pathological complete response (pCR) rate and long-term survival. This contributed to its further clinical utilization.

Laparoscopy is a representative of minimally invasive surgery techniques in the 21st century. Since Kitano *et al*[10] reported the first laparoscopic gastrectomy in 1994, laparoscopy has emerged as a standard surgical approach especially for distal gastrectomy proved by several high-quality trials[11,12].




**DOI:** 10.4240/wjgs.v14.i5.452 

**Figure 1 Flow diagram of patient enrollment.** NACT: Neoadjuvant chemotherapy.

Laparoscopic total gastrectomy (LTG) was carried out relatively late due to its complex surgical procedure and anastomotic technical difficulty. Although LTG has been proved safer than open total gastrectomy (OTG) for clinical stage I GC by CLASS-02 study[13], the option of LTG is still conservative in the treatment of advanced GC (AGC). At present, a multitude of retrospective articles conducted in experienced medical centers demonstrated comparable short- and long-term outcomes between LTG and OTG[14,15], but prospective studies have not acquired final results.

Currently, surgical safety and oncological outcomes after NACT have gradually attracted surgeons' attention. Based on standardization of NACT for AGC in Western countries, which was advised by European guidelines, van der Wielen *et al*[16] conducted STOMACH trial as the first multi-institutional RCT study which demonstrated the comparable complication rate and non-inferiority of 1-year overall survival (OS) and disease-free survival (DFS) between LTG and OTG after NACT in Western countries [16]. However, it is still unclear whether LTG has superior short and long-term outcomes compared with OTG or not for AGC patients who accepted NACT in China. As minimally invasive surgery is gaining popularization and great importance is attached to NACT in China, more studies should be conducted for the proper application of LTG after NACT.

## MATERIALS AND METHODS

### Patients

This is a retrospective study conducted at the General Surgery Department of the Chinese PLA General Hospital. Clinical and pathological data of patients with AGC who accepted NACT before LTG or OTG plus D2 lymphadenectomy from June 2012 to June 2019 were collected. The eligible criteria were: (1) Clinical tumor stage II-III (including Bulky N or large type 3-4) proved by endoscopic ultrasonography, abdominal computed tomography (CT), and positron emission tomography-CT (PET-CT); (2) Histologically proved gastric adenocarcinoma by preoperative gastroscopy and biopsy; (3) Ages ranging from 18 to 75 years; (4) ASA score ≤ III; (5) Integrated clinical and pathological data; and (6) No conversion to OTG in the LTG group. All patients accepted LTG or OTG followed by NACT (chemotherapeutic regimen: SOX, XELOX, SF, or DCF) according to the consultation of a multi-disciplinary team.

### Surgical approach

Surgical procedures were conducted according to Japanese Gastric Cancer Treatment Guidelines[17]. D2 lymphadenectomy was performed, including resection of No. 1, 2, 3a, 4sa, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, 11d, and 12a. Dissection of No. 10 lymph nodes was performed when a tumor was located in the upper stomach invading the greater curvature. Roux-en-Y reconstruction was achieved after tumor dissection. One month after surgery, residual adjuvant chemotherapy was carried out under the guidance of surgeons with rich experience.

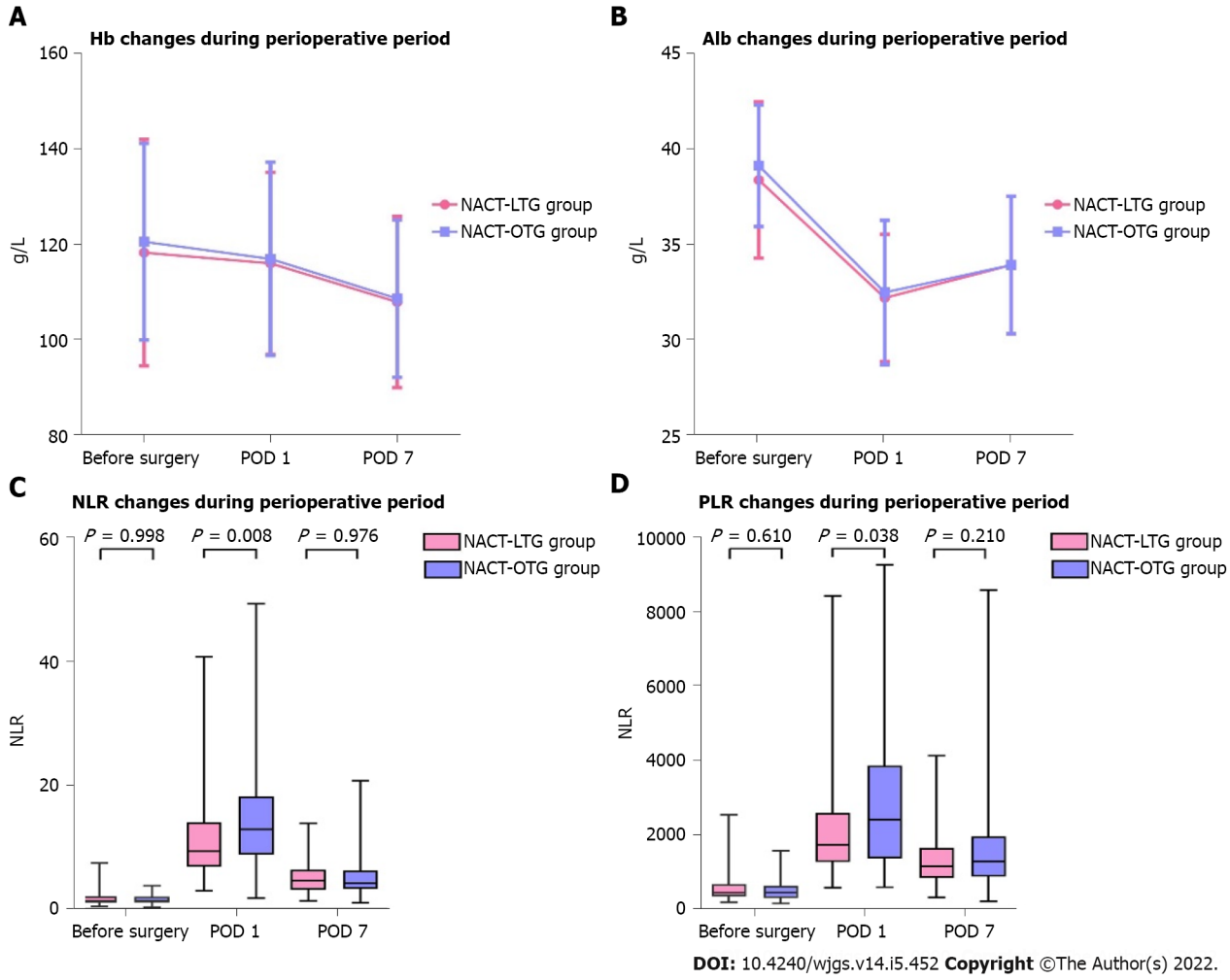



**Figure 2 Comparisons of laboratorial indexes during the perioperative period.** A: Hemoglobin changes between laparoscopic total gastrectomy (LTG) and open total gastrectomy (OTG) groups; B: Albumin changes between LTG and OTG groups; C: Neutrophil-to-lymphocyte ratio changes between LTG and OTG groups; D: Platelet-to-lymphocyte ratio changes between LTG and OTG groups. NACT: Neoadjuvant chemotherapy; LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio.

### *Perioperative indexes*

We retrospectively collected clinicopathologic indicators including blood loss, operation time, time to first flatus (days), postoperative hospitalization days, surgical and hospitalized cost, retrieved lymph nodes, tumor length, *etc*. The 30-d morbidity and mortality were recorded from case report form and its severe degree was assessed in accordance with the Clavien-Dindo classification[18]. We defined Clavien-Dindo classification ≥ IIIa as severe complication.

Follow-up started 3 mo after operation by outpatient visit or telephone until patients' death. Frequency of adjuvant chemotherapy, survival status, and recurrence or not were mentioned during inquiries. If patients dropped out, the time of last accessible follow-up or last discharge was defined as cutoff value.

### *Statistical analysis*

We used SPSS statistical package, version 26 (IBM software), R software, and GraphPad PRISM 8.0 software to perform statistical analyses. Continuous variables are described as mean ± SD for normal distributions, while medians and interquartile ranges are used to represent skew distributions. Comparison tests were performed by the Student's *t* test and Mann–Whitney U test as appropriate. Categorical variables are described as frequencies with percent, and Chi square test was performed to demonstrate difference of categorical variables between two groups. Moreover, the difference of perioperative laboratorial index between two groups is vividly presented by line chart and box diagram.

To show long-term oncological outcomes, overall survival and disease-free survival were analyzed using Kaplan-Meier method and log-rank test was used to determine significance. We used univariate cox analyses to explore the related indexes and put indicators with $P < 0.10$ into multivariate analysis. Multivariate analyses, with backward variable selection, were conducted using the Cox proportional hazards regression model. All tests were two-sided and statistical significance was set at $P < 0.05$.

**Table 1 Baseline characteristics of 136 gastric cancer patients after neoadjuvant chemotherapy (mean ± SD)**

| Clinical characteristic | LTG group (*n* = 61) | OTG group (*n* = 75) | *P* value |
|---|---|---|---|
| **Gender** | | | 0.821 |
| Male | 47 | 59 | |
| Female | 14 | 16 | |
| Age (yr) | 57.56 ± 10.35 | 56.84 ± 11.95 | 0.712 |
| BMI (kg/m$^2$) | 22.81 ± 2.67 | 23.67 ± 3.31 | 0.099 |
| **CCI score, *n* (%)** | | | 0.982 |
| 0-2 | 43 | 53 | |
| > 2 | 18 | 22 | |
| **History of abdominal surgery** | | | 0.179 |
| No | 54 | 60 | |
| Yes | 7 | 15 | |
| **Clinical tumor stage** | | | |
| **cT** | | | 0.695 |
| T2 | 1 | 6 | |
| T3 | 22 | 23 | |
| T4 | 38 | 46 | |
| **cN** | | | 0.191 |
| N0 | 7 | 4 | |
| N+ | 54 | 71 | |
| **cTNM** | | | 0.468 |
| II | 5 | 9 | |
| III | 56 | 66 | |
| **Historical factor** | | | 0.088 |
| 2012-2015 | 22 | 38 | |
| 2016-2019 | 39 | 37 | |

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; CCI: Comprehensive complication index; BMI: Body mass index; NACT: Neoadjuvant chemotherapy.

## RESULTS

### *Clinicopathologic characteristics*

We collected the clinical data of 2102 patients who underwent total gastrectomy from June 2012 to June 2019 at the Chinese PLA General Hospital. After screening as described in Figure 1, 136 patients were included into this case-control study with 61 patients in NACT-LTG group and 75 patients in NACT-OTG group. Clinicopathologic characteristics of patients in the two groups are summarized in Tables 1 and 2. Groups were comparable according to sex, age, body mass index (BMI), comprehensive complication index score, proportion of previous abdominal surgery, tumor diameter, clinical and pathologic TNM stage, tumor location, nerve or vascular invasion, and histological type with no significant difference.

### *NACT*

All the 136 patients accepted NACT before surgery. Among them, 113 patients adopted SOX regimen (48 in LTG group and 65 in OTG group), 17 used XELOX regimen (8 in LTG group and 9 in OTG group), and 6 accepted other regimens like DCF and SF; no significant difference was found in the utilization of chemotherapy regimen between the two groups ($P$ = 0.143). Cycles of NACT was determined mainly by patients' chemotherapeutic reaction and tumor response, with no significant difference between the two groups ($P$ = 0.467). We recorded adverse events during chemotherapy by patients' self-report and

**Table 2 Pathological characteristics of 136 gastric cancer patients after neoadjuvant chemotherapy**

| Pathological characteristic | LTG group (*n* = 61) | OTG group (*n* = 75) | *P* value |
|---|---|---|---|
| Tumor diameter, cm (median, IQR) | 4.0 (2.5-6.5) | 4.0 (2.0-6.0) | 0.366 |
| **Site of tumor** | | | 0.244 |
| Upper 1/3 | 30 | 27 | |
| Middle 1/3 | 21 | 29 | |
| Diffused | 10 | 19 | |
| **ypT** | | | 0.751 |
| T0 | 1 | 7 | |
| T1 | 5 | 5 | |
| T2 | 10 | 14 | |
| T3 | 34 | 30 | |
| T4 | 11 | 19 | |
| **ypN** | | | 0.190 |
| N0 | 19 | 35 | |
| N1 | 14 | 11 | |
| N2 | 12 | 11 | |
| N3 | 16 | 18 | |
| **ypTNM** | | | 0.300 |
| 0 | 1 | 7 | |
| I | 8 | 17 | |
| II | 22 | 16 | |
| III | 29 | 34 | |
| IV | 1 | 1 | |
| **Nerve invasion** | | | 0.545 |
| Yes | 20 | 21 | |
| No | 41 | 54 | |
| **Vascular invasion** | | | 0.982 |
| Yes | 18 | 22 | |
| No | 43 | 53 | |
| **Differentiation** | | | 0.616 |
| Well/moderate | 27 | 30 | |
| Poor/undifferentiated | 34 | 45 | |

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; NACT: Neoadjuvant chemotherapy.

laboratorial index, and classified severe degree *via* CTCAE version 4.0. We found that patients in the two groups had comparable adverse events with no significant difference ($P$ = 0.535). The LTG group had significantly longer chemotherapy–surgical procedure interval compared with the OTG group (5.07 ± 1.67 wk *vs* 4.55 ± 1.33 wk; $P$ = 0.047). There was no significant difference in adjuvant therapy between the two groups ($P$ = 0.545) (Table 3).

Clinical response was another factor defined in accordance with RECIST criteria[19]. In this study, 8 (5.9%) patients achieved a completed response while 57 (41.9%) had a partial response. However, other patients did not have obvious downstage after NACT and were defined as stable disease (62 patients) and progressive disease (9 patients).

**Table 3 Neoadjuvant chemotherapy characteristics**

| Variable | LTG group (*n* = 61) | OTG group (*n* = 75) | *P* value |
|---|---|---|---|
| **Number of cycles of NACT** | | | 0.467 |
| 1-2 | 13 | 12 | |
| 3-4 | 45 | 59 | |
| > 4 | 3 | 4 | |
| **NACT regimen** | | | 0.143 |
| SOX | 48 | 65 | |
| XELOX | 8 | 9 | |
| Other | 5 | 1 | |
| **Clinical response** | | | 0.659 |
| CR | 1 | 7 | |
| PR | 28 | 29 | |
| SD | 28 | 34 | |
| PD | 4 | 5 | |
| **Adverse effects after NACT** | | | 0.535 |
| Grade 0 | 13 | 17 | |
| Grade I | 16 | 21 | |
| Grade II | 17 | 23 | |
| Grade III | 11 | 12 | |
| Grade IV | 4 | 2 | |
| Chemotherapy–surgical procedure interval (wk) | 5.07 ± 1.67 | 4.55 ± 1.33 | 0.047 |
| **Adjuvant therapy** | | | 0.545 |
| Yes | 52 | 61 | |
| No | 9 | 14 | |

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; NACT: Neoadjuvant chemotherapy; CR: Complete response; PR: Partial response; PD: Progressive disease.

### *Surgical indicators and postoperative recovery*

Of 58 (95.1%) patients in the LTG group and 74 (98.7%) patients in the OTG group acquired R0 resection ($P$ = 0.471). Compared with the OTG group, the LTG group had longer operation time (255.66 ± 40.10 min *vs* 238.59 ± 40.30 min, $P$ = 0.015) and less blood loss [150 (100-300) mL *vs* 200 (200-300) mL, $P$ = 0.003]. The number of retrieved lymph nodes was similar between the two groups (33.38 ± 13.26 in LTG group *vs* 34.75 ± 16.69 in OTG group, $P$ = 0.603).

Regarding postoperative recovery, we found that the LTG group showed advantages of enhanced recovery after surgery in comparison with the OTG group with regard to days to first flatus (4.36 ± 1.28 d *vs* 5.41 ± 1.16 d, $P$ < 0.001) and postoperative hospitalization days (9.48 ± 3.98 d *vs* 11.89 ± 3.36 d, $P$ < 0.001).

Perioperative expenditure was another concern to evaluate cost-effectiveness of different surgical approaches. In this study, even though LTG spent more surgical cost than OTG ($P$ < 0.001), LTG seemed more economical compared with OTG in terms of total hospitalized cost ($P$ < 0.001). Specific indicators mentioned above are presented in Table 4.

In subgroup analysis, we compared the difference between the LTG and OTG groups on the basis of different pathological tumor stages. After balancing the baseline characteristics, similar results were obtained like above in ypTNM 0-II patients (Table 5). Whereas, for patients with ypTNM III-IV, no significant difference was observed on surgical time ($P$ = 0.332) or blood loss ($P$ = 0.159) between the two groups (Table 6).

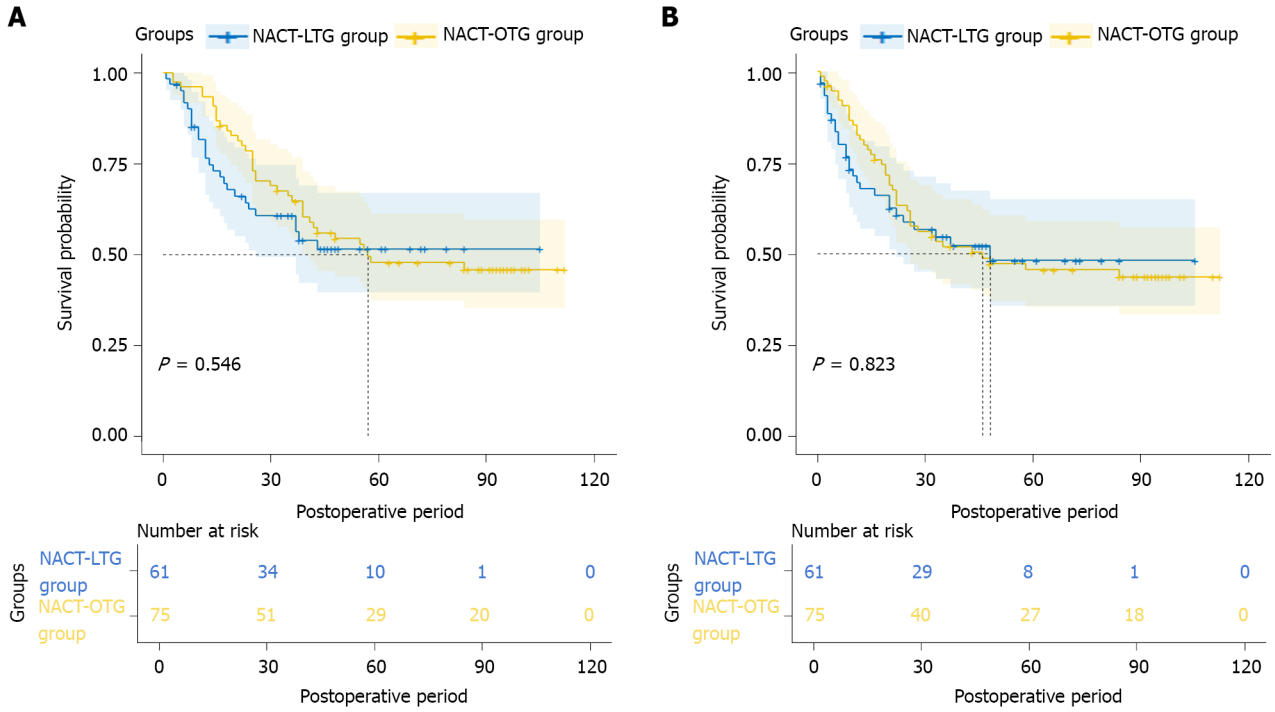
### *Laboratorial indexes before surgery and at postoperative days 1 and 7*

We selected partial laboratorial indexes like hemoglobin (Hb) and albumin (Alb) in the perioperative

**Table 4 Perioperative clinical indexes and postoperative outcomes between laparoscopic total gastrectomy and open total gastrectomy groups after neoadjuvant chemotherapy (mean ± SD)**

| Variable | LTG group (*n* = 61) | OTG group (*n* = 75) | *P* value |
|---|---|---|---|
| Surgical time, min | 255.66 ± 40.10 | 238.59 ± 40.30 | 0.015 |
| Blood loss, mL (median, IQR) | 150 (100-300) | 200 (200-300) | 0.003 |
| **Blood loss (mL), *n* (%)** | | | 0.003 |
| < 200 | 31 | 13 | |
| 200-400 | 20 | 51 | |
| > 400 | 10 | 11 | |
| Retrieved lymph nodes, *n* | 33.38 ± 13.26 | 34.75 ± 16.69 | 0.603 |
| **No. 10 lymph nodes dissection** | | | 0.339 |
| No | 41 | 56 | |
| Yes | 20 | 19 | |
| **Extent of resection** | | | 0.471 |
| R0 | 58 | 74 | |
| R1/R2 | 3 | 1 | |
| Time to first flatus, d | 4.36 ± 1.28 | 5.41 ± 1.16 | 0.000 |
| Postoperative stay, d | 9.48 ± 3.98 | 11.89 ± 3.36 | 0.000 |
| Surgery costs, $ | 5419.99 ± 1315.39 | 4162.36 ± 791.93 | 0.000 |
| Hospitalization costs, $ (median, IQR) | 13105.92 (11713.18-14640.53) | 14873.96 (13501.66-17131.31) | 0.000 |
| Total complication rate (%) | 14 (23.0) | 21 (28.0) | 0.503 |
| Clavien-Dindo classification | | | |
| **Grade II** | 12 | 19 | |
| Peritoneal infection | 2 | 2 | |
| Lymphatic leakage | 2 | 0 | |
| Anastomotic leakage | 1 | 0 | |
| Pancreatic fistula | 1 | 1 | |
| Ileus | 1 | 2 | |
| Cardiac failure | 1 | 0 | |
| Hypoproteinemia | 2 | 8 | |
| Anemia | 2 | 2 | |
| Cholecystitis | 0 | 1 | |
| Incision infection | 0 | 2 | |
| Pneumonia | 0 | 1 | |
| **Grade IIIa** | 1 | 2 | |
| Deep venous thrombosis | 1 | 0 | |
| Pleural effusion | 0 | 1 | |
| Anastomotic leakage | 0 | 1 | |
| **Grade V** | 1 | 0 | |
| Septic shock | 1 | 0 | |
| Severe complication rate (%) | 2 (3.3) | 2 (2.7) | 1.000 |

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; NACT: Neoadjuvant chemotherapy.




**DOI:** 10.4240/wjgs.v14.i5.452 

**Figure 3 Overall survival and disease-free survival in neoadjuvant chemotherapy-laparoscopic total gastrectomy and neoadjuvant chemotherapy-open total gastrectomy groups.** A: Overall survival between the two groups; B: Disease-free survival between the two groups. NACT: Neoadjuvant chemotherapy; LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy.

period to figure out the changes of perioperative nutritional status between LTG and OTG. In spite of different timelines including before surgery, postoperative day 1 (POD 1), and POD 7, there were no significant difference in Hb or Alb between the two groups.

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were also calculated through laboratory tests. In this study, except for a higher NLR in the OTG group compared with the LTG group at POD 1 ($P$ = 0.008) and PLR in the OTG compared with the LTG group at POD 1 ($P$ = 0.038), no significant difference was observed between the two groups in other periods. Visualized comparison is depicted in Figure 2.

### *30-d postoperative morbidity*

Of the 136 patients who underwent surgery after NACT, 21 (28.0%) in the OTG group and 14 (23.0%) in the LTG group developed Grade II or above postoperative complications evaluated by the Clavien-Dindo classification, with no significant difference between the two groups ($P$ = 0.503). Two (3.3%) patients who underwent LTG had severe complications, wherein one patient died because of septic shock at POD 3. The rate of severe complications after OTG (2/75, 2.7%) did not differ significantly from that in the LTG group ($P$ = 1.000). Table 4 gives the detailed items of complications.

Subgroup analysis showed that regardless of ypTNM 0-II or ypTNM III-IV patients, there was no significant difference in overall or severe complication rate between the two groups ($P$ > 0.05) (Tables 5 and 6).

### *Long-term oncological outcomes*

Of the 136 patients included, 127 (93.4%) completed follow-up. The last follow-up day was December 30, 2021. The median follow-up period was 69 (range, 1–112) mo. The 3-year OS rate was 60.6% and 64.6% in the LTG and OTG groups, respectively [hazard ratio (HR) = 0.859, 95% confidence interval (CI): 0.522-1.412], which demonstrated no significant difference between the two groups (log-rank $\chi^2$ = 0.364, $P$ = 0.546). The 3-year DFS rate was 54.5% and 51.8% in the LTG and OTG groups, respectively (HR = 0.947, 95%CI: 0.582-1.539), which presented no significant difference (log-rank $\chi^2$ = 0.05, $P$ = 0.823). Kaplan-Meier curves are shown in Figure 3.

Additionally, we set up two subgroups according to different ypTNM stages to explore the oncological impact of the two surgical approaches. For ypTNM 0-II patients, there was no significant difference in 3-year OS rate ($P$ = 0.264) or DFS rate ($P$ = 0.262) between LTG and OTG, neither were the subgroup of ypTNM III-IV patients ($P$ > 0.05).These results illustrated the similar long-term outcomes between LTG and OTG after NACT no matter what ypTNM stage was. Kaplan-Meier curves for different subgroups are shown in Supplementary Figure 1.

**Table 5 Clinical characteristics and perioperative indexes in ypTNM 0-II patients after neoadjuvant chemotherapy (mean ± SD)**

| Variable | LTG group (*n* = 31) | OTG group (*n* = 40) | *P* value |
|---|---|---|---|
| **Gender** | | | 0.841 |
| Male | 25 | 33 | |
| Female | 6 | 7 | |
| Age (yr) | 59.10 ± 10.51 | 57.63 ± 11.16 | 0.574 |
| BMI (kg/m$^2$) | 22.58 ± 2.77 | 23.72 ± 2.93 | 0.102 |
| **CCI score** | | | 0.594 |
| 0-2 | 22 | 26 | |
| > 2 | 9 | 14 | |
| Tumor diameter, cm (median, IQR) | 3.00 (2.20-4.50) | 2.30 (1.42-4.00) | 0.158 |
| Surgical time, min | 260.97 ± 37.20 | 237.93 ± 35.51 | 0.010 |
| Blood loss, mL (median, IQR) | 150 (100-200) | 200 (200-300) | 0.002 |
| **Blood loss (mL), *n* (%)** | | | 0.000 |
| 0-200 | 19 | 5 | |
| 200-400 | 9 | 31 | |
| > 400 | 3 | 4 | |
| Retrieved lymph nodes, *n* | 34.00 ± 15.11 | 36.38 ± 17.64 | 0.552 |
| Time to first flatus, d | 4.32 ± 1.28 | 5.45 ± 1.24 | 0.000 |
| Postoperative stay, d | 8.94 ± 3.63 | 11.65 ± 3.03 | 0.001 |
| Surgery costs, $ | 5641.18 ± 1351.17 | 4163.48 ± 627.86 | 0.000 |
| Hospitalization costs, $ | 13389.70 ± 2254.38 | 15024.88 ± 23358.95 | 0.004 |
| **Total complication rate (%), C-D classification** | 5 (16.1) | 9 (22.5) | 0.503 |
| II | 4 | 8 | |
| IIIa | 0 | 1 | |
| V | 1 | 0 | |
| Severe complication rate (%) | 1(3.2) | 1 (2.5) | 1.000 |

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; NACT: Neoadjuvant chemotherapy; CCI: Comprehensive complication index; BMI: Body mass index; C-D classification: Clavien-Dindo classification

### *Multivariate Cox analysis of OS and DFS*

Multivariate Cox analyses are shown in Tables 7 and 8. In the univariate analysis, BMI, pTNM stage, tumor diameter, estimated blood loss, and vascular and nerve invasion were significantly correlated with OS ($P < 0.10$), and pTNM stage, tumor diameter, estimated blood loss, and vascular invasion were significantly correlated with DFS ($P < 0.10$). In the multivariate analysis, BMI and pTNM stage were independent risk factors for OS while vascular invasion and pTNM stage were independent risk factors for DFS ($P < 0.05$). Historical factor was not significantly associated with OS or DFS ($P > 0.05$).

## DISCUSSION

The application of NACT to AGC rapidly increased because of its potential oncological benefit[20]. At present, surgeons focus mainly on the impact of NACT on gastrectomy[16,21]. In this study, we reported mono-institutional retrospective outcomes aiming to evaluate surgical safety and oncological efficacy between LTG and OTG after NACT in China, which could provide a reference to the reasonable utilization of minimally invasive surgery for AGC patients who accepted NACT.

NACT before surgery has several advantages over surgery first for AGC, such as tumor regression, better tolerance, and improved R0 resection. Previous studies which consisted of over 100 cases of NACT showed that pCR rate ranged from 5%-17.2%[22]. In the present research, 8 (5.9%) patients

**Table 6 Clinical characteristics and perioperative index in ypTNM III-IV patients after neoadjuvant chemotherapy (mean ± SD)**

| Variable | LTG group (*n* = 30) | OTG group (*n* = 35) | *P* value |
|---|---|---|---|
| **Gender** | | | 0.931 |
| Male | 22 | 26 | |
| Female | 8 | 9 | |
| Age (yr) | 55.97 ± 10.10 | 55.94 ± 12.90 | 0.993 |
| BMI (kg/m$^2$) | 23.03 ± 2.60 | 23.63 ± 3.73 | 0.468 |
| **CCI score** | | | 0.514 |
| 0-2 | 21 | 27 | |
| > 2 | 9 | 8 | |
| Tumor diameter, cm | 5.5 (3.5-8.0) | 5.0 (4.0-8.0) | 0.916 |
| Surgical time, min | 250.17 ± 42.99 | 239.34 ± 45.69 | 0.332 |
| Blood loss, mL (median, IQR) | 200 (100-350) | 300 (200-400) | 0.159 |
| **Blood loss (mL), *n* (%)** | | | 0.404 |
| 0-200 | 12 | 8 | |
| 200-400 | 11 | 20 | |
| > 400 | 7 | 7 | |
| Retrieved lymph nodes, *n* | 32.73 ± 11.24 | 32.89 ± 15.58 | 0.965 |
| Time to first flatus, d | 4.40 ± 1.30 | 5.37 ± 1.09 | 0.002 |
| Postoperative stay, d | 10.03 ± 4.30 | 12.17 ± 3.73 | 0.036 |
| Surgery costs, $ | 4793.57 (4032.20-6242.77) | 3871.55 (3686.28-4416.86) | 0.000 |
| Hospitalization costs, $ | 13190.05 (12036.98-14591.47) | 15263.28 (13162.85-17143.01) | 0.000 |
| **Total complication rate (%), C-D classification** | 9 (30.0) | 12 (34.3) | 0.647 |
| II | 8 | 11 | |
| IIIa | 1 | 1 | |
| Severe complication rate (%) | 1 (3.3) | 1 (2.9) | 1.000 |

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; NACT: Neoadjuvant chemotherapy; CCI: Comprehensive complication index; BMI: Body mass index; C-D classification: Clavien-Dindo classification.

achieved a pathologic complete response while 65 (47.8%) gained an objective response that was consistent with the results mentioned above. Better chemotherapeutic response was the crucial premise of radical gastrectomy. In this study, 58 (95.1%) patients in the LTG group and 74 (98.7%) in the OTG group achieved R0 resection, and no significant difference ($P$ = 0.471) was found between the two groups. These results indicated that LTG could ensure considerable R0 resection in comparison to OTG after NACT.

Perioperative laboratorial indexes could evaluate the extent of surgical damage and nutritional status, and even might predict prognosis[23]. In our series, no significant difference was observed in Alb and Hb between LTG and OTG at three time points, including before surgery, POD 1, and POD 7. The incidence of hypoproteinemia seemed lower in the LTG group (3.3%) compared with the OTG group (10.7%), but the difference was not significant ($P$ = 0.190), which indicated that LTG after NACT did not obviously improve postoperative nutritional status with advantages of minimally invasive surgery. NLR and PLR were regarded as potential markers to predict further prognosis[24]. Our results found no significant difference in PLR or NLR between the LTG and OTG groups before surgery and at POD 7, which implied that LTG and OTG after NACT had analogical long-term outcomes up to a point. However, higher NLR and PLR were observed at POD 1 in the OTG group than in the LTG group. We attributed this interesting phenomenon to stronger stress response at early period after OTG[25], which might elevate inflammation and suppress inherit immunity, leading to higher NLR and PLR. Hence, most studies selected pre-operation as a factor rather than other time points[26].

Adhesion of tissues, lack of anatomical layer, and peri-gastric edema and fibrosis might occur after NACT, which increased the surgical difficulty. Laparoscopy has several advantages like delicate

**Table 7 Univariate and multivariate analyses for overall survival**

| Factor | Univariate analysis | | *P* value | Multivariate analysis | | *P* value |
|---|---|---|---|---|---|---|
| | HR | 95%CI | | HR | 95%CI | |
| **Sex** | | | 0.127 | | | |
| Male | 1.000 | | | | | |
| Female | 1.541 | 0.885-2.684 | | | | |
| **Age** | | | 0.647 | | | |
| < 65 | 1.000 | | | | | |
| ≥ 65 | 1.129 | 0.671-1.900 | | | | |
| **BMI (kg/m$^2$)** | | | 0.091 | | | 0.049 |
| < 25 | 1.000 | | | 1.000 | | |
| ≥ 25 | 0.601 | 0.333-1.086 | | 0.547 | 0.300-0.998 | |
| **Surgical approach** | | | 0.549 | | | |
| Laparoscopy | 1.000 | | | | | |
| Open | 1.164 | 0.708-1.914 | | | | |
| **CCI score** | | | 0.438 | | | |
| 0-2 | 1.000 | | | | | |
| ≥ 2 | 1.225 | 0.733-2.049 | | | | |
| **pTNM stage** | | | 0.000 | | | 0.006 |
| 0-II | 1.000 | | | 1.000 | | |
| III-IV | 2.632 | 1.569-4.413 | | 2.224 | 1.258-3.930 | |
| **Tumor diameter (cm)** | | | 0.039 | | | 0.153 |
| ≤ 3 | 1.000 | | | 1.000 | | |
| > 3 | 1.838 | 1.031-3.277 | | 1.577 | 0.844-2.945 | |
| **Operation time (min)** | | | 0.483 | | | |
| ≤ 240 | 1.000 | | | | | |
| > 240 | 1.192 | 0.730-1.948 | | | | |
| **Estimated blood loss (mL)** | | | 0.074 | | | 0.588 |
| ≤ 200 | 1.000 | | | 1.000 | | |
| > 200 | 1.559 | 0.958-2.536 | | 1.154 | 0.688-1.935 | |
| **Vascular invasion** | | | 0.008 | | | 0.062 |
| No | 1.000 | | | 1.000 | | |
| Yes | 1.987 | 1.200-3.289 | | 1.712 | 0.974-3.010 | |
| **Nerve invasion** | | | 0.079 | | | 0.567 |
| No | 1.000 | | | 1.000 | | |
| Yes | 1.580 | 0.949-2.632 | | 0.838 | 0.456-1.537 | |
| **Differentiation** | | | 0.261 | | | |
| Well/moderate | 1.000 | | | | | |
| Poor/undifferentiated | 1.335 | 0.806-2.212 | | | | |
| **Complications** | | | 0.662 | | | |
| No | 1.000 | | | | | |
| Yes | 1.131 | 0.651-1.968 | | | | |
| **Historical factor** | | | 0.861 | | | |

| | | |
|---|---|---|
| 2012-2015 | 1.000 | |
| 2016-2019 | 0.957 | 0.587-1.560 |

HR: Hazard ratio; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; CCI: Comprehensive complication index; BMI: Body mass index.

manipulation, regional amplification, faster recovery, and damage control that might reduce the surgical risk of NACT. Li *et al*[21] found that laparoscopic distal gastrectomy had remarkably lower postoperative morbidity compared with open distal gastrectomy (20% *vs* 46%, $P = 0.007$) for patients with AGC who received NACT[21]. In this study, our perioperative clinical indicators showed that LTG offered benefits of less blood loss ($P = 0.003$), shorter days to first flatus, and shorter postoperative hospitalization dasy ($P < 0.001$) compared with OTG, which illuminated specific superiority of minimally invasive surgery. LTG also could achieve adequate lymph nodes dissection with a comparable number of retrieved lymph nodes between LTG and OTG (33.38 ± 13.26 *vs* 34.75 ± 16.69, $P = 0.603$). Meanwhile, an interesting phenomenon was found that LTG cost more on operation and less on total hospitalization than OTG, which was similar to the results of the studies by Tegels *et al*[27] and Hoya *et al*[28]. Gosselin-Tardif *et al*[29] also found that the application of laparoscopic gastrectomy was more cost-effective compared with open gastrectomy in Canadians. We reckon that the fact that expensive disposable surgical instruments mostly relied on import might elevate surgical cost in LTG, but fast postoperative recovery could offset deviations by reducing other costs, which suggested LTG as a probable cost-effective alternative surgical approach after NACT.

In terms of perioperative complications, CLASS-02 trial conducted in China demonstrated that LTG performed by experienced surgeons had acceptable postoperative morbidity (19.1%) for clinical stage I GC[13]. STOMACH trial showed no significant difference in the rate of postoperative complications between OTG (42.9%) and LTG (34.0%) in LTG after NACT in Western countries ($P = 0.408$). Wang *et al*[30] demonstrated that LTG had comparable safety to OTG after NACT in the perioperative period and patients in the LTG group could benefit from less intravenous patient-controlled analgesia (IV-PCA) use [30]. Back to our study, we found that LTG did not significantly increase or decrease 30-d postoperative complications compared with OTG after NACT (overall morbidity of LTG *vs* OTG: 23.0% *vs* 28.0%, $P = 0.503$; severe morbidity of LTG *vs* OTG: 3.3% *vs* 2.7%, $P = 1.000$), which was similar to the results of the studies mentioned above. These results still existed in different ypTNM stage patients. Thus, we consider that the application of LTG after NACT could be safe and feasible whatever tumor stage was and we recommend to initiate prospective studies to give high-grade evidence in East Asia.

Long-term outcomes were inevitable to evaluate oncological benefit caused by different surgical approaches. The studies by Gambhir *et al*[14] and Komatsu *et al*[31] both pointed out a comparable long-term survival between LTG and OTG, nevertheless it remained uncertain between the LTG and OTG group after NACT. Our results of follow-up focused on 3-year OS and DFS rates showed no significant difference between the two groups (LTG compared to OTG: 3-year OS: 60.6% *vs* 64.6%, $P = 0.546$; 3-year DFS: 54.5% *vs* 51.8%, $P = 0.823$). Subgroup analysis according to different ypTNM stages also showed no significant difference in 3-year OS or DFS rate. These findings suggested that patients with LTG after NACT had similar oncological benefits compared with those in the OTG group irrespective of stage, and LTG after NACT could be regarded as an alternative surgical approach with acceptable short and long-term outcomes.

Our study has several limitations. Principally, this is not a prospective study which lacked of authentic evidence-based support and existed selection bias. Under the trend of climbing application of NACT as a promising treatment for AGC in East Asia[32], large-scale retrospective or even multi-institutional RCT studies are required to better understand the association between LTG and OTG after NACT. Moreover, small sample size increased the probability of type II error and reduced the power of test. To decrease such impact, we combined patients with adjacent ypTNM stages into one group to ensure enough sample size in subgroup analysis. Third, although SOX regimen was the main NACT treatment in our study, other regimens like XELOX and DCF were also used for a small portion of appropriate patients, which may slightly influence short or long-term outcomes. In addition, even the baseline characteristics of patients included in this study were comparable between the LTG and OTG groups, some potential imbalance caused by unknown indicators may affect the validity of results.

## CONCLUSION

To sum up, this study suggested that there are no significant disparities between LTG and OTG in postoperative complication rates, 3-year OS rates, and 3-year DFS rates after NACT for AGC patients. LTG performed by experienced surgeons after NACT has several advantages including less blood loss, faster postoperative recovery, and less hospitalized cost, which could be regarded as an alternative surgical approach with its safety, feasibility, and comparable oncological benefits at any ypTNM stage.

**Table 8 Univariate and multivariate analyses for disease-free survival**

| Factor | Univariate analysis | | *P* value | Multivariate analysis | | *P* value |
|---|---|---|---|---|---|---|
| | HR | 95%CI | | HR | 95%CI | |
| **Sex** | | | 0.259 | | | |
| Male | 1.000 | | | | | |
| Female | 0.851 | 0.642-1.127 | | | | |
| **Age** | | | 0.267 | | | |
| < 65 | 1.000 | | | | | |
| ≥ 65 | 1.326 | 0.806-2.181 | | | | |
| **BMI (kg/m2)** | | | 0.706 | | | |
| < 25 | 1.000 | | | | | |
| ≥ 25 | 0.706 | 0.403-1.237 | | | | |
| **Surgical approach** | | | 0.825 | | | |
| Laparoscopy | 1.000 | | | | | |
| Open | 0.947 | 0.582-1.539 | | | | |
| **CCI score** | | | 0.707 | | | |
| 0-2 | 1.000 | | | | | |
| ≥ 2 | 1.104 | 0.660-1.847 | | | | |
| **pTNM stage** | | | 0.000 | | | 0.022 |
| 0-II | 1.000 | | | 1.000 | | |
| III-IV | 2.418 | 1.471-3.973 | | 1.854 | 1.095-3.140 | |
| **Tumor diameter (cm)** | | | 0.022 | | | 0.200 |
| ≤ 3 | 1.000 | | | 1.000 | | |
| > 3 | 1.954 | 1.100-3.470 | | 1.484 | 0.812-2.710 | |
| **Operation time (min)** | | | 0.710 | | | |
| ≤ 240 | 1.000 | | | | | |
| > 240 | 1.095 | 0.679-1.765 | | | | |
| **Estimated blood loss (mL)** | | | 0.024 | | | 0.204 |
| ≤ 200 | 1.000 | | | 1.000 | | |
| > 200 | 1.730 | 1.075-2.785 | | 1.379 | 0.840-2.263 | |
| **Vascular invasion** | | | 0.001 | | | 0.020 |
| No | 1.000 | | | 1.000 | | |
| Yes | 2.245 | 1.378-3.659 | | 1.824 | 1.101-3.022 | |
| **Nerve invasion** | | | 0.203 | | | |
| No | 1.000 | | | | | |
| Yes | 1.387 | 0.838-2.295 | | | | |
| **Differentiation** | | | 0.283 | | | |
| Well/moderate | 1.000 | | | | | |
| Poor/undifferentiated | 1.311 | 0.800-2.148 | | | | |
| **Complications** | | | 0.751 | | | |
| No | 1.000 | | | | | |
| Yes | 1.093 | 0.631-1.894 | | | | |
| **Historical factor** | | | 0.691 | | | |

| | | |
|---|---|---|
| 2012-2015 | 1.000 | |
| 2016-2019 | 1.102 | 0.683-1.779 |

HR: Hazard ratio; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; CCI: Comprehensive complication index; BMI: Body mass index.

## ARTICLE HIGHLIGHTS

### *Research background*

Neoadjuvant chemotherapy (NACT) combined with surgery is regarded as an effective treatment for advanced gastric cancer (AGC). Laparoscopic surgery represents the mainstream of minimally invasive surgery.

### *Research motivation*

Currently, surgeons focus more on surgical safety and oncological outcomes of laparoscopic gastrectomy after NACT.

### *Research objectives*

We sought to evaluate short- and long-term outcomes between laparoscopic total gastrectomy (LTG) and open total gastrectomy (OTG) after NACT.

### *Research methods*

We retrospectively collected the clinicopathological data of 136 patients who accepted gastrectomy after NACT from June 2012 to June 2019, including 61 patients in the LTG group and 75 patients in the OTG group. Clinicopathological characteristics between the LTG and OTG groups showed no significant difference. We compared the perioperative indexes and long-term outcomes between the LTG and OTG groups after NACT. SPSS 26.0, R software, and GraphPad PRISM 8.0 were used to perform statistical analyses.

### *Research results*

In this study, we found that LTG had longer operation time, less blood loss, shorter days to first flatus, and shorter postoperative hospitalization days compared with OTG. LTG showed comparable 30-d postoperative morbidity as well as 3-year OS and DFS rate to OTG.

### *Research conclusions*

This study suggested that there are no significant disparities between LTG and OTG in postoperative complication rates, 3-year OS rates, and 3-year DFS rates after NACT for AGC patients. LTG performed by experienced surgeons after NACT has several advantages including less blood loss, faster postoperative recovery, and less hospitalized cost, which could be regarded as an alternative surgical approach with its safety, feasibility, and comparable oncological benefits at any ypTNM stage.

### *Research perspectives*

We recommend that experienced surgeons could select LTG for proper patients after NACT. Large-scale retrospective or even multi-institutional RCT studies are required to better understand the association between LTG and OTG after NACT.

## FOOTNOTES

**Author contributions:** Cui H, Zhang KC, Cao B, Chen L, and Wei B designed the study; Cao B, Deng H, and Zhao RY collected the data; Liu Y analyzed and interpreted the data; Cui H and Zhang KC prepared the manuscript; all the authors read and approved the final manuscript.

**Supported by** National Basic Research Program of China (973 Program), No. 2019YFB1311505; National Natural Science Foundation of China, No. 81773135 and No. 82073192.

**Institutional review board statement:** The study involving human participants was reviewed and approved by the Research Ethics Committee of Chinese PLA General Hospital.

**Informed consent statement:** The patients and participants provided their written informed consent to participate in this study.

**Conflict-of-interest statement:** All authors have completed the ICMJE uniform disclosure form. They declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Data sharing statement:** The datasets generated and/or analyzed during the current study are not publicly available due to hospital policy but are available from the corresponding author on reasonable request.



**Country/Territory of origin:** China

**ORCID number:** Hao Cui 0000-0003-1185-5322; Ke-Cheng Zhang 0000-0002-9257-5607; Bo Cao 0000-0003-4623-7348; Huan Deng 0000-0002-6144-2289; Gui-Bin Liu 0000-0002-2785-5848; Li-Qiang Song 0000-0001-5893-0727; Rui-Yang Zhao 0000-0001-6619-9532; Yi Liu 0000-0002-0973-4241; Lin Chen 0000-0002-3507-673X; Bo Wei 0000-0001-7386-2689.

**S-Editor:** Fan JR
**L-Editor:** Wang TQ
**P-Editor:** Fan JR

## REFERENCES

1 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]
2 **Sun D**, Cao M, Li H, He S, Chen W. Cancer burden and trends in China: A review and comparison with Japan and South Korea. *Chin J Cancer Res* 2020; **32**: 129-139 [PMID: 32410791 DOI: 10.21147/j.issn.1000-9604.2020.02.01]
3 **Yu JH**, Wang ZZ, Fan YC, Liu MX, Xu K, Zhang N, Yao ZD, Yang H, Zhang CH, Xing JD, Cui M, Su XQ. Comparison of neoadjuvant chemotherapy followed by surgery vs. surgery alone for locally advanced gastric cancer: a meta-analysis. *Chin Med J (Engl)* 2021; **134**: 1669-1680 [PMID: 34397593 DOI: 10.1097/CM9.0000000000001603]
4 **Umeda S**, Kanda M, Nakanishi K, Ito S, Mochizuki Y, Teramoto H, Ishigure K, Murai T, Asada T, Ishiyama A, Matsushita H, Shimizu D, Kobayashi D, Tanaka C, Fujiwara M, Murotani K, Kodera Y. Short-term outcomes of gastrectomy after neoadjuvant chemotherapy for clinical stage III gastric cancer: propensity score-matched analysis of a multi-institutional database. *Surg Today* 2021; **51**: 821-828 [PMID: 33170366 DOI: 10.1007/s00595-020-02179-0]
5 **Fujisaki M**, Mitsumori N, Shinohara T, Takahashi N, Aoki H, Nyumura Y, Kitazawa S, Yanaga K. Short- and long-term outcomes of laparoscopic versus open gastrectomy for locally advanced gastric cancer following neoadjuvant chemotherapy. *Surg Endosc* 2021; **35**: 1682-1690 [PMID: 32277356 DOI: 10.1007/s00464-020-07552-1]
6 **Cunningham D**, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355**: 11-20 [PMID: 16822992 DOI: 10.1056/NEJMoa055531]
7 **Al-Batran SE**, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, Kopp HG, Mayer F, Haag GM, Luley K, Lindig U, Schmiegel W, Pohl M, Stoehlmacher J, Folprecht G, Probst S, Prasnikar N, Fischbach W, Mahlberg R, Trojan J, Koenigsmann M, Martens UM, Thuss-Patience P, Egger M, Block A, Heinemann V, Illerhaus G, Moehler M, Schenk M, Kullmann F, Behringer DM, Heike M, Pink D, Teschendorf C, Löhr C, Bernhard H, Schuch G, Rethwisch V, von Weikersthal LF, Hartmann JT, Kneba M, Daum S, Schulmann K, Weniger J, Belle S, Gaiser T, Oduncu FS, Güntner M, Hozaeel W, Reichart A, Jäger E, Kraus T, Mönig S, Bechstein WO, Schuler M, Schmalenberg H, Hofheinz RD; FLOT4-AIO Investigators. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet* 2019; **393**: 1948-1957 [PMID: 30982686 DOI: 10.1016/S0140-6736(18)32557-1]
8 **Zhang X**, Liang H, Li Z, Xue Y, Wang Y, Zhou Z, Yu J, Bu Z, Chen L, Du Y, Wang X, Wu A, Li G, Su X, Xiao G, Cui M, Wu D, Wu X, Zhou Y, Zhang L, Dang C, He Y, Zhang Z, Sun Y, Li Y, Chen H, Bai Y, Qi C, Yu P, Zhu G, Suo J, Jia B, Li L, Huang C, Li F, Ye Y, Xu H, Yuan Y, E JY, Ying X, Yao C, Shen L, Ji J; RESOLVE study group. Perioperative or postoperative adjuvant oxaliplatin with S-1 versus adjuvant oxaliplatin with capecitabine in patients with locally advanced gastric or gastro-oesophageal junction adenocarcinoma undergoing D2 gastrectomy (RESOLVE): an open-label, superiority and non-inferiority, phase 3 randomised controlled trial. *Lancet Oncol* 2021; **22**: 1081-1092 [PMID: 34252374 DOI: 10.1016/S1470-2045(21)00297-7]
9 **Wang X**, Li S, Sun Y, Li K, Shen X, Xue Y, Liang P, Li G, Chen L, Zhao Q, Fu W, Liang H, Xin H, Suo J, Fang X, Zheng Z, Xu Z, Chen H, Zhou Y, He Y, Huang H, Zhu L, Yang K, Ji J, Ye Y, Zhang Z, Li F, Wang X, Tian Y, Park S. The protocol of a prospective, multicenter, randomized, controlled phase III study evaluating different cycles of oxaliplatin combined with S-1 (SOX) as neoadjuvant chemotherapy for patients with locally advanced gastric cancer: RESONANCE-

II trial. *BMC Cancer* 2021; **21**: 20 [PMID: 33402102 DOI: 10.1186/s12885-020-07764-7]
10 **Kitano S**, Iso Y, Moriyama M, Sugimachi K. Laparoscopy-assisted Billroth I gastrectomy. *Surg Laparosc Endosc* 1994; **4**: 146-148 [PMID: 8180768]
11 **Yu J**, Huang C, Sun Y, Su X, Cao H, Hu J, Wang K, Suo J, Tao K, He X, Wei H, Ying M, Hu W, Du X, Hu Y, Liu H, Zheng C, Li P, Xie J, Liu F, Li Z, Zhao G, Yang K, Liu C, Li H, Chen P, Ji J, Li G; Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) Group. Effect of Laparoscopic vs Open Distal Gastrectomy on 3-Year Disease-Free Survival in Patients With Locally Advanced Gastric Cancer: The CLASS-01 Randomized Clinical Trial. *JAMA* 2019; **321**: 1983-1992 [PMID: 31135850 DOI: 10.1001/jama.2019.5359]
12 **Katai H**, Mizusawa J, Katayama H, Morita S, Yamada T, Bando E, Ito S, Takagi M, Takagane A, Teshima S, Koeda K, Nunobe S, Yoshikawa T, Terashima M, Sasako M. Survival outcomes after laparoscopy-assisted distal gastrectomy versus open distal gastrectomy with nodal dissection for clinical stage IA or IB gastric cancer (JCOG0912): a multicentre, non-inferiority, phase 3 randomised controlled trial. *Lancet Gastroenterol Hepatol* 2020; **5**: 142-151 [PMID: 31757656 DOI: 10.1016/S2468-1253(19)30332-2]
13 **Liu F**, Huang C, Xu Z, Su X, Zhao G, Ye J, Du X, Huang H, Hu J, Li G, Yu P, Li Y, Suo J, Zhao N, Zhang W, Li H, He H, Sun Y; Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) Group. Morbidity and Mortality of Laparoscopic vs Open Total Gastrectomy for Clinical Stage I Gastric Cancer: The CLASS02 Multicenter Randomized Clinical Trial. *JAMA Oncol* 2020; **6**: 1590-1597 [PMID: 32815991 DOI: 10.1001/jamaoncol.2020.3152]
14 **Gambhir S**, Inaba CS, Whealon M, Sujatha-Bhaskar S, Pejcinovska M, Nguyen NT. Short- and long-term survival after laparoscopic versus open total gastrectomy for gastric adenocarcinoma: a National database study. *Surg Endosc* 2021; **35**: 1872-1878 [PMID: 32394166 DOI: 10.1007/s00464-020-07591-8]
15 **Oh Y**, Kim MS, Lee YT, Lee CM, Kim JH, Park S. Laparoscopic total gastrectomy as a valid procedure to treat gastric cancer option both in early and advanced stage: A systematic review and meta-analysis. *Eur J Surg Oncol* 2020; **46**: 33-43 [PMID: 31477462 DOI: 10.1016/j.ejso.2019.08.018]
16 **van der Wielen N**, Straatman J, Daams F, Rosati R, Parise P, Weitz J, Reissfelder C, Diez Del Val I, Loureiro C, Parada-González P, Pintos-Martínez E, Mateo Vallejo F, Medina Achirica C, Sánchez-Pernaute A, Ruano Campos A, Bonavina L, Asti ELG, Alonso Poza A, Gilsanz C, Nilsson M, Lindblad M, Gisbertz SS, van Berge Henegouwen MI, Fumagalli Romario U, De Pascale S, Akhtar K, Jaap Bonjer H, Cuesta MA, van der Peet DL. Open versus minimally invasive total gastrectomy after neoadjuvant chemotherapy: results of a European randomized trial. *Gastric Cancer* 2021; **24**: 258-271 [PMID: 32737637 DOI: 10.1007/s10120-020-01109-w]
17 **Japanese Gastric Cancer Association**. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer* 2021; **24**: 1-21 [PMID: 32060757 DOI: 10.1007/s10120-020-01042-y]
18 **Katayama H**, Kurokawa Y, Nakamura K, Ito H, Kanemitsu Y, Masuda N, Tsubosa Y, Satoh T, Yokomizo A, Fukuda H, Sasako M. Extended Clavien-Dindo classification of surgical complications: Japan Clinical Oncology Group postoperative complications criteria. *Surg Today* 2016; **46**: 668-685 [PMID: 26289837 DOI: 10.1007/s00595-015-1236-x]
19 **Eisenhauer EA**, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228-247 [PMID: 19097774 DOI: 10.1016/j.ejca.2008.10.026]
20 **Das M**. Neoadjuvant chemotherapy: survival benefit in gastric cancer. *Lancet Oncol* 2017; **18**: e307 [PMID: 28483410 DOI: 10.1016/S1470-2045(17)30321-2]
21 **Li Z**, Shan F, Ying X, Zhang Y, E JY, Wang Y, Ren H, Su X, Ji J. Assessment of Laparoscopic Distal Gastrectomy After Neoadjuvant Chemotherapy for Locally Advanced Gastric Cancer: A Randomized Clinical Trial. *JAMA Surg* 2019; **154**: 1093-1101 [PMID: 31553463 DOI: 10.1001/jamasurg.2019.3473]
22 **Petrelli F**, Ghidini M, Barni S, Sgroi G, Passalacqua R, Tomasello G. Neoadjuvant chemoradiotherapy or chemotherapy for gastroesophageal junction adenocarcinoma: A systematic review and meta-analysis. *Gastric Cancer* 2019; **22**: 245-254 [PMID: 30483986 DOI: 10.1007/s10120-018-0901-3]
23 **Wang Y**, Wang H, Jiang J, Cao X, Liu Q. Early decrease in postoperative serum albumin predicts severe complications in patients with colorectal cancer after curative laparoscopic surgery. *World J Surg Oncol* 2018; **16**: 192 [PMID: 30253767 DOI: 10.1186/s12957-018-1493-4]
24 **Miyamoto R**, Inagawa S, Sano N, Tadano S, Adachi S, Yamamoto M. The neutrophil-to-lymphocyte ratio (NLR) predicts short-term and long-term outcomes in gastric cancer patients. *Eur J Surg Oncol* 2018; **44**: 607-612 [PMID: 29478743 DOI: 10.1016/j.ejso.2018.02.003]
25 **Novitsky YW**, Litwin DE, Callery MP. The net immunologic advantage of laparoscopic surgery. *Surg Endosc* 2004; **18**: 1411-1419 [PMID: 15791361 DOI: 10.1007/s00464-003-8275-x]
26 **Hirahara T**, Arigami T, Yanagita S, Matsushita D, Uchikado Y, Kita Y, Mori S, Sasaki K, Omoto I, Kurahara H, Maemura K, Okubo K, Uenosono Y, Ishigami S, Natsugoe S. Combined neutrophil-lymphocyte ratio and platelet-lymphocyte ratio predicts chemotherapy response and prognosis in patients with advanced gastric cancer. *BMC Cancer* 2019; **19**: 672 [PMID: 31286873 DOI: 10.1186/s12885-019-5903-y]
27 **Tegels JJ**, Silvius CE, Spauwen FE, Hulsewé KW, Hoofwijk AG, Stoot JH. Introduction of laparoscopic gastrectomy for gastric cancer in a Western tertiary referral centre: A prospective cost analysis during the learning curve. *World J Gastrointest Oncol* 2017; **9**: 228-234 [PMID: 28567187 DOI: 10.4251/wjgo.v9.i5.228]
28 **Hoya Y**, Taki T, Tanaka Y, Yano H, Hirabayashi T, Okamoto T, Kashiwagi H, Yanaga K. Disadvantage of operation cost in laparoscopy-assisted distal gastrectomy under the national health insurance system in Japan. *Dig Surg* 2010; **27**: 343-346 [PMID: 20838052 DOI: 10.1159/000318774]
29 **Gosselin-Tardif A**, Abou-Khalil M, Mata J, Guigui A, Cools-Lartigue J, Ferri L, Lee L, Mueller C. Laparoscopic versus open subtotal gastrectomy for gastric adenocarcinoma: cost-effectiveness analysis. *BJS Open* 2020; **4**: 830-839 [PMID: 32762036 DOI: 10.1002/bjs5.50327]
30 **Wang Y**, Lei X, Liu Z, Shan F, Ying X, Li Z, Ji J. Short-term outcomes of laparoscopic versus open total gastrectomy after neoadjuvant chemotherapy: a cohort study using the propensity score matching method. *J Gastrointest Oncol* 2021; **12**:

237-248 [PMID: 34012622 DOI: 10.21037/jgo-20-374]

31 **Komatsu S**, Kosuga T, Kubota T, Okamoto K, Konishi H, Shiozaki A, Fujiwara H, Ichikawa D, Otsuji E. Comparison of short- and long-term outcomes following laparoscopy and open total gastrectomy for gastric cancer: a propensity score-matched analysis. *Am J Transl Res* 2020; **12**: 2225-2233 [PMID: 32509214]

32 **Terashima M**, Yoshikawa T, Boku N, Ito S, Tsuburaya A, Iwasaki Y, Fukagawa T, Tokunaga M, Sano T, Sasako M; Stomach Cancer Study Group, Japan Clinical Oncology Group. Current status of perioperative chemotherapy for locally advanced gastric cancer and JCOG perspectives. *Jpn J Clin Oncol* 2020; **50**: 528-534 [PMID: 32134452 DOI: 10.1093/jjco/hyaa005]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 May 27; 14(5): 470-481

DOI: 10.4240/wjgs.v14.i5.470

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

# Are laparoscopic cholecystectomy and natural orifice transluminal endoscopic surgery gallbladder preserving cholecystolithotomy truly comparable? A propensity matched study

Saif Ullah, Bao-Hong Yang, Dan Liu, Xue-Yang Lu, Zhen-Zhen Liu, Li-Xia Zhao, Ji-Yu Zhang, Bing-Rong Liu

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Cianci P, Italy; Tantau AI, Romania

**Received:** November 6, 2021
**Peer-review started:** November 6, 2021
**First decision:** January 9, 2022
**Revised:** January 18, 2022
**Accepted:** April 9, 2022
**Article in press:** April 9, 2022
**Published online:** May 27, 2022

**Saif Ullah, Bao-Hong Yang, Dan Liu, Xue-Yang Lu, Zhen-Zhen Liu, Li-Xia Zhao, Ji-Yu Zhang, Bing-Rong Liu,** Department of Gastroenterology and Hepatology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan Province, China

**Bao-Hong Yang,** Department of Oncology, Weifang People's Hospital, Weifang 261000, Shandong Province, China

**Bing-Rong Liu,** State Key Laboratory of Esophageal Cancer Prevention and Treatment, Zhengzhou University, Zhengzhou 450052, Henan Province, China

**Corresponding author:** Bing-Rong Liu, PhD, Director, Professor, Department of Gastroenterology and Hepatology, The First Affiliated Hospital of Zhengzhou University, No. 1 Eastern Jianshe Road, Zhengzhou 450052, Henan Province, China. fccliubr@zzu.edu.cn

## Abstract

***BACKGROUND***

Cholecystectomy is the preferred treatment option for symptomatic gallstones. However, another option is gallbladder-preserving cholecystolithotomy which preserves the normal physiological functions of the gallbladder in patients desiring to avoid surgical resection.

***AIM***

To compare the feasibility, safety and effectiveness of pure natural orifice transluminal endoscopic surgery (NOTES) gallbladder-preserving cholecystolithotomy *vs* laparoscopic cholecystectomy (LC) for symptomatic gallstones.

***METHODS***

We adopted propensity score matching (1:1) to compare trans-rectal NOTES cholecystolithotomy and LC patients with symptomatic gallstones. We reviewed 2511 patients with symptomatic gallstones from December 2017 to December 2020; 517 patients met the matching criteria (NOTES, 110; LC, 407), yielding 86 pairs.

***RESULTS***

The technical success rate for the NOTES group was 98.9% *vs* 100% for the LC group. The median procedure time was 119 min [interquartile ranges (IQRs), 95-

175] with NOTES *vs* 60 min (IQRs, 48-90) with LC ($P < 0.001$). The frequency of post-operative pain was similar between NOTES and LC: 4.7% (4/85) *vs* 5.8% (5/95) ($P = 0.740$). The median duration of post-procedure fasting with NOTES was 1 d (IQRs, 1-2) *vs* 2 d with LC (IQRs, 1-3) ($P < 0.001$). The median post-operative hospital stay for NOTES was 4 d (IQRs, 3-6) *vs* 4 d for LC (IQRs, 3-5), ( $P = 0.092$). During follow-up, diarrhea was significantly less with NOTES (5.8%) compared to LC (18.6%) ($P = 0.011$). Gallstones and cholecystitis recurrence within a median of 12 mo (range: 6-40 mo) following NOTES was 10.5% and 3.5%, respectively. Concerns regarding the presence of abdominal wall scars were present in 17.4% ($n = 15/86$) of patients following LC (mainly women).

*CONCLUSION*

NOTES provides a feasible new alternative scar-free treatment for patients who are unwilling or unable to undergo cholecystectomy. This minimally invasive organ-sparing procedure both removes the gallstones and preserves the physiological function of the gallbladder. Reducing gallstone recurrence is essential to achieving widespread clinical adoption of NOTES.

**Key Words:** Gallstones; Trans-rectal; Natural orifice transluminal endoscopic surgery; Minimally invasive surgery; Gallbladder preservation; Cholecystolithotomy; Laparoscopic cholecystectomy



**Core Tip:** Laparoscopic cholecystectomy (LC) is the current gold standard for treating gallstones. However, long-term complications of LC such as duodenogastric reflux, post-cholecystectomy syndrome, bile duct injuries and an increase in colonic cancer remain largely unreported/unstudied. Some experts now advocate simple gallstone extraction with gallbladder preservation (cholecystolithotomy) in order to avoid post-cholecystectomy syndrome, bile duct injury, and its association with colon cancer. The authors' developed the pure natural orifice transluminal endoscopic surgery trans-rectal gallbladder preserving cholecystolithotomy technique for removal of gallbladder stones. This study compared trans-rectal gallbladder preserving cholecystolithotomy with traditional LC.

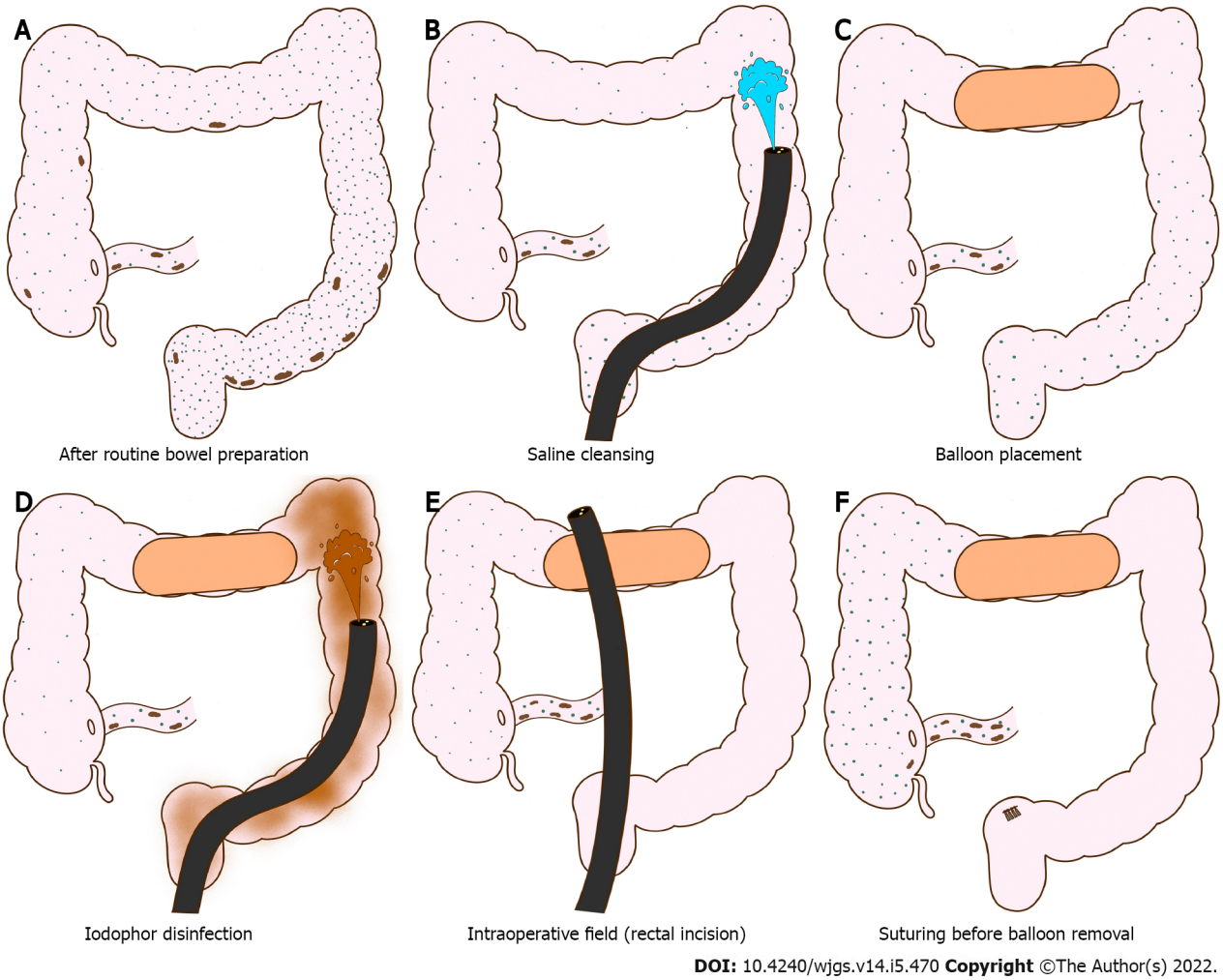
**Citation:** Ullah S, Yang BH, Liu D, Lu XY, Liu ZZ, Zhao LX, Zhang JY, Liu BR. Are laparoscopic cholecystectomy and natural orifice transluminal endoscopic surgery gallbladder preserving cholecystolithotomy truly comparable? A propensity matched study. *World J Gastrointest Surg* 2022; 14(5): 470-481
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i5/470.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i5.470

## INTRODUCTION

Approximately 25 million people in the United States have gallstones, resulting in more than one million hospitalizations each year[1-4]. Cholecystectomy is the gold standard treatment for symptomatic gallstones[5]. For the past three decades, laparoscopic cholecystectomy (LC) has been the treatment of choice[6-8] as it is minimally invasive. However, since Rao *et al*[9]'s description of the first human NOTES trans-gastric appendectomy in 2004, ultra-minimally invasive techniques have evolved including natural orifice transluminal endoscopic surgery (NOTES) cholecystectomy[9]. Some experts now advocate cholecystolithotomy without gallbladder excision in order to preserve gallbladder function and to avoid gallbladder resection-related complications[10-13]. In addition, cholecystectomy is associated with post-cholecystectomy syndrome, surgical incision complications, and bile duct injury [14-16]. The reasons given for gallbladder preservation include the reported associations of colon cancer, functional gastrointestinal and psychological conditions following cholecystectomy[15-17].

Experimental studies using flexible endoscopic trans-rectal NOTES have suggested this approach as an attractive alternative option for intra-abdominal procedures[18-21]. However, concern regarding peritoneal contamination with trans-rectal NOTES limited the adoption of trans-rectal NOTES as a routine clinical practice. The problem of peritoneal contamination during trans-rectal NOTES has now been largely overcome with the use of a detachable obstructive colonic balloon which prevents distal colonic contamination (Figure 1)[22-24].

No comparison of NOTES and LC for symptomatic gallstones has previously been reported. Therefore, we performed a comparative study of pure NOTES gallbladder preservation cholecystolithotomy and LC to examine relative effectiveness as well as differences in post-operative pain, infection, time to normal diet intake, hospital duration, short- and long-term complications.




**DOI:** 10.4240/wjgs.v14.i5.470 

**Figure 1 Schematic of colonic cleansing, detachable balloon placement, and colonic disinfection.** A: Colon after bowel preparations; B: Colon cleansing using saline solution; C: Placement of detachable balloon in the transverse colon; D: Distal colon disinfection using iodophor; E: Endoscopy insertion to peritoneal cavity *via* rectal incision; F: Suturing of rectal incision before balloon removal.

## MATERIALS AND METHODS

### *Study design*

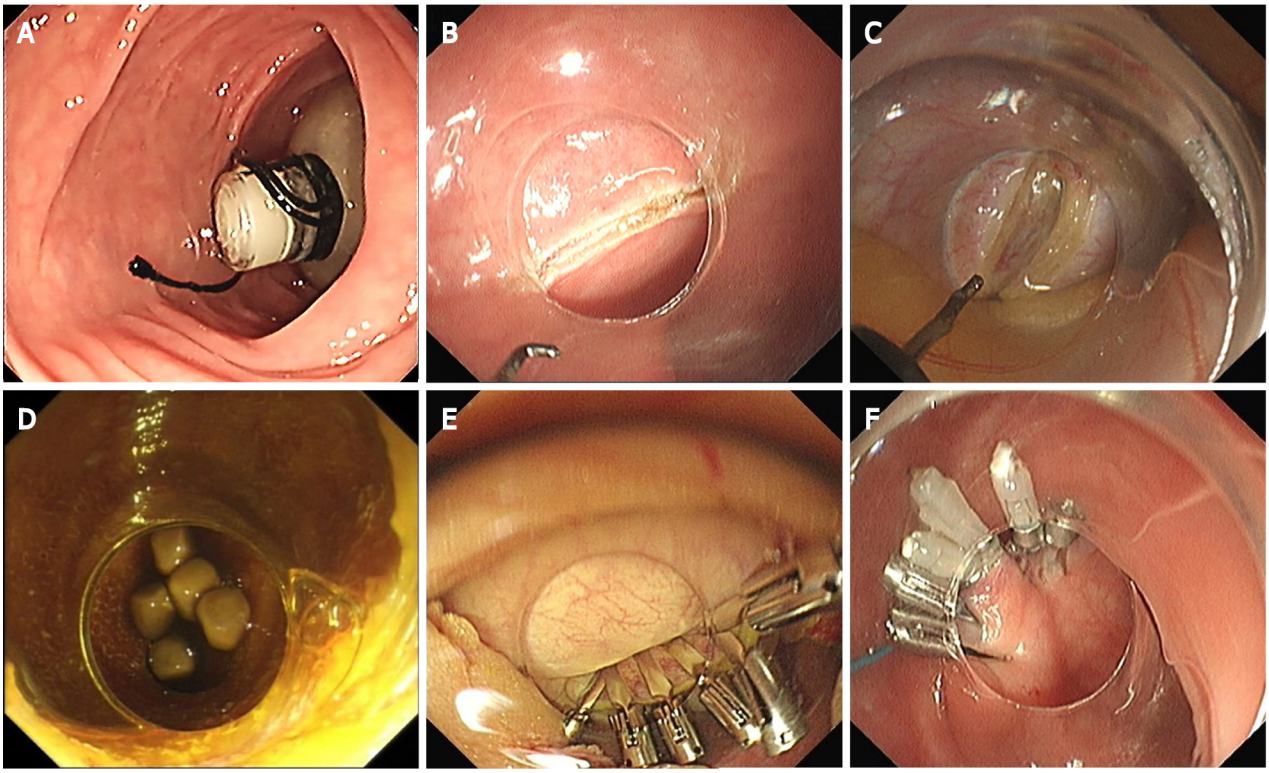
The study protocol was approved by the independent ethics committee of the Second Affiliated Hospital of Harbin University. Written informed consent was obtained from all patients before the procedure. All NOTES procedures were performed by an expert gastroenterologist with experience of more than 150 NOTES procedures. The research was carried out in accordance with the Helsinki Declaration. All authors had access to the study data, and reviewed and approved the final manuscript.

### *Patient selection for NOTES*

We extracted patient data from the inpatient database of the First Affiliated Hospital of Zhengzhou University who were treated for gallbladder disease from December 2017 to December 2020. The inclusion criteria were: (1) Patients over the age of 18 years and less than 80 years of age; (2) Patients with symptomatic cholelithiasis confirmed by B-ultrasound or other imaging examination (CT/MRI); (3) Patients with no history of major upper abdominal surgery; (4) A strong desire by the patient to retain the gallbladder; and (5) No absolute surgical contraindications, including severe hepatic, renal, cardiac and pulmonary insufficiency, history of cerebral coma and allergy to anesthesia *etc*. Exclusion criteria included: (1) Patients younger than 18 years or older than 80 years of age; (2) Patients with acute cholecystitis, chronic atrophic cholecystitis, atrophy of the gallbladder due to any reason and suspicion of gallbladder cancer; (3) Unable to undergo endoscopic surgery for various reasons such as associated other diseases or age factor; and (4) Could not be contacted or loss of information.

### *Interventions*

**Description of trans-rectal NOTES technique:** After routine bowel preparation, all procedures were




**DOI:** 10.4240/wjgs.v14.i5.470 **Copyright** ©The Author(s) 2022.

**Figure 2 Natural orifice transluminal endoscopic surgery trans-rectal gallbladder preserving cholecystolithotomy.** A: Detachable balloon placement in the colonic lumen; B: Rectum incision for trans-rectal access; C: Gallbladder incision; D: Visualization of gallbladder stones; E: Closure of the gallbladder wall with endoclips; F: Closure of the rectal incision with endoclips and endoloops.

performed under general anesthesia. With the patients in the lithotomy position, a colonoscope (EVIS GIF-Q260J, Olympus, Tokyo, Japan) was advanced into the transverse colon for colonic cleansing. A detachable colonic exclusion balloon was placed into the transverse colon with help of the colonoscope and inflated to 3.0-3.5 cm in diameter by injecting 120 to 140 mL of air into the balloon to occlude the transverse colonic lumen (Figure 2A). Cleansing and disinfection of the distal colonic and rectal lumen was then completed with a 0.1% povidone-iodine solution. A disinfected (a low temperature ethylene oxide processed) gastroscope with a transparent cap attached to the tip of the endoscope was inserted and an incision was made on the right anterior wall of the rectum 15 to 20 cm from the anal verge using Hook and IT knives (Figure 2B). The endoscope was advanced upward through the inter-bowel space into the upper peritoneal cavity where the liver and gallbladder were identified. A full-thickness longitudinal incision was created in the gallbladder wall using the Hook and IT knifes (Figure 2C). The tip of the endoscope was inserted into the gallbladder cavity and the bile was aspirated. The lumen was then cleansed with normal saline and the gallstones were extracted from the gallbladder using a biliary stone extractor (E151186, GMBH FLEX, Germany) and removed *via* the trans-rectal incision (Figure 2D). The gallbladder incision was closed with endoclips (longclip, HX-610-090, Olympus, Tokyo, Japan) (Figure 2E). The endoscope was then withdrawn and the stomal opening in the rectum was closed with endoclips and endoloops (HX-20L-1, Olympus, Tokyo, Japan) (Figure 2F). The colon occlusion balloon was deflated and removed and the colonic mucosa at the site of balloon occlusion was inspected (Videos 1 and 2
).

**Description of laparoscopic technique:** LC was performed by expert gastroenterology surgeons with experience of more than 500 cholecystectomies. LC was performed using a standard laparoscopic approach.

### Outcomes

The two methods of therapy were compared with regard to treatment success, procedure time, post-operative pain, time to normal diet intake, duration of hospital stay, and post-operative short- and long-term complications, and recurrence rate.

### Follow-up

The median follow-up period was one year (range: 6-40 mo). The primary outcome was treatment

success. In the NOTES-treated group, treatment success was defined as successful if the procedure was completed using endoscopic surgery without conversion to laparoscopic or open surgery. In the LC group, treatment success was identified as a successful cholecystectomy without converting to open surgery.

Secondary outcomes included procedure time, post-operative pain, duration of post-operative hospital stay, duration of fasting, and post-operative short-term (within 2 wk) and long-term complications, and recurrence rate. In the NOTES group, short-term complications included biliary peritonitis, fever, nausea and vomiting, bleeding and systemic complications (pulmonary embolism, stroke, cardiac events, acute renal failure, and sepsis). Long-term complications included recurrent gallstone, recurrent cholecystitis, diarrhea, constipation, and malignant tumors of the gallbladder. In the LC group, short-term complications included incisional infection, incisional pain, bile duct injury, anesthesia-related complications, and systemic complications. Long-term complications included abdominal pain, hernia, and digestive symptoms. All enrolled patients were followed up by telephone and/or medical records.

### Statistical analysis

We used logistic regression models for the calculation of propensity scores. We used a 1:1 propensity score matching (PSM) with the NOTES and LC groups and the caliper value fixed at 0.1 for the propensity matching score. The study matched clinical baseline indicators including age, sex, bilirubin levels, gallbladder stones, temperature, white blood cell count, and hemoglobin. An absolute standard difference of less than 0.1 was considered negligible between both groups. Categorical variables were expressed as frequency and percentages with 95%CI, and continuous variables (operative time, post-operative hospital stay, fasting time, and recurrent time) were expressed as medians with interquartile ranges (IQRs). The Pearson × 2 and Fisher's exact tests were used for categorical variables, and the Mann-Whitney test was applied for continuous variables. Gender, age, baseline leukocytes, total bilirubin, and number of gallbladder stones were analyzed by univariate Cox proportional risk regression for the 1-year recurrence-free outcome. PSM and all calculations were conducted with Stata/SE 15.0 (Stata Corp., College Station, TX, United States). A two-sided $P$ value less than 0.05 was considered statistically significant.

## RESULTS

### Population characteristics before and after PSM

We extracted data from 2511 patients from the inpatient database of patients treated for gallbladder disease. We excluded 15 patients younger than 18 years of age, 201 patients older than 80 years of age, 55 patients with malignant gallbladder tumor, 112 patients with open surgery, 1281 patients with chronic atrophic cholecystitis and/or atrophy of the gallbladder, 159 patients unable to undergo endoscopic surgery, and 171 patients who could not be contacted (lost to follow-up). Consequently, there were 517 patients eligible for matching (NOTES, 110; LC, 407), and yielded 86 patient pairs (Figure 3). Table 1 shows the characteristics of the patients before and after PSM.

### Short-term complications

In the NOTES group, one patient ($n$ = 85/86) was referred to open surgery for removal of the gallbladder due to adhesions between the gallbladder and surrounding tissue. The overall success rate was 98.9% (95%CI: 94.3%-99.8%; $n$ = 85/86). All the patients in the LC group successfully underwent LC with a success rate of 100%. Subsequent pathology confirmed chronic cholecystitis in all. The median operative time was 119 min (IQRs, 95-175) in the NOTES group which was longer than the LC group with a median time of 60 min (IQRs, 48-90), (difference, 59 min; $P$ < 0.001). The median duration of fasting in the NOTES group was 1 d (IQRs, 1-2) *vs* 2 d (IQRs, 1-3) in the LC group, (difference, 1 d; $P$ < 0.001). The median post-operative hospital stay was 4 d (IQRs, 3-6) in the NOTES group *vs* 4 d in the LC group (IQRs, 3-5), ($P$ = 0.092).

In the NOTES group, 2.3% (95%CI: 0.6%-8.9%; $n$ = 2/85) of patients developed post-operative biliary peritonitis. All the peritonitis patients recovered with abdominal irrigation (percutaneous flushing of the peritoneal cavity with saline solution) and combined antibiotic treatment. In the LC group, 2.3% (95%CI: 0.6%-7.4%; $n$ = 2/86) of patients developed lung infections, 5.8% (95%CI: 2.3%-11.7%; $n$ = 5/86) of patients had severe abdominal pain, 1 (1%, 95%CI: 0.2%-5.7%) patient had a wound infection with fever, and one patient had urinary retention. The mortality rate in both groups was 0%.

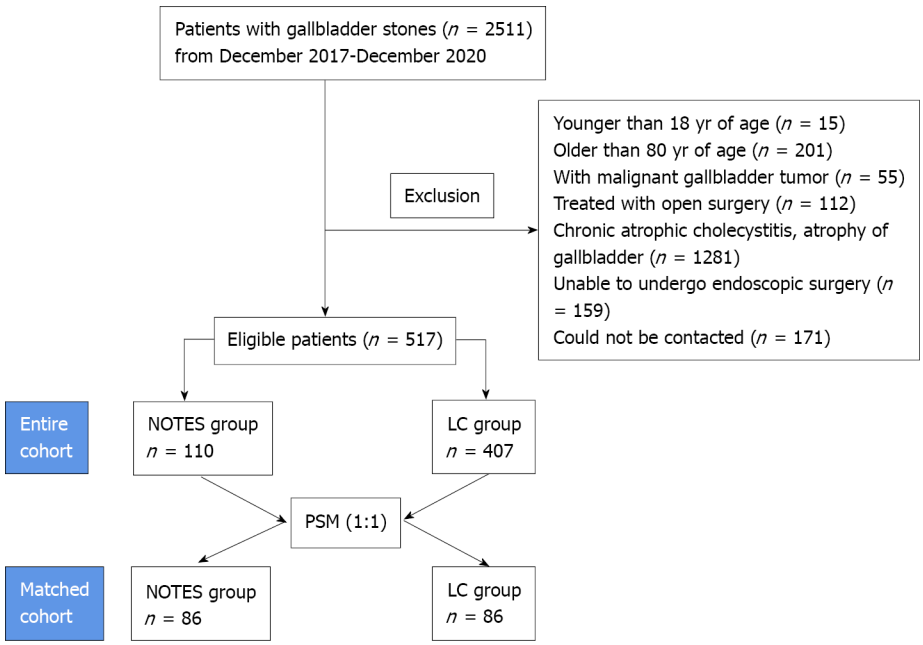
### Long-term complications (post-cholecystectomy syndrome)

During the follow-up period, all patients in the two groups are alive. In the LC group, 18.6% (95%CI: 10.6%-25.6%; $n$ = 16/86) of patients developed diarrhea, of which 8 (8.4%, 95%CI: 4.3%-15.7%) had frequent diarrhea, 5 (5.3%, 95%CI: 2.3%-11.7%) patients were prone to diarrhea after eating fatty foods, 3 (3.3%, 95%CI: 1.1%-8.9%) patients had occasional diarrhea, and diarrhea symptoms were not relieved by symptomatic treatment. In comparison, 5.8% (95%CI: 2.3%-11.8%; $n$ = 5/85) of NOTES patients

**Table 1 Baseline patient characteristics after propensity score matching**

| Variable | NOTES group (*n* = 86) | LA group (*n* = 86) | *P* value |
|---|---|---|---|
| Age, *n* (%) | | | 0.88 |
| ≤ 60 yr | 51 (59.3) | 50 (58.1) | |
| > 60 yr | 35 (40.7) | 36 (41.2) | |
| Sex, *n* (%) | | | 0.53 |
| Male | 55 (63.9) | 51 (59.3) | |
| Female | 31 (36.1) | 35 (40.7) | |
| Total bilirubin levels[1], *n* (%) | | | 0.72 |
| 0-25 | 83 (96.5) | 81 (94.2) | |
| > 25 | 3 (3.5) | 5 (5.8) | |
| Temperature[2], *n* (%) | | | 0.75 |
| ≤ 37.2°C | 6 (6.9) | 5 (5.8) | |
| > 37.2°C | 80 (93.1) | 81 (94.2) | |
| Gallbladder stones, *n* (%) | | | 0.75 |
| ≤ 3 | 6 (6.9) | 5 (5.8) | |
| > 3 (or Mud-like gallstones) | 80 (93.1) | 81 (94.2) | |

[1]Total bilirubin levels, reference: 0-25 μmol/L.
[2]Baseline temperature, reference: 36.3-37.2 °C.
The data are presented in the form *n* (%). NOTES: Natural orifice transluminal endoscopic surgery.




**DOI:** 10.4240/wjgs.v14.i5.470 

**Figure 3 Flow chart of the entire and matched cohort.** NOTES: Natural orifice transluminal endoscopic surgery.

presented with diarrhea, 3 of them after undergoing cholecystectomy which was significantly less frequent than after LC [difference, 11.5 percentage points (95%CI: 2.5-20.8); *P* = 0.011]. 2.3% (95%CI: 0.6%-7.4%; *n* = 2/85) of NOTES patients presented with constipation *vs* 3.5% (95%CI: 1.1%-8.9%; *n* = 3/86) of LC patients [difference, 1.03 percentage points (95%CI: -0.5-7); *P* = 0.663].

In the LC group, 5.8% (95%CI: 2.3%-11.7%; *n* = 5/86) of patients had pain in the surgical area with anxiety; 17.4% (95%CI: 9.8%-24.4%; *n* = 15/86) of patients were concerned about scars on the abdominal wall (mainly women). 11.6% (95%CI: 5.8%-18.3%; *n* = 10/86) of patients had decreased appetite and

reduced their diet compared to their preoperative status. Only 2.3% ($n$ = 2/85) of NOTES patients had decreased appetite [difference, 8.4 percentage points (95%CI: 1.3-16.3); $P$ = 0.018]. Two (2.3%, 95%CI: 0.6%-7.4%) patients had back pain after exertion, and one (1.06%, 95%CI: 0.2%-5.7%) patient had chest tightness. One (1.06%, 95%CI: 0.2%-5.7%) patient developed renal calculi (Table 2).

### *Risk factors for patients with recurrent gallbladder stones*

Nine NOTES patients had recurrence of gallbladder stones suggested by abdominal ultrasound. The recurrent gallbladder stones were all mud-like stones with a median recurrence time of 210 d (IQRs, 165-255). The recurrence rate was 10.5% (95%CI: 5.1%-17.2%; $n$ = 9/85); 5 underwent cholecystectomy; 4 patients were asymptomatic and they did not wish to undergo further therapy with either NOTES or LC. We recommended re-NOTES or LC for recurrent cases. The post-operative pathology revealed chronic cholecystitis; 3.5% (95%CI: 1.1%-9%; $n$ = 3/85) of patients had pain in the right upper abdomen and the diagnosis of cholecystitis recurrence was made by ultrasound and CT examination, of which 1 (1.1%, 95%CI: 0.2%-5.8%) patient had gallbladder stones combined with cholecystitis. In patients with recurrence who did not receive surgical treatment, symptoms were significantly reduced after antibiotic treatment. Figure 4A shows the cumulative incidence of recurrent gallbladder stones and Figure 4B shows recurrent cholecystitis in the NOTES patients. To identify risk factors for recurrence of gallbladder stones, we performed univariate Cox regression analysis of gender, baseline leukocytes, number of gallstones, and age, and none of these factors were statistically significant for recurrence of gallbladder stones.

## DISCUSSION

Symptomatic gallstones are common and cholecystectomy remains the 'gold standard' for their management[25,26]. In 1987, the first LC was conducted which ushered in the age of cholecystectomy with minimal trauma and rapid recovery. This approach demonstrated superiority and created a precedent for minimally invasive operations. Subsequently, with improved technology, many patients with cholelithiasis worldwide have undergone LC and this technique has become the standard treatment for cholelithiasis. However, simple gallstone extraction with gallbladder preservation (cholecystolithotomy) has been proposed in order to preserve the normal physiological function of the gallbladder, avoid post-cholecystectomy syndrome, bile duct injury, complications due to abdominal wall incisions, bile reflux gastritis, and reduce the incidence of gastrointestinal cancer[27-29]. The justification for this practice includes considerations regarding safety, reduced short- and long-term complications as well as cosmetic results and patient satisfaction. Besides this, in clinical practice, we have found that many Chinese patients express a strong desire for preservation of their gallbladder. In response to the clinical desires and importance of gallbladder preservation in a large number of patients, we developed pure NOTES trans-rectal gallbladder preserving cholecystolithotomy as an ultra-minimally invasive technique for removal of gallbladder stones and gallbladder preservation.

Both LC and NOTES approaches have advantages and disadvantages. The advantages of NOTES cholecystolithotomy include: (1) Organ retention and preserved biological function; (2) No incision on the body surface; (3) Early diet intake (*e.g.*, 6 h after the procedure patients are able to take a liquid diet); (4) Reduced post-operative pain; and (5) Fewer long-term complications compared to LC.

The problem with this approach is the current longer procedure time than that for LC and the potential for recurrence of gallstones. Long operative time is expected during the early clinical stage. During initial laparoscopic surgery, a 2-3 h operation was common. With experience and improved techniques, the operative time for NOTES cholecystolithotomy is expected to decrease.

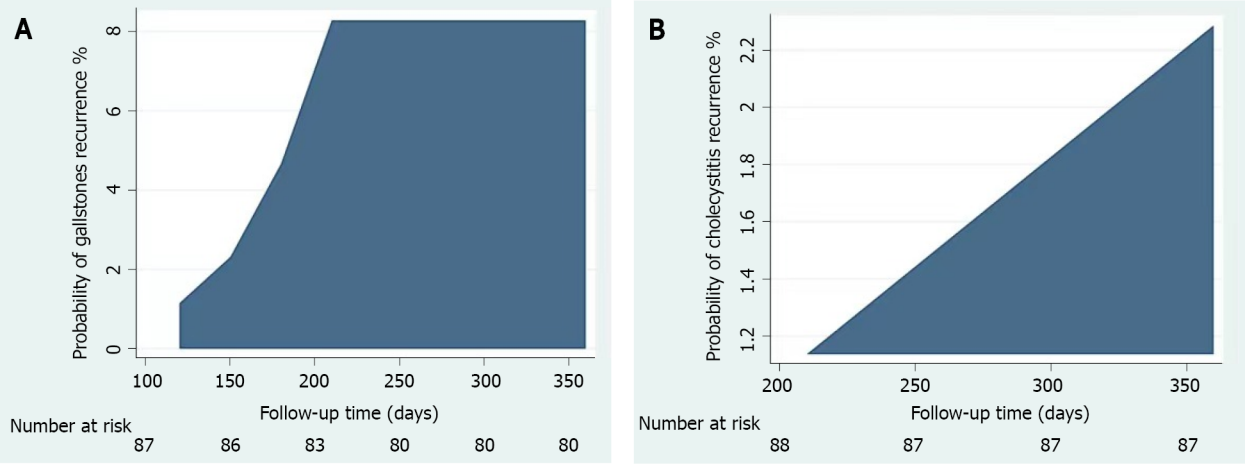
Gallstone recurrence remains a concern. A recent report showed that the average recurrence risk for percutaneous cholecystolithotomy was 3% in 4 years and 10% in 15 years[30]. In China, a long-term analysis of the gallstone recurrence rate after laparoscopic cholecystolithotomy over more than 15 years reported a rate of 10.1% within both 10 and 15 years[31]. In our study, the recurrence risk of gallstones was 9.8% (9/94) during 6 to 40 mo of follow-up. Widespread use of NOTES cholecystolithotomy may require development of a reliable method to prevent recurrence of gallstones. A randomized, double-blind placebo-controlled multicenter clinical trial reported that ursodeoxycholic acid is a safe and effective drug for the prevention of gallstone recurrence[32]. In an another meta-analysis Li *et al*[33] noted that not taking oral ursodeoxycholic acid after gallbladder preserving therapy increased the rate of stone recurrence[33]. Therefore, we recommend that patients who undergo cholecystolithotomy take ursodeoxycholic acid orally to prevent the recurrence of stones. However, further studies are needed to explore the mechanism, dosing and duration of therapy to prevent recurrence of gallstones before final recommendations are made.

The advantage of LC is a shorter procedure time than with NOTES. Disadvantages include: (1) The organ is resected so the loss of its biological function may result in long-term complications; (2) A scar on the body surface; (3) Diet intake is delayed (*e.g.* on day 2); (4) Risk of incision-related complications; and (5) More short- and long-term complications than that with NOTES (abdominal pain, nausea, diarrhea, constipation, fatty food intolerance, indigestion, association with colon cancer, functional

**Table 2 Short- and long-term complications in the laparoscopic cholecystectomy and natural orifice transluminal endoscopic surgery cholecystolithotomy treatment groups**

| | NOTES group, *n* (%), (95%CI) | Laparoscopic group, *n* (%), (95%CI) | Differences |
|---|---|---|---|
| **Short-term complications** | | | |
| Biliary peritonitis | 2 (2.3), 0.6-8.9 | 0 (0), - | < 0.497 |
| Post-operative pain (Abdominal or incisional) | 4 (4.7), 1.8-11.4 | 5 (5.8), 2.5-12.9 | 0.740 |
| Lung infection | 0 (0), - | 2 (2.3), 0.6-9.9 | |
| Incisional infection | 0 (0), - | 1 (1.2), 0.2-6.3 | |
| Urinary retention | 0 (0), - | 1 (1.2), 0.2-6.3 | |
| **Long-term complications** | | | |
| Diarrhea | 5 (5.8), 2.5-12.9 | 16 (18.6), 11.8-28.1 | 0.011 |
| Constipation | 2 (2.3), 0.6-8.9 | 3 (3.5), 1.2-9.8 | 0.063 |
| Decreased appetite | 2 (2.3), 0.6-8.9 | 10 (11.6), 6.4-20.1 | 0.018 |
| Pain with anxiety in surgical area | - | 5 (5.8), 2.5-12.9 | |
| **Concerned about scars** | - | 15 (17.4), 10.9-26.8 | |
| **Gallstones recurrence** | 9 (10.5), 5.6-18.7 | | |
| **Cholecystitis recurrence** | 3 (3.5), 1.2-9.8 | | |

NOTES: Natural orifice transluminal endoscopic surgery.




**DOI:** 10.4240/wjgs.v14.i5.470 

**Figure 4 The cumulative incidence of recurrent gallbladder stones and recurrent cholecystitis in the natural orifice transluminal endoscopic surgery group.** A: Cumulative incidence of recurrent gallbladder stones in natural orifice transluminal endoscopic surgery (NOTES) patients; B: Cumulative incidence of recurrent cholecystitis in the NOTES patients.

gastrointestinal and psychological conditions)[14-18].

There was no significant difference in duration of hospital stay between the two groups. Initially, we admitted patients after undergoing NOTES procedure for a longer than usual time as this was a preliminary study with a limited sample size. Post-operative stay ranged between 3 and 5 d *vs* same day surgery for LC in the United States and western world, which might raise questions. The explanation for this is that in China the standard of post-operative care is different, and after all types of abdominal surgery (laparoscopic or open surgery) patients remain in hospital under observation for 3-5 d.

In our study, the most significant differences between the two groups were long-term complications and no wound infections. Although, LC seems to be a 50 min procedure with a good outcome, its long-time complications are largely unstudied including post-cholecystectomy syndrome and a possible association with colon cancer. On the other hand, the only long-term reported (10-15 years of follow-up) complication of percutaneous cholecystolithotomy has been gallstones recurrence. The main reported factors associated with the recurrence of gallstones are a family history of cholelithiasis, a preference for

greasy food and gallbladder dysfunction prior to cholecystolithotomy[29-33].

Compared with LC, NOTES is more than a cosmetic technique to perform surgery as it also has the potential to reduce anesthesia requirements, accelerate patient recovery, and, above all, provide minimally invasive access to organs that are otherwise difficult to access with conventional open or laparoscopic approaches. In addition, some patients refuse surgery and some older patients are not considered candidates for surgical procedures. NOTES provides an alternative option to treat gallstone disease. Although we found short-term complications and recurrences, overall, the safety and efficacy were good with NOTES. With time and improved technology these complications will likely be reduced.

This study has some limitations, including NOTES is a new technique, a retrospective study design, small cohort, and absence of a control group which makes the study prone to attrition and possible loss of clinical data. The same limits the generalizability of the study. Additional studies especially larger multi-center trials are needed to confirm the advantages shown here, and to understand the future for this innovative new approach in the treatment of symptomatic gallstones.

## CONCLUSION

In conclusion, NOTES appears to be a minimally invasive and feasible alternative technique for the management of patients with symptomatic gallstones. In our study more than 85% of patients showed good results without complications. Its advantages include no skin wound, organ retention, quick recovery, fewer post-operative complications, and patient satisfaction. Although, this procedure is unlikely to immediately replace LC, it proved useful for patients wishing to avoid surgical resection, and produced good results. Reducing the recurrence of gallstones is essential to achieve widespread clinical adoption of NOTES.

## ARTICLE HIGHLIGHTS

### *Research background*

Laparoscopic cholecystectomy (LC) remains the preferred option for symptomatic gallstones. However, the gallbladder functions in regulating bile flow and storing bile, and cholecystectomy may disrupt the whole biliary system and induce subsequent complications. Simple gallstone extraction with gallbladder preservation (cholecystolithotomy) has been proposed in order to preserve gallbladder function and to avoid gallbladder resection-related complications.

### *Research motivation*

In response to the clinical desires and importance of gallbladder retention in a large number of patients, we developed pure natural orifice transluminal endoscopic surgery (NOTES) trans-rectal gallbladder preserving cholecystolithotomy as an ultra-minimally invasive technique for removal of gallbladder stones and gallbladder preservation.

### *Research objectives*

To compare the feasibility, safety and effectiveness of pure NOTES gallbladder-preserving cholecystolithotomy *vs* LC for symptomatic gallstones.

### *Research methods*

We extracted patient data from the inpatient database and adopted propensity score matching (1:1) to compare trans-rectal NOTES cholecystolithotomy and LC in patients with symptomatic gallstones.

### *Research results*

The technical success rate for the NOTES group *vs* the LC group was 98.9% *vs* 100%. Post-operative pain was similar between NOTES and LC; however, the median duration of fasting was less in NOTES patients. During the follow-up period, diarrhea was significantly less with NOTES (5.8%) compared to LC (18.6%). The recurrence rate of stones and cholecystitis within a median of 12 mo (range: 6-40 mo) following NOTES was 10.5% and 3.5%, respectively. Concerns regarding the presence of abdominal wall scars were present in patients following LC.

### *Research conclusions*

NOTES appears to be a minimally invasive and feasible alternative scar-free technique for the management of patients with symptomatic gallstones. Reducing the recurrence of gallstones is essential to achieve widespread clinical adoption of NOTES.

### *Research perspectives*

Although cholecystectomy remains the mainstay in gallstones treatment due to its unique merits, it may not be feasible in surgical patients at high-risk or with biliary deformity. In addition, since post-operative adverse events after removal of the gallbladder are inevitable in some patients, more and more endoscopists are interested in preservation of gallbladder function during the management of gallstones. Therefore, in our opinion NOTES cholecystolithotomy may be an alternative treatment for symptomatic gallstones, especially for patients wishing to avoid surgical resection.

## ACKNOWLEDGEMENTS

We express our gratitude to Professor David Y Graham, Baylor College of Medicine, Houston, United States, for his encouragement and assistance in revising the manuscript.

## FOOTNOTES

**Author contributions:** Liu BR, Saif U and Yang BH contributed to the design of the study, collected data and drafted the manuscript; Yang BH, Lu XY performed the data analyses and revised the manuscript; Zhao LX, Liu D, and Liu ZZ helped perform the analysis with constructive discussions; Zhang JY and Saif U contributed to manuscript preparation data for the work; Liu BR conceived the work that led to the submission and approved the final version; all authors issued final approval for the version to be submitted.

**Supported by** Outstanding Foreign Scientist Studio Project of Henan Province, No. GZS2020006.

**Institutional review board statement:** This study was reviewed and approved by the Independent Ethics Committee of the Second Affiliated Hospital of Harbin University and the First Affiliated Hospital of Zhengzhou University.

**Informed consent statement:** All study participants or their legal guardian provided informed written consent regarding personal and medical data collection prior to study enrolment.

**Conflict-of-interest statement:** We have no financial relationships to disclose.

**Data sharing statement:** No additional data are available.



**Country/Territory of origin:** China

**ORCID number:** Saif Ullah 0000-0003-0064-8942; Bao-Hong Yang 0000-0003-3286-1967; Dan Liu 0000-0001-8313-4343; Xue-Yang Lu 0000-0002-8468-8425; Zhen-Zhen Liu 0000-0001-6674-5396; Li-Xia Zhao 0000-0002-1114-9754; Ji-Yu Zhang 0000-0003-1919-4418; Bing-Rong Liu 0000-0001-6101-8675.

**S-Editor:** Fan JR
**L-Editor:** Webster JR
**P-Editor:** Fan JR

## REFERENCES

1 **Zeng Q**, He Y, Qiang DC, Wu LX. Prevalence and epidemiological pattern of gallstones in urban residents in China. *Eur J Gastroenterol Hepatol* 2012; **24**: 1459-1460 [PMID: 23111386 DOI: 10.1097/MEG.0b013e3283583d13]
2 **Bar-Meir S**. Gallstones: prevalence, diagnosis and treatment. *Isr Med Assoc J* 2001; **3**: 111-113 [PMID: 11344819]
3 **Festi D**, Dormi A, Capodicasa S, Staniscia T, Attili AF, Loria P, Pazzi P, Mazzella G, Sama C, Roda E, Colecchia A. Incidence of gallstone disease in Italy: results from a multicenter, population-based Italian study (the MICOL project). *World J Gastroenterol* 2008; **14**: 5282-5289 [PMID: 18785280 DOI: 10.3748/wjg.14.5282]
4 **Duncan CB**, Riall TS. Evidence-based current surgical practice: calculous gallbladder disease. *J Gastrointest Surg* 2012; **16**: 2011-2025 [PMID: 22986769 DOI: 10.1007/s11605-012-2024-1]
5 **Litynski GS**. Highlights in the History of Laparoscopy. *Barbara Bernert Verlag* 1996; 165-168 [DOI: 10.1080/110241598750005336]
6 **Reynolds W Jr**. The first laparoscopic cholecystectomy. *JSLS* 2001; **5**: 89-94 [PMID: 11304004]

7 **Zanghì G**, Leanza V, Vecchio R, Malaguarnera M, Romano G, Rinzivillo NM, Catania V, Basile F. Single-Incision Laparoscopic Cholecystectomy: our experience and review of literature. *G Chir* 2015; **36**: 243-246 [PMID: 26888698 DOI: 10.11138/gchir/2015.36.6.243]

8 **Talseth A**, Lydersen S, Skjedlestad F, Hveem K, Edna TH. Trends in cholecystectomy rates in a defined population during and after the period of transition from open to laparoscopic surgery. *Scand J Gastroenterol* 2014; **49**: 92-98 [PMID: 24354967 DOI: 10.3109/00365521.2013.853828]

9 **Rao GV**, Reddy DN, Banerjee R. NOTES: human experience. *Gastrointest Endosc Clin N Am* 2008; **18**: 361-70; x [PMID: 18381176 DOI: 10.1016/j.giec.2008.01.007]

10 **Akiyama H**, Nagusa Y, Fujita T, Shirane N, Sasao T, Iwamori S, Hidaka T, Okuhara T. A new method for nonsurgical cholecystolithotomy. *Surg Gynecol Obstet* 1985; **161**: 72-74 [PMID: 4012547]

11 **Kerlan RK Jr**, LaBerge JM, Ring EJ. Percutaneous cholecystolithotomy: preliminary experience. *Radiology* 1985; **157**: 653-656 [PMID: 4059554 DOI: 10.1148/radiology.157.3.4059554]

12 **Pai RD**, Fong DG, Bundga ME, Odze RD, Rattner DW, Thompson CC. Transcolonic endoscopic cholecystectomy: a NOTES survival study in a porcine model (with video). *Gastrointest Endosc* 2006; **64**: 428-434 [PMID: 16923495 DOI: 10.1016/j.gie.2006.06.079]

13 **Ye L**, Liu J, Tang Y, Yan J, Tao K, Wan C, Wang G. Endoscopic minimal invasive cholecystolithotomy *vs* laparoscopic cholecystectomy in treatment of cholecystolithiasis in China: a meta-analysis. *Int J Surg* 2015; **13**: 227-238 [PMID: 25527194 DOI: 10.1016/j.ijsu.2014.12.014]

14 **Jaunoo SS**, Mohandas S, Almond LM. Postcholecystectomy syndrome (PCS). *Int J Surg* 2010; **8**: 15-17 [PMID: 19857610 DOI: 10.1016/j.ijsu.2009.10.008]

15 **Barrett M**, Asbun HJ, Chien HL, Brunt LM, Telem DA. Bile duct injury and morbidity following cholecystectomy: a need for improvement. *Surg Endosc* 2018; **32**: 1683-1688 [PMID: 28916877 DOI: 10.1007/s00464-017-5847-8]

16 **Lum YW**, House MG, Hayanga AJ, Schweitzer M. Postcholecystectomy syndrome in the laparoscopic era. *J Laparoendosc Adv Surg Tech A* 2006; **16**: 482-485 [PMID: 17004873 DOI: 10.1089/Lap.2006.16.482]

17 **Zhang Y**, Peng J, Li X, Liao M. Endoscopic-Laparoscopic Cholecystolithotomy in Treatment of Cholecystolithiasis Compared With Traditional Laparoscopic Cholecystectomy. *Surg Laparosc Endosc Percutan Tech* 2016; **26**: 377-380 [PMID: 27579981 DOI: 10.1097/SLE.0000000000000305]

18 **Tsai MC**, Chen CH, Lee HC, Lin HC, Lee CZ. Increased Risk of Depressive Disorder following Cholecystectomy for Gallstones. *PLoS One* 2015; **10**: e0129962 [PMID: 26053886 DOI: 10.1371/journal.pone.0129962]

19 **Renz BW**, Bösch F, Angele MK. Bile Duct Injury after Cholecystectomy: Surgical Therapy. *Visc Med* 2017; **33**: 184-190 [PMID: 28785565 DOI: 10.1159/000471818]

20 **Abbasoğlu O**, Tekant Y, Alper A, Aydın Ü, Balık A, Bostancı B, Coker A, Doğanay M, Gündoğdu H, Hamaloğlu E, Kapan M, Karademir S, Karayalçın K, Kılıçturgay S, Şare M, Tümer AR, Yağcı G. Prevention and acute management of biliary injuries during laparoscopic cholecystectomy: Expert consensus statement. *Ulus Cerrahi Derg* 2016; **32**: 300-305 [PMID: 28149133 DOI: 10.5152/UCD.2016.3683]

21 **Zha Y**, Chen XR, Luo D, Jin Y. The prevention of major bile duct injures in laparoscopic cholecystectomy: the experience with 13,000 patients in a single center. *Surg Laparosc Endosc Percutan Tech* 2010; **20**: 378-383 [PMID: 21150413 DOI: 10.1097/SLE.0b013e3182008efb]

22 **Liu B**, Du B, Pan Y. Video of the Month: Transrectal Gallbladder-Preserving Cholecystolithotomy *via* Pure Natural Orifice Transluminal Endoscopic Surgery: First Time in Humans. *Am J Gastroenterol* 2015; **110**: 1655 [PMID: 26673494 DOI: 10.1038/ajg.2015.266]

23 **Du B**, Fan YJ, Zhao LX, Geng XY, Li L, Wu XW, Zhang K, Liu BR. A reliable detachable balloon that prevents abdominal cavity contamination during transrectal natural orifice transluminal endoscopic surgery. *J Dig Dis* 2019; **20**: 383-390 [PMID: 31069947 DOI: 10.1111/1751-2980.12757]

24 **Zhao LX**, Liu ZZ, Ullah S, Liu D, Yang HY, Liu BR. The detachable balloon: A novel device for safe trans-rectal natural orifice transluminal endoscopic surgery. *Dig Liver Dis* 2021; **53**: 931-934 [PMID: 33994130 DOI: 10.1016/j.dld.2021.04.019]

25 **Lammert F**, Gurusamy K, Ko CW, Miquel JF, Méndez-Sánchez N, Portincasa P, van Erpecum KJ, van Laarhoven CJ, Wang DQ. Gallstones. *Nat Rev Dis Primers* 2016; **2**: 16024 [PMID: 27121416 DOI: 10.1038/nrdp.2016.24]

26 **Qu Q**, Chen W, Liu X, Wang W, Hong T, Liu W, He X. Role of gallbladder-preserving surgery in the treatment of gallstone diseases in young and middle-aged patients in China: results of a 10-year prospective study. *Surgery* 2020; **167**: 283-289 [PMID: 31606197 DOI: 10.1016/j.surg.2019.09.001]

27 **Du S**, Zhu L, Sang X, Mao Y, Lu X, Zhong S, Huang J. Gallbladder carcinoma post gallbladder-preserving cholecystolithotomy: a case report. *Hepatobiliary Surg Nutr* 2012; **1**: 61-63 [PMID: 24570906 DOI: 10.3978/j.issn.2304-3881.2012.07.01]

28 **Tan YY**, Zhao G, Wang D, Wang JM, Tang JR, Ji ZL. A new strategy of minimally invasive surgery for cholecystolithiasis: calculi removal and gallbladder preservation. *Dig Surg* 2013; **30**: 466-471 [PMID: 24481280 DOI: 10.1159/000357823]

29 **Zhu X**, Liu J, Wang F, Zhao Q, Zhang X, Gu J. Influence of traditional Chinese culture on the choice of patients concerning the technique for treatment of cholelithiasis: Cultural background and historical origins of gallbladder-preserving surgery. *Surgery* 2020; **167**: 279-282 [PMID: 31590916 DOI: 10.1016/j.surg.2019.05.037]

30 **Gao DK**, Wei SH, Li W, Ren J, Ma XM, Gu CW, Wu HR. Totally laparoscopic gallbladder-preserving surgery: A minimally invasive and favorable approach for cholelithiasis. *Exp Ther Med* 2015; **9**: 395-398 [PMID: 25574204 DOI: 10.3892/etm.2014.2107]

31 **Liu J**, Li J, Zhao Q. The analyses of the results of 612 cases with gallbladder stones who underwent fibrocholedocoscope cholecystectomy for removal of caculas and preservation of gallbladder (Chinese Article). *Mag Chin Surg* 2009; **47**: 279-281 [DOI: 10.1007/978-981-15-6010-1_28]

32 **Kosters A**, Jirsa M, Groen AK. Genetic background of cholesterol gallstone disease. *Biochim Biophys Acta* 2003; **1637**: 1-19 [PMID: 12527402 DOI: 10.1016/s0925-4439(02)00173-4]

33 **Li W**, Huang P, Lei P, Luo H, Yao Z, Xiong Z, Liu B, Hu K. Risk factors for the recurrence of stones after endoscopic minimally invasive cholecystolithotomy in China: a meta-analysis. *Surg Endosc* 2019; **33**: 1802-1810 [PMID: 30701362 DOI: 10.1007/s00464-018-6455-y]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 May 27; 14(5): 482-493

DOI: 10.4240/wjgs.v14.i5.482

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Observational Study

# Application of omental interposition to reduce pancreatic fistula and related complications in pancreaticoduodenectomy: A propensity score-matched study

Yang Li, Yun Liang, Yao Deng, Zhi-Wei Cai, Ming-Jian Ma, Long-Xiang Wang, Meng Liu, Hong-Wei Wang, Chong-Yi Jiang

**Specialty type:** Surgery

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Kessel B, Israel; Suc B, France; Vasavada B, India

**Received:** December 16, 2021
**Peer-review started:** December 16, 2021
**First decision:** March 13, 2022
**Revised:** March 16, 2022
**Accepted:** April 24, 2022
**Article in press:** April 24, 2022
**Published online:** May 27, 2022

**Yang Li, Yun Liang, Yao Deng, Zhi-Wei Cai, Ming-Jian Ma, Long-Xiang Wang, Meng Liu, Hong-Wei Wang, Chong-Yi Jiang,** Department of General Surgery, Huadong Hospital Affiliated to Fudan University, Shanghai 200040, China

**Yun Liang,** Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center, Shanghai 200032, China

**Corresponding author:** Chong-Yi Jiang, MD, Chief Doctor, Department of General Surgery, Huadong Hospital Affiliated to Fudan University, No. 221 West Yan'an Road, Shanghai 200040, China. jiangzhongyi9@sina.com

## Abstract

***BACKGROUND***

The life-threatening complications following pancreatoduodenectomy (PD), intra-abdominal hemorrhage, and postoperative infection, are associated with leaks from the anastomosis of pancreaticoduodenectomy. Although several methods have attempted to reduce the postoperative pancreatic fistula (POPF) rate after PD, few have been considered effective. The safety and short-term clinical benefits of omental interposition remain controversial.

***AIM***

To investigate the safety and feasibility of omental interposition to reduce the POPF rate and related complications in pancreaticoduodenectomy.

***METHODS***

In total, 196 consecutive patients underwent PD performed by the same surgical team. The patients were divided into two groups: An omental interposition group (127, 64.8%) and a non-omental interposition group (69, 35.2%). Propensity score-matched (PSM) analyses were performed to compare the severe complication rates and mortality between the two groups.

***RESULTS***

Following PSM, the clinically relevant POPF (CR-POPF, 10.1% *vs* 24.6%; $P = 0.025$) and delayed postpancreatectomy hemorrhage (1.4% *vs* 11.6%; $P = 0.016$) rates were significantly lower in the omental interposition group. The omental inter-

position technique was associated with a shorter time to resume food intake (7 d *vs* 8 d; $P = 0.048$) and shorter hospitalization period (16 d *vs* 21 d; $P = 0.031$). Multivariate analyses showed that a high body mass index, nonapplication of omental interposition, and a main pancreatic duct diameter < 3 mm were independent risk factors for CR-POPF.

*CONCLUSION*
The application of omental interposition is an effective and safe approach to reduce the CR-POPF rate and related complications after PD.

**Key Words:** Pancreaticoduodenectomy; Pancreatic fistula; Complication; Omental interposition



**Core Tip:** Postoperative pancreatic fistula (POPF) is a life-threatening complication after pancreaticoduodenectomy. Multiple methods have been described in the literature to prevent POPF; however, few trials have demonstrated that a certain method can achieve good clinical outcomes. In this study, we proved that the application of omental interposition can reduce the incidence of clinically relevant POPF, which is associated with a trend towards accelerated recovery.

**Citation:** Li Y, Liang Y, Deng Y, Cai ZW, Ma MJ, Wang LX, Liu M, Wang HW, Jiang CY. Application of omental interposition to reduce pancreatic fistula and related complications in pancreaticoduodenectomy: A propensity score-matched study. *World J Gastrointest Surg* 2022; 14(5): 482-493
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i5/482.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i5.482

## INTRODUCTION

Pancreaticoduodenectomy is the gold standard for benign or malignant tumors in the periampullary region. Despite advances in surgical techniques and perioperative care, the postoperative morbidity rate remains high (20-50%), even in high-volume comprehensive hospitals[1-3]. Postoperative pancreatic fistula (POPF) is a life-threatening complication because of its interrelationship with delayed postpancreatectomy hemorrhage (PPH) and postoperative intraabdominal infection[4]. POPF is responsible for erosion of the gastroduodenal artery stump (GDAS), skeletonized hepatic artery (HA), or other adjacent abdominal vessels due to activated pancreatic enzymes.

During the last quarter of the 20$^{th}$ century, multiple methods have been described in the literature to prevent POPF and subsequent complications, including the usage of somatostatin or octreotide, introduction of pancreatic duct stenting, creation of various anastomosis techniques (*e.g.*, duct-to-mucosa, pancreatogastrostomy, invagination), use of polyethylene glycolic acid mesh to reinforce around the pancreatojejunostomy (PJ) site, and use of fibrin glue over the PJ site[5-9]. However, few trials have demonstrated that a certain method will reinforce the PJ site in PD with favorable clinical outcomes.

Currently, the greater omentum has been widely used to reinforce anastomoses and compensate for tissue defects in the fields of thoracic, urinary, and general surgery[10-12]. Recently, some centers have shown that fixing the omental interposition behind the anastomotic site of the PJ to protect the GDAS and nearby HA from erosive pancreatic juices is the most promising approach to reduce the incidence of severe complications[13,14], but they did not have control group data.

Our study investigated whether the application of the omental interposition could effectively reduce the incidence of POPF and its related complications after pancreaticoduodenectomy.

## MATERIALS AND METHODS

### *Patients*

Between January 2015 and December 2019, 196 consecutive patients underwent pancreaticoduodenectomy performed by the same surgical team at our institution. The first 69 consecutive patients did not use omental interpositions, and the remaining 127 used omental interpositions. According to whether the omental interposition was applied, the patients were divided into two groups: the omental group (79 males, 48 females; mean age: 64.8 years) and the non-omental interposition group (44 males, 25 females; mean age: 62.1 years). Propensity score matching (PSM) was used to minimize bias from the

nonrandomized treatment assignments. We summarized the data on the general clinical characteristics, short-term surgical outcomes, and recovery. Moreover, the laboratory data on the drain fluid amylase obtained on the first postoperative day (DFA1) were pooled. All data were prospectively collected in our electronic media database. This study was approved by the ethics review committee of Huadong Hospital Affiliated to Fudan University (2019K087; Shanghai, China).

### Surgical technique

At our institution, PD was accomplished with a standard approach. After the head of the pancreas had been removed, intestinal reconstruction was achieved with a modified version of the method described by Child. A reconstruction PJ was performed (by duct-to-mucosa, end-to-side reconstruction) and a pancreatic drainage tube was placed. (1) Insert the pancreatic juice drainage tube into 3-5 cm and use 4-0 polydioxanone suture to insert the needle from the ventral side of the pancreatic duct, penetrate the anterior and posterior walls of the pancreatic juice drainage tube, and suture from the back of the pancreatic duct to fix the drainage tube; (2) Place the pancreatic juice drainage tube into the distal end of the jejunal loop, and purse suture of the jejunal incision; and (3) Use 3-0 prolene to suture of seromuscular layer of pancreas and jejunum. Hepaticojejunostomy (HJ) was performed with continuous barbed sutures or interrupted sutures. Gastrojejunostomy (GJ) was performed with interrupted 3-0 polypropylene monofilament sutures.

In the omental interposition group, following complete anastomosis, we routinely placed a pedicled omental interposition in front of the adjacent vessels (HA, PV, and GDAS) and behind the anastomosis where the pancreas stump was fixed to the jejunum[15]. The omental interposition was fixed to the hepatic portal and hepatogastric ligament with several sutures to prevent postoperative mobilization (Figure 1). Generally, the upper boundary of the omental interposition was the level of the hepatogastric ligament, the left boundary was the level of the pancreatic body, and the right boundary was the right margin of the inferior vena cava, so that the omental interposition could separate skeletonized vessels from a possible anastomotic leakage. Then two double catheterization cannulas (PJ tube and HJ tube) were placed at the left anterior of the PJ anastomosis site and right posterior of the HJ anastomosis site, respectively. The blood flow of the omental interposition was reconfirmed before the abdominal cavity was closed. The application of the omental interposition in PD is shown in Figure 2.

In the non-omental interposition group, we simply placed the two drainage tubes at the aforementioned positions after completing the anastomosis. After the operation, the amylase concentration from the drainage fluid was measured daily. If the drain fluid amylase obtained on DFA1 exceeded 2000 U/L, abdominal irrigation was used to dilute the concentration of pancreatic juice around the anastomosis as soon as possible. Approximately 3000 mL normal saline was irrigated every day, with a flow rate of 200 mL/h. The flow of irrigation was modulated frequently according to the character of the secretion. The suction pressure was set with low-pressure suction between 20 and 30 cm water. Once the amylase level of the dilution fluid was lower than 30 U/L, the use of abdominal irrigation was stopped. The drainage tubes were removed until the amylase concentration was less than three times the upper limit of the normal serum level. All patients underwent routine postoperative computed tomography (CT) examinations before the drain tubes were removed to assess the presence of potential complications and peritoneal effusion.

### Definitions

POPF was defined and graded according to the modified definition by the International Study Group of Pancreatic Fistula (ISGPF)[16]. Clinically relevant POPF (CR-POPF) was considered grades B and C. Delayed gastric emptying (DGE) and PPH were defined and classified by the International Study Group for Pancreatic Surgery[17,18]. Intra-abdominal infections were diagnosed according to the definition proposed by the Surgical Infection Society and the Infectious Diseases Society of America[19].

### Statistical analysis

All statistical analyses were conducted using SPSS 23.0. The $\chi^2$ test or Fisher's exact test was used for categorical variables, whereas the Student's *t*-test or Wilcoxon rank-sum test (whether the variables were normally distributed) were used for continuous variables. $P < 0.05$ was considered statistically significant. After matching, each patient who received an omental interposition was matched to a patient in the non-omental interposition group by using nearest-neighbor matching in a 1:1 ratio. A PSM analysis was used to reduce the impact of the treatment selection bias when estimating the omental interposition values using original observational indicators. Multivariable logistic regression was performed with adjustments for the propensity scores using the associated covariates.

## RESULTS

### Analyses of all unmatched patients

The demographic and clinically related variables of all patients including age, sex, body mass index


**DOI:** 10.4240/wjgs.v14.i5.482 

**Figure 1 Omental interposition was placed in front of the adjacent vessels and behind the anastomosis where the pancreas stump was fixed to the jejunum.** 1: Liver; 2: Portal vein; 3: Hepatic artery; 4: Common bile duct; 5: Hepaticojejunostomy; 6: Gastrojejunostomy; 7: Celiac artery; 8: Pancreaticojejunostomy site; 9: Gastrojejunostomy. site; 10: Omental interposition; 11: Transverse colon.

(BMI), American Society of Anesthesiologists score, serum albumin content, main pancreatic duct size and pathology were similar between the two groups ($P > 0.05$). However, patients in the omental interposition group had a higher median serum bilirubin than those in the non-omental interposition group (96.5 [17.9-107.0] *vs* 20.5 [9.6-148.5]; $P = 0.015$). Laparoscopic pancreaticoduodenectomy (LPD) was more frequently performed in the omental interposition group than in the non-omental interposition group (69, 54.3% *vs* 19, 27.5%; $P < 0.001$). The details are shown in Table 1.

Regarding postoperative complications, a comparison revealed that the rates of CR-POPF (13, 10.2% *vs* 17, 24.6%; $P = 0.028$), biliary fistula (BF, 2,1.6% *vs* 5, 7.2%; $P = 0.041$), delayed PPH associated with POPF (1, 0.8% *vs* 8, 11.6%; $P = 0.002$), and postoperative transfusion (18,14.2% *vs* 20, 29.0%; $P = 0.012$) were significantly lower in the omental interposition group than in the non-omental interposition group. The rates of other surgery-related complications, including DGE, intra-abdominal abscess, and reoperation, did not significantly differ between the two groups. Regarding mortality, there was no significant difference between the two groups (2, 1.6% *vs* 5, 7.2%; $P = 0.101$). However, the CR-POPF-related mortality in the omental interposition group was significantly lower than the mortality in the non-omental interposition group (1, 0.8% *vs* 5, 7.2%; $P = 0.021$). The details on the deaths that occurred are shown in Table 2 and Figure 3. Fewer complications in the omental group may be related to passing the laparoscopic learning curve. However, among the 108 cases of OPD, 58 cases applied the omental interposition technique, and the omental interposition group had lower incidence of complications (6, 10.3% *vs* 9, 18%; $P = 0.008$) and lower mortality rate (0, 0% *vs* 4, 8%; $P = 0.007$).

When comparing relevant data on the enhanced recovery after surgery between the two groups, the HJ and PJ drainage tubes were removed earlier in the omental interposition group than in the non-omental interposition group (both $P < 0.05$). The omental interposition group of patients had significantly shorter postoperative durations of restarting their diet and shorter length of hospital stay than the non-omental interposition group patients (both $P < 0.01$). Based on the laboratory test results, the DFA1 around the HJ in the omental interposition group was dramatically lower than that in the non-omental interposition group (300.0 [74.3-893.0] *vs* 599.8 [171.1-2064.7]; $P = 0.002$). In the omental interposition group, the drain amylase values from the tube around the HJ were lower than those around the PJ (300.0 [74.3-893.0] *vs* 546.8 [76.4-3094.0]; $P < 0.001$). However, the difference disappeared in the non-omental interposition group. The details are shown in Table 2 and Figure 4A.

### *Analyses of all matched patients*

To reduce the impact of selection bias and the role of the procedure (LPD and OPD), PSM was performed using nine selected baseline characteristics. After PSM, the patient demographic and clinically related characteristics, including preoperative serum bilirubin and operation methods, were similar between the two groups. The rates of CR-POPF (7, 10.1% *vs* 17, 24.6%; $P = 0.025$), delayed PPH associated with POPF (1, 1.4% *vs* 8, 11.6%; $P = 0.016$) and postoperative transfusion (9, 13.0% *vs* 20, 29.0%; $P = 0.022$) remained significantly lower in the omental interposition group than in the non-

**Table 1 Comparisons of patients' characteristics between the two groups**

| | Before PSM | | | After PSM | | |
|---|---|---|---|---|---|---|
| | Omental interposition group (127) | Non-omental interposition group (69) | *P* value | Omental interposition group (69) | Non-omental interposition group (69) | *P* value |
| Male/female | 79/48 | 44/25 | 0.919 | 46/23 | 44/25 | 0.721 |
| Age (yr) | 64.8 ± 10.5 | 62.1 ± 9.9 | 0.083 | 64.2 ± 9.5 | 62.1 ± 9.9 | 0.210 |
| BMI (mean ± SD, kg/m$^2$) | 21.9 ± 3.0 | 22.0 ± 2.8 | 0.844 | 21.9 ± 3.2 | 22.0 ± 2.9 | 0.933 |
| ASA score, *n* (%) | | | 0.126 | | | 0.168 |
| I | 65 (51.2) | 42 (60.9) | | 34 (49.3) | 42 (60.9) | |
| II | 60 (47.2) | 24 (34.8) | | 34 (49.3) | 24 (34.8) | |
| III | 2 (1.6) | 3 (4.3) | | 1 (1.4) | 3 (4.3) | |
| Serum ALB [*n* (%), g/L] | | | 0.152 | | | 1.00 |
| < 35 | 13 (10.2) | 12 (17.4) | | 12 (17.4) | 12 (17.4) | |
| ≥ 35 | 114 (89.8) | 57 (82.6) | | 57 (82.6) | 57 (82.6) | |
| Serum bilirubin (μmol/L) | 96.5 (17.9-107.0) | 20.5 (9.6-148.5) | 0.015 | 29.8 (12.4-153.7) | 20.5 (9.6-148.5) | 0.753 |
| Main pancreatic duct size [*n* (%), mm] | | | 0.080 | | | 0.173 |
| < 3 | 57 (44.9) | 40 (58.0) | | 32 (46.4) | 40 (58.0) | |
| ≥ 3 | 70 (55.1) | 29 (42.0) | | 37 (53.6) | 29 (42.0) | |
| Operation method, *n* (%) | | | 0.005 | | | 0.708 |
| LPD | 69 (54.3) | 19 (27.5) | | 21 (30.4) | 19 (27.5) | |
| OPD | 58 (45.7) | 50 (72.5) | | 48 (69.6) | 50 (72.5) | |
| Pathology, *n* (%) | | | 0.009 | | | 0.151 |
| PDAC | 53 (41.7) | 25 (36.2) | | 36 (52.2) | 25 (36.2) | |
| Bile duct cancer | 10 (7.9) | 13 (18.8) | | 4 (5.8) | 13 (18.8) | |
| Ampulla of Vater cancer | 18 (14.2) | 15 (21.7) | | 10 (14.5) | 15 (21.7) | |
| Duodenal cancer | 11 (8.7) | 2 (2.9) | | 2 (2.9) | 2 (2.9) | |
| Other carcinoma | 19 (15.0) | 2 (2.9) | | 3 (4.3) | 2 (2.9) | |
| Benign tumor | 16 (12.6) | 12 (17.4) | | 14 (20.3) | 12 (17.4) | |

ALB: Albumin; ASA: American Society of Anesthesiologist score; BMI: Body mass index LPD: Laparoscopic pancreaticoduodenectomy; OPD: Open pancreaticoduodenectomy.

omental interposition group after PSM. The operation time in the omental interposition group was slightly longer both before (388.3 ± 68.8 *vs* 365.2 ± 75.0) and after (392.6 ± 74.1 *vs* 365.2 ± 75.0) the match, which may be related to the selection, cutting, and fixing of the omental interposition. Moreover, the omental interposition group of patients had a significantly shorter postoperative duration to restart their diet (7 [5-8] *vs* 8 [6-15]; $P = 0.048$) and shorter hospital stays (16 [12-24] *vs* 21 [13-32]; $P = 0.031$] than the non-omental interposition group of patients. The non-omental interposition group had greater mortality related to POPF than the omental interposition group (5 [7.2%] *vs* 1 [1.4%]), but there was no significant difference, which may be related to the small number of cases. The details are shown in Table 2.

Following PSM, the omental interposition group had dramatically lower DFA1 around the HJ than the non-omental interposition group (200.0 [58-610.6] *vs* 599.8 [171.1-2064.7] $P = 0.003$). In the omental interposition group, the DFA1 around the HJ was lower than the DFA1 around the PJ (200.0 [58-610.6] *vs* 325.0 [75.3-2869], $P < 0.001$). The details on DFA1 are shown in Table 2 and Figure 4B.

**Table 2 Comparisons of the postoperative outcomes between the two groups**

| | Before PSM | | | After PSM | | |
|---|---|---|---|---|---|---|
| | Omental interposition group (127) | Non-omental interposition group (69) | *P* value | Omental interposition group (69) | Non-omental interposition group (69) | *P* value |
| CR-POPF | 13 (10.2%) | 17 (24.6%) | 0.028 | 7 (10.1%) | 17 (24.6%) | 0.025 |
| Operation time (mean ± SD, min) | 388.3 ± 68.8 | 365.2 ± 75.0 | 0.031 | 392.6 ± 74.1 | 365.2 ± 75.0 | 0.033 |
| BF, *n* (%) | 2 (1.6) | 5 (7.2) | 0.041 | 1 (1.4) | 5 (7.2) | 0.208 |
| DGE, *n* (%) | 4 (3.1) | 6 (8.7) | 0.178 | 1 (1.4) | 6 (8.7) | 0.115 |
| PPH, *n* (%) | 1 (0.8) | 8 (11.6) | 0.002 | 1 (1.4) | 8 (11.6) | 0.016 |
| Intra-abdominal abscess, *n* (%) | 15 (11.8) | 12 (17.4) | 0.286 | 8 (11.6) | 12 (17.4) | 0.333 |
| Reoperation, *n* (%) | 3 (2.4) | 6 (8.7) | 0.096 | 2 (2.9) | 6 (8.7) | 0.274 |
| Mortality in 30 d, *n* (%) | 2 (1.6) | 5 (7.2) | 0.101 | 2 (2.9) | 5 (7.2) | 0.438 |
| Mortality related to POPF, *n* (%) | 1 (0.8) | 5 (7.2) | 0.038 | 1 (1.4) | 5 (7.2) | 0.210 |
| DFA1 around the HJ site (U/L) | 300.0 (74.3-893.0) | 599.8 (171.1-2064.7) | 0.002 | 200.0 (57.5-659.8) | 599.8 (171.1-2064.7) | 0.003 |
| DFA1 around the PJ site (U/L) | 546.8 (76.4-3094.0) | 350.0 (50.0-2577.4) | 0.255 | 325.0 (69.5-2972.5) | 350.0 (50.0-2577.4) | 0.951 |
| Duration until removal of the tube around the HJ site (d) | 7 (5-9) | 9 (7-14) | 0.000 | 8 (6-11) | 9 (7-14) | 0.115 |
| Duration until removing the tube around the PJ site (d) | 7 (6-11) | 10 (7-15) | 0.004 | 8 (6-12) | 10 (7-15) | 0.100 |
| Required blood transfusions, *n* (%) | 18 (14.2) | 20 (29.0) | 0.012 | 9 (13.0) | 20 (29.0) | 0.022 |
| Length of hospital stay (d) | 15 (11-22) | 21 (13-32) | 0.004 | 16 (12-24) | 21 (13-32) | 0.031 |
| Duration until restarting diet (d) | 6 (5-8) | 8 (6-15) | 0.001 | 7 (5-8) | 8 (6-15) | 0.048 |

BF: Biliary fistula; CR-POPF: Clinically relevant postoperative pancreatic fistula; DFA1: Drain fluid amylase obtained on the first postoperative day; DGE: Delayed gastric emptying; HJ: Hepaticojejunostomy; PJ: Pancreaticojejunostomy; PPH: Postpancreatectomy hemorrhage.

### *Factors associated with CR-POPF after PD*

Table 3 shows the univariate and multivariate analyses of the PSM data to evaluate the risk factors associated with CR-POPF after PD. Male sex, BMI ≥ 23 kg/m$^2$, nonapplication of omental interposition, DFA1 around HJ ≥ 1000 U/L, and main pancreatic duct size < 3 mm were significantly associated with the development of CR-POPF after PD. Multivariate logistic regression analyses showed that a high BMI (odds ratio [OR] = 6.094, 95% confidence interval [CI]: 2.021-18.374; $P$ = 0.001), nonapplication of omental interposition (OR = 3.145, 95%CI: 1.040-9.509; $P$ = 0.042), and main pancreatic duct diameter < 3 mm (OR = 5.663, 95%CI: 1.456-22.033; $P$ = 0.012) were independent factors that were significantly associated with the development of CR-POPF after PD.

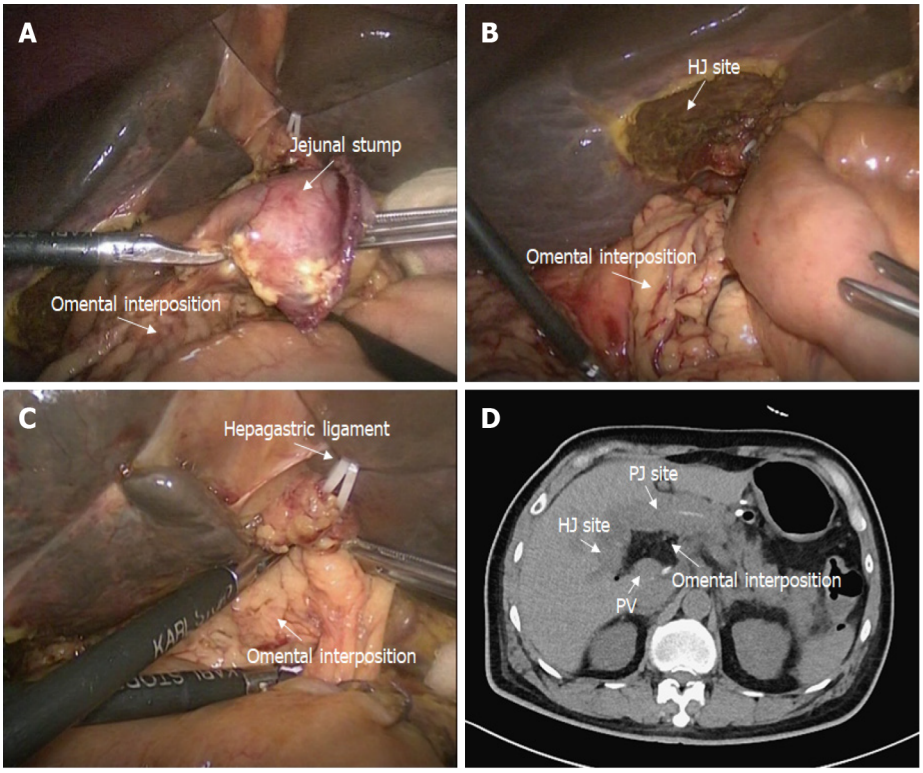
## DISCUSSION

To date, POPF remains the most fatal complication after PD. Pancreatic fistula, especially clinically related postoperative fistula, is the most common cause of delayed PPH and intra-abdominal infections after PD[1-4]. Leaked activated pancreatic juice is highly corrosive. Once the drainage tubes fail to effectively work, pancreatic juice accumulates in the potential cavity gap around the anastomosis. This condition may erode the vulnerable anastomosis and adjacent vascular wall. Various efforts[5-8] have been tested for their ability to reduce the incidence of CR-POPF after PD, such as improved anastomosis and the use of somatostatin. However, few randomized control trials have significantly prevented CR-POPF.

**Table 3 The univariate and multivariate analyses of the propensity score-matched data to evaluate the risk factors associated with clinically relevant postoperative pancreatic fistula after pancreaticoduodenectomy**

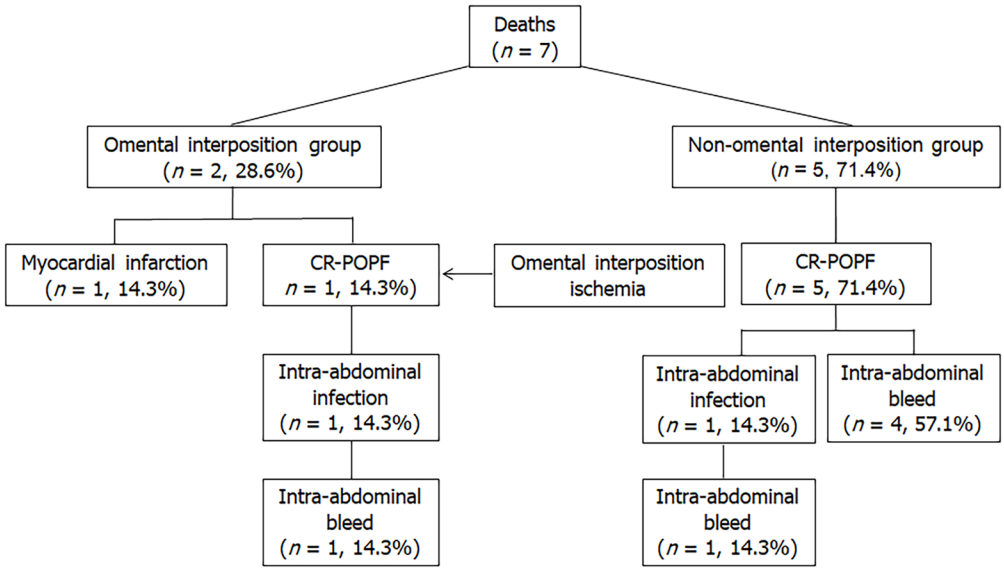
| | CR-POPF (24) | No CR-POPF (114) | *P* value | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | | | | OR | 95%CI | *P* value |
| Age (mean ± SD, yr) | 63.5 ± 7.9 | 63.1 ± 10.1 | 0.829 | | | |
| Sex, *n* (%) | | | 0.040 | | | |
| Male | 20 (83.3%) | 70 (61.4%) | | 2.436 | 0.692-8.574 | 0.165 |
| Female | 4 (16.7%) | 44 (38.6%) | | Reference | | |
| Operation method, *n* (%) | | | 0.143 | | | |
| LPD | 4 (16.7%) | 36 (31.6%) | | | | |
| OPD | 20 (83.3%) | 78 (68.4%) | | | | |
| BMI (kg/m$^2$) | | | 0.000 | | | |
| ≥ 23 | 18 (75.0%) | 33 (28.9%) | | 6.094 | 2.021-18.374 | 0.001 |
| < 23 | 6 (25.0%) | 81 (71.1%) | | Reference | | |
| Serum bilirubin (μmol/L) | 96.6 (16.1-180.4) | 67 (13.8-111.2) | 0.185 | | | |
| Serum ALB (g/L) | | | 0.843 | | | |
| ≥ 35 | 21 (87.5%) | 98 (86.0%) | | | | |
| < 35 | 3 (12.5%) | 16 (14.0%) | | | | |
| ASA score, *n* (%) | | | 0.122 | | | |
| Grade I | 11 (45.8%) | 66 (57.9%) | | | | |
| Grade II | 11 (45.8%) | 47 (41.2%) | | | | |
| Grade III | 2 (8.3%) | 1 (0.9%) | | | | |
| Pathology, *n* (%) | | | 0.196 | | | |
| Malignancy | 23 (95.8%) | 96 (84.2%) | | | | |
| Benign | 1 (4.2%) | 18 (15.8%) | | | | |
| Omental interposition, *n* (%) | | | 0.025 | | | |
| Yes | 7 (29.2%) | 62 (54.4%) | | Reference | | |
| No | 17 (70.8%) | 52 (45.6%) | | 3.145 | 1.040-9.509 | 0.042 |
| Operating time (mean ± SD, min) | 387.1±82.5 | 377.7±71.2 | 0.609 | | | |
| HJ DFA1 (U/L) | | | 0.010 | | | |
| ≥ 1000 | 13 (54.2%) | 31 (27.2%) | | 1.000 | 1.000-1.000 | 0.834 |
| < 1000 | 11 (45.8%) | 83 (72.8%) | | Reference | | |
| PJ DFA1 (U/L) | | | 0.115 | | | |
| ≥ 1000 | 13 (54.2%) | 42 (36.8%) | | | | |
| < 1000 | 11 (45.8%) | 72 (63.2%) | | | | |
| Main pancreatic duct size [*n* (%), mm] | | | 0.000 | | | |
| ≥ 3 | 3 (12.5%) | 64 (56.1%) | | Reference | | |
| < 3 | 21 (87.5%) | 50 (43.9%) | | 5.663 | 1.456-22.033 | 0.012 |

ALB: Albumin; ASA: American Society of Anesthesiologist score; BMI: Body mass index; DFA1: Drain fluid amylase obtained on the first postoperative day; HJ: Hepaticojejunostomy; LPD: Laparoscopic pancreaticoduodenectomy; OPD: Open pancreaticoduodenectomy; PJ: Pancreaticojejunostomy.




**DOI:** 10.4240/wjgs.v14.i5.482 **Copyright** ©The Author(s) 2022.

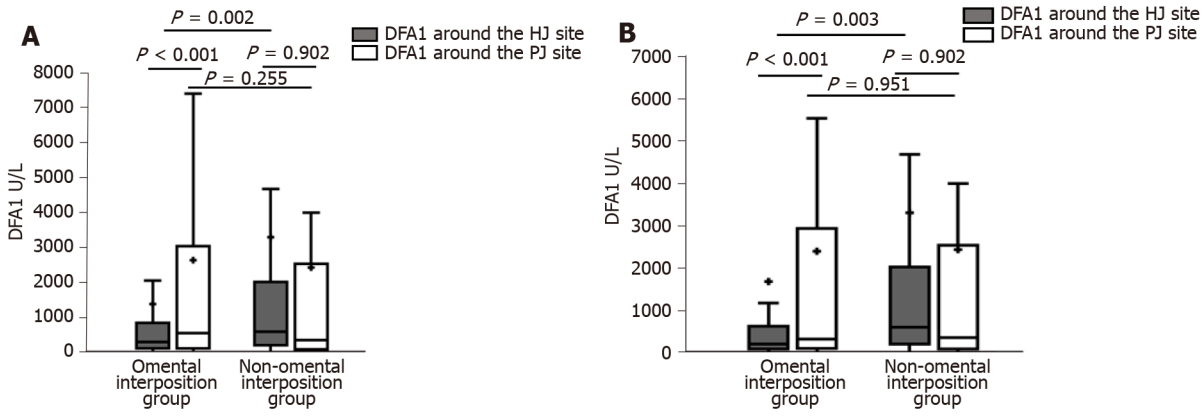
**Figure 2 Application of the omental interposition in pancreaticoduodenectomy.** A: The pedicled omental interposition was placed in front of the adjacent vessels (hepatic artery, portal vein, and gastroduodenal artery stump) and behind the pancreaticojejunostomy site; B: The right boundary of the omental interposition was the right margin of the inferior vena cava; C: The upper boundary of the omental interposition was the hepatogastric ligament; the omental interposition was fixed to the hepatic portal and hepatogastric ligament with several sutures to prevent postoperative mobilization; D: Postoperative computed tomography images. The omental interposition elevated the hepaticojejunostomy site and filled the potential cavity.




**DOI:** 10.4240/wjgs.v14.i5.482 **Copyright** ©The Author(s) 2022.

**Figure 3 Causes of death in the two groups.**

Since pancreatic fistulas are almost inevitable after PD, it is necessary to improve the surgical techniques and accelerate the healing process of fistulas to strive for "harmless" pancreatic fistulas. Experimental results have shown that the greater omentum can resist corrosion, provide anti-infection properties, absorb the peritoneal effusion, regenerate blood vessels and repair tissue defects. Thus, we hypothesized that the omental interposition could seal the posterior wall of the PJ anastomosis, fill the potential cavity to avoid effusion at the surgical site, cover the skeletonized vessels to avoid erosion and




**DOI:** 10.4240/wjgs.v14.i5.482 

**Figure 4 Differences between the two groups.** A: Drain fluid amylase obtained on the first postoperative day (DFA1) before propensity score-matching (PSM); B: DFA1 after PSM.

accelerate the regeneration of blood vessels to improve the blood supply of the anastomosis. The study shows that the incidence of CR-POPF and delayed PPH were lower in the omental interposition group than in the non-omental interposition group. As a result of the reduced complications, the average duration to restart diet and the length of hospital stay were shorter in the omental interposition group. Previous studies on OPD have reached similar conclusions. Maeda[14] covered the major splanchnic arteries and the PV with an omental flap in 100 patients. Although the author concluded that the incidence of POPF (20%) was not significantly different from that in other articles, he did not rule out biochemical fistulas based on the modified definition by the ISGPF. Matsuda *et al*[20] emphasized the preventive effect of omental flaps in PD against postoperative pseudoaneurysm formation. Shah *et al*[21] wrapped the omental flap around the PJ site in 101 patients and showed that it could reduce the incidence of POPF (4.0% *vs* 17.4%), PPH (0% *vs* 6.5%), BF (1.0% *vs* 13.0%), and DGE (4.0% *vs* 17.4%) compared to those in the non-omental interposition group.

In addition to the physiological function of the omental interposition, our method could elevate the height of the anastomosis and fill the potential cavity due to the physical characteristics. Because the omental interposition can elevate the position of the HJ anastomosis (Figure 2D), the erosive pancreatic fluid will flow to the left instead of remaining around the skeletonized vessels in the right upper quadrant of the abdomen. The difference in DFA1 between HJ and PJ sites confirm these physical characteristics in the omental interposition group. This finding also confirms that the application of the omental interposition, by preventing leakage from the anastomosis, reduces the incidence of delayed PPH. Because of the effective control of serious complications, the omental interposition group had their drainage tubes removed earlier, required fewer postoperative transfusions, restarted their diet earlier and had a shorter hospital stay than the non-omental interposition group. These findings are highly consistent with the aforementioned studies showing the efficacy of the omental interposition in PD.

PSM of nine baseline characteristics was performed to reduce selection bias and potential confounding factors between the two groups. After matching, the incidences of CR-POPF and delayed PPH remain significantly lower in the omental interposition group. Similarly, the difference in median DFA1 values between HJ and PJ sites in the omental interposition group remained observable. However, in the non-omental interposition group, the DFA1 around the PJ site was significantly higher than the DFA1 around the HJ site. Due to the physical characteristics of the omental interposition, the corrosive pancreatic juice would flow to the left upper quadrant of the abdomen because of gravity. Obviously, these details matter tremendously.

Previous studies[22-24] have reported that the risk factors for POPF include a high BMI, soft pancreatic texture, and small pancreatic duct size. In our study, univariate and multivariate analyses revealed that a high BMI, nonapplication of omental interposition, and main pancreatic duct diameter < 3 mm were independent factors significantly associated with the development of CR-POPF after PD. The developed statistical model had a c-index of 0.848. These findings were partially consistent with previous POPF risk scores.

Only one patient in the omental group died of delayed PPH caused by ischemic infection due to poor blood supply of the omental interposition, which resulted in delayed hemorrhage. This was the eighth case in which we applied the omental interposition with insufficient emphasis on ensuring good blood supply to the omental interposition. Since then, we detached the gastrocolic ligament along the gastric wall to ensure good blood supply to the omental interposition.

This study had several limitations, including its design as a single-center, retrospective observational study. However, all clinically related data were prospectively collected, and all operations were performed by the same surgical group with the same surgical technology. Thus, the majority of the

potential confounding factors were controlled.

## CONCLUSION

In conclusion, we believe that the application of the omental interposition is technically simple and may help prevent CR-POPF and the associated complications following PD.

## ARTICLE HIGHLIGHTS

### *Research background*

Postoperative pancreatic fistula (POPF) is a life-threatening complication after pancreaticoduodenectomy (PD).

### *Research motivation*

Several methods have attempted to reduce the POPF after PD, few have been considered effective. The safety and short-term clinical benefits of omental interposition remain controversial.

### *Research objectives*

To investigate the safety and feasibility of omental interposition to reduce the POPF rate and related complications in PD.

### *Research methods*

In total, 196 consecutive patients underwent PD performed by the same surgical team, the patients were divided into two groups: an omental interposition group (127, 64.8%) and a non-omental interposition group (69, 35.2%). Propensity score-matched analyses were performed to compare the severe complication rates and mortality between the two groups.

### *Research results*

The clinically relevant POPF (CR-POPF; 10.1% *vs* 24.6%; $P = 0.025$) and delayed postpancreatectomy hemorrhage (1.4% *vs* 11.6%; $P = 0.016$) rates were significantly lower in the omental interposition group. The omental interposition technique was associated with a shorter time to resume food intake (7 *vs* 8 d; $P = 0.048$) and a shorter hospitalization period (16 *vs* 21 d; $P = 0.031$).

### *Research conclusions*

The application of the omental interposition is an effective and safe approach to reduce the CR-POPF rate and related complications after PD.

### *Research perspectives*

Prospective studies are needed on the role of omental interposition in reducing CR-POPF.

## FOOTNOTES

**Author contributions:** Li Y, Liang Y, and Deng Y contributed equally to this manuscript; Jiang CY participated in the conception and design of this study; Deng Y, Cai ZW, Ma MJ, Wang LX, Liu M, and Wang HW participated in the data collection; Li Y participated in the data collection, analysis, and drafting of the article; Liang Y participated in the design of the study and data analyses; All authors have read and approved the final manuscript.

**Supported by** the Shanghai Science and Technology Commission of Shanghai Municipality, No. 20Y11908600; the Shanghai Shenkang Hospital Development Center, No. SHDC2020CR5008; and Shanghai Municipal Health Commission, No. 20194Y0195.

**Institutional review board statement:** The study was reviewed and approved by the Ethics Review Committee of Huadong Hospital (Shanghai).

**Conflict-of-interest statement:** The authors have no conflicts of interest to declare.

**Data sharing statement:** No additional data are available

**STROBE statement:** The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

**Country/Territory of origin:** China

**ORCID number:** Yang Li 0000-0003-1422-3013; Yun Liang 0000-0002-1605-2994; Yao Deng 0000-0002-3691-1856; Zhi-Wei Cai 0000-0002-5121-0687; Ming-Jian Ma 0000-0001-9381-9311; Long-Xiang Wang 0000-0003-2711-3198; Meng Liu 0000-0002-0481-2968; Hong-Wei Wang 0000-0003-2432-3608; Chong-Yi Jiang 0000-0002-9691-4055.

**S-Editor:** Ma YJ
**L-Editor:** Filipodia
**P-Editor:** Ma YJ

## REFERENCES

1 **Ellis RJ**, Brock Hewitt D, Liu JB, Cohen ME, Merkow RP, Bentrem DJ, Bilimoria KY, Yang AD. Preoperative risk evaluation for pancreatic fistula after pancreaticoduodenectomy. *J Surg Oncol* 2019; **119**: 1128-1134 [PMID: 30951614 DOI: 10.1002/jso.25464]
2 **Satoi S**, Toyokawa H, Yanagimoto H, Yamamoto T, Yamao J, Kim S, Matsui Y, Takai S, Mergental H, Kamiyama Y; Department of Surgery, Kansai Medical University, Osaka, Japan. A new guideline to reduce postoperative morbidity after pancreaticoduodenectomy. *Pancreas* 2008; **37**: 128-133 [PMID: 18665071 DOI: 10.1097/MPA.0b013e318162cb53]
3 **Roberts KJ**, Sutcliffe RP, Marudanayagam R, Hodson J, Isaac J, Muiesan P, Navarro A, Patel K, Jah A, Napetti S, Adair A, Lazaridis S, Prachalias A, Shingler G, Al-Sarireh B, Storey R, Smith AM, Shah N, Fusai G, Ahmed J, Abu Hilal M, Mirza DF. Scoring System to Predict Pancreatic Fistula After Pancreaticoduodenectomy: A UK Multicenter Study. *Ann Surg* 2015; **261**: 1191-1197 [PMID: 25371115 DOI: 10.1097/SLA.0000000000000997]
4 **Chen JF**, Xu SF, Zhao W, Tian YH, Gong L, Yuan WS, Dong JH. Diagnostic and therapeutic strategies to manage post-pancreaticoduodenectomy hemorrhage. *World J Surg* 2015; **39**: 509-515 [PMID: 25287917 DOI: 10.1007/s00268-014-2809-3]
5 **Kang JS**, Han Y, Kim H, Kwon W, Kim SW, Jang JY. Prevention of pancreatic fistula using polyethylene glycolic acid mesh reinforcement around pancreatojejunostomy: the propensity score-matched analysis. *J Hepatobiliary Pancreat Sci* 2017; **24**: 169-175 [PMID: 28054751 DOI: 10.1002/jhbp.428]
6 **Hong S**, Wang H, Yang S, Yang K. External stent versus no stent for pancreaticojejunostomy: a meta-analysis of randomized controlled trials. *J Gastrointest Surg* 2013; **17**: 1516-1525 [PMID: 23568149 DOI: 10.1007/s11605-013-2187-4]
7 **Martin I**, Au K. Does fibrin glue sealant decrease the rate of anastomotic leak after a pancreaticoduodenectomy? *HPB (Oxford)* 2013; **15**: 561-566 [PMID: 23458447 DOI: 10.1111/hpb.12018]
8 **Kurumboor P**, Palaniswami KN, Pramil K, George D, Ponnambathayil S, Varma D, Aikot S. Octreotide Does Not Prevent Pancreatic Fistula Following Pancreatoduodenectomy in Patients with Soft Pancreas and Non-dilated Duct: A Prospective Randomized Controlled Trial. *J Gastrointest Surg* 2015; **19**: 2038-2044 [PMID: 26302879 DOI: 10.1007/s11605-015-2925-x]
9 **Montorsi M**, Zerbi A, Bassi C, Capussotti L, Coppola R, Sacchi M; Italian Tachosil Study Group. Efficacy of an absorbable fibrin sealant patch (TachoSil) after distal pancreatectomy: a multicenter, randomized, controlled trial. *Ann Surg* 2012; **256**: 853-9; discussion 859 [PMID: 23095631 DOI: 10.1097/SLA.0b013e318272dec0]
10 **Ye P**, Cao JL, Li QY, Wang ZT, Yang YH, Lv W, Hu J. Mediastinal transposition of the omentum reduces infection severity and pharmacy cost for patients undergoing esophagectomy. *J Thorac Dis* 2016; **8**: 1653-1660 [PMID: 27499954 DOI: 10.21037/jtd.2016.05.92]
11 **Ye J**, Li Q, Liu R, Zhang K, Nie Z, Chen J, Jin F, Huo W. Pedicled greater omentum graft: a new technique to repair recurrent urinary fistulae after kidney transplantation. *Cell Biochem Biophys* 2012; **62**: 69-72 [PMID: 21833672 DOI: 10.1007/s12013-011-9260-y]
12 **Karabulut B**, Sönmez K, Türkyilmaz Z, Demiroğullari B, Karabulut R, Sezer C, Sultan N, Başaklar AC, Kale N. Omentum prevents intestinal adhesions to mesh graft in abdominal infections and serosal defects. *Surg Endosc* 2006; **20**: 978-982 [PMID: 16738996 DOI: 10.1007/s00464-005-0473-2]
13 **Seyama Y**, Kubota K, Kobayashi T, Hirata Y, Itoh A, Makuuchi M. Two-staged pancreatoduodenectomy with external drainage of pancreatic juice and omental graft technique. *J Am Coll Surg* 1998; **187**: 103-105 [PMID: 9660033 DOI: 10.1016/s1072-7515(98)00127-6]
14 **Maeda A**, Ebata T, Kanemoto H, Matsunaga K, Bando E, Yamaguchi S, Uesaka K. Omental flap in pancreaticoduodenectomy for protection of splanchnic vessels. *World J Surg* 2005; **29**: 1122-1126 [PMID: 16132400 DOI: 10.1007/s00268-005-7900-3]
15 **Jiang CY**, Liang Y, Wang HW, Hu PF, Cai ZW, Wang W. Management of the uncinate process *via* the artery first approach in laparoscopic pancreatoduodenectomy. *J Hepatobiliary Pancreat Sci* 2019; **26**: 410-415 [PMID: 31218822 DOI: 10.1002/jhbp.647]
16 **Bassi C**, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, Allen P, Andersson R, Asbun HJ, Besselink MG, Conlon K, Del Chiaro M, Falconi M, Fernandez-Cruz L, Fernandez-Del Castillo C, Fingerhut A, Friess H, Gouma DJ,

Hackert T, Izbicki J, Lillemoe KD, Neoptolemos JP, Olah A, Schulick R, Shrikhande SV, Takada T, Takaori K, Traverso W, Vollmer CR, Wolfgang CL, Yeo CJ, Salvia R, Buchler M; International Study Group on Pancreatic Surgery (ISGPS). The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. *Surgery* 2017; **161**: 584-591 [PMID: 28040257 DOI: 10.1016/j.surg.2016.11.014]

17 **Wente MN**, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Traverso LW, Yeo CJ, Büchler MW. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2007; **142**: 761-768 [PMID: 17981197 DOI: 10.1016/j.surg.2007.05.005]

18 **Wente MN**, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Yeo CJ, Büchler MW. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery* 2007; **142**: 20-25 [PMID: 17629996 DOI: 10.1016/j.surg.2007.02.001]

19 **Solomkin JS**, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, O'Neill PJ, Chow AW, Dellinger EP, Eachempati SR, Gorbach S, Hilfiker M, May AK, Nathens AB, Sawyer RG, Bartlett JG. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Surg Infect (Larchmt)* 2010; **11**: 79-109 [PMID: 20163262 DOI: 10.1089/sur.2009.9930]

20 **Matsuda H**, Sadamori H, Umeda Y, Shinoura S, Yoshida R, Satoh D, Utsumi M, Yagi T, Fujiwara T. Preventive effect of omental flap in pancreaticoduodenectomy against postoperative pseudoaneurysm formation. *Hepatogastroenterology* 2012; **59**: 578-583 [PMID: 21940374 DOI: 10.5754/hge11452]

21 **Shah OJ**, Bangri SA, Singh M, Lattoo RA, Bhat MY. Omental flaps reduces complications after pancreaticoduodenectomy. *Hepatobiliary Pancreat Dis Int* 2015; **14**: 313-319 [PMID: 26063034 DOI: 10.1016/s1499-3872(15)60372-1]

22 **Sugimoto M**, Takahashi S, Gotohda N, Kato Y, Kinoshita T, Shibasaki H, Konishi M. Schematic pancreatic configuration: a risk assessment for postoperative pancreatic fistula after pancreaticoduodenectomy. *J Gastrointest Surg* 2013; **17**: 1744-1751 [PMID: 23975030 DOI: 10.1007/s11605-013-2320-4]

23 **El Nakeeb A**, Salah T, Sultan A, El Hemaly M, Askr W, Ezzat H, Hamdy E, Atef E, El Hanafy E, El-Geidie A, Abdel Wahab M, Abdallah T. Pancreatic anastomotic leakage after pancreaticoduodenectomy. Risk factors, clinical predictors, and management (single center experience). *World J Surg* 2013; **37**: 1405-1418 [PMID: 23494109 DOI: 10.1007/s00268-013-1998-5]

24 **Polanco PM**, Zenati MS, Hogg ME, Shakir M, Boone BA, Bartlett DL, Zeh HJ, Zureikat AH. An analysis of risk factors for pancreatic fistula after robotic pancreaticoduodenectomy: outcomes from a consecutive series of standardized pancreatic reconstructions. *Surg Endosc* 2016; **30**: 1523-1529 [PMID: 26139506 DOI: 10.1007/s00464-015-4366-8]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 May 27; 14(5): 494-505

DOI: 10.4240/wjgs.v14.i5.494

ISSN 1948-9366 (online)

SCIENTOMETRICS

# Global research production pertaining to gastrointestinal involvement in COVID-19: A bibliometric and visualised study

Sa'ed H Zyoud, Samah W Al-Jabi, Moyad Jamal Shahwan, Ammar Abdulrahman Jairoun

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Guo F, China; Song B, China; Wang MK, China

**Received:** March 16, 2021
**Peer-review started:** March 16, 2021
**First decision:** May 4, 2021
**Revised:** May 26, 2021
**Accepted:** May 7, 2022
**Article in press:** May 7, 2022
**Published online:** May 27, 2022

**Sa'ed H Zyoud, Samah W Al-Jabi,** Department of Clinical and Community Pharmacy, College of Medicine and Health Sciences, An-Najah National University, Nablus 44839, Palestine

**Sa'ed H Zyoud,** Poison Control and Drug Information Center, College of Medicine and Health Sciences, An-Najah National University, Nablus 44839, Palestine

**Sa'ed H Zyoud,** Clinical Research Centre, An-Najah National University Hospital, Nablus 44839, Palestine

**Moyad Jamal Shahwan,** Department of Clinical Sciences, College of Pharmacy and Health Sciences, Ajman University, Ajman 346, United Arab Emirates

**Moyad Jamal Shahwan,** Centre of Medical and Bio-allied Health Sciences Research, Ajman University, Ajman 346, United Arab Emirates

**Ammar Abdulrahman Jairoun,** Department of Health and Safety, Dubai Municipality, Dubai 67, United Arab Emirates

**Corresponding author:** Sa'ed H Zyoud, PhD, Associate Professor, Director, Department of Clinical and Community Pharmacy, College of Medicine and Health Sciences, An-Najah National University, Academic Street, Nablus 44839, Palestine. saedzyoud@yahoo.com

## Abstract

### *BACKGROUND*

Coronavirus disease 2019 (COVID-19) is a global pandemic that can cause diarrhoea, nausea/vomiting, and abdominal pain, among other gastrointestinal (GI) symptoms.

### *AIM*

To perform a bibliometric analysis of the global research production pertaining to GI involvement in COVID-19.

### *METHODS*

The Scopus database was used to search the global literature on GI involvement in COVID-19 during 2020. A bibliometric review of these publications was also performed using VOSviewer.

### *RESULTS*

Scopus had published 95615 documents on COVID-19 in all areas of research at the time of data collection. In total, 1267 publications on the topic of GI and

COVID-19 were identified. Research articles ($n$ = 606; 47.83%), letters (293; 23.13%), and reviews (186; 14.68%) were the most popular types of documents. The most productive countries and institutions in this field were the United States and Huazhong University of Science and Technology. The most cited paper was Xiao *et al*, which was published in *Gastroenterology* as a brief communication, with 798 citations. This paper provides evidence for GI infection of COVID-19 and its possible faecal–oral transmission route. In the term cluster analysis, there were two frontiers in this field: GI manifestations among COVID-19 patients and the implications of COVID-19 for the gastroenterologist.

***CONCLUSION***

GI manifestations among COVID-19 patients and implications of COVID-19 for gastroenterologists were of interest, especially in the early stages of the pandemic.

**Key Words:** COVID-19; Gastrointestinal; Symptoms; Bibliometric; Scopus



**Core Tip:** This bibliometric analysis provides the first concise summary of global gastrointestinal (GI) publications related to coronavirus disease 2019 (COVID-19). It highlights the benefits of bibliometric analysis in a systematic and structured way to measure the productivity of studies. GI manifestations among COVID-19 patients and the implications of COVID-19 for gastroenterologists were of interest, especially in the early stage of the pandemic. The results will form the basis for future research and guide decision-making in research related to GI symptoms and treatments in COVID-19.

**Citation:** Zyoud SH, Al-Jabi SW, Shahwan MJ, Jairoun AA. Global research production pertaining to gastrointestinal involvement in COVID-19: A bibliometric and visualised study. *World J Gastrointest Surg* 2022; 14(5): 494-505

**URL:** https://www.wjgnet.com/1948-9366/full/v14/i5/494.htm

**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i5.494

## INTRODUCTION

In December 2019, coronavirus disease (coronavirus disease 2019, COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spread quickly from China to nearly every country in the world, and is now considered the world's most significant public health threat, causing a massive crisis for global health[1-3]. The 2019 new coronavirus was named SARS-CoV-2 by the World Health Organization (WHO), with COVID-19 being given as the disease name[4]. As of March 13, 2021, there were over 118 million confirmed cases worldwide, with more than 2.6 million associated global deaths, according to a WHO report[5].

In most studies, patients with COVID-19 have gastrointestinal (GI) manifestations, such as diarrhoea, nausea, anorexia, vomiting, abdominal pain, and GI bleeding[6-11], in addition to fever and common respiratory symptoms including cough, and shortness of breath[3,12]. However, some patients have developed various fatal complications including severe pneumonia, pulmonary oedema, acute respiratory distress syndrome, septic shock, and organ failure[13-15]. Several studies have shown that SARS-CoV-2 can interact with angiotensin-converting enzyme 2 (ACE2) receptors on ileal enterocytes and colon epithelial cells, implying a trophism for the GI tract[7]. The pathophysiology of GI symptoms is unclear, but it appears that SARS-CoV-2 binds to ACE2, which regulates amino acid homeostasis and microbiome balance in the intestine, causing a change in physiological function that leads to GI symptoms[16-18].

Several systematic reviews and meta-analyses have indicated that during the pandemic, there was an increase in the number of publications discussing the impact of COVID-19 on the GI system in several countries[6,9-11,19-27]. To date, there has not been a global bibliometric review of research related to GI and COVID-19. Bibliometrics aims to determine the depth of information in a given field[28]. In other areas of COVID-19, this approach has been used to quantify and categorise research output, allowing for mapping the area in question based on the most involved authors, institutions, countries, citations, journals, and hot topics in this field[29-32]. Therefore, the purpose of this study was to report a bibliometric analysis of the global research production pertaining to GI involvement in COVID-19 to determine the most widely cited papers and most prolific countries, institutions, and journals related to this topic. Our results will help to guide priority setting and policy formulation for long-term strategies to improve the outcomes of COVID-19 patients with GI manifestations.

## MATERIALS AND METHODS

### Data sources

The publications were retrieved on the same day from the Scopus on March 20, 2021, to prevent bias due to the daily database updates. Since Scopus is the most commonly accepted and regularly used database for analysing scientific articles in the field of bibliometrics, it was chosen as the search engine. Although we recognise the existence of other databases, we acted in accordance with the methodological approach of previous research[33,34].

### Search strategies

The search was restricted to publications between January 1 and December 31, 2020. The following search strategy was used in this bibliometric study to retrieve data.

**Step 1:** To achieve the goals of this bibliometric review, the terms related to COVID-19 entered into the Scopus engine were chosen from the literature related to COVID-19[35-38]. All of the following terms were used as Article Title/Abstract/Keyword: "COVID 19" OR "2019 novel coronavirus" OR "coronavirus 2019" OR "SARS-CoV-2" OR "SARS-CoV 2" or "coronavirus disease 2019" OR "2019-novel CoV" OR "2019 ncov" OR "COVID 2019" OR "corona virus 2019" OR "nCoV-2019" OR nCoV2019 OR "nCoV 2019" OR 2019-ncov OR COVID-19 OR "Severe acute respiratory syndrome coronavirus 2" OR Novel Coronavirus.

**Step 2:** We confined the publications that we obtained in Step 1 to those with the terms gastrointestinal and related words in their title. The terms relevant to GI that were entered into the Scopus engine were selected from previous GI meta-analyses[6,39]. All of the following terms were entered as Article Title: gastrointestinal OR "GI tract" OR gastr* OR Diarrh* OR Constipation OR Vomiting OR *intestin* OR dysphagia OR "Abdominal pain" OR Nausea OR heartburn OR Bowel OR Gut OR digest* OR stomach OR duodenal OR colon OR colorectal anorectum. The asterisk (*) was used as a truncator or wildcard to capture all of the term variants that shared a core.

### Bibliometric analysis

The data collected included the following bibliometric parameters: type of documents, number of publications, citation count, country, institution, and journals. The impact index per article is presented for the top ten most-cited papers as determined by *Reference Citation Analysis* (RCA). Baishideng Publishing Group Inc. owns RCA, an open, multidisciplinary citation analysis database (Pleasanton, CA, United States) (https://www.referencecitationanalysis.com/).

### Visualise analysis

VOSviewer version 1.6.16 (Leiden University, Leiden, The Netherlands) was used for bibliometric visualisation[40]. In this study, VOSviewer was used for collaborative patterns between countries and term co-occurrence analysis. As a result, we decided to build and visualise the network terms used in the title/abstract of publications to define the hot topics in this field. The relationship between terms is based on the number of publications in which they appear together, according to co-occurrence analysis [40]. Therefore, the aim of this study was to identify research areas as hot topics, and it is a valuable indicator for tracking scientific progress[41].

## RESULTS

### Volume and types of publications

Scopus had published 95615 documents on COVID-19 in all areas of research at the time of data collection. In total, 1267 publications on the topic of GI and COVID-19 were identified during the period of study (January 1 to December 31, 2020). A total of 1267 documents (1.33%) were used in this study. Research articles ($n$ = 606; 47.83%), letters (293; 23.13%), and reviews (186; 14.68%) were the most popular types of documents.

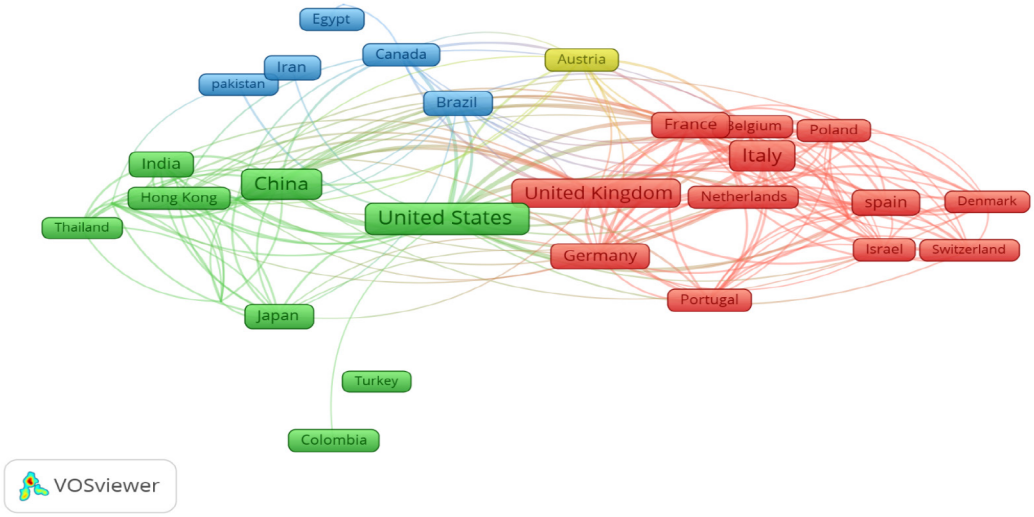
### Active countries and international research collaboration

The United States was the leader in this field, with 278 publications (21.94%). Other top countries were China (222, 17.52%), Italy (184, 14.52%), and the United Kingdom (159, 12.55%) (Table 1). Several studies reported the symptoms of GI to be present in 2.6% and 75% patients with COVID 19 infection (Table 1). There were 33 countries included (the minimum number of publications for each country was 10), and their network collaboration maps were visualised by VOSviewer (Figure 1). The top four countries by centrality were the United States, China, Italy, and the United Kingdom. According to their centrality, these countries showed close collaboration with each other and a strong research influence with other countries.

**Table 1 List of the top 10 countries pertaining to gastrointestinal publications involvement in coronavirus disease 2019**

| Ranking | Country | No. of documents | % | Study population | Sample size | Prevalence of GI symptoms (%) | Common GI symptoms |
|---|---|---|---|---|---|---|---|
| 1st | United States | 278 | 21.94 | Multicentre Cohort Study [48] | 318 | 61.3 | Loss of appetite, diarrhoea, and nausea |
| 2nd | China | 222 | 17.52 | Retrospective study[51] | 1320 | 14.5 | Diarrhoea, anorexia, and nausea and vomiting |
| 3rd | Italy | 184 | 14.52 | Prospective case-control study[47] | 34 | 8.8 | Diarrhoea, abdominal pain, and nausea |
| 4th | United Kingdom | 159 | 12.55 | Prospective observational cohort study[42] | 20, 133 | 23 | Diarrhoea, nausea/vomiting, and abdominal pain |
| 5th | Spain | 61 | 4.81 | Retrospective study[49] | 76 | 75 | Diarrhoea, nausea/vomiting, and abdominal pain |
| 6th | France | 59 | 4.66 | Retrospective study[45] | 114 | 2.6 | Diarrhoea |
| 7th | Germany | 56 | 4.42 | Retrospective study[43] | 50 | > 16 | Diarrhoea, nausea/vomiting |
| 8th | India | 51 | 4.03 | Prospective study[44] | 252 | 10.3 | anorexia, nausea, vomiting, abdominal pain |
| 9th | Australia | 37 | 2.92 | Epidemiological study[50] | 295 | > 16 | Diarrhoea, nausea/vomiting, and abdominal pain |
| 10th | Iran | 33 | 2.60 | Retrospective study[46] | 611 | 25.4 | Nausea/vomiting, diarrhoea, and abdominal pain |

GI: Gastrointestinal.




**DOI:** 10.4240/wjgs.v14.i5.494 

**Figure 1 Network visualisation map of international research collaborations among the top 33 active countries with at least 10 articles published each.**

### *Active institutions/organisations*

Table 2 shows the top 10 institutions in terms of publication numbers. The Huazhong University of Science and Technology, China ($n$ = 33 publications), Humanitas Research Hospital, Italy ($n$ = 23 publications), the Humanitas University, Italy ($n$ = 30 publications), and the Tongji Medical College, China ($n$ = 29 publications) were the top four productive and influential institutions, indicating that they have achieved significant scientific achievements and research capability.

### *Active journals*

Regarding journals, *Gastroenterology* ranked first with 457 publications (4.50%), followed by *American Journal of Gastroenterology* ($n$ = 34; 2.68%), *Inflammatory Bowel Diseases* ($n$ = 34; 2.68%), and *Lancet Gastroenterology and Hepatology* ($n$ = 34; 2.68%). Table 3 presents the top 10 most popular journals with

**Table 2 List of the top 10 institutions pertaining to gastrointestinal publication involvement in coronavirus disease 2019**

| Ranking | Institution | Country | *n* | % |
|---|---|---|---|---|
| 1st | Huazhong University of Science and Technology | China | 33 | 2.60 |
| 2nd | Humanitas Research Hospital | Italy | 32 | 2.53 |
| 3rd | Humanitas University | Italy | 30 | 2.37 |
| 4th | Tongji Medical College | China | 29 | 2.29 |
| 5th | INSERM | France | 27 | 2.13 |
| 6th | Chinese University of Hong Kong | China | 26 | 2.05 |
| 7th | Fondazione Policlinico Universitario Agostino Gemelli IRCCS Università Cattolica del Sacro Cuore | Italy | 25 | 1.97 |
| 8th | Università degli Studi di Roma La Sapienza | Italy | 22 | 1.74 |
| 9th | Università degli Studi di Milano | Italy | 21 | 1.66 |
| 10th | Università degli Studi di Padova | Italy | 20 | 1.58 |
| 10th | University Hospitals Birmingham NHS Foundation Trust | United Kingdom | 20 | 1.58 |

**Table 3 List of the top 10 journals pertaining to gastrointestinal publications involvement in coronavirus disease 2019**

| Ranking | Journal | *n* | % | Impact factors |
|---|---|---|---|---|
| 1st | *Gastroenterology* | 57 | 4.50 | 17.373 |
| 2nd | *American Journal of Gastroenterology* | 34 | 2.68 | 10.171 |
| 2nd | *Inflammatory Bowel Diseases* | 34 | 2.68 | 4.261 |
| 2nd | *Lancet Gastroenterology and Hepatology* | 34 | 2.68 | 14.789 |
| 5th | *Digestive and Liver Disease* | 33 | 2.60 | 3.570 |
| 6th | *British Journal of Surgery* | 29 | 2.29 | 5.676 |
| 7th | *Alimentary Pharmacology and Therapeutics* | 25 | 1.97 | 7.515 |
| 8th | *Clinical Gastroenterology and Hepatology* | 21 | 1.66 | 8.549 |
| 9th | *Colorectal Disease* | 20 | 1.58 | 2.769 |
| 10th | *Journal of Gastroenterology and Hepatology* | 18 | 1.42 | 3.437 |

Impact factors were retrieved from the 2019 Journal Citation Reports (Clarivate Analytics).

the highest number of global research productions pertaining to GI involvement in COVID-19.

### *Top cited documents*

The number of citations is an important measure of the impact and recognition that a paper has received from the scientific community. Table 4 presents the 10 most cited studies found in the Scopus database. The top 10 most cited publications had citation counts ranging from 269 to 798. Furthermore, the ten most cited articles have an impact index per article of 189 to 617.5 (Table 4).

### *Most frequent terms (research themes)*

Using VOSviewer, we examined the term occurrence from 1267 publications. As seen in Figure 2, 270 words were identified and grouped into two clusters based on the number of times they appeared in the titles and abstracts of all publications. The red cluster involved GI manifestations including terms such as “gastrointestinal”, “symptoms”; “nausea”, “vomiting”, and “diarrhoea”. The green cluster involved implications of COVID-19 for the gastroenterologist including terms such as “recommendations”, "procedure”, “impact”, “surgery”, “endoscopy”, “strategy”, “practice”, and “prevention”.

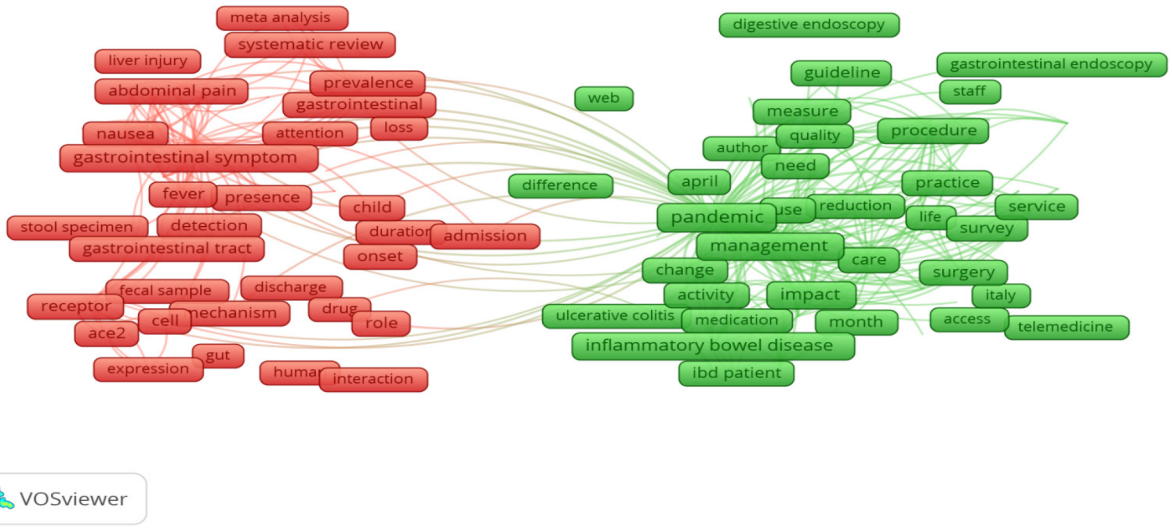
## DISCUSSION

The use of bibliometric analysis to review the patterns and development of various fields and areas of

**Table 4 List of the top 10 cited articles for gastrointestinal publications involvement in coronavirus disease 2019**

| Ranking | Ref. | Title | Source title | Cited by | Impact index per article[1] |
|---|---|---|---|---|---|
| 1st | Xiao *et al* [58], 2020 | "Evidence for Gastrointestinal Infection of SARS-CoV-2" | *Gastroenterology* | 798 | 617.5 |
| 2nd | Xu *et al*[59], 2020 | "Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding" | *Nature Medicine* | 525 | 384.0 |
| 3rd | Gu *et al*[52], 2020 | "COVID-19: Gastrointestinal Manifestations and Potential Fecal–Oral Transmission" | *Gastroenterology* | 507 | 342.5 |
| 4th | Pan *et al*[55], 2020 | "Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: A descriptive, cross-sectional, multicenter study" | *American Journal of Gastroenterology* | 464 | 352.5 |
| 5th | Wu *et al*[57], 2020 | "Prolonged presence of SARS-CoV-2 viral RNA in faecal samples" | *Lancet Gastroenterology and Hepatology* | 451 | 374.5 |
| 6th | Jin *et al*[53], 2020 | "Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms" | *Gut* | 362 | 277.0 |
| 7th | Cheung *et al* [10], 2020 | "Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis" | *Gastroenterology* | 356 | 269.5 |
| 8th | Lamers *et al* [54], 2020 | "SARS-CoV-2 productively infects human gut enterocytes" | *Science* | 338 | 317.5 |
| 9th | Yeo *et al*[60], 2020 | "Enteric involvement of coronaviruses: is faecal–oral transmission of SARS-CoV-2 possible?" | *Lancet Gastroenterology and Hepatology* | 323 | 202.0 |
| 10th | Tian *et al* [56], 2020 | "Gastrointestinal features in COVID-19 and the possibility of faecal transmission" | *Alimentary Pharmacology and Therapeutics* | 269 | 189.0 |

[1]The impact index per article is presented based on *Reference Citation Analysis* [source: Baishideng Publishing Group Inc. (Pleasanton, CA 94566, United States)].




**DOI:** 10.4240/wjgs.v14.i5.494 

**Figure 2 Network visualisation map of the most frequent terms in titles/abstracts of the retrieved literature pertaining to gastrointestinal publications involvement in coronavirus disease 2019.** The terms were divided into two clusters based on the various colours created by default, namely, gastrointestinal manifestations coronavirus disease 2019 (COVID-19) patients (red), and implications of COVID-19 for gastroenterologists (green). The large icon indicates the terms that appeared at a high frequency. Among the 13932 terms, only 270 (defined as terms that occurred > 15 times) appeared in titles and abstracts in all publications.

research is becoming more common. The current data analysis reflects various facets of GI publication involvement in COVID-19, including the top countries, institutions, cited articles, journals generating COVID-19 publications, and hot topics in this field. It is critical to determine scientific output through bibliometric analysis to guide researchers on what has already been developed and what is currently

being researched so that future research can resolve information gaps.

Following the COVID-19 pandemic, high-income countries such as the United States, China, Italy, the United Kingdom, Spain, France and Germany are the world leaders in GI publications in COVID-19. A potential reason for these findings is the high prevalence of COVID-19 in countries that experienced the initial outbreak[61-66]. In the most recent studies, nearly 60% of the COVID-19 publications in the Web of Science come from the United States, China, Italy and the United Kingdom[67]. According to the research, the United States contributed the most scientific papers published during the COVID-19 pandemic. This is due to the fact that it has the most academic journals on the search sites in use, as well as being a country where researchers from all over the world want to publish their findings[68]. China was second in the ranking. This is demonstrated by the fact that China has over 3.61 million licensed doctors[13]. Furthermore, Chinese institutions contributed various papers to the COVID-19 research initiative and played a crucial role in the pandemic response[69].

This study found that many publications focused on GI manifestations among COVID-19 patients and implications of COVID-19 for gastroenterologists. So far, COVID-19-related research has involved disease transmission, virology and immunology, epidemiology, clinical characteristics, nonpharmaceutical interventions, detection and diagnosis, treatment, vaccines, and other categories including the psychological status of the medical staff and public during the pandemic[67,70].

The current study used a bibliometric review to discuss the top 10 cited publications about GI involvement in COVID-19. Just three articles addressed GI intervention in COVID-19 patients, while the rest of the widely cited literature centred on GI characteristics and disease features in COVID-19 patients. The most-cited paper was Xiao *et al*[58], which was published in *Gastroenterology* as a brief communication, with 798 citations. This paper provides evidence for GI infection in COVID-19 and its possible faecal-oral transmission route. The second most-cited paper was by Xu *et al*[59] from *Nature Medicine* as a brief communication. According to the results of that study, rectal swab testing may be more helpful than nasopharyngeal swab testing in assessing the efficacy of management and timing of quarantine termination. However, replication-competent virus in faecal swabs was not demonstrated in the study, and this is necessary to confirm the possibility of faecal-oral transmission. The third most-cited paper was by Gu *et al*[52] in *Gastroenterology* as a commentary, which stated that COVID-19 could be present in the oral cavity and faeces of infected people. Moreover, that study recommended that the initial digestive symptoms of COVID-19 should be an alert for early isolation, detection, diagnosis and intervention.

Therefore, our study provides an understanding of the research on GI symptoms in COVID-19, and citation rates can indicate important research topics, development trends in COVID-19 and GI-related research, and provide a reference for research cooperation. However, the mechanism of intestinal infection, its relationship to cytokine release syndrome, and the probability of faecal-oral transmission all require further research in larger populations, especially prospective validation studies with well-designed questions.

This bibliometric analysis provides the first concise summary of global GI publications related to COVID-19. It highlights the benefits of bibliometric analysis in a systematic and structured way to measure the productivity of studies. However, no search strategy is flawless, and the dropout of false-positive or false-negative results is also expected. We attempted to be as comprehensive as possible, using all terms related to GI and COVID-19 listed in the literature. However, there was a possibility of missing some terms. Therefore, we did our best to retrieve all GI publications concerning COVID-19 and sought to verify their study approach using techniques introduced in previously published bibliometric studies. Furthermore, the number of citations will fluctuate over time due to the rapidly changing existence of COVID-19 science. The final limitation is that the authors did not search all scientific databases; however, this limitation is present in almost all bibliometric studies.

## CONCLUSION

This research offers a detailed overview of the position of GI publications in COVID-19 research evolution during the early stages of the outbreak. In a short timespan (1 year) following the start of the COVID-19 pandemic, high-income countries such as the United States, China, Italy, the United Kingdom, Spain, France and Germany became the global leaders of GI-related publications, and were responsible for the bulk of the literature written in this field. This study has found that many publications focused on GI manifestations among COVID-19 patients and the implications of COVID-19 for gastroenterologists. While GI symptoms play an important role in COVID-19, there are still many knowledge gaps about their pathophysiology and prognostic value. Prospective studies with well-designed questions can be used to perform further research. The results of this bibliometric study will act as a basis for future research and guide decision-makers for research related to GI symptoms and treatment in COVID-19.

## ARTICLE HIGHLIGHTS

### *Research background*

Fever and respiratory symptoms are common in coronavirus disease 2019 (COVID-19) patients. Gastrointestinal (GI) symptoms such as diarrhoea, vomiting, and stomach pain may also occur in some patients.

### *Research motivation*

There was an increase in the number of publications addressing the effect of COVID-19 on the GI system in a variety of countries during the outbreak, according to several systematic reviews and meta-analyses. There has not been a comprehensive bibliometric analysis of research on GI and COVID-19. The aim of bibliometrics is to determine the depth of knowledge in a given area.

### *Research objectives*

The purpose of this study was to report a bibliometric analysis of the global research pertaining to GI involvement in COVID-19 to determine the most widely cited papers and most prolific countries, institutions, and journals related to this topic.

### *Research methods*

We searched Scopus for publications during 2020, and selected articles focused on GI and COVID-19.

### *Research results*

The current data analysis reflects various facets of GI-related publications in COVID-19, including the top countries, institutions, cited articles, journals generating COVID-19 publications, and hot topics in this field. It is critical to determine scientific output through bibliometric analysis to guide researchers on what has already been developed and what is currently being researched so that future research can resolve information gaps.

### *Research conclusions*

COVID-19 GI manifestations and implications for gastroenterologists were of increasing concern, especially in the early stages of the pandemic. As a result, it is suggested that research on this subject be focused on the connection between GI manifestations and potential COVID-19 outcomes.

### *Research perspectives*

Our results will help to guide priority setting and policy formulation for long-term strategies to improve the outcomes of COVID-19 patients with GI manifestations.

## FOOTNOTES

**Author contributions:** Zyoud SH designed the study, collected the data, analyzed the data, made major contributions to the manuscript's existing literature search and interpretation, and drafted the manuscript; Al-Jabi SW participated in the study design, was involved in interpretation of the data, made revisions to the initial draft, and answered the reviewers' comments; Jairoun AA and Shahwan MJ corrected the manuscript and answered the reviewers' comments; all authors provided a critical review and approved the final manuscript before submission.

**Conflict-of-interest statement:** The authors have no financial disclosures or conflicts of interest to declare.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.



**Country/Territory of origin:** Palestine

**ORCID number:** Sa'ed H Zyoud 0000-0002-7369-2058; Samah W Al-Jabi 0000-0002-4414-9427; Moyad Jamal Shahwan 0000-0001-8367-4841; Ammar Abdulrahman Jairoun 0000-0002-4471-0878.

**S-Editor:** Gao CC
**L-Editor:** Kerr C

**P-Editor:** Gao CC

## REFERENCES


1 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]

2 **Zhu N**, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; **382**: 727-733 [PMID: 31978945 DOI: 10.1056/NEJMoa2001017]

3 **Adhikari SP**, Meng S, Wu YJ, Mao YP, Ye RX, Wang QZ, Sun C, Sylvia S, Rozelle S, Raat H, Zhou H. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. *Infect Dis Poverty* 2020; **9**: 29 [PMID: 32183901 DOI: 10.1186/s40249-020-00646-x]

4 **World Health Organization**. WHO Director-General's Remarks at the Media Briefing on 2019-nCoV on 11 February 2020. [cited 13 March 2021]. In: World Health Organization [Internet]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020

5 **World Health Organization**. Coronavirus disease (COVID-19) outbreak situation. [cited 13 March 2021]. In: World Health Organization [Internet]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019

6 **Rokkas T**. Gastrointestinal involvement in COVID-19: a systematic review and meta-analysis. *Ann Gastroenterol* 2020; **33**: 355-365 [PMID: 32624655 DOI: 10.20524/aog.2020.0506]

7 **Cha MH**, Regueiro M, Sandhu DS. Gastrointestinal and hepatic manifestations of COVID-19: A comprehensive review. *World J Gastroenterol* 2020; **26**: 2323-2332 [PMID: 32476796 DOI: 10.3748/wjg.v26.i19.2323]

8 **Galanopoulos M**, Gkeros F, Doukatas A, Karianakis G, Pontas C, Tsoukalas N, Viazis N, Liatsos C, Mantzaris GJ. COVID-19 pandemic: Pathophysiology and manifestations from the gastrointestinal tract. *World J Gastroenterol* 2020; **26**: 4579-4588 [PMID: 32884218 DOI: 10.3748/wjg.v26.i31.4579]

9 **Parasa S**, Desai M, Thoguluva Chandrasekar V, Patel HK, Kennedy KF, Roesch T, Spadaccini M, Colombo M, Gabbiadini R, Artifon ELA, Repici A, Sharma P. Prevalence of Gastrointestinal Symptoms and Fecal Viral Shedding in Patients With Coronavirus Disease 2019: A Systematic Review and Meta-analysis. *JAMA Netw Open* 2020; **3**: e2011335 [PMID: 32525549 DOI: 10.1001/jamanetworkopen.2020.11335]

10 **Cheung KS**, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, Ng YY, Chu MY, Chung TWH, Tam AR, Yip CCY, Leung KH, Fung AY, Zhang RR, Lin Y, Cheng HM, Zhang AJX, To KKW, Chan KH, Yuen KY, Leung WK. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis. *Gastroenterology* 2020; **159**: 81-95 [PMID: 32251668 DOI: 10.1053/j.gastro.2020.03.065]

11 **Zarifian A**, Zamiri Bidary M, Arekhi S, Rafiee M, Gholamalizadeh H, Amiriani A, Ghaderi MS, Khadem-Rezaiyan M, Amini M, Ganji A. Gastrointestinal and hepatic abnormalities in patients with confirmed COVID-19: A systematic review and meta-analysis. *J Med Virol* 2021; **93**: 336-350 [PMID: 32681674 DOI: 10.1002/jmv.26314]

12 **Zhou P**, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; **579**: 270-273 [PMID: 32015507 DOI: 10.1038/s41586-020-2012-7]

13 **Chen N**, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507-513 [PMID: 32007143 DOI: 10.1016/S0140-6736(20)30211-7]

14 **Zaim S**, Chong JH, Sankaranarayanan V, Harky A. COVID-19 and Multiorgan Response. *Curr Probl Cardiol* 2020; **45**: 100618 [PMID: 32439197 DOI: 10.1016/j.cpcardiol.2020.100618]

15 **Wu Z**, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020; **323**: 1239-1242 [PMID: 32091533 DOI: 10.1001/jama.2020.2648]

16 **Ye Q**, Wang B, Zhang T, Xu J, Shang S. The mechanism and treatment of gastrointestinal symptoms in patients with COVID-19. *Am J Physiol Gastrointest Liver Physiol* 2020; **319**: G245-G252 [PMID: 32639848 DOI: 10.1152/ajpgi.00148.2020]

17 **Troisi J**, Venutolo G, Pujolassos Tanyà M, Delli Carri M, Landolfi A, Fasano A. COVID-19 and the gastrointestinal tract: Source of infection or merely a target of the inflammatory process following SARS-CoV-2 infection? *World J Gastroenterol* 2021; **27**: 1406-1418 [PMID: 33911464 DOI: 10.3748/wjg.v27.i14.1406]

18 **Zhang J**, Garrett S, Sun J. Gastrointestinal symptoms, pathophysiology, and treatment in COVID-19. *Genes Dis* 2021; **8**: 385-400 [PMID: 33521210 DOI: 10.1016/j.gendis.2020.08.013]

19 **Aziz M**, Haghbin H, Lee-Smith W, Goyal H, Nawras A, Adler DG. Gastrointestinal predictors of severe COVID-19: systematic review and meta-analysis. *Ann Gastroenterol* 2020; **33**: 615-630 [PMID: 33162738 DOI: 10.20524/aog.2020.0527]

20 **Wang H**, Qiu P, Liu J, Wang F, Zhao Q. The liver injury and gastrointestinal symptoms in patients with Coronavirus Disease 19: A systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol* 2020; **44**: 653-661 [PMID: 32418852 DOI: 10.1016/j.clinre.2020.04.012]

21 **Dong ZY**, Xiang BJ, Jiang M, Sun MJ, Dai C. The Prevalence of Gastrointestinal Symptoms, Abnormal Liver Function, Digestive System Disease and Liver Disease in COVID-19 Infection: A Systematic Review and Meta-Analysis. *J Clin Gastroenterol* 2021; **55**: 67-76 [PMID: 33116063 DOI: 10.1097/MCG.0000000000001424]

22 **Dorrell RD**, Dougherty MK, Barash EL, Lichtig AE, Clayton SB, Jensen ET. Gastrointestinal and hepatic manifestations of COVID-19: A systematic review and meta-analysis. *JGH Open* 2020 [PMID: 33363257 DOI: 10.1002/jgh3.12456]

23 **Gul F**, Lo KB, Peterson J, McCullough PA, Goyal A, Rangaswami J. Meta-analysis of outcomes of patients with COVID-19 infection with *vs* without gastrointestinal symptoms. *Proc (Bayl Univ Med Cent)* 2020; **33**: 366-369 [PMID: 32669979 DOI: 10.1080/08998280.2020.1771164]

24 **Kumar A**, Arora A, Sharma P, Anikhindi SA, Bansal N, Singla V, Khare S, Srivastava A. Gastrointestinal and hepatic manifestations of Corona Virus Disease-19 and their relationship to severe clinical course: A systematic review and meta-analysis. *Indian J Gastroenterol* 2020; **39**: 268-284 [PMID: 32749643 DOI: 10.1007/s12664-020-01058-3]

25 **Mao R**, Qiu Y, He JS, Tan JY, Li XH, Liang J, Shen J, Zhu LR, Chen Y, Iacucci M, Ng SC, Ghosh S, Chen MH. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020; **5**: 667-678 [PMID: 32405603 DOI: 10.1016/S2468-1253(20)30126-6]

26 **Suresh Kumar VC**, Mukherjee S, Harne PS, Subedi A, Ganapathy MK, Patthipati VS, Sapkota B. Novelty in the gut: a systematic review and meta-analysis of the gastrointestinal manifestations of COVID-19. *BMJ Open Gastroenterol* 2020; **7** [PMID: 32457035 DOI: 10.1136/bmjgast-2020-000417]

27 **Tariq R**, Saha S, Furqan F, Hassett L, Pardi D, Khanna S. Prevalence and Mortality of COVID-19 Patients With Gastrointestinal Symptoms: A Systematic Review and Meta-analysis. *Mayo Clin Proc* 2020; **95**: 1632-1648 [PMID: 32753138 DOI: 10.1016/j.mayocp.2020.06.003]

28 **Hicks D**, Wouters P, Waltman L, de Rijcke S, Rafols I. Bibliometrics: The Leiden Manifesto for research metrics. *Nature* 2015; **520**: 429-431 [PMID: 25903611 DOI: 10.1038/520429a]

29 **Chahrour M**, Assi S, Bejjani M, Nasrallah AA, Salhab H, Fares M, Khachfe HH. A Bibliometric Analysis of COVID-19 Research Activity: A Call for Increased Output. *Cureus* 2020; **12**: e7357 [PMID: 32328369 DOI: 10.7759/cureus.7357]

30 **DE Felice F**, Polimeni A. Coronavirus Disease (COVID-19): A Machine Learning Bibliometric Analysis. *In Vivo* 2020; **34**: 1613-1617 [PMID: 32503819 DOI: 10.21873/invivo.11951]

31 **Gong Y**, Ma TC, Xu YY, Yang R, Gao LJ, Wu SH, Li J, Yue ML, Liang HG, He X, Yun T. Early Research on COVID-19: A Bibliometric Analysis. *Innovation (N Y)* 2020; **1**: 100027 [PMID: 32914141 DOI: 10.1016/j.xinn.2020.100027]

32 **Yu Y**, Li Y, Zhang Z, Gu Z, Zhong H, Zha Q, Yang L, Zhu C, Chen E. A bibliometric analysis using VOSviewer of publications on COVID-19. *Ann Transl Med* 2020; **8**: 816 [PMID: 32793661 DOI: 10.21037/atm-20-4235]

33 **Sweileh WM**. Bibliometric analysis of peer-reviewed literature on antimicrobial stewardship from 1990 to 2019. *Global Health* 2021; **17**: 1 [PMID: 33397377 DOI: 10.1186/s12992-020-00651-7]

34 **Dehghanbanadaki H**, Aazami H, Keshavarz Azizi Raftar S, Ashrafian F, Ejtahed HS, Hashemi E, Hoseini Tavassol Z, Ahmadi Badi S, Siadat SD. Global scientific output trend for Akkermansia muciniphila research: a bibliometric and scientometric analysis. *BMC Med Inform Decis Mak* 2020; **20**: 291 [PMID: 33167984 DOI: 10.1186/s12911-020-01312-w]

35 **Andersen N**, Bramness JG, Lund IO. The emerging COVID-19 research: dynamic and regularly updated science maps and analyses. *BMC Med Inform Decis Mak* 2020; **20**: 309 [PMID: 33256719 DOI: 10.1186/s12911-020-01321-9]

36 **Aristovnik A**, Ravšelj D, Umek L. A Bibliometric Analysis of COVID-19 across Science and Social Science Research Landscape. *Sustainability* 2020; **12**: 9132 [DOI: 10.3390/su12219132]

37 **Furstenau LB**, Rabaioli B, Sott MK, Cossul D, Bender MS, Farina EMJM, Filho FNB, Severo PP, Dohan MS, Bragazzi NL. A Bibliometric Network Analysis of Coronavirus during the First Eight Months of COVID-19 in 2020. *Int J Environ Res Public Health* 2021; **18** [PMID: 33499127 DOI: 10.3390/ijerph18030952]

38 **Borku Uysal B**, Islamoglu MS, Koc S, Karadag M, Dokur M. Most notable 100 articles of COVID-19: an Altmetric study based on bibliometric analysis. *Ir J Med Sci* 2021; **190**: 1335-1341 [PMID: 33459942 DOI: 10.1007/s11845-020-02460-8]

39 **Huang ZD**, Gu HY, Zhu J, Luo J, Shen XF, Deng QF, Zhang C, Li YB. The application of enhanced recovery after surgery for upper gastrointestinal surgery: Meta-analysis. *BMC Surg* 2020; **20**: 3 [PMID: 31900149 DOI: 10.1186/s12893-019-0669-3]

40 **van Eck NJ**, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. *Scientometrics* 2010; **84**: 523-538 [PMID: 20585380 DOI: 10.1007/s11192-009-0146-3]

41 **Wang K**, Xing D, Dong S, Lin J. The global state of research in nonsurgical treatment of knee osteoarthritis: a bibliometric and visualized study. *BMC Musculoskelet Disord* 2019; **20**: 407 [PMID: 31484517 DOI: 10.1186/s12891-019-2804-9]

42 **Docherty AB**, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, Holden KA, Read JM, Dondelinger F, Carson G, Merson L, Lee J, Plotkin D, Sigfrid L, Halpin S, Jackson C, Gamble C, Horby PW, Nguyen-Van-Tam JS, Ho A, Russell CD, Dunning J, Openshaw PJ, Baillie JK, Semple MG; ISARIC4C investigators. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* 2020; **369**: m1985 [PMID: 32444460 DOI: 10.1136/bmj.m1985]

43 **Dreher M**, Kersten A, Bickenbach J, Balfanz P, Hartmann B, Cornelissen C, Daher A, Stöhr R, Kleines M, Lemmen SW, Brokmann JC, Müller T, Müller-Wieland D, Marx G, Marx N. The Characteristics of 50 Hospitalized COVID-19 Patients With and Without ARDS. *Dtsch Arztebl Int* 2020; **117**: 271-278 [PMID: 32519944 DOI: 10.3238/arztebl.2020.0271]

44 **Ghoshal UC**, Ghoshal U, Mathur A, Singh RK, Nath A, Garg A, Singh D, Singh S, Singh J, Pandey A, Rai S, Vasanth S, Dhiman RK. The Spectrum of Gastrointestinal Symptoms in Patients With Coronavirus Disease-19: Predictors, Relationship With Disease Severity, and Outcome. *Clin Transl Gastroenterol* 2020; **11**: e00259 [PMID: 33463978 DOI: 10.14309/ctg.0000000000000259]

45 **Klopfenstein T**, Kadiane-Oussou NJ, Royer PY, Toko L, Gendrin V, Zayet S. Diarrhea: An underestimated symptom in Coronavirus disease 2019. *Clin Res Hepatol Gastroenterol* 2020; **44**: 282-283 [PMID: 32371006 DOI: 10.1016/j.clinre.2020.04.002]

46 **Montazeri M**, Maghbouli N, Jamali R, Sharifi A, Pazoki M, Salimzadeh A, Barzegari B, Rafiei N, Mansouri ES, Hadadi A. Clinical Characteristics of COVID-19 Patients with Gastrointestinal Symptoms. *Arch Iran Med* 2021; **24**: 131-138 [PMID: 33636982 DOI: 10.34172/aim.2021.21]

47 **Papa A**, Covino M, Pizzolante F, Miele L, Lopetuso LR, Bove V, Iorio R, Simeoni B, Vetrone LM, Tricoli L, Mignini I, Schepis T, D'Alessandro A, Coppola G, Nicoletti T, Visconti E, Rapaccini G. Gastrointestinal symptoms and digestive

comorbidities in an Italian cohort of patients with COVID-19. *Eur Rev Med Pharmacol Sci* 2020; **24**: 7506-7511 [PMID: 32706091 DOI: 10.26355/eurrev_202007_21923]

48 **Redd WD**, Zhou JC, Hathorn KE, McCarty TR, Bazarbashi AN, Thompson CC, Shen L, Chan WW. Prevalence and Characteristics of Gastrointestinal Symptoms in Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection in the United States: A Multicenter Cohort Study. *Gastroenterology* 2020; **159**: 765-767.e2 [PMID: 32333911 DOI: 10.1053/j.gastro.2020.04.045]

49 **Rivera-Izquierdo M**, Valero-Ubierna MDC, Martínez-Diz S, Fernández-García MÁ, Martín-Romero DT, Maldonado-Rodríguez F, Sánchez-Pérez MR, Martín-delosReyes LM, Martínez-Ruiz V, Lardelli-Claret P, Jiménez-Mejías E. Clinical Factors, Preventive Behaviours and Temporal Outcomes Associated with COVID-19 Infection in Health Professionals at a Spanish Hospital. *Int J Environ Res Public Health* 2020; **17** [PMID: 32560180 DOI: 10.3390/ijerph17124305]

50 **COVID-19 National Incident Room Surveillance Team**. COVID-19, Australia: Epidemiology Report 7 (Reporting week ending 19:00 AEDT 14 March 2020). *Commun Dis Intell (2018)* 2020; **44** [PMID: 32192424 DOI: 10.33321/cdi.2020.44.23]

51 **Zheng T**, Yang C, Wang HY, Chen X, Yu L, Wu ZL, Sun H. Clinical characteristics and outcomes of COVID-19 patients with gastrointestinal symptoms admitted to Jianghan Fangcang Shelter Hospital in Wuhan, China. *J Med Virol* 2020; **92**: 2735-2741 [PMID: 32510173 DOI: 10.1002/jmv.26146]

52 **Gu J**, Han B, Wang J. COVID-19: Gastrointestinal Manifestations and Potential Fecal-Oral Transmission. *Gastroenterology* 2020; **158**: 1518-1519 [PMID: 32142785 DOI: 10.1053/j.gastro.2020.02.054]

53 **Jin X**, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM, Hao SR, Jia HY, Cai H, Zhang XL, Yu GD, Xu KJ, Wang XY, Gu JQ, Zhang SY, Ye CY, Jin CL, Lu YF, Yu X, Yu XP, Huang JR, Xu KL, Ni Q, Yu CB, Zhu B, Li YT, Liu J, Zhao H, Zhang X, Yu L, Guo YZ, Su JW, Tao JJ, Lang GJ, Wu XX, Wu WR, Qv TT, Xiang DR, Yi P, Shi D, Chen Y, Ren Y, Qiu YQ, Li LJ, Sheng J, Yang Y. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut* 2020; **69**: 1002-1009 [PMID: 32213556 DOI: 10.1136/gutjnl-2020-320926]

54 **Lamers MM**, Beumer J, van der Vaart J, Knoops K, Puschhof J, Breugem TI, Ravelli RBG, Paul van Schayck J, Mykytyn AZ, Duimel HQ, van Donselaar E, Riesebosch S, Kuijpers HJH, Schipper D, van de Wetering WJ, de Graaf M, Koopmans M, Cuppen E, Peters PJ, Haagmans BL, Clevers H. SARS-CoV-2 productively infects human gut enterocytes. *Science* 2020; **369**: 50-54 [PMID: 32358202 DOI: 10.1126/science.abc1669]

55 **Pan L**, Mu M, Yang P, Sun Y, Wang R, Yan J, Li P, Hu B, Wang J, Hu C, Jin Y, Niu X, Ping R, Du Y, Li T, Xu G, Hu Q, Tu L. Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. *Am J Gastroenterol* 2020; **115**: 766-773 [PMID: 32287140 DOI: 10.14309/ajg.0000000000000620]

56 **Tian Y**, Rong L, Nian W, He Y. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. *Aliment Pharmacol Ther* 2020; **51**: 843-851 [PMID: 32222988 DOI: 10.1111/apt.15731]

57 **Wu Y**, Guo C, Tang L, Hong Z, Zhou J, Dong X, Yin H, Xiao Q, Tang Y, Qu X, Kuang L, Fang X, Mishra N, Lu J, Shan H, Jiang G, Huang X. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. *Lancet Gastroenterol Hepatol* 2020; **5**: 434-435 [PMID: 32199469 DOI: 10.1016/S2468-1253(20)30083-2]

58 **Xiao F**, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. *Gastroenterology* 2020; **158**: 1831-1833.e3 [PMID: 32142773 DOI: 10.1053/j.gastro.2020.02.055]

59 **Xu Y**, Li X, Zhu B, Liang H, Fang C, Gong Y, Guo Q, Sun X, Zhao D, Shen J, Zhang H, Liu H, Xia H, Tang J, Zhang K, Gong S. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat Med* 2020; **26**: 502-505 [PMID: 32284613 DOI: 10.1038/s41591-020-0817-4]

60 **Yeo C**, Kaushal S, Yeo D. Enteric involvement of coronaviruses: is faecal-oral transmission of SARS-CoV-2 possible? *Lancet Gastroenterol Hepatol* 2020; **5**: 335-337 [PMID: 32087098 DOI: 10.1016/S2468-1253(20)30048-0]

61 **Bernard Stoecklin S**, Rolland P, Silue Y, Mailles A, Campese C, Simondon A, Mechain M, Meurice L, Nguyen M, Bassi C, Yamani E, Behillil S, Ismael S, Nguyen D, Malvy D, Lescure FX, Georges S, Lazarus C, Tabaï A, Stempfelet M, Enouf V, Coignard B, Levy-Bruhl D; Investigation Team. First cases of coronavirus disease 2019 (COVID-19) in France: surveillance, investigations and control measures, January 2020. *Euro Surveill* 2020; **25** [PMID: 32070465 DOI: 10.2807/1560-7917.ES.2020.25.6.2000094]

62 **Marchand-Senécal X**, Kozak R, Mubareka S, Salt N, Gubbay JB, Eshaghi A, Allen V, Li Y, Bastien N, Gilmour M, Ozaldin O, Leis JA. Diagnosis and Management of First Case of COVID-19 in Canada: Lessons Applied From SARS-CoV-1. *Clin Infect Dis* 2020; **71**: 2207-2210 [PMID: 32147731 DOI: 10.1093/cid/ciaa227]

63 **Wells CR**, Sah P, Moghadas SM, Pandey A, Shoukat A, Wang Y, Wang Z, Meyers LA, Singer BH, Galvani AP. Impact of international travel and border control measures on the global spread of the novel 2019 coronavirus outbreak. *Proc Natl Acad Sci U S A* 2020; **117**: 7504-7509 [PMID: 32170017 DOI: 10.1073/pnas.2002616117]

64 **Livingston E**, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. *JAMA* 2020; **323**: 1335 [PMID: 32181795 DOI: 10.1001/jama.2020.4344]

65 **Spiteri G**, Fielding J, Diercke M, Campese C, Enouf V, Gaymard A, Bella A, Sognamiglio P, Sierra Moros MJ, Riutort AN, Demina YV, Mahieu R, Broas M, Bengnér M, Buda S, Schilling J, Filleul L, Lepoutre A, Saura C, Mailles A, Levy-Bruhl D, Coignard B, Bernard-Stoecklin S, Behillil S, van der Werf S, Valette M, Lina B, Riccardo F, Nicastri E, Casas I, Larrauri A, Salom Castell M, Pozo F, Maksyutov RA, Martin C, Van Ranst M, Bossuyt N, Siira L, Sane J, Tegmark-Wisell K, Palmérus M, Broberg EK, Beauté J, Jorgensen P, Bundle N, Pereyaslov D, Adlhoch C, Pukkila J, Pebody R, Olsen S, Ciancio BC. First cases of coronavirus disease 2019 (COVID-19) in the WHO European Region, 24 January to 21 February 2020. *Euro Surveill* 2020; **25** [PMID: 32156327 DOI: 10.2807/1560-7917.ES.2020.25.9.2000178]

66 **Sjölander-Lindqvist A**, Larsson S, Fava N, Gillberg N, Marcianò C, Cinque S. Communicating About COVID-19 in Four European Countries: Similarities and Differences in National Discourses in Germany, Italy, Spain, and Sweden. *Front Commun* 2020; **5**: 593325 [DOI: 10.3389/fcomm.2020.593325]

67 **Wang P**, Tian D. Bibliometric analysis of global scientific research on COVID-19. *J Biosaf Biosecur* 2021; **3**: 4-9 [PMID: 33521590 DOI: 10.1016/j.jobb.2020.12.002]

68 **Oliveira EMN**, Carvalho ARB, Silva JSE, Sousa Neto AR, Moura MEB, Freitas DRJ. Analysis of scientific production on the new coronavirus (COVID-19): a bibliometric analysis. *Sao Paulo Med J* 2021; **139**: 3-9 [PMID: 33656129 DOI: 10.1590/1516-3180.2020.0449.R1.01102020]

69 **Xiang YT**, Li W, Zhang Q, Jin Y, Rao WW, Zeng LN, Lok GKI, Chow IHI, Cheung T, Hall BJ. Timely research papers about COVID-19 in China. *Lancet* 2020; **395**: 684-685 [PMID: 32078803 DOI: 10.1016/S0140-6736(20)30375-5]

70 **Pfefferbaum B**, North CS. Mental Health and the Covid-19 Pandemic. *N Engl J Med* 2020; **383**: 510-512 [PMID: 32283003 DOI: 10.1056/NEJMp2008017]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 May 27; 14(5): 506-513

DOI: 10.4240/wjgs.v14.i5.506

ISSN 1948-9366 (online)

*CASE REPORT*

# Aorto-oesophageal fistula after corrosive ingestion: A case report

Matthias Frank Scriba, Urda Kotze, Nadraj Naidoo, Eduard Jonas, Galya Eileen Chinnery

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Chiu CC, Taiwan; Lim KT, Singapore; Link A, Germany

**Received:** August 31, 2021
**Peer-review started:** August 31, 2021
**First decision:** March 11, 2022
**Revised:** March 23, 2022
**Accepted:** April 15, 2022
**Article in press:** April 15, 2022
**Published online:** May 27, 2022

**Matthias Frank Scriba, Eduard Jonas, Galya Eileen Chinnery,** Surgical Gastroenterology Unit, Department of Surgery, Groote Schuur Hospital, University of Cape Town, Cape Town 7925, Western Cape, South Africa

**Urda Kotze,** Surgical Gastroenterology Unit, Department of Surgery, University of Cape Town, Faculty of Health Sciences, Cape Town 7925, Western Cape, South Africa

**Nadraj Naidoo,** Vascular and Endovascular Surgery Unit, Department of Surgery, Groote Schuur Hospital, University of Cape Town, Cape Town 7925, Western Cape, South Africa

**Corresponding author:** Matthias Frank Scriba, MBChB, Surgeon, Surgical Gastroenterology, Department of Surgery, Groote Schuur Hospital, University of Cape Town, Anzio Road, Observatory, Cape Town 7925, Western Cape, South Africa. matthias.scriba@gmail.com

## Abstract

*BACKGROUND*

Aorto-oesophageal fistula (AOF) are uncommon and exceedingly rare after corrosive ingestion. The authors report a case of AOF after corrosive ingestion that survived. A comprehensive literature review was performed to identify all cases of AOF after corrosive ingestion to determine the incidence of this condition, how it is best managed and what the outcomes are.

*CASE SUMMARY*

A previously healthy 30-year-old male, presented with a corrosive oesophageal injury after drain cleaner ingestion. He did not require acute surgical resection, but developed long-segment oesophageal stricturing, which was initially managed with cautious dilatation and later stenting. An AOF was suspected at endoscopy performed two months after the ingestion, when the patient represented with massive upper gastrointestinal bleeding. The fistula was confirmed on computerised tomographic angiography. The initial bleeding at endoscopy was temporised by oesophageal stenting; a second stent was placed when bleeding recurred later the same day. The stenting successfully achieved temporary bleeding control, but resulted in sudden respiratory distress, which was found to be due to left main bronchus compression caused by the overlapping oesophageal stents. Definitive bleeding control was achieved by endovascular aortic stent-grafting. A retrosternal gastroplasty was subsequently performed to achieve gastrointestinal diversion to reduce the risk of stent-graft sepsis. He was subsequently successfully discharged and remains well one year post injury.

*CONCLUSION*

AOF after corrosive ingestion is exceedingly rare, with a very high mortality. Most occur weeks to months after the initial corrosive ingestion. Conservative management is ill-advised.

**Key Words:** Aorto-oesophageal fistula; Corrosive/caustic injury; Corrosive ingestion; Case report



**Core Tip:** Aorto-oesophageal fistula (AOF) after corrosive ingestion is exceedingly rare, but is usually catastrophic. We present a case of AOF after corrosive ingestion which was successfully managed with a combination of oesophageal stenting to achieve temporary bleeding control, and endovascular aortic stent-grafting with retrosternal gastroplasty as definitive management. Including this case, only 16 individual cases of this rare condition are found in the literature, with only two survivors prior to this case. Fistula formation usually only occurs weeks to months after the ingestion incident and as such a high level of suspicion is needed to diagnose this illusive and difficult to manage condition.

**Citation:** Scriba MF, Kotze U, Naidoo N, Jonas E, Chinnery GE. Aorto-oesophageal fistula after corrosive ingestion: A case report. *World J Gastrointest Surg* 2022; 14(5): 506-513
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i5/506.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i5.506

## INTRODUCTION

Aorto-oesophageal fistula (AOF) is a rare, but deadly entity. Chiari's classic triad of midthoracic pain, a herald bleed, followed by exsanguinating haemorrhage was initially described for AOF after foreign body ingestion but has since been applied to any AOF[1]. The most common causes include complicated thoracic aortic aneurysms, oesophageal foreign bodies and oesophageal carcinoma[1]. Confirming the diagnosis can be challenging and in most cases is only made at post-mortem examination. Management remains controversial and overall survival is low. AOF after corrosive or caustic ingestion are exceedingly rare and only a few cases have been described in the literature. We report a case of an AOF survivor after corrosive ingestion. A comprehensive literature review was performed to identify all cases of AOF after corrosive ingestion to assess how common the condition is, how it is best managed and what the outcomes are.

A comprehensive search of the literature up to March 31, 2021 was performed with the help of a clinical librarian in the following databases: PubMed, PubMed Central, Scopus, Web of Science Core Collection and Cochrane Library. No language or time constraints were set. The following keyword search terms were used: [(Aorta OR aorta OR aortas OR aortic) AND (oesophagus OR esophagus OR oesophageal OR esophageal) AND (fistula OR fistulae OR fistulas) AND (corrosive OR corrosion OR corroding OR caustic OR caustics OR lye OR abrasive OR abrasives OR acid OR acids OR alkaline)]. The following MESH terms were also included in the search: ["Aorta" (Mesh) OR "Aortic Diseases" (Mesh)] AND [Esophageal Fistula (Mesh)] AND ["Caustics" (Mesh)] (Supplementary Table 1).

A total of 2460 studies were identified after the initial search, of which only 11 publications met the final inclusion criteria, rendering a total of 15 individual cases of AOF after corrosive ingestion (not including our own case, reported in this publication).

## CASE PRESENTATION

### *Chief complaints*

A 30-year-old male, known with a long-segment oesophageal stricture two months after corrosive ingestion, underwent an urgent gastroscopy for an upper gastrointestinal bleed. During the procedure he was noted to have massive bleeding from the oesophagus and an AOF was suspected.

### *History of present illness*

The patient initially presented to our institution five days after accidentally consuming a corrosive substance, later identified as drain cleaner (sodium hydroxide). He was dared to consume the substance at a party and was unaware that it contained a corrosive. Except for a mild tachycardia, vital signs and routine blood work on initial admission were normal. He had an inflamed oropharyngeal mucosa and careful early upper gastrointestinal endoscopy indicated a severe corrosive injury with extensive necrosis of almost the entire oesophageal mucosa, but with viable visible underlying oesophageal

muscle (Zargar grade IIb[2]). He also had a milder gastric injury, with superficial focal ulceration but no necrosis, limited to the gastric antrum (Zargar grade IIa[2]). With no features of full thickness gastric or oesophageal necrosis, an endoscopic nasojejunal feeding tube was placed and he was admitted for continued observations and nutritional support.

Contrast swallow examination on day nine post injury (Figure 1) confirmed the extensive oesophageal injury with irregular mucosa and already showed early long-segment stricturing. The feeding tube was removed fourteen days later after successful early cautious serial bougie dilatation to 14 mm. He was discharged home three days later tolerating a soft diet.

At his two-weekly review, he again complained of near-complete dysphagia. Upper gastrointestinal endoscopy with fluoroscopy now confirmed an established high-grade, long oesophageal stricture extending from 25 cm from the front incisors to the oesophagogastric junction. Due to the risk of perforation associated with pneumatic or repeat bougie dilatation, a more gradual dilatation with temporary stenting was opted for. Two overlapping 120 mm × 20 mm fully covered self-expanding metal stents were placed (Taewoong Medical Company, Gojeong, South Korea). He remained well after this, tolerating a soft diet at home.

He returned three weeks later reporting a single episode of haematemesis, but was haemodynamically and generally well. He did not complain of dysphagia. Gastroscopy was again performed, which revealed both stents in-situ and patent. However, the most proximal stent had migrated distally by some 2 cm with an area of stricturing above this. The scope was passed beyond this with complete endoscopic examination down to the second part of the duodenum revealing no signs of gastrointestinal bleeding or pathology. On pulling back the proximal stent to cover the area of developing stricturing, brisk bleeding occurred which was controlled after placement of a third oesophageal stent.

### History of past illness

The patient was previously healthy, with no known prior medical or surgical history.

### Personal and family history

There was no other relevant personal history or family history of note. Other than social alcohol use he denied any other substance use.

### Physical examination

After the bleeding from the suspected AOF was temporised, his vital signs showed a blood pressure of 105/67 mmHg, a heart rate of 150 beats/minute, a respiratory rate of 18 breaths/minute with oxygen saturation of 97% on room air and a normal Glascow Coma Scale of 15/15. His general examination was normal with no signs of pallor or other abnormalities.

### Laboratory examinations

Full blood count showed a formal haemoglobin of 9.3 g/dL and a mild leukocytosis of 11.59 × $10^9$/L. Urea, creatinine and electrolytes were normal.

### Imaging examinations

On suspicion of an AOF, an urgent computerised tomographic angiogram (CTA) was performed, which confirmed the fistula in the region of the proximal thoracic oesophagus with an aberrant right-sided aortic arch (Figure 2).

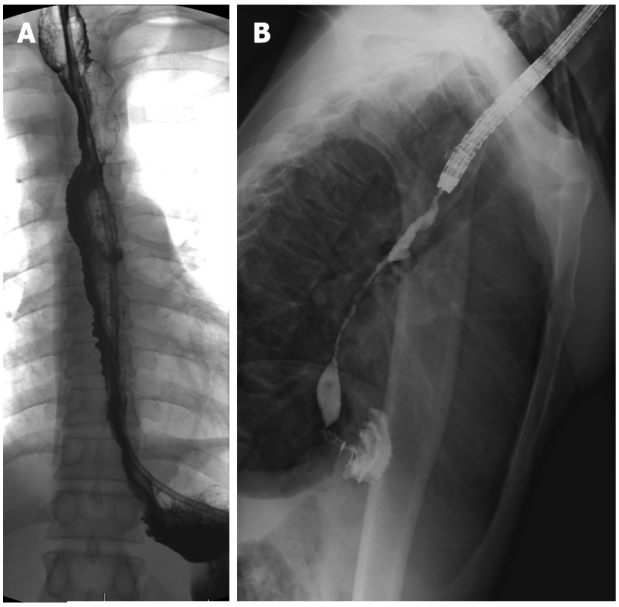
## FINAL DIAGNOSIS

AOF after corrosive ingestion.

## TREATMENT

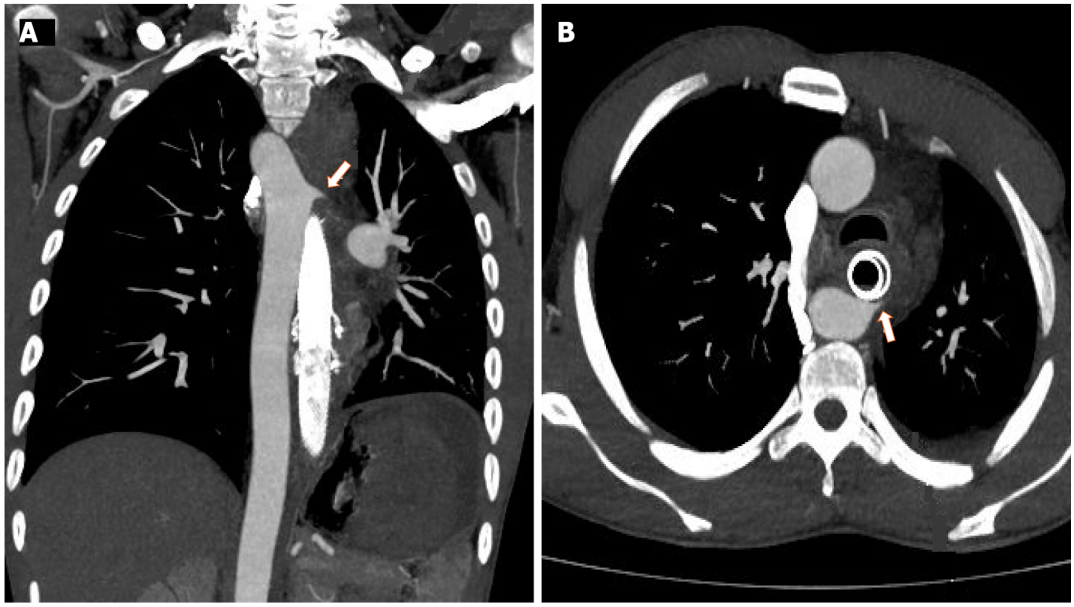
After the bleeding was stopped, the patient was resuscitated with intravenous fluids and admitted. After CTA confirmation of the AOF, an endovascular aortic repair was planned but another massive bleed occurred which was temporised with a fourth oesophageal stent. This was followed by transient respiratory distress and chest X-ray showed a near-complete "white-out" of the left chest (Figure 3). A thoracic endovascular aortic repair *via* a right femoral approach using a 28 mm (proximal diameter) × 28 mm (distal diameter) × 157 mm (covered length) Valiant thoracic stent graft (Medtronic, Dublin, Ireland) was then successfully performed.

To prevent endovascular stent contamination, an oesophageal exclusion with a retrosternal gastric conduit was performed five days after the endovascular procedure. On-table bronchoscopy showed extrinsic compression with near-complete occlusion of the left main bronchus. On-table oesophagoscopy with successful retrieval of the four oesophageal stents was performed. Repeat bronchoscopy now




**DOI:** 10.4240/wjgs.v14.i5.506 **Copyright** ©The Author(s) 2022.

**Figure 1 Contrast swallow examination on day nine post injury.** A: Contrast swallow study performed 9 d post injury, already confirming early long-segment stricturing of the oesophagus; B: Fluoroscopic study during endoscopy performed 4 wk post injury, showing high-grade, long-segment oesophageal stricturing.



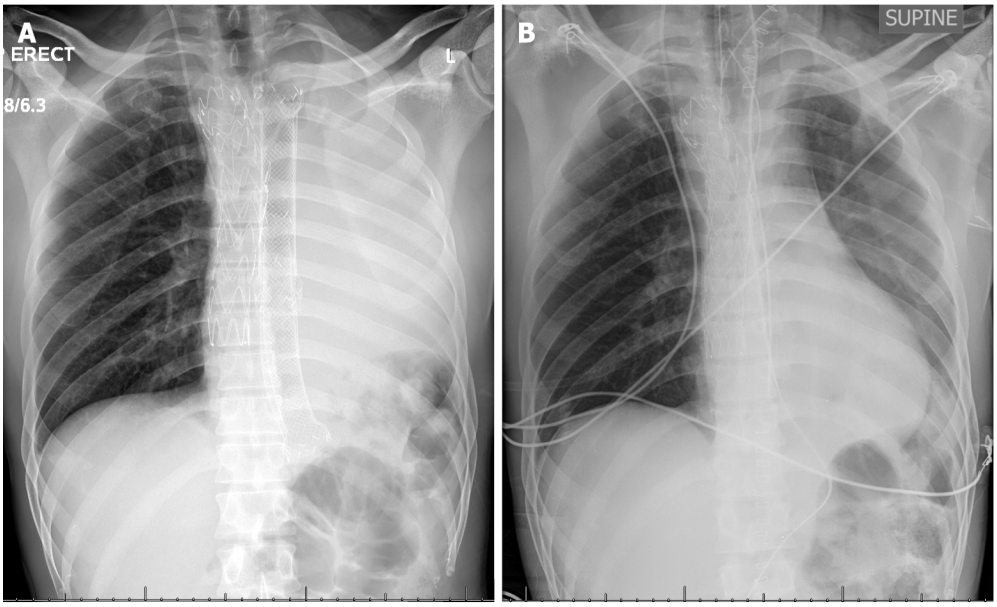

**DOI:** 10.4240/wjgs.v14.i5.506 **Copyright** ©The Author(s) 2022.

**Figure 2 Computed tomography angiogram images confirming the site of the proximal aorto-oesophageal fistula (arrows).** A: Coronal image; B: Axial image.

revealed a patent left main bronchus, confirming that the extrinsic bronchial occlusion was due to the radial pressure of the oesophageal stents. The oesophageal exclusion was then performed, leaving the native, severely strictured and adherent oesophagus in-situ.

## OUTCOME AND FOLLOW-UP

The patient was discharged 13 d later without complication. He subsequently developed mild stricturing of the proximal oesophagogastric anastomosis, which was successfully treated with serial dilatations. At one year post the initial corrosive injury the patient is well and dysphagia-free.




**DOI:** 10.4240/wjgs.v14.i5.506 

**Figure 3 Chest X-ray.** A: Chest X-ray post aortic endovascular repair, showing aortic stent-graft, multiple overlapping stents in the oesophagus and white-out of the left lung, caused by left main bronchus compression by the oesophageal stents; B: Chest X-ray immediately post-operative after retrosternal gastric pull-up and removal of oesophageal stents showing good left lung re-expansion.

## DISCUSSION

AOF are uncommon. In an extensive literature review in 1991 Hollander and Quick[1] identified a total of only 500 AOF cases of all aetiologies, with 51% being related to thoracic aortic aneurysms, 19% related to foreign body ingestion and 17% related to oesophageal malignancy[1]. Aorta-oesophageal fistula after corrosive ingestion is exceedingly rare. Our own comprehensive literature review on AOF after corrosive ingestion yielded only 15 cases other than our own, with only two other reported survivors. Table 1 outlines numerous characteristics of the entire cohort of 16 cases. Unfortunately, as most cases pre-date 2000, missing data was common in many cases. In the 13 cases where the mode of diagnoses was specified, the diagnosis was only made on imaging in two patients, at surgical exploration in two patients and in the remaining nine at post-mortem examination. The time from corrosive ingestion to AOF formation ranged from 2–62 d, with a median time of 14 d (IQR: 11.5–35.5 d). In only four cases (25%) was a herald bleed prior to massive haemorrhage reported. Five cases had a concomitant fistula between the oesophagus and respiratory tract (four tracheo-oesophageal fistulae and one broncho-oesophageal fistula), while in seven cases a concomitant gastric injury was described. Of the 16 described cases, 13 died resulting in a mortality rate of 81.2%. In four patients (25%) management of the AOF was attempted, of whom three survived.

Diagnosis remains challenging. Chiari's triad is of limited diagnostic value with only a minority of patients in this review having evidence of a herald bleed. Although endoscopy may be useful in suspecting the injury, vascular imaging with angiography or CTA is required to make a definitive diagnosis. Fistulae following corrosive ingestion typically occur more than two weeks post injury. In the context of the case reported the significant radial force exerted by self-expanding oesophageal stents needs to be considered. We postulate that the AOF likely formed due to a combination of factors, including the initial corrosive injury, but cannot exclude that the radial force of the stents placed was contributory. This force was also responsible for bronchial compression, which has previously been described in the literature[3,4]. It needs to be highlighted that using oesophageal stenting in the early management of the corrosive stricture is controversial, but was made by the treating team in light of the severity and length of the corrosive stricture where the risk of perforation using bougie or balloon dilatation was considered too high. Using an oesophageal stent to temporise bleeding was performed as the patient was present in the endoscopy suite where fluoroscopy was readily available, but using balloon tamponade to achieve haemostasis is another option and may be more suitable in other settings.

Conservative management of AOF is invariably fatal and should be reserved for patients not fit for intervention. Effective management of any AOF requires management of the fistula from both the oesophageal and aortic sides. The decision between open and endovascular management of the aorta is controversial and although contemporary guidelines consider open repair the gold standard, this is mostly based on fistulae secondary to thoracic aortic aneurysms, where the primary pathology is vascular[5]. With corrosive ingestion the primary pathology is in the oesophagus. Attempted definitive repair using an endovascular stent-graft leaves the significant concern of oesophageal content gaining

**Table 1 Summary of all aorto-oesophageal fistula after corrosive ingestion publications and individual patient cases (total cases *n* = 16)**

| Ref. | Age (yr) | Sex | Corrosive agent | Ingestion intent | Days to presentation | Herald bleed | Diagnosis | Management of AOF | Outcome | Associated corrosive injuries |
|---|---|---|---|---|---|---|---|---|---|---|
| Schranz[9], 1934 | 16 | F | Alkali | [1] | 7 | N | Autopsy | - | D | BOF |
| Singh *et al* [10], 1976 | [1] | [1] | [1] | [1] | [1] | [1] | Autopsy | - | D | - |
| Waller and Rumler[11], 1963 | 10 | M | Alkali | A | 10 | N | Autopsy | - | D | TOF, gastric (necrosis) |
| Rabinovitz *et al*[12], 1990 | 23 | F | [1] | [1] | 12 | Y | Autopsy | - | D | TOF, gastric and duodenal injuries |
| Singh *et al* [10], 1976 | 54 | M | Alkali | [1] | 27 | N | Autopsy | - | D | TOF, diaphragm (necrosis, perforation) |
| Ottosson [13], 1981 | 14 | M | Alkali | A | 44 | N | Surgery | Primary repair of the oesophagus and aorta | D | - |
| Sarfati *et al* [14], 1987 | [1] | [1] | [1] | [1] | 14 | [1] | [1] | [1] | D | [1] |
| | [1] | [1] | [1] | [1] | 14 | [1] | [1] | [1] | D | [1] |
| | [1] | [1] | [1] | [1] | 14 | [1] | [1] | [1] | D | [1] |
| Rabinovitz *et al*[12], 1990 | 34 | M | Alkali | S | 23 | Y | Autopsy | - | D | TOF, gastric (necrosis with perforation) |
| Marone *et al* [7], 2006 | 20 | M | Acid | S | 25 | N | Surgery | Open local aortic repair, then endovascular stent repair. Oesophageal bypass (colon conduit) | S | Gastric necrosis with perforation |
| Yegane *et al* [15], 2008 | 37 | M | Acid | S | 11 | N | Autopsy | - | D | - |
| | 40 | M | Acid | [1] | 2 | N | Autopsy | - | D | - |
| | 67 | M | Acid | [1] | 60 | Y | Autopsy | - | D | Gastric (di Constanzo grade II injury) |
| Lee *et al*[8], 2011 | 75 | F | Alkali | [1] | 60 | N | CT | Open aortic repair, total oesophago-gastrectomy | S | Gastric (total gastrectomy) |
| This study[2] | 30 | M | Alkali | A | 62 | Y | CT, Endoscopy | Oesophageal stenting endovascular aortic repair, oesophageal bypass (gastric conduit) | S | Gastric (Zargar IIa injury) |

[1]Not mentioned.

[2]Authors own case report, not previously published.

F: Female; M: Male; A: Accidental; S: Suicidal; N: No; Y: Yes; CT: Computed tomography; D: Deceased; S: Survived; AOF: Aorto-oesophageal fistula; BOF: Broncho-oesophageal fistula; TOF: Trachea-oesophageal fistula.

access to the synthetic graft *via* the fistula, with the risk of prosthetic sepsis. For this reason, management of the fistula from the oesophageal side is mandatory. Although oesophageal stenting could facilitate temporizing the bleeding and divert content away from the fistula, long-term results in terms of preventing graft infection are lacking. While a surgical conduit will effectively divert luminal content, leaving the native oesophagus in-situ is associated with a risk of mucocoele formation and possible future risk of malignant transformation[6]. However, this must be weighed up against a difficult oesophageal resection due to extensive mediastinal fibrosis with a high risk of associated surgical morbidity[6].

The patient described in this case report was managed with minimally invasive interventions for temporizing control using oesophageal stenting and definitive management of the aortic defect with endovascular stenting. Surgical management was reserved for the oesophageal reconstruction. Marone *et al*[7] reported the first successfully managed patient with AOF after corrosive, which involved initial local closure of the fistula *via* open surgical access followed by endovascular stent repair of the aorta and oesophageal replacement with a retrosternal colonic conduit. Lee *et al*[8] reported a patient that was

successfully managed with surgical repair of the aorta, followed by oesophagogastrectomy.

In view of the extreme rarity of this condition, with only five other cases described in the last 30 years, creating evidence-based management algorithms or follow-up protocols is truly challenging. We do however advise clinicians treating patients after corrosive ingestion to ensure there is regular, planned patient follow-up in all those who sustain significant oesophageal corrosive injuries (Zargar IIb and above) who survive the initial management period. This should be done primarily due to the very high incidence of subsequent stricture formation frequently requiring long term endoscopic treatment. The common scenario of multi-level or long-segment stricturing seen with severe corrosive injuries poses challenging management problems[6]. Clinicians should be alerted to the fact that any reported gastro-intestinal bleeding in these patients, even months after the initial injury, may represent an AOF. We recommend CT angiography as the diagnostic modality of choice and strongly advocate that all diagnosed fistulae be treated on an individualised basis in a multi-disciplinary environment *via* combined approaches from the vascular and gastro-intestinal sides of the fistula.

## CONCLUSION

Outcomes for AOF after corrosive ingestion remain dismal. Although a rare cause of upper gastrointestinal bleeding, it should be considered as a cause following corrosive injury and requires a high level of suspicion as fistula formation often occurs in a delayed fashion after the ingestion event. Management should be individualised as guidelines to aid decision-making are lacking. Optimal outcomes are best achieved with multimodality therapy in a multidisciplinary setting.

## ACKNOWLEDGEMENTS

The authors would like to thank Dr. Chanel Robinson (PhD) for providing formal biostatistical support and in revising parts of the paper.

## FOOTNOTES

**Author contributions:** Scriba MF, Chinnery GE and Kotze U performed the literature review; Jonas E and Naidoo N assisted in writing up the paper and critically reviewing it; all authors read and approved the final manuscript

**Informed consent statement:** Informed written consent was obtained from the patient for the publication of this report and for any accompanying images.

**Conflict-of-interest statement:** The authors declare they have no conflicts of interest.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).



**Country/Territory of origin:** South Africa

**ORCID number:** Matthias Frank Scriba 0000-0001-8903-0510; Urda Kotze 0000-0003-1405-474X; Nadraj Naidoo 0000-0003-2202-9691; Eduard Jonas 0000-0003-0123-256X; Galya Eileen Chinnery 0000-0002-9097-8648.

**S-Editor:** Fan JR
**L-Editor:** A
**P-Editor:** Fan JR

## REFERENCES

1 **Hollander JE**, Quick G. Aortoesophageal fistula: a comprehensive review of the literature. *Am J Med* 1991; **91**: 279-287 [PMID: 1892150 DOI: 10.1016/0002-9343(91)90129-L]
2 **Zargar SA**, Kochhar R, Nagi B, Mehta S, Mehta SK. Ingestion of corrosive acids. Spectrum of injury to upper

gastrointestinal tract and natural history. *Gastroenterology* 1989; **97**: 702-707 [PMID: 2753330 DOI: 10.1016/0016-5085(89)90641-0]

3 **Farivar AS**, Vallières E, Kowdley KV, Wood DE, Mulligan MS. Airway obstruction complicating esophageal stent placement in two post-pneumonectomy patients. *Ann Thorac Surg* 2004; **78**: e22-e23 [PMID: 15276582 DOI: 10.1016/j.athoracsur.2003.09.118]

4 **Aneeshkumar S**, Sundararajan L, Santosham R, Palaniappan R, Dhus U. Erosion of esophageal stent into left main bronchus causing airway compromise. *Lung India* 2017; **34**: 76-78 [PMID: 28144066 DOI: 10.4103/0970-2113.197114]

5 **Chakfé N**, Diener H, Lejay A, Assadian O, Berard X, Caillon J, Fourneau I, Glaudemans AWJM, Koncar I, Lindholt J, Melissano G, Saleem BR, Senneville E, Slart RHJA, Szeberin Z, Venermo M, Vermassen F, Wyss TR; Esvs Guidelines Committee, de Borst GJ, Bastos Gonçalves F, Kakkos SK, Kolh P, Tulamo R, Vega de Ceniga M, Document Reviewers, von Allmen RS, van den Berg JC, Debus ES, Koelemay MJW, Linares-Palomino JP, Moneta GL, Ricco JB, Wanhainen A. Editor's Choice - European Society for Vascular Surgery (ESVS) 2020 Clinical Practice Guidelines on the Management of Vascular Graft and Endograft Infections. *Eur J Vasc Endovasc Surg* 2020; **59**: 339-384 [PMID: 32035742 DOI: 10.1016/j.ejvs.2019.10.016]

6 **Chirica M**, Bonavina L, Kelly MD, Sarfati E, Cattan P. Caustic ingestion. *Lancet* 2017; **389**: 2041-2052 [PMID: 28045663 DOI: 10.1016/S0140-6736(16)30313-0]

7 **Marone EM**, Baccari P, Brioschi C, Tshomba Y, Staudacher C, Chiesa R. Surgical and endovascular treatment of secondary aortoesophageal fistula. *J Thorac Cardiovasc Surg* 2006; **131**: 1409-1410 [PMID: 16733185 DOI: 10.1016/j.jtcvs.2006.01.036]

8 **Lee YH**, Han HY. CT Findings of an Aortoesophageal Fistula due to Lye Ingestion: A Case Report. *J Korean Soc Radiol* 2011; **64**: 553 [DOI: 10.3348/jksr.2011.64.6.553]

9 **Schranz D**. Ueber eigenartige Faelle von Laugenaetzung. *Dtsch Z Gesamte Gerichtl Med* 1934; **23**: 152-159

10 **Singh AK**, Kothawla LK, Karlson KE. Tracheoesophageal and aortoesophageal fistulae complicating corrosive esophagitis. *Chest* 1976; **70**: 549-551 [PMID: 975960 DOI: 10.1378/chest.70.4.549]

11 **Waller H**, Rumler W. Ueber den ungewoehnlichen Ausgang einer Laugenveraetzung. *Med Klin* 1963; **58**: 1719-1721

12 **Rabinovitz M**, Udekwu AO, Campbell WL, Kumar S, Razack A, Van Thiel DH. Tracheoesophageal-aortic fistula complicating lye ingestion. *Am J Gastroenterol* 1990; **85**: 868-871 [PMID: 2196788]

13 **Ottosson A**. Late aortic rupture after lye ingestion. *Arch Toxicol* 1981; **47**: 59-62 [PMID: 7283741 DOI: 10.1007/BF00297131]

14 **Sarfati E**, Gossot D, Assens P, Celerier M. Management of caustic ingestion in adults. *Br J Surg* 1987; **74**: 146-148 [PMID: 3815035 DOI: 10.1002/bjs.1800740225]

15 **Yegane RA**, Bashtar R, Bashashati M. Aortoesophageal fistula due to caustic ingestion. *Eur J Vasc Endovasc Surg* 2008; **35**: 187-189 [PMID: 17981058 DOI: 10.1016/j.ejvs.2007.09.002]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 May 27; 14(5): 514-520

DOI: 10.4240/wjgs.v14.i5.514

ISSN 1948-9366 (online)

CASE REPORT

# Castleman disease of the pancreas mimicking pancreatic malignancy on $^{68}$Ga-DOTATATE and $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography: A case report

Sheng-Lu Liu, Ming Luo, Hao-Xian Gou, Xiao-Li Yang, Kai He

**Specialty type:** Surgery

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Jian X, China; Velikova TV, Bulgaria

**Received:** January 8, 2022
**Peer-review started:** January 8, 2022
**First decision:** March 13, 2022
**Revised:** April 1, 2022
**Accepted:** May 7, 2022
**Article in press:** May 7, 2022
**Published online:** May 27, 2022

**Sheng-Lu Liu, Ming Luo, Hao-Xian Gou, Xiao-Li Yang, Kai He,** Department of General Surgery (Hepatobiliary Surgery), The Affiliated Hospital of Southwest Medical University, Luzhou 646000, Sichuan Province, China

**Sheng-Lu Liu, Kai He,** Nuclear Medicine and Molecular Imaging Key Laboratory of Sichuan Province, The Affiliated Hospital of Southwest Medical University, Luzhou 646000, Sichuan Province, China

**Sheng-Lu Liu, Kai He,** Academician (Expert) Workstation of Sichuan Province, The Affiliated Hospital of Southwest Medical University, Luzhou 646000, Sichuan Province, China

**Corresponding author:** Kai He, MM, Professor, Department of General Surgery (Hepatobiliary Surgery), The Affiliated Hospital of Southwest Medical University, No. 25 Taiping Street, Jiangyang District, Luzhou 646000, Sichuan Province, China. hekai615@126.com

## Abstract

*BACKGROUND*

Castleman disease is an uncommon nonclonal lymphoproliferative disorder, which frequently mimics both benign and malignant abnormalities in several regions. Depending on the number of lymph nodes or regions involved, Castleman disease (CD) varies in diagnosis, treatment and prognosis. It rarely occurs in the pancreas alone without any distinct clinical feature and tends to be confused with pancreatic paraganglioma (PGL), neuroendocrine tumors (NETs), and primary tumors, thus impeding proper diagnosis and treatment.

*CASE SUMMARY*

A 28-year-old woman presented with a lesion on the neck of the pancreas, detected by ultrasound during a health examination. Physical examination and laboratory findings were normal. The mass showed hypervascularity on enhanced computed tomography (CT), significantly increased $^{18}$F-fluorodeoxyglucose uptake on positron emission tomography (PET)/CT, and slightly increased somatostatin receptor (SSTR) expression on $^{68}$Ga-DOTATATE PET/CT, suggesting no distant metastases and subdiagnoses such as pancreatic PGL, NET, or primary tumor. Intraoperative pathology suggested lymphatic hyperplasia, and only simple tumor resection was performed. The patient was diagnosed with the hyaline vascular variant of CD, which was confirmed by postoperative immuno-

histochemistry. The patient was discharged successfully, and no recurrence was observed on regular review.

*CONCLUSION*
High glucose uptake and slightly elevated SSTR expression are potentially new diagnostic features of CD of the pancreas.

**Key Words:** Castleman disease; Pancreatic malignancy; Pancreatic neuroendocrine tumors; Pancreatic paraganglioma; Positron emission tomography; Case report



**Core tip:** Some rare tumors with high blood supply to the pancreas, such as Castleman disease (CD), paraganglioma, and neuroendocrine tumors are difficult for clinicians to differentially diagnose based on conventional imaging and clinical presentation. In our case, CD of the pancreas had no obvious clinical features as previously reported but showed higher glucose uptake and mildly increased somatostatin receptor expression on positron emission tomography/computed tomography, which might help in the diagnosis.

**Citation:** Liu SL, Luo M, Gou HX, Yang XL, He K. Castleman disease of the pancreas mimicking pancreatic malignancy on $^{68}$Ga-DOTATATE and $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography: A case report. *World J Gastrointest Surg* 2022; 14(5): 514-520
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i5/514.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i5.514

## INTRODUCTION

Castleman disease (CD), a rare nonclonal lymphoproliferative disorder of unknown etiology, is alternatively known as giant lymph node hyperplasia or angiofollicular lymph node hyperplasia, first described by Dr. Benjamin Castleman in 1954[1]. Variably manifested and capable of influencing any region in the body, CD largely imitates both benign and malignant tumors in the neck, thorax, abdomen and pelvis[2]. Despite increasing reports on CD, the condition remains difficult to diagnose, particularly when it appears as a pancreatic mass[3]. With the ability to collect structural and metabolic information, $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) plays a pivotal role in the early diagnosis, robust characterization, and therapeutic evaluation of CD[4]. However, no $^{18}$F-FDG PET/CT images of pancreatic CD have thus far been reported. $^{68}$Ga-DOTATATE PET/CT is the first choice for evaluating the well-differentiated histologic subtypes of neuroendocrine tumors (NETs), but its diagnostic value for identifying CD has yet to be determined[5].

## CASE PRESENTATION

### *Chief complaints*

A 28-year-old woman presented to our department with the complaint of a pancreatic lesion, which was detected by ultrasound during a physical examination conducted 1 wk earlier.

### *History of present illness*

The patient showed a feel-good self-report without abdominal pain, distension, diarrhea, fever, and other discomforts.

### *History of past illness*

The patient had good health history.

### *Personal and family history*

The personal and family history of the patient was unremarkable.

### *Physical examination*

The vital signs of the patient were within the normal range. No yellow staining of skin and sclera was

observed. Abdominal physical examination revealed no positive signs without tenderness and lumps in the abdomen.

### *Laboratory examinations*

Blood analysis revealed mild anemia, with low hemoglobin concentration (102 g/L), normal leukocyte count, and normal platelet count. All liver function indexes were normal. The following were also normal: levels of serum amylase, lipase and alkaline phosphatase; plasma or urinary metanephrine levels; and tumor markers for alpha-fetoprotein (1.97 ng/mL), carcinoembryonic antigen (3.63 ng/mL), carbohydrate antigen (CA) 153 (16.40 U/mL), and CA199 (19.66 U/mL). Endoscopic results suggested chronic nonatrophic gastritis with erosion. Fasting and postprandial insulin levels were within the normal range.

### *Imaging examinations*

A plain CT scan (Figure 1A) showed a hyperdense lesion (arrow) measuring 3.0 cm × 2.0 cm × 2.5 cm in the neck of the pancreas. On contrast-enhanced CT, the lesion (arrow) showed significant enhancement in the arterial phase (Figure 1B), evenly distributed with smooth and well-defined boundaries, and gradually washed out in the venous phase (Figure 1C). $^{18}$F-FDG PET/CT images (Figure 2) showed glucose hypermetabolism with an standardized uptake value $(SUV)_{max}$ of 3.6 in the pancreatic mass. $^{68}$Ga-DOTATATE PET/CT images (Figure 3) revealed minimally increased expression of somatostatin receptor (SSTR) on the pancreatic mass (arrows) with a $SUV_{max}$ of 5.8.

## FINAL DIAGNOSIS

The final diagnosis of the presented case was pancreatic hypervascular malignancy, not excluding CD, paraganglioma (PGL), and NETs.

## TREATMENT

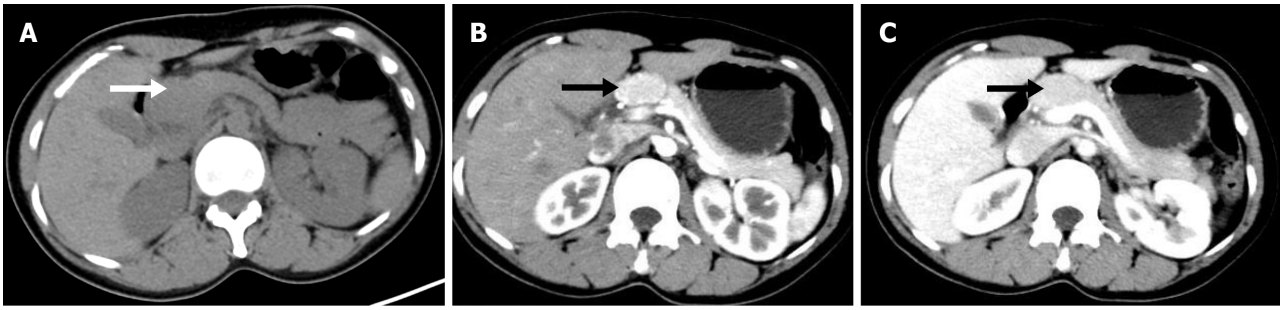
On the basis of neoplastic etiology, we intended to perform pancreaticoduodenectomy. During exploratory laparotomy, we found that the mass had a rich blood supply. We completely separated it from the pancreatic tissue. The size of the tumor was 3.5 cm × 3 cm with a complete envelope (Figure 4A). Intraoperative frozen section examination (hematoxylin–eosin staining) suggested lymphatic hyperplasia, germinal centers with regressive transformation, and expanded mantle with "an onion skin" rimming of small lymphocytes (Figure 4B). Given the high probability of a benign mass, we performed simple tumor resection.

## OUTCOME AND FOLLOW-UP

Immunohistochemistry: CD3 and CD5 (T zone +), CD20 (B zone +), CD10 and BCL-6 (germinal center +), BCL-2 (low expression in the germinal center, high expression outside the germinal center), CD21 (Figure 4C) and CD23 (follicular dendritic cell proliferation in the germinal center), Ki-67 (Figure 4D, high expression in the germinal center, low expression outside the germinal center), and Cyclin D1(). The immunohistochemical profile was consistent with the hyaline vascular variant of CD. The patient showed no apparent discomfort after surgery and was discharged after 1 wk. No recurrence of abdominal ultrasonography was reported after half a year.

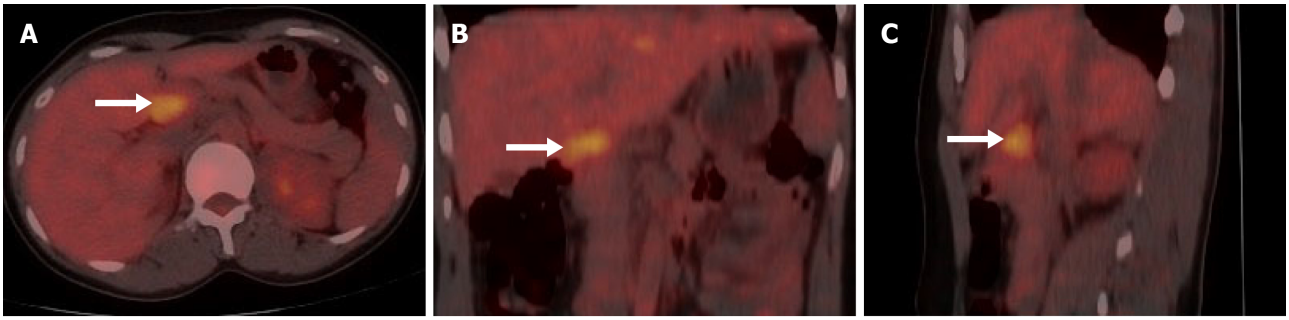
## DISCUSSION

CD occurs throughout the body. Approximately 70% of the condition presents in the chest, 15% in the neck, and 15% in the abdomen–pelvis, principally involving lymphoid tissues. Castleman disease also occasionally occurs in extralymphatic sites, such as the larynx, lungs, pancreas, meninges, and muscles [6-8]. It is subclassified because of the number of enlarged lymph nodes[9]. The involvement of a single lymph node or region is referred to as unicentric CD (UCD), whereas that of multiple lymph nodes is known as multicentric CD (MCD). A battery of pathological variants includes the classic hyaline vascular type, the less common plasma cell variant and human-herpesvirus-8-associated type, and the multicentric type, not otherwise specified[10]. Moreover, 90% of the cases of hyaline vascular CD are unicentric[11]. UCD typically manifests as an asymptomatic mass with a benign growth, but MCD presents with diffuse lymphadenopathy, organ dysfunction, and systemic inflammation.



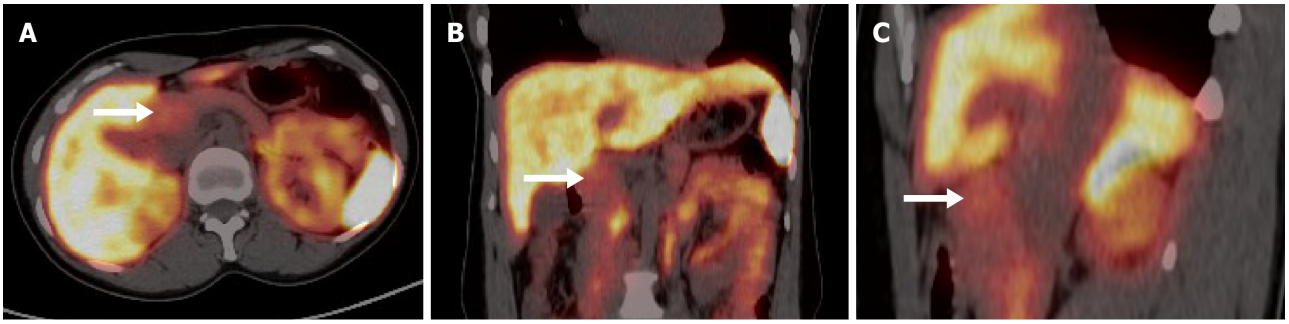

**DOI:** 10.4240/wjgs.v14.i5.514 **Copyright** ©The Author(s) 2022.

**Figure 1 Preoperative computed tomography of the abdomen.** A: A plain computed tomography (CT) scan showed a hyperdense lesion measuring 3.0 cm × 2.0 cm × 2.5 cm in the neck of the pancreas; B: On enhanced CT, the lesion showed significant enhancement in the arterial phase, evenly distributed with smooth and well-defined boundaries; C: In the venous phase, the lesion was gradually washed out.




**DOI:** 10.4240/wjgs.v14.i5.514 **Copyright** ©The Author(s) 2022.

**Figure 2 $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography showing glucose hypermetabolism in the pancreatic mass.** A: Axial positron emission tomography/computed tomography (PET/CT); B: Coronal PET/CT; C: Sagittal PET/CT.

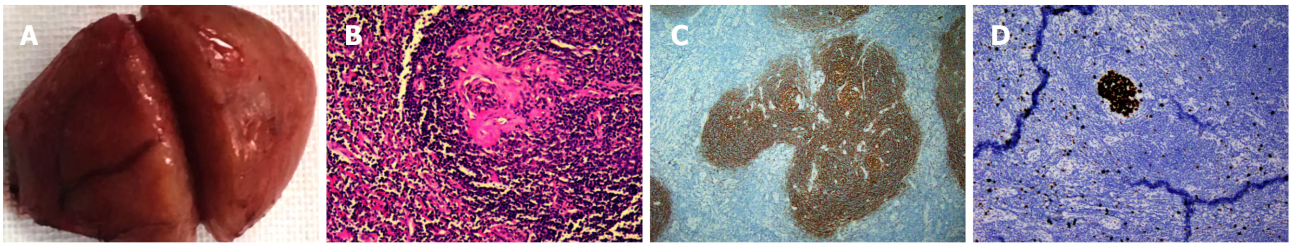



**DOI:** 10.4240/wjgs.v14.i5.514 **Copyright** ©The Author(s) 2022.

**Figure 3 $^{68}$Ga-DOTATATE positron emission tomography/computed tomography revealing slightly elevated somatostatin receptor expression on the pancreatic mass.** A: Axial positron emission tomography/computed tomography (PET/CT); B: Coronal PET/CT; C: Sagittal PET/CT.

Complete removal of lymph nodes is an effective and usually curative treatment for UCD, and the recurrence rate is low. Chemotherapy and radiotherapy are alternative therapies when the mass cannot be completely removed surgically[9,12]. By contrast, MCD has a poor prognosis, with a high recurrence rate associated with clinicopathological features and a high risk of malignancy leading to possible transformation into malignant lymphoma, plasmacytoma and Kaposi's sarcoma, among others[4]. Meanwhile, treatment options for MCD are complex and include steroid therapy, chemotherapy, antiviral drugs, or the use of antiproliferative regimens[4,13]. Therefore, the clinical typing of CD determines the corresponding diagnosis and prognosis.

Conventional imaging [CT/magnetic resonance imaging (MRI)] is not widely used to guide typing because it fails to distinguish clearly between reactive hyperplasia and pathological enlargement of lymph nodes, nor does it sensitively detect the involvement of normal-sized lymph nodes[4]. However, $^{18}$F-FDG PET/CT can be used to assess the metabolism of lymph node enlargement. Although lymph node biopsy is the only method for the definitive diagnosis of CD, available evidence suggests that previous FDG-PET/CT can help differentiate CD subtypes and guide subsequent treatment and




**DOI:** 10.4240/wjgs.v14.i5.514 

**Figure 4 Specimen photograph and pathological photographs.** A: The pancreatic mass with an intact envelope, measuring approximately 3.5 cm × 3 cm; B: Photomicrograph (hematoxylin-eosin stain) suggesting a germinal center with the classic "onionskin" appearance (magnification × 200); C: Immunohistochemistry of CD21 (magnification × 200); D: Immunohistochemistry of Ki-67 (magnification × 200).

monitoring[13]. In our case, the $^{18}$F-FDG PET/CT results showed that the mass was solitary in the pancreas with high glucose metabolism and no distant metastases, consistent with the diagnosis of UCD. CD is rarely reported on $^{68}$Ga-DOTATATE PET/CT, and the ability and accuracy of its classification are unknown. In our case, UCD showed higher SSTR expression.

When the tumor is located in the pancreas and is highly vascularized, some rare conditions other than CD including PGL and NETs should also be considered[14].

PGL, a rare type of vascular NET, results from a paraganglial cell cluster that develops from the ectoderm of the neural crest[15]. The majority of the tumors are benign, and only 10% of the tumors are malignant. Although up to 77% of the tumors are commonly located retroperitoneally, the PGL is rarely located in the pancreas. A retrospective analysis of 15 cases diagnosed with PGL located in the pancreas summarized the clinical and imaging features of the disease[14]. Most patients exhibit no apparent symptoms or abdominal discomfort caused by compression. Enhanced CT suggests significant enhancement of the mass at the early stage. MR images reveal tumor isointensity for the T1-weighted image and hyperintensity, hypointensity, or mixed intensity for the T2-weighted image. PGL located in the chest and pelvis may overproduce some hormones, particularly catecholamine which causes sweating, palpitations, and hypertension. PGLs most commonly overexpress SSTR2. [$^{68}$Ga]-Somatostatin agonists (SSTas) target SSTR2 and are internalized into the cells. DOTA-coupled SSTas exhibit excellent affinity for SSTR2[16]. Owing to its ultrahigh detection rate, [$^{68}$Ga] DOTA-somatostatin analog PET/CT has become the preferred imaging approach to diagnosing retroperitoneal PGL[17]. However, [$^{68}$Ga] SSTas PET can inevitably lead to false-positive findings, including metastatic lymph nodes owing to various cancers, meningioma, the pituitary gland, inflammatory diseases, and some rare conditions, such as fibrous dysplasia[18] Focal pancreatic accumulation in the uncinate process may mimic pancreatic NETs.

Pancreatic NETs (pNETs) are heterogeneous epithelial neoplasms derived from pluripotent stem cells of the neuroendocrine system[19]. The tumor is malignant and classified as either functional or nonfunctional[14]. Nonfunctional pNETs are asymptomatic or manifest local compression, whereas functional pNETs cause clinical syndromes associated with hormone hypersecretion according to the cell of origin. In MRI, the tumor presents with hypointensity on T1-weighted imaging and mostly hyperintensity on T2-weighted imaging; however, few are isointense or hypointense. In enhanced CT images, the functional pNET shows a clear boundary and rich blood supply, and the diameter of the tumor is generally < 2 cm[14]. The nonfunctional pNET presents heterogeneous enhancement, necrosis, and cystic degeneration in enhanced CT images and often has a larger diameter (> 5 cm) than that of the functional pNET. $^{68}$Ga-DOTATATE PET/CT, the first choice for evaluating well-differentiated histological subtypes of NETs, provides staging with improved accuracy and additional treatment choices[20].

## CONCLUSION

CD rarely occurs in the pancreas. CD of the pancreas often presents with an abundant blood supply, which, together with the lack of specificity in the clinical presentation, further blurs the distinction of the disease from NETs and PGL. PET/CT is supposed to be selected to guide the typing and subsequent treatment choices for CD. In our case, PET/CT showed that CD was solitary in the pancreas, and complete surgical resection led to a good prognosis. In addition to abundant blood supply, high glucose uptake and slightly elevated SSTR expression are potentially new diagnostic features of CD of the pancreas.

## ACKNOWLEDGMENTS

We are grateful to the patient for providing the information, support, and the written informed consent allowing us to publish their data. We thank Dr. Liu (Department of pathology, the Affiliated Hospital of Southwest Medical University) for providing pathological data.

## FOOTNOTES

**Author contributions:** He K and Yang XL proposed the idea and supervised, revised the writing; Liu SL collected the data, analyzed the literature, and wrote the manuscript; Luo M assisted with data collection and imaging guidance; He K, Gou HX were the patient's surgeons and participated in the entire operation; all authors read and approved the manuscript.

**Informed consent statement:** Informed written consent was obtained from the patient for publication of this report and any accompanying images.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).



**Country/Territory of origin:** China

**ORCID number:** Kai He 0000-0003-1247-7749.

**S-Editor:** Gong ZM
**L-Editor:** Kerr C
**P-Editor:** Gong ZM

## REFERENCES

1 **Castleman B**, Towne VW. Case records of the Massachusetts General Hospital: Case No. 40231. *N Engl J Med* 1954; **250**: 1001-1005 [PMID: 13165944 DOI: 10.1056/NEJM195406102502308]
2 **Bonekamp D**, Horton KM, Hruban RH, Fishman EK. Castleman disease: the great mimic. *Radiographics* 2011; **31**: 1793-1807 [PMID: 21997995 DOI: 10.1148/rg.316115502]
3 **Huang Z**, Jin T, Zhang X, Wu Z. Pancreatic mass found to be Castleman disease, a rare case report. *Asian J Surg* 2020; **43**: 767-768 [PMID: 32171606 DOI: 10.1016/j.asjsur.2020.02.007]
4 **Koa B**, Borja AJ, Aly M, Padmanabhan S, Tran J, Zhang V, Rojulpote C, Pierson SK, Tamakloe MA, Khor JS, Werner TJ, Fajgenbaum DC, Alavi A, Revheim ME. Emerging role of 18F-FDG PET/CT in Castleman disease: a review. *Insights Imaging* 2021; **12**: 35 [PMID: 33709329 DOI: 10.1186/s13244-021-00963-1]
5 **Verçosa AFA**, Flamini MEDM, Loureiro LVM, Flamini RC. 68Ga-DOTATATE and 18F-FDG in Castleman Disease. *Clin Nucl Med* 2020; **45**: 868-870 [PMID: 32969902 DOI: 10.1097/RLU.0000000000003277]
6 **Johkoh T**, Müller NL, Ichikado K, Nishimoto N, Yoshizaki K, Honda O, Tomiyama N, Naitoh H, Nakamura H, Yamamoto S. Intrathoracic multicentric Castleman disease: CT findings in 12 patients. *Radiology* 1998; **209**: 477-481 [PMID: 9807577 DOI: 10.1148/radiology.209.2.9807577]
7 **Keller AR**, Hochholzer L, Castleman B. Hyaline-vascular and plasma-cell types of giant lymph node hyperplasia of the mediastinum and other locations. *Cancer* 1972; **29**: 670-683 [PMID: 4551306 DOI: 10.1002/1097-0142(197203)29:3<670::aid-cncr2820290321>3.0.co;2-#]
8 **McAdams HP**, Rosado-de-Christenson M, Fishback NF, Templeton PA. Castleman disease of the thorax: radiologic features with clinical and histopathologic correlation. *Radiology* 1998; **209**: 221-228 [PMID: 9769835 DOI: 10.1148/radiology.209.1.9769835]
9 **Mitsos S**, Stamatopoulos A, Patrini D, George RS, Lawrence DR, Panagiotopoulos N. The role of surgical resection in Unicentric Castleman's disease: a systematic review. *Adv Respir Med* 2018; **86**: 36-43 [PMID: 29490420 DOI: 10.5603/ARM.2018.0008]
10 **Cronin DM**, Warnke RA. Castleman disease: an update on classification and the spectrum of associated lesions. *Adv Anat Pathol* 2009; **16**: 236-246 [PMID: 19546611 DOI: 10.1097/PAP.0b013e3181a9d4d3]
11 **Tey HL**, Tang MB. A case of paraneoplastic pemphigus associated with Castleman's disease presenting as erosive lichen planus. *Clin Exp Dermatol* 2009; **34**: e754-e756 [PMID: 19663833 DOI: 10.1111/j.1365-2230.2009.03479.x]
12 **Zhang X**, Rao H, Xu X, Li Z, Liao B, Wu H, Li M, Tong X, Li J, Cai Q. Clinical characteristics and outcomes of

Castleman disease: A multicenter study of 185 Chinese patients. *Cancer Sci* 2018; **109**: 199-206 [PMID: 29124835 DOI: 10.1111/cas.13439]

13 **Barker R**, Kazmi F, Stebbing J, Ngan S, Chinn R, Nelson M, O'Doherty M, Bower M. FDG-PET/CT imaging in the management of HIV-associated multicentric Castleman's disease. *Eur J Nucl Med Mol Imaging* 2009; **36**: 648-652 [PMID: 19050873 DOI: 10.1007/s00259-008-0998-4]

14 **Wang W**, Qin Y, Zhang H, Chen K, Liu Z, Zheng S. A rare case of retroperitoneal paraganglioma located in the neck of the pancreas: a case report and literature review. *Gland Surg* 2021; **10**: 1523-1531 [PMID: 33968704 DOI: 10.21037/gs-20-758]

15 **Corssmit EP**, Romijn JA. Clinical management of paragangliomas. *Eur J Endocrinol* 2014; **171**: R231-R243 [PMID: 25063320 DOI: 10.1530/EJE-14-0396]

16 **Wild D**, Mäcke HR, Waser B, Reubi JC, Ginj M, Rasch H, Müller-Brand J, Hofmann M. 68Ga-DOTANOC: a first compound for PET imaging with high affinity for somatostatin receptor subtypes 2 and 5. *Eur J Nucl Med Mol Imaging* 2005; **32**: 724 [PMID: 15551131 DOI: 10.1007/s00259-004-1697-4]

17 **Taïeb D**, Hicks RJ, Hindié E, Guillet BA, Avram A, Ghedini P, Timmers HJ, Scott AT, Elojeimy S, Rubello D, Virgolini IJ, Fanti S, Balogova S, Pandit-Taskar N, Pacak K. European Association of Nuclear Medicine Practice Guideline/Society of Nuclear Medicine and Molecular Imaging Procedure Standard 2019 for radionuclide imaging of phaeochromocytoma and paraganglioma. *Eur J Nucl Med Mol Imaging* 2019; **46**: 2112-2137 [PMID: 31254038 DOI: 10.1007/s00259-019-04398-1]

18 **Archier A**, Varoquaux A, Garrigue P, Montava M, Guerin C, Gabriel S, Beschmout E, Morange I, Fakhry N, Castinetti F, Sebag F, Barlier A, Loundou A, Guillet B, Pacak K, Taïeb D. Prospective comparison of (68)Ga-DOTATATE and (18)F-FDOPA PET/CT in patients with various pheochromocytomas and paragangliomas with emphasis on sporadic cases. *Eur J Nucl Med Mol Imaging* 2016; **43**: 1248-1257 [PMID: 26637204 DOI: 10.1007/s00259-015-3268-2]

19 **Yao JC**, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008; **26**: 3063-3072 [PMID: 18565894 DOI: 10.1200/JCO.2007.15.4377]

20 **Deroose CM**, Hindié E, Kebebew E, Goichot B, Pacak K, Taïeb D, Imperiale A. Molecular Imaging of Gastroenteropancreatic Neuroendocrine Tumors: Current Status and Future Directions. *J Nucl Med* 2016; **57**: 1949-1956 [PMID: 27811124 DOI: 10.2967/jnumed.116.179234]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 May 27; 14(5): 521-524

DOI: 10.4240/wjgs.v14.i5.521

ISSN 1948-9366 (online)

LETTER TO THE EDITOR

# Applying refined pancreaticogastrostomy techniques in pancreatic trauma

Jake Krige, Marc Bernon, Eduard Jonas

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Li JT, China

**Received:** July 31, 2021
**Peer-review started:** July 31, 2021
**First decision:** October 3, 2021
**Revised:** November 10, 2021
**Accepted:** April 29, 2022
**Article in press:** April 29, 2022
**Published online:** May 27, 2022

**Jake Krige, Marc Bernon, Eduard Jonas,** Department of Surgery, University of Cape Town Health Sciences Faculty, Cape Town 7925, South Africa

**Corresponding author:** Eduard Jonas, MBChB, PhD, Professor, Department of Surgery, University of Cape Town Health Sciences Faculty, Anzio Road, Cape Town 7925, South Africa. eduard.jonas@uct.ac.za

## Abstract

We comment on a study titled "Feasibility and safety of "bridging" pancreaticogastrostomy for pancreatic trauma in Landrace pigs" in which ten pigs were randomized to either experimental "bridging" pancreaticogastrostomy (PG) or a control group with a routine mucosa-to-mucosa PG. At six months anastomoses had strictured and closed in both groups. The authors concluded that "bridging" PG is feasible and safe in damage control surgery during the early stage of pancreatic injury. In this letter we comment on the study design, specifically leaving a 2 cm gap between the pancreatic stump and the stomach and highlight the complexity of performing pancreatic anastomoses following trauma pancreaticoduodenectomy as to our experience in a high volume trauma centre. Our data emphasize that pancreatic anastomoses in trauma are complex procedures with significant postoperative morbidity and are best managed collaboratively by trauma and hepatopancreaticobiliary surgical teams with the required technical skills.

**Key Words:** Pancreatic trauma; Pancreatic anastomoses; Pancreaticogastrostomy; Complications



**Core Tip:** In the elective setting a number of different pancreatic anastomotic methods have been proposed with variations in the site of implantation (stomach or jejunum), the anastomotic technique and the use of pancreatic duct stenting. These techniques need to be adapted to the prevailing operative circumstances. We recommend a pancreaticogastrostomy rather than a pancreaticojejunostomy in the presence of severe shock, prolonged resuscitation and associated major vascular injuries. We routinely use a 5 Fr silastic intraluminal pancreatic duct stent through the anastomoses.

**Citation:** Krige J, Bernon M, Jonas E. Applying refined pancreaticogastrostomy techniques in pancreatic trauma. *World J Gastrointest Surg* 2022; 14(5): 521-524
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i5/521.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i5.521

## TO THE EDITOR

We read with interest the research study by Feng *et al*[1] in the *World Journal of Gastrointestinal Surgery* entitled "Feasibility and safety of bridging pancreaticogastrostomy for pancreatic trauma in Landrace pigs" which was designed to simulate damage control surgery in pancreatic trauma[1]. In their study ten Landrace pigs were randomized into an experimental group in which a "bridging" pancreaticogastrostomy (PG) was performed while in a control group a routine mucosa-to-mucosa PG was constructed. Amylase levels in drainage fluid, fasting and two-hour postprandial blood glucose, insulin levels in peripheral blood, and insulin levels in portal vein blood were measured six months after the operation. Repeat surgery was undertaken one and six months to examine the condition of the abdominal cavity and pancreas and evaluate the patency of the PG.

After surgery, the authors found that the fasting and two-hour postprandial blood glucose levels were similar. There was also no difference in the fasting and two-hour insulin values of postprandial peripheral blood and portal vein blood six months after the operation between the two groups. One month after the operation, the tract in the bridging group and the conventional PG were patent. However, after six months both groups had strictured and closed with chronic pancreatitis present in both. The authors concluded that a "bridging" PG is a practical and secure method of damage control surgery during the initial management of a pancreatic injury.

The authors are to be congratulated on this innovative study evaluating a "bridging" PG in order to overcome the difficulties related to a PG after trauma. All pancreatic surgeons will concede that the pancreatic anastomosis is the Achilles' heel of pancreatic surgery, especially so when circumstances are unfavorable, as occurs in pancreatic trauma. The authors acknowledge that using this method the bridging tubes invariably became dislodged with time and that all the PG anastomoses eventually strictured with resultant chronic pancreatitis in both groups. We are however puzzled why the authors left a 2 cm gap between the pancreatic stump and the stomach bridged by the tube because this space will inevitably fibrose and stricture. Intuitively it makes more sense to create a sutured and stent-splinted apposition PG which provides a tight seal without a gap between the pancreas and stomach and would theoretically be less prone to fibrosis and stricturing. Two further observations which test the validity of their study are that the operations undertaken on the pigs were elective procedures which did not simulate a pancreatic trauma situation as occurs in reality, nor do the authors provide any evidence in their study that the bridging procedure is indeed quicker than a conventional anastomosis.

We, too, have grappled with the complexities of establishing a safe method for a pancreatic anastomosis in pancreatic trauma[2]. Our clinical experience is based on one of the largest active databases of complex pancreatic injuries in the world. We have shown that when a trauma pancreaticoduodenectomy has been completed, several important assessments are necessary with regard to the timing and type of reconstruction. The crucial factor in the eventual result is the quality of the pancreatic anastomosis. As is relevant during elective resections, the pancreatic to bowel anastomosis after a pancreaticoduodenectomy for trauma is the Achilles' heel of the operation and a leak from the pancreatic anastomosis failure is the most important reason for the considerable incidence of complications which may occur after the operation. Even when the pancreatic anastomosis is performed during elective operations the fistula rate is significant and the incidence is greatest in patients who have a soft pancreatic parenchyma when combined with a small main pancreatic duct. These important risk factors which are relevant when the pancreas is injured are further aggravated by a pancreas that is may be hemorrhagic, as well as a jejunal wall thickened by edema, which makes the circumstances even more difficult and hazardous for a sound anastomosis.

During elective surgery several techniques have been suggested to minimize the possibility of pancreatic fistulas occurring after the operation. These include the location of implantation (stomach or jejunum), the technique used for the anastomosis and whether a stent is used to splint the pancreatic duct and bowel. These techniques may need to be modified according to the existing conditions. PG and pancreaticojejunostomy each have their own benefits and disadvantages but neither are consistently appropriate after a serious pancreatic injury where edema and substantial damage to tissues are critical influences deciding whether a particular type or method should be used in the anastomotic reconstruction. In our clinical studies we routinely used a PG when prolonged hypotension, extended fluid resuscitation and associated venous injuries resulted in an edematous small bowel which jeopardized the anastomosis. Under these unfavorable conditions there are several rational and technical reasons for doing a PG in preference to a pancreaticojejunostomy. The posterior gastric wall is conveniently contiguous to the pancreatic remnant and approximation is never a problem. The

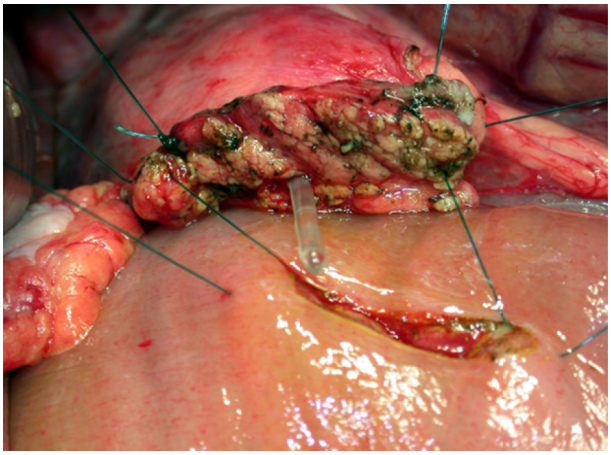


**Figure 1 Construction of a single layer stented pancreaticogastrostomy.** Citation: Feng J, Zhang HY, Yan L, Zhu ZM, Liang B, Wang PF, Zhao XQ, Chen YL. Feasibility and safety of "bridging" pancreaticogastrostomy for pancreatic trauma in Landrace pigs. *World J Gastrointest Surg* 2021; 13: 419-428. Copyright ©The Authors 2021. Published by Baishideng Publishing Group Inc.

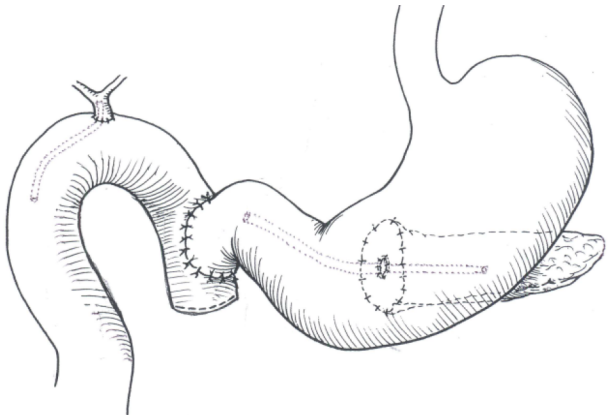


**Figure 2 Stented pancreaticogastrostomy with an Imanaga configuration.** Citation: Krige JE, Jonas E, Thomson SR, Kotze UK, Setshedi M, Navsaria PH, Nicol AJ. Resection of complex pancreatic injuries: Benchmarking postoperative complications using the Accordion classification. *World J Gastrointest Surg* 2017; 9: 82-91. Copyright ©The Authors 2021. Published by Baishideng Publishing Group Inc.

gastrostomy can be created to the precise dimension required without any difference in size to allow a tension-free anastomosis. In addition, the gastric wall is thick, sutures hold well, has a generous blood supply and is less likely than the jejunum to develop ischemic complications. Gastric and pancreatic secretions are easily drained *via* a well-placed nasogastric tube after a PG and the pancreatic exocrine enzymes remain inactivated with a low pH in the absence of enterokinase. We prefer to use a modified single layer interrupted suture technique which includes the pancreatic capsule and parenchyma and we routinely place a 5 Fr silastic intraluminal stent rather than to attempt a more complicated duct to mucosa technique which escalates the level of complexity (Figure 1). If circumstances dictate we apply the Imanaga method of reconstruction which, with minor modifications, allows endoscopic access to the biliary system subsequently if required for retrieval of biliary stents and balloon-enhanced cholangiography through the duodenojejunal anastomosis (Figure 2).

Our data emphasize that pancreatic anastomoses in trauma are technically complicated procedures which may have substantial sequelae postoperatively and are best treated collaboratively by trauma and hepatopancreaticobiliary surgical teams who have the requisite technical skills to recognize and deal with high-risk pancreatic anastomoses.

## FOOTNOTES

**Author contributions:** Krige J, Bernon M and Jonas E have contributed equally to the writing of this letter to the editor and approved the final manuscript.

**Conflict-of-interest statement:** The authors have no conflict of interest to declare.

**Country/Territory of origin:** South Africa

**ORCID number:** Jake Krige 0000-0002-7057-9156; Marc Bernon 0000-0002-7967-8548; Eduard Jonas 0000-0003-0123-256X.

**S-Editor:** Fan JR
**L-Editor:** A
**P-Editor:** Fan JR

## REFERENCES

1 **Feng J**, Zhang HY, Yan L, Zhu ZM, Liang B, Wang PF, Zhao XQ, Chen YL. Feasibility and safety of "bridging" pancreaticogastrostomy for pancreatic trauma in Landrace pigs. *World J Gastrointest Surg* 2021; **13**: 419-428 [PMID: 34122732 DOI: 10.4240/wjgs.v13.i5.419]

2 **Krige JE**, Jonas E, Thomson SR, Kotze UK, Setshedi M, Navsaria PH, Nicol AJ. Resection of complex pancreatic injuries: Benchmarking postoperative complications using the Accordion classification. *World J Gastrointest Surg* 2017; **9**: 82-91 [PMID: 28396721 DOI: 10.4240/wjgs.v9.i3.82]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 May 27; 14(5): 525-527

DOI: 10.4240/wjgs.v14.i5.525

ISSN 1948-9366 (online)

LETTER TO THE EDITOR

# Providing higher value care for hepatocellular carcinoma rather than diagnosis: What can current radiologists do?

Shan Yao, Yi Wei, Bin Song

**Specialty type:** Radiology, nuclear medicine and medical imaging

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Papadopoulos N, Greece; Tovoli F, Italy

**Received:** January 6, 2022
**Peer-review started:** January 6, 2022
**First decision:** March 12, 2022
**Revised:** March 16, 2022
**Accepted:** May 13, 2022
**Article in press:** May 13, 2022
**Published online:** May 27, 2022

**Shan Yao, Yi Wei, Bin Song,** Department of Radiology, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

**Corresponding author:** Bin Song, MD, PhD, Chief Doctor, Director, Professor, Department of Radiology, West China Hospital, Sichuan University, No. 37 Guoxue Alley, Wuhou District, Chengdu 610041, Sichuan Province, China. cjr.songbin@vip.163.com

## Abstract

Medical imaging is of great value for the comprehensive evaluation of hepatocellular carcinoma from diagnosis to prognosis, which contributes to optimal clinical management making.

**Key Words:** Hepatocellular carcinoma; Medical imaging; Clinical management



**Core Tip:** Medical imaging plays a vital role in the accurate diagnosis and grading of hepatocellular carcinoma as clinical treatment decision-making. Moreover, it is of powerful value for noninvasively preoperative evaluation of the treatment outcomes, prognosis, and survival with high sensitivity and repeatability. The comprehensive assessment involving preoperative, perioperative, and postoperative indicators for treatment option selection will assist surgeons precisely and maximize the benefits for patients.

**Citation:** Yao S, Wei Y, Song B. Providing higher value care for hepatocellular carcinoma rather than diagnosis: What can current radiologists do? *World J Gastrointest Surg* 2022; 14(5): 525-527
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i5/525.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i5.525

## TO THE EDITOR

In the current issue, we read with interest a retrospective study by Delvecchio *et al*[1], where liver resection (LR) and radiofrequency ablation (RFA) were evaluated as the

treatment of choice for single hepatocellular carcinoma (HCC) (≤ 30 mm) located in posterosuperior segments (PSS) in elderly patients. Based on operative time, hospital stay, and short- and long-term outcomes, RFA was recommended as a suitable option.

The critical value of tumor size for LR or RFA differs in various criteria and guidelines, most of which is 20 mm. Single HCC with a tumor size of ≤ 30 mm was mainly targeted in this study. Locations with difficulties in surgery (PSS) and age (for the elderly ≥ 70 years old) were considered while making the treatment decision. It offered an insightful perspective and a specific focus, providing a supplement to this field with certain guiding significance for clinical management practice.

As described in the study, all subjects underwent computed tomography (CT) or magnetic resonance imaging (MRI) before treatment to access the tumor location and size, which are the two key points of this study. The diagnosis and stage of HCC were based on the European Association for the Study of the Liver criteria[2], which also regard medical imaging manifestations as a dominant support. Thus, medical imaging plays a vital role in the accurate diagnosis and qualitative evaluation of HCC. Along with morphological features, such as tumor location and size, satellite nodules, portal vein embolus, and invasion of adjacent tissues can be evaluated using CT or MRI, which are also of prognostic significance for patients with HCC after treatment.

Apart from the abovementioned perioperative and postoperative indicators for selecting treatment option, preoperative evaluation can be performed using noninvasive medical imaging with high sensitivity and repeatability. In a study by Cha *et al*[3], pretreatment imaging was utilized to compare the outcomes of RFA and LR for HCC ≤ 30 mm, and a high positive predictive value was achieved. Burgeoning functional imaging technologies, such as gadoxetic acid-enhanced MRI, intravoxel incoherent motion, T1 mapping, have enabled insightful assessment of microvascular invasion, hepatocyte membrane function, hepatocyte density changes, tissue microcirculation, and liver reserve function. Meanwhile, artificial intelligence-imaging combining radiomics has been empowering deep data mining of CT or MRI images of HCC from diagnosis to prognosis. In prior studies, we found that preoperative CT imaging combined with clinical features could predict the rate of liver regeneration after right hepatectomy for HCCs with an accuracy of 0.78 and an area under the curve (AUC) of 0.84 [4]. Gadoxetic acid-enhanced MRI-derived features showed great potential for preoperative prediction of early recurrence of LR for HCCs, with the related model demonstrating a significant AUC of 0.841 (95%CI: 0.769-0.919)[5]. Taken together, medical imaging is closely related to optimal treatment decision-making and survival quality for patients. In future clinical practice, it is necessary to take full advantage of medical imaging to comprehensively evaluate tumor and liver conditions preoperatively as a treatment plan trade-off, so as to maximize the benefits for patients with HCC and meet the demands of precision medicine.

## FOOTNOTES

**Author contributions:** Yao S and Song B designed the research; Yao S and Wei Y conducted literature search and analysis; Yao S wrote the letter and made critical revisions to the letter; Song B and Wei Y provided material and funding support for the article.

**Supported by** the Science and Technology Support Program of Sichuan Province, No. 2021YFS0144 and No. 2021YFS0021; and China Postdoctoral Science Foundation, No. 2021M692289.

**Conflict-of-interest statement:** All authors declared no potential conflict of interests related to this publication.



**Country/Territory of origin:** China

**ORCID number:** Shan Yao 0000-0002-0665-2566; Yi Wei 0000-0003-3993-9747; Bin Song 0000-0001-7007-6367.

**S-Editor:** Gong ZM
**L-Editor:** A
**P-Editor:** Gong ZM

## REFERENCES

1 **Delvecchio A**, Inchingolo R, Laforgia R, Ratti F, Gelli M, Anelli MF, Laurent A, Vitali G, Magistri P, Assirati G, Felli E,

Wakabayashi T, Pessaux P, Piardi T, di Benedetto F, de'Angelis N, Briceño J, Rampoldi A, Adam R, Cherqui D, Aldrighetti LA, Memeo R. Liver resection vs radiofrequency ablation in single hepatocellular carcinoma of posterosuperior segments in elderly patients. *World J Gastrointest Surg* 2021; **13**: 1696-1707 [PMID: 35070074 DOI: 10.4240/wjgs.v13.i12.1696]

2 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018; **69**: 182-236 [PMID: 29628281 DOI: 10.1016/j.jhep.2018.03.019]

3 **Cha DI**, Song KD, Kang TW, Lee MW, Rhim H. Small masses (≤3 cm) diagnosed as hepatocellular carcinoma on pre-treatment imaging: comparison of therapeutic outcomes between hepatic resection and radiofrequency ablation. *Br J Radiol* 2020; **93**: 20190719 [PMID: 31670571 DOI: 10.1259/bjr.20190719]

4 **Zhang T**, Wei Y, He X, Yuan Y, Yuan F, Ye Z, Li X, Tang H, Song B. Prediction of Remnant Liver Regeneration after Right Hepatectomy in Patients with Hepatocellular Carcinoma Using Preoperative CT Texture Analysis and Clinical Features. *Contrast Media Mol Imaging* 2021; **2021**: 5572470 [PMID: 34220379 DOI: 10.1155/2021/5572470]

5 **Zhang Z**, Jiang H, Chen J, Wei Y, Cao L, Ye Z, Li X, Ma L, Song B. Hepatocellular carcinoma: radiomics nomogram on gadoxetic acid-enhanced MR imaging for early postoperative recurrence prediction. *Cancer Imaging* 2019; **19**: 22 [PMID: 31088553 DOI: 10.1186/s40644-019-0209-5]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
**Telephone:** +1-925-3991568
**E-mail:** bpgoffice@wjgnet.com
**Help Desk:** https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

ISSN 1948-9366 (online)

# World Journal of

# *Gastrointestinal Surgery*

*World J Gastrointest Surg* 2022 June 27; 14(6): 528-631

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 14 Number 6 June 27, 2022

*World Journal of Gastrointestinal Surgery*

**Monthly Volume 14 Number 6 June 27, 2022**

## Contents

### LETTER TO THE EDITOR

*World Journal of Gastrointestinal Surgery*

**Monthly Volume 14 Number 6 June 27, 2022**

## Contents

## ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Arun Prasad, FACS, FRCS (Ed), FRCS (Gen Surg), MBBS, Adjunct Professor, Doctor, Professor, Surgeon, Department of Minimal Access, Thoracoscopic, Bariatric and Robotic Surgery, Apollo Hospital, New Delhi 110044, India. surgerytimes@gmail.com

## AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJGS* mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

## INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJGS* as 2.582; IF without journal self cites: 2.564; 5-year IF: 3.378; Journal Citation Indicator: 0.53; Ranking: 97 among 212 journals in surgery; Quartile category: Q2; Ranking: 73 among 92 journals in gastroenterology and hepatology; and Quartile category: Q4.

## RESPONSIBLE EDITORS FOR THIS ISSUE

**Production Editor:** *Rui-Rui Wu*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Ya-Juan Ma*.

**NAME OF JOURNAL**
*World Journal of Gastrointestinal Surgery*

**ISSN**
ISSN 1948-9366 (online)

**LAUNCH DATE**
November 30, 2009

**FREQUENCY**
Monthly

**EDITORS-IN-CHIEF**
Peter Schemmer

**EDITORIAL BOARD MEMBERS**
https://www.wjgnet.com/1948-9366/editorialboard.htm

**PUBLICATION DATE**
June 27, 2022



**INSTRUCTIONS TO AUTHORS**
https://www.wjgnet.com/bpg/gerinfo/204

**GUIDELINES FOR ETHICS DOCUMENTS**
https://www.wjgnet.com/bpg/GerInfo/287

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**
https://www.wjgnet.com/bpg/gerinfo/240

**PUBLICATION ETHICS**
https://www.wjgnet.com/bpg/GerInfo/288

**PUBLICATION MISCONDUCT**
https://www.wjgnet.com/bpg/gerinfo/208

**ARTICLE PROCESSING CHARGE**
https://www.wjgnet.com/bpg/gerinfo/242

**STEPS FOR SUBMITTING MANUSCRIPTS**
https://www.wjgnet.com/bpg/GerInfo/239

**ONLINE SUBMISSION**
https://www.f6publishing.com

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 June 27; 14(6): 528-537

DOI: 10.4240/wjgs.v14.i6.528

ISSN 1948-9366 (online)

*MINIREVIEWS*

# Transarterial chemoembolization failure/refractoriness: A scientific concept or pseudo-proposition

Shen Zhang, Bin-Yan Zhong, Lei Zhang, Wan-Sheng Wang, Cai-Fang Ni

**Specialty type:** Oncology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Elshimi E, Egypt; Kumar SKY, India
**A-Editor:** Chan KM, Taiwan

**Received:** December 13, 2021
**Peer-review started:** December 13, 2021
**First decision:** January 27, 2022
**Revised:** February 8, 2022
**Accepted:** June 4, 2022
**Article in press:** June 4, 2022
**Published online:** June 27, 2022

**Shen Zhang, Bin-Yan Zhong, Lei Zhang, Wan-Sheng Wang, Cai-Fang Ni,** Department of Interventional Radiology, The First Affiliated Hospital of Soochow University, Suzhou 215006, Jiangsu Province, China

**Corresponding author:** Cai-Fang Ni, MD, PhD, Chief Doctor, Department of Interventional Radiology, The First Affiliated Hospital of Soochow University, No. 899 Pinghai Road, Suzhou 215006, Jiangsu Province, China. szncf@suda.edu.cn

## Abstract

Multi-session transarterial chemoembolization (TACE) is usually needed for the treatment of intermediate-stage hepatocellular carcinoma (HCC), but it may not always have a positive influence on prognosis due to high heterogeneity of HCC. To avoid ineffective repeated TACE, the concept of TACE failure/refractoriness has been proposed by several organizations and is being addressed using tyrosine kinase inhibitors. The concept of TACE failure/refractoriness is controversial due to ambiguous definitions and low evidence-based data. To date, only a few studies have examined the rationality concerning the definition of TACE failure/refractoriness, although the concept has been introduced and applied in many TACE-related clinical trials. This review focuses on some of the issues related to different versions of TACE failure/refractoriness, the rationality of related definitions, and the feasibility of continuing TACE after so-called failure/refractoriness based on published evidence. A suggestion to re-define TAEC failure/refractoriness is also put forward.

**Key Words:** Hepatocellular carcinoma; Transarterial chemoembolization; Failure; Refractoriness



**Core Tip:** The definitions in the current concept of transarterial chemoembolization (TACE) failure/refractoriness are not capable of guiding clinical practice. A persistent viable tumor lesion is a well-accepted item of TACE failure/refractoriness, but that is not the case when it comes to new lesions, portal vein tumor thrombosis or extrahepatic spread. Patients with recurrent hepatocellular carcinoma after TACE constitute a heterogenous group and the treatment modalities need to be individualized.

**Citation:** Zhang S, Zhong BY, Zhang L, Wang WS, Ni CF. Transarterial chemoembolization failure/refractoriness: A scientific concept or pseudo-proposition. *World J Gastrointest Surg* 2022; 14(6): 528-537
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i6/528.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i6.528

## INTRODUCTION

According to the Barcelona Clinic Liver Cancer (BCLC) staging system, transarterial chemoembolization (TACE) is the standard approach for patients with intermediate stage (BCLC-B) hepatocellular carcinoma (HCC)[1-3]. Nevertheless, the overall prognosis for patients undergoing TACE varies considerably due to the high heterogeneity of BCLC-B stage HCC[4]. In addition, repeated TACE courses are associated with an increase in angiogenesis and embolization-related liver damage, all of which may negate the benefits achieved in the tumor or even adversely affect overall survival (OS)[4-6]. Thus, many investigations have been carried out in order to identify a turning point where subsequent repeated TACE is not any more beneficial than alternative treatments or best supportive care for patients[7,8]. With the clinical application of tyrosine kinase inhibitors (TKIs), some scholars have proposed a new treatment paradigm where patients with intermediate stage HCC should switch to TKIs monotherapy when tumor progression occurs after TACE procedures[9,10], and as a consequence, the concept of TACE failure/refractoriness was introduced and proposed.

## REVIEW OF DIFFERENT DEFINITIONS OF TACE FAILURE/REFRACTORINESS

The concept of TACE failure/refractoriness was initially proposed by the Japan Society of Hepatology (JHS) in 2010[11] and revised by the JSH-Liver Cancer Study Group of Japan (LCSGJ) in 2014 (Table 1) during a consensus meeting[6]. According to the definition, persistent viable treated lesions, consecutive emergence of new intrahepatic tumors and disease stage progression as well as continuous elevation of tumor markers were scenarios for terminating repeated TACE. However, Korean scholars did not take the same view and they concluded that 3 conditions, namely 3 or more TACE procedures within 6 mo, advancing to portal vein tumor thrombosis (PVTT) and extrahepatic spread (EHS) was TACE failure/refractoriness[12]. These suggestions were also supported by the International Association for the Study of the Liver (Table 1)[13]. Notably, the concept from Europeans seems to be more reliable in clinical practice (Table 1)[14]. They suggested that the determination of TACE failure/refractoriness should be in line with the indications of TACE. If stable disease (SD) of HCC is achieved when TACE is used as a palliative therapy it is regarded as effective. Conversely, when TACE acts as a curative treatment, the outcome of SD or progressive disease is identified as TACE failure/refractoriness. Currently, the concept of TACE failure/refractoriness has been widely introduced, especially in clinical trials for HCC[5,9,10,15,16]. However, these concepts require further discussion due to low evidence-based data. This article attempts to provide a comprehensive understanding concerning the omissions in the current definitions based on published evidence.

## COMPREHENSIVE ANALYSES OF THE ENDPOINTS FOR TACE IN TACE FAILURE/REFRACTORINESS

### *Persistent viable targeted lesion(s) after consecutive treatments*

When insufficient response in intrahepatic tumor occurs after multi-session TACE, it is sensible to define TACE failure/refractoriness and to stop TACE. The peripheral region as well as the capsular region of HCC nodules may be nourished by both the hepatic artery and portal vein and, as a result, substantial tumor necrosis by arterial embolization is not always guaranteed[17-19]. It has been reported that nourishing vessels of residual tumors may change from the hepatic artery to the portal vein after repeated TACE[20]. In addition, repeated chemoembolization increases pressure in the tumor microenvironment and may lead to phenotypic variation in surviving tumor cells, which tend to be more malignant and chemoembolization-resistant[21-23]. It has been reported that locally recurrent HCC after TACE has a significantly shorter doubling time than primary HCC nodules[24].

The number of TACE sessions performed before abandoning TACE in the case of insufficient tumor necrosis is a crucial issue. Georgiades *et al*[25] reported that 47% of non-responders to the first TACE ultimately achieved partial response (PR) or complete response (CR) after the second procedure, and median OS between patients who achieved response at the first or the second chemoembolization was comparable. Some experts suggested that if target nodule(s) show no response after at least two consecutive sessions of TACE, it is reasonable to define TACE-failure and trigger treatment stage

**Table 1 Different concepts of transarterial chemoembolization failure/refractoriness**

| Guidelines/articles | Contents |
|---|---|
| JSH-LCSGJ criteria 2014 [6] | (1) Intrahepatic lesion: Two or more consecutive insufficient responses of the treated tumor (viable lesion > 50%) even after changing the chemotherapeutic agents and/or reanalysis of the feeding artery seen on response evaluation CT/MRI at 1-3 mo after having adequately performed selective TACE; two or more consecutive progressions in the liver (tumor number increases as compared with tumor number before the previous TACE procedure) even after having changed the chemotherapeutic agents and/or reanalysis of the feeding artery seen on response evaluation CT/MRI at 1-3 mo after having adequately performed selective TACE; (2) Continuous elevation of tumor markers immediately after TACE even though a slight transient decrease is observed; (3) Appearance of vascular invasion; and (4) Appearance of extrahepatic spread |
| International Association for the Study of the Liver [13] | No response after 3 or more TACE procedures within a 6 mo period, to the same area. |
| Europe[14] | Depending on the purpose of TACE, if TACE is used as palliative therapy, stable lesions can be regarded as effective. Conversely, if TACE is used as a curative therapy, stable lesions are considered TACE-failure |

JSH-LCSGJ: JSH-Liver Cancer Study Group of Japan; TACE: Transarterial chemoembolization; CT: Computed tomography; MRI: Magnetic resonance imaging.

migration[2,4,16,26]. Based on a large cohort study of 4154 patients with HCC, Chen *et al*[27] found that HCC nodules became insensitive to chemoembolization after 3 sessions of TACE, with an objective response rate (ORR) < 10%. Furthermore, patients with tumors eventually attaining CR or PR within the first 3 TACE sessions had a longer median OS than those who did not (43.4 mo *vs* 16.6 mo, $P < 0.001$). As a consequence, three sessions were recommended before abandoning TACE.

However, residual tumors with persistent viability may not be an absolute indication for systemic monotherapy owing to the unsatisfactory anti-tumor effect[28]. Other locoregional interventional methods, with curative potential, are preferred options once tumor size meets the indications. Chen *et al*[17] reported that subsequent microwave ablation (MWA) yielded a better survival time than sorafenib in patients with incomplete remission of targeted lesions after multiple sessions of TACE, with a longer progression-free survival (PFS) time (9.0 mo *vs* 2.8 mo, $P = 0.006$) and OS (not reached *vs* 16.6 mo, $P = 0.001$). In addition, Yttrium-90 radioembolization and Iodine-125 ($^{125}$I) seed brachytherapy have been adopted to control target lesions[29-31]. TACE combined with systemic therapy or loco-regional therapy revealed favorable outcomes and good tolerance[15,31,32].

### *New intrahepatic lesion(s) appearing after consecutive treatments*

Vascular endothelial growth factor (VEGF), which is regulated by hypoxia-inducible factor-1α, has been demonstrated to be the most important element in neovascularization[33]. Substantial evidence has been elucidated on the intrinsic connection between the transient upregulation of VEGF after TACE and intrahepatic metastasis. Tumor recurrences are frequently reported after TACE, whereas it is arbitrary to describe this scenario as an absolute contraindication to repeated TACE[34,35]. First, TACE is traditionally recognized as a palliative, loco-regional therapy and it is unreasonable to define the occurrence of new lesions outside treated areas as disease progression[4,27,35]. Second, frequent intrahepatic metastasis is the inherent nature of HCC and it occurs in the very early-stage. A clinicopathologic study found that nearly 19% of small HCC patients (solitary nodule with a diameter no more than 3 cm) had satellite lesions, located 2 cm or less from the main tumor and were 1 mm to 5 mm in diameter[36]. Although these undetectable and untypical micro-metastases are too small to be diagnosed as tumors according to the European Association for the Study of the Liver (EASL)[3], they possess enormous potential to develop into typical tumor lesions and appear as local recurrence or intrahepatic metastases[37]. In addition, the malignancy of HCC is positively associated with tumor size. It has been reported that approximately 51.3% of HCC nodules (with an average size of 5 cm) had microvascular invasion (MVI) and 42.4% of the nuclei were severely atypical[38]. For patients with intermediate- or advanced-stage HCC, early tumor progression after locoregional therapy was almost inevitable due to heavy tumor burden and frequent MVI[15,32,39]. Combination therapy was expected to delay tumor recurrence[16]. Even the supporters of TACE failure/refractoriness are ambivalent on the issue of whether new lesion(s) after TACE is a condition of TACE failure/refractoriness[6,16,35]. In the TACTICS trial, the first randomized control trial (RCT) demonstrating the superiority of TACE plus sorafenib compared to TACE monotherapy in unresectable HCC, "TACE failure/refractoriness" was one of the major endpoints for TACE treatment. However, the study simultaneously emphasized that multicentric occurrence and intrahepatic recurrence/metastases were the unique biological features of HCC[35], and therefore it was reasonable to perform demand TACE to control new tumor lesions[40]. To date, there is still no convincing evidence to conclude that new intrahepatic tumor lesions attribute to the biological features of HCC, whereas consecutive intrahepatic metastasis should be defined as TACE failure/refractoriness.

On-demand TACE for new intrahepatic lesions is safe and efficient in selected patients[12,41]. In a large cohort study, 264 patients with intermediate-stage HCC underwent TACE with "on demand" mode (range: 1-13 times; mean: 3 times)[12]. During the follow-up, patients experiencing intrahepatic metastasis or a total target tumor diameter increase of 20% were defined as having progressive disease (PD), while those having PVTT invasion or EHS were defined as having stage progression (SP). The results showed that median OS was comparable between patients in the PD (-) and SP (-) group (36.6 mo) and in the PD (+) and SP (-) group (35.5 mo). However, evidence from these studies only supports the feasibility of repeated TACE in new lesions, but by no means indicates that TACE can be implemented unrestrainedly. Liver function deterioration and hypoxia-induced pressure on residual HCCs have a great influence on patients' survival. Additional systemic therapies including TKIs may prolong the interval between two TACE sessions and hamper intrahepatic micro-metastases[16,42]. Hence, the treatment decision has to be individualized according to expert evaluation. Several nomograms have been established to identify patients who may benefit from repeated TACE, but the rationality of these nomograms is still controversial[7,8,43].

### *Continuous elevation of tumor markers*

On-schedule tumor marker assessment is a crucial adjuvant method for evaluating tumor response and monitoring tumor recurrence. A sudden increase in α-fetoprotein (AFP), AFP-L3 and/or des-gamma-carboxy prothrombin after treatment was thought to show tumor progression or greater malignancy of the tumor[44,45]. However, that does not indicate a definitive correlation with TACE failure/refractoriness. On the one hand, a well-designed control study is expected to clarify the superiority of TKIs to TACE in patients who experienced tumor marker flare after TACE. Although previous evidence has shown that rapid reductions in tumor markers were positive predictors of TACE and vice versa[46], subsequent treatments to deal with elevated tumor markers were not explored and recommended. Up to now, all TKIs targeting HCC, except ramucirumab which demonstrated apparent benefits in patients with AFP ≥ 400 ng/mL, are not designed for the biomarker-selected population[47]. On the other hand, the significance of the tumor marker trends has not yet been fully elucidated in the management of HCC and the relationship between different tumor markers and morphological changes is unclear[21,46]. As shown by the EASL clinical practice guideline, the use of changes in serum biomarker levels for assessment of response (*i.e.*, AFP levels) is under investigation[3]. Hence, when tumor markers are increased after TACE, subsequent treatment should be codetermined by tumor burden, liver function and tumor response to previous TACE, rather than abandoning TACE blindly[3,48]. Furthermore, "continuous elevation" is a vague definition and an immature quantification of "elevation" brings many factors into the clinical decision. Ogasawara *et al*[10] suggested an increase in the level of AFP of 20% from baseline as a cut-off value. However, other researchers have different opinions[8,45].

### *Appearance of vascular invasion or extrahepatic spread*

Neither the EASL nor the American Association for the Study of Liver Disease guidelines recommend TACE for the treatment of HCC with PVTT or EHS[1,3]. However, according to the BRIDGE study that documented real-world clinical practice in HCC, TACE was still the most frequent first treatment in advanced-stage HCC[49]. A national questionnaire conducted in Korea also indicated that nearly half of clinicians would not abandon TACE in the case of PVTT or EHS due to the heterogeneity of HCC[48]. Outcomes from the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) and Oriental clinical trials and the corresponding subgroup analyses showed a marginal improvement for sorafenib over placebo in terms of PVTT with/without EHS[28,50-52]. Lenvatinib exhibited a promising short-term anti-tumor effect compared with sorafenib in patients suffering PVTT with/without EHS [Hazard ratio (HR): 0.64; 95% confidence interval (CI): 0.54-0.77], while the long-term prognosis was undefined (HR: 0.87; 95%CI: 0.73-1.04). It is worth stressing that although the BCLC stage system recommends systemic therapy as the initial treatment for advanced-stage HCC, a special profile of an individual patient may induce a different option in clinical practice[48,49,53-55].

### *Vascular invasion*

With the development of embolization techniques, TACE has been safely and effectively performed in some patients with adequate collateral pathways around the occluded portal vein[15,48,55-58]. These advanced stage populations were defined as "Quasi-C" patients (segmental PVTT, Child-Pugh A, and acceptable performance status). A meta-analysis showed that TACE conferred a longer OS in patients with branch PVTT than those with main trunk PVTT (11 mo *vs* 5 mo, $P < 0.001$)[59]. Significantly, for PVTT invading the main trunk, initial portal vein re-canalization using irradiation and a stent with subsequent selective TACE was effective in hampering disease progression, with a median stent patency of 8 mo and median OS of 12.5 mo[60]. Wang *et al*[61] introduced modified $^{125}$I seed brachytherapy to treat main trunk PVTT and exhibited favorable outcomes when combined with TACE (median OS: 9.8 mo). In addition, combination therapy of TACE and TKIs demonstrated better results for selected patients with PVTT[62]. According to a large cohort study, compared with sorafenib monotherapy, TACE combined with sorafenib showed a trend towards significant risk reduction in patients ($n$ = 1136) with vascular invasion (HR: 0.78; 95%CI: 0.59-1.02)[63]. Recently, a RCT conducted

by Ding *et al*[62] reported that TACE plus lenvatinib had a more favorable efficacy *vs* TACE plus sorafenib in patients with PVTT, especially those with Vp1-3 type (HR: 0.12; 95%CI: 0.03-0.42, $P < 0.01$) or heavy tumor burden (HR: 0.30; 95%CI: 0.15-0.61, $P < 0.01$). It should be emphasized that PVTT is a complex system and the optimal treatment strategy is individual rather than univocal. For patients whose tumor thrombus involves a segment of the portal vein or above, surgery is a potential option once tumor burden is downstaged to the Milan criteria in the liver; for patients who miss curative treatment, TACE, TKIs and other modalities may play a complementary role in controlling disease progression[57]. So far, many novel treatment strategies for PVTT have been investigated and have yielded exciting results, providing patients with more treatment options[30,57,60,64,65].

### *Extrahepatic spread*

Subgroup analysis from the SHARP clinical trial revealed that sorafenib only conferred an additional survival time of 0.6 mo compared with placebo[52]. Due to the fact that more than two-thirds of patients with EHS died of intrahepatic tumor progression rather than extrahepatic disease, aggressive treatment targeting intrahepatic disease might be beneficial in selected patients with EHS[15,53,63]. The results from Kirstein *et al*[53] suggested that TACE was not inferior to sorafenib in patients with limited EHS of HCC, with a median OS of 8.8 mo *vs* 7.0 mo for sorafenib *vs* TACE ($P = 0.312$) before propensity score matching (PSM) analysis and 4.0 mo *vs* 8.0 mo after PSM ($P = 0.613$). In another large cohort study of 186 patients with EHS, TACE appeared to be more beneficial in patients aged below 60 years (HR: 0.58, 95%CI: 0.37-0.91, $P = 0.017$) or complicated with PVTT (HR: 0.44, 95%CI: 0.25-0.79, $P < 0.001$)[66]. Choi *et al*[55] compared combination treatment (TACE plus sorafenib) with sorafenib alone in advanced stage patients. The combination group demonstrated a more significant survival benefit than monotherapy both in time to progression (2.7 mo *vs* 2.1 mo, $P = 0.011$) and median OS (8.9 mo *vs* 5.9 mo; $P = 0.009$). Subgroup analysis revealed that combination therapy was more efficacious in patients who had good liver function and EHS. Hence, although systemic therapy is recommended as the first choice for patients with EHS, TACE may still be a potential alternative in selected patients.

## SUGGESTIONS TO DEFINE TACE FAILURE/REFRACTORINESS

For patients with intermediate-stage HCC, multidisciplinary treatment is compulsory to overcome the vast heterogeneity in HCC and different treatment modalities are cooperators rather than competitors. The term "failure" or "refractoriness" was initially derived from systemic chemotherapy in oncology where the current chemotherapeutic strategy failed to prevent overall tumor progression including tumor recurrences and new lesions. TACE is only a locoregional therapy but disease progression of HCC involves intrahepatic areas and extrahepatic tissues. In the absence of prospective well-designed studies, a persuasive definition of TACE failure/refractoriness should largely rely on the nature of the treatment, that is, a locoregional therapy. In 2020, a nationwide online survey of 257 clinicians in 184 hospitals was conducted to recognize TACE failure/refractoriness among clinicians treating HCC in China[67]. The survey showed that 89.1% ($n = 229$) of participants deemed TACE as a palliative therapy although sometimes could be a curative modality. While the outcome of TACE was full of variation ($n = 244$), almost all the participants ($n = 252$) would still choose TACE as the first choice for intermediate-stage HCC. In terms of TACE failure/refractoriness, nearly three-quarters ($n = 199$) acknowledged the rationality of the concept, whereas 91.4% ($n = 235$) of the respondents did not agree with the current definitions. A clear majority of clinicians would perform TACE combined with therapy in patients with segmental PVTT ($n = 242$) or EHS ($n = 253$) if liver function was well preserved. In addition, only 42 (16.3%) respondents unequivocally stated that new intrahepatic tumor lesions were an indication of TACE failure/refractoriness; and 36.6% ($n = 94$) gave an equivocal answer. Among the remaining 121 respondents who answered "No" to the question, most preferred combination therapy, including TACE ($n = 80$) and ablation ($n = 80$), to control new lesions. Additionally, 166 (64.6%) participants agreed that repeated TACE can be performed if tumor necrosis was insufficient and feeding arteries were available. Whereas, 150 participants (58.4%) believed that repeated TACE on pre-treated lesions should be limited to 3 times. Notably, 98.1% ($n = 252$) of the respondents expressed a strong desire for the improvement of TACE, including preferable embolization agents, chemotherapeutic drugs followed by embolization technique and more advanced microcatheters. Based on the above discussion and evidence, if intrahepatic targeted lesions are well controlled by appropriate TACE regimens, TACE should not be indiscriminately abandoned in the context of disease progression including new lesions, PVTT and EHS. However, if three consecutive insufficient tumor responses in targeted lesions occur, TACE should not be repeated and TACE failure/refractoriness proposed.

## FUTURE OF TACE FAILURE/REFRACTORINESS

Treatment modalities for unresectable HCC have undergone profound changes and TACE faces

unprecedented challenges, where novel treatment strategies may substitute for TACE as the first treatment option in selected patients with intermediate-stage HCC (ABC-HCC, NCT04803994; RENOTACE, NCT04777851). As a consequence, the concept of TACE failure/refractoriness may be expanded or re-defined as other proposals, for example, TACE unsuitability and TACE impossible. However, such concepts should not be overemphasized before substantial evidence is published, as the management of unresectable HCC is no longer the conversion between various monotherapies in the era of comprehensive therapy. The evolution of TACE will continue and many options are being investigated, including new embolic or chemotherapeutic agents in order to ensure complete tumor necrosis, and combination treatments with newly-developed immune checkpoint inhibitors (LEAP-012, NCT04246177; EMERALD-1, NCT03778957; CheckMate74W, NCT04340193; IMMUTACE, NCT03572582). In the near future, the outcomes of these RCTs may re-position the role of TACE in the management of HCC.

## CONCLUSION

TACE failure/refractoriness is a scientific proposal for HCC but certain definitions in current concepts are debatable. Tumor progression after TACE is due to high heterogeneity and therefore subsequent treatment is an individual profile rather than a univocal recommendation. We put forward new opinions concerning TACE failure/refractoriness which might be more reasonable in clinical practice.

## FOOTNOTES

**Author contributions:** Zhang S and Zhong BY contributed equally to drafting the manuscript; Zhang L polished the vocabulary and the grammar; Wang WS and Ni CF shared responsibility for the study concept and design; all authors contributed to reviewing and criticizing revision of the manuscript and approving the final version of the manuscript.

**Supported by** the National Natural Science Foundation of China, No. 81901847; Natural Science Foundation of Jiangsu Province, No. BK20190177; and the Suzhou Science and Technology Youth Plan, No. KJXW2018003.

**Conflict-of-interest statement:** There are no conflicts of interest to report.



**Country/Territory of origin:** China

**ORCID number:** Shen Zhang 0000-0001-7363-351X; Bin-Yan Zhong 0000-0001-9716-1211; Lei Zhang 0000-0002-2564-3948; Wan-Sheng Wang 0000-0001-9539-4425; Cai-Fang Ni 0000-0003-2693-367X.

**S-Editor:** Chen YL
**L-Editor:** Webster JR
**P-Editor:** Chen YL

## REFERENCES

1 **Heimbach JK**, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, Zhu AX, Murad MH, Marrero JA. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018; **67**: 358-380 [PMID: 28130846 DOI: 10.1002/hep.29086]
2 **Kokudo N**, Takemura N, Hasegawa K, Takayama T, Kubo S, Shimada M, Nagano H, Hatano E, Izumi N, Kaneko S, Kudo M, Iijima H, Genda T, Tateishi R, Torimura T, Igaki H, Kobayashi S, Sakurai H, Murakami T, Watadani T, Matsuyama Y. Clinical practice guidelines for hepatocellular carcinoma: The Japan Society of Hepatology 2017 (4th JSH-HCC guidelines) 2019 update. *Hepatol Res* 2019; **49**: 1109-1113 [PMID: 31336394 DOI: 10.1111/hepr.13411]
3 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018; **69**: 182-236 [PMID: 29628281 DOI: 10.1016/j.jhep.2018.03.019]
4 **Raoul JL**, Sangro B, Forner A, Mazzaferro V, Piscaglia F, Bolondi L, Lencioni R. Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. *Cancer Treat Rev* 2011; **37**: 212-220 [PMID: 20724077 DOI: 10.1016/j.ctrv.2010.07.006]
5 **Kudo M**, Ueshima K, Chan S, Minami T, Chishina H, Aoki T, Takita M, Hagiwara S, Minami Y, Ida H, Takenaka M,

Sakurai T, Watanabe T, Morita M, Ogawa C, Wada Y, Ikeda M, Ishii H, Izumi N, Nishida N. Lenvatinib as an Initial Treatment in Patients with Intermediate-Stage Hepatocellular Carcinoma Beyond Up-To-Seven Criteria and Child-Pugh A Liver Function: A Proof-Of-Concept Study. *Cancers (Basel)* 2019; **11** [PMID: 31370183 DOI: 10.3390/cancers11081084]

6 **Kudo M**, Matsui O, Izumi N, Kadoya M, Okusaka T, Miyayama S, Yamakado K, Tsuchiya K, Ueshima K, Hiraoka A, Ikeda M, Ogasawara S, Yamashita T, Minami T; Liver Cancer Study Group of Japan. Transarterial chemoembolization failure/refractoriness: JSH-LCSGJ criteria 2014 update. *Oncology* 2014; **87** Suppl 1: 22-31 [PMID: 25427730 DOI: 10.1159/000368142]

7 **Sieghart W**, Hucke F, Pinter M, Graziadei I, Vogel W, Müller C, Heinzl H, Trauner M, Peck-Radosavljevic M. The ART of decision making: retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma. *Hepatology* 2013; **57**: 2261-2273 [PMID: 23316013 DOI: 10.1002/hep.26256]

8 **Adhoute X**, Penaranda G, Naude S, Raoul JL, Perrier H, Bayle O, Monnet O, Beaurain P, Bazin C, Pol B, Folgoc GL, Castellani P, Bronowicki JP, Bourlière M. Retreatment with TACE: the ABCR SCORE, an aid to the decision-making process. *J Hepatol* 2015; **62**: 855-862 [PMID: 25463541 DOI: 10.1016/j.jhep.2014.11.014]

9 **Arizumi T**, Ueshima K, Minami T, Kono M, Chishina H, Takita M, Kitai S, Inoue T, Yada N, Hagiwara S, Minami Y, Sakurai T, Nishida N, Kudo M. Effectiveness of Sorafenib in Patients with Transcatheter Arterial Chemoembolization (TACE) Refractory and Intermediate-Stage Hepatocellular Carcinoma. *Liver Cancer* 2015; **4**: 253-262 [PMID: 26734579 DOI: 10.1159/000367743]

10 **Ogasawara S**, Chiba T, Ooka Y, Kanogawa N, Motoyama T, Suzuki E, Tawada A, Kanai F, Yoshikawa M, Yokosuka O. Efficacy of sorafenib in intermediate-stage hepatocellular carcinoma patients refractory to transarterial chemoembolization. *Oncology* 2014; **87**: 330-341 [PMID: 25227534 DOI: 10.1159/000365993]

11 **Kudo M**, Izumi N, Kokudo N, Matsui O, Sakamoto M, Nakashima O, Kojiro M, Makuuchi M; HCC Expert Panel of Japan Society of Hepatology. Management of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. *Dig Dis* 2011; **29**: 339-364 [PMID: 21829027 DOI: 10.1159/000327577]

12 **Kim HY**, Park JW, Joo J, Jung SJ, An S, Woo SM, Kim HB, Koh YH, Lee WJ, Kim CM. Severity and timing of progression predict refractoriness to transarterial chemoembolization in hepatocellular carcinoma. *J Gastroenterol Hepatol* 2012; **27**: 1051-1056 [PMID: 22098152 DOI: 10.1111/j.1440-1746.2011.06963.x]

13 **Park JW**, Amarapurkar D, Chao Y, Chen PJ, Geschwind JF, Goh KL, Han KH, Kudo M, Lee HC, Lee RC, Lesmana LA, Lim HY, Paik SW, Poon RT, Tan CK, Tanwandee T, Teng G, Cheng AL. Consensus recommendations and review by an International Expert Panel on Interventions in Hepatocellular Carcinoma (EPOIHCC). *Liver Int* 2013; **33**: 327-337 [PMID: 23331661 DOI: 10.1111/liv.12083]

14 **Raoul JL**, Gilabert M, Piana G. How to define transarterial chemoembolization failure or refractoriness: a European perspective. *Liver Cancer* 2014; **3**: 119-124 [PMID: 24945002 DOI: 10.1159/000343867]

15 **Lin PT**, Teng W, Jeng WJ, Hsieh YC, Hung CF, Huang CH, Lui KW, Chen YC, Lin CC, Lin CY, Sheen IS, Lin SM. Add-on sorafenib is beneficial for hepatocellular carcinoma patients with transarterial chemoembolization refractoriness: a real-world experience. *Eur J Gastroenterol Hepatol* 2020; **32**: 1192-1199 [PMID: 31851084 DOI: 10.1097/MEG.0000000000001637]

16 **Kudo M**, Ueshima K, Ikeda M, Torimura T, Tanabe N, Aikata H, Izumi N, Yamasaki T, Nojiri S, Hino K, Tsumura H, Kuzuya T, Isoda N, Yasui K, Aino H, Ido A, Kawabe N, Nakao K, Wada Y, Yokosuka O, Yoshimura K, Okusaka T, Furuse J, Kokudo N, Okita K, Johnson PJ, Arai Y; TACTICS study group. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. *Gut* 2020; **69**: 1492-1501 [PMID: 31801872 DOI: 10.1136/gutjnl-2019-318934]

17 **Chen S**, Shi M, Shen L, Qi H, Wan W, Cao F, Xie L, Wu Y, Chen G, Mo J, Zhu G, Ye D, Zhang Y, Feng Z, Xu L, Fan W. Microwave ablation versus sorafenib for intermediate-Stage Hepatocellular carcinoma with transcatheter arterial chemoembolization refractoriness: a propensity score matching analysis. *Int J Hyperthermia* 2020; **37**: 384-391 [PMID: 32323585 DOI: 10.1080/02656736.2020.1752400]

18 **Yoshimitsu K**. Transarterial chemoembolization using iodized oil for unresectable hepatocellular carcinoma: perspective from multistep hepatocarcinogenesis. *Hepat Med* 2014; **6**: 89-94 [PMID: 25114603 DOI: 10.2147/hmer.s31440]

19 **International Consensus Group for Hepatocellular NeoplasiaThe International Consensus Group for Hepatocellular Neoplasia**. Pathologic diagnosis of early hepatocellular carcinoma: a report of the international consensus group for hepatocellular neoplasia. *Hepatology* 2009; **49**: 658-664 [PMID: 19177576 DOI: 10.1002/hep.22709]

20 **Miyayama S**, Matsui O, Zen Y, Yamashiro M, Hattori Y, Orito N, Matsui K, Tsuji K, Yoshida M, Sudo Y. Portal blood supply to locally progressed hepatocellular carcinoma after transcatheter arterial chemoembolization: Observation on CT during arterial portography. *Hepatol Res* 2011; **41**: 853-866 [PMID: 21699636 DOI: 10.1111/j.1872-034X.2011.00836.x]

21 **Park H**, Park JY. Clinical significance of AFP and PIVKA-II responses for monitoring treatment outcomes and predicting prognosis in patients with hepatocellular carcinoma. *Biomed Res Int* 2013; **2013**: 310427 [PMID: 24455683 DOI: 10.1155/2013/310427]

22 **Kojiro M**, Sugihara S, Kakizoe S, Nakashima O, Kiyomatsu K. Hepatocellular carcinoma with sarcomatous change: a special reference to the relationship with anticancer therapy. *Cancer Chemother Pharmacol* 1989; **23** Suppl: S4-S8 [PMID: 2466583 DOI: 10.1007/BF00647229]

23 **Zen C**, Zen Y, Mitry RR, Corbeil D, Karbanová J, O'Grady J, Karani J, Kane P, Heaton N, Portmann BC, Quaglia A. Mixed phenotype hepatocellular carcinoma after transarterial chemoembolization and liver transplantation. *Liver Transpl* 2011; **17**: 943-954 [PMID: 21491582 DOI: 10.1002/lt.22314]

24 **Tezuka M**, Hayashi K, Kubota K, Sekine S, Okada Y, Ina H, Irie T. Growth rate of locally recurrent hepatocellular carcinoma after transcatheter arterial chemoembolization: comparing the growth rate of locally recurrent tumor with that of primary hepatocellular carcinoma. *Dig Dis Sci* 2007; **52**: 783-788 [PMID: 17268830 DOI: 10.1007/s10620-006-9537-y]

25 **Georgiades C**, Geschwind JF, Harrison N, Hines-Peralta A, Liapi E, Hong K, Wu Z, Kamel I, Frangakis C. Lack of response after initial chemoembolization for hepatocellular carcinoma: does it predict failure of subsequent treatment? *Radiology* 2012; **265**: 115-123 [PMID: 22891361 DOI: 10.1148/radiol.12112264]

26 **Reig M**, Forner A, Rimola J, Ferrer-Fabrega J, Burrel M, Garcia-Criado A, Kelley RK, Galle PR, Mazzaferro V, Salem R, Sangro B, Singal AG, Vogel A, Fuster J, Ayuso C, Bruix J. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. *J Hepatol* 2021 [DOI: 10.1016/j.jhep.2021.11.018]

27 **Chen S**, Peng Z, Zhang Y, Chen M, Li J, Guo R, Li B, Mei J, Feng S, Kuang M. Lack of Response to Transarterial Chemoembolization for Intermediate-Stage Hepatocellular Carcinoma: Abandon or Repeat? *Radiology* 2021; **298**: 680-692 [PMID: 33464183 DOI: 10.1148/radiol.2021202289]

28 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]

29 **Li M**, He J, Pan M, Yu Y, Pan Z, Xu B, Zhu J. Iodine-125 implantation plus transarterial chemoembolization for the treatment of hepatocellular carcinoma of 3-5cm: A propensity score matching study. *Dig Liver Dis* 2016; **48**: 1082-1087 [PMID: 27365224 DOI: 10.1016/j.dld.2016.06.007]

30 **Bekki Y**, Marti J, Toshima T, Lewis S, Kamath A, Argiriadi P, Simpson W, Facciuto L, Patel RS, Gunasekaran G, Kim E, Schiano TD, Facciuto ME. A comparative study of portal vein embolization versus radiation lobectomy with Yttrium-90 micropheres in preparation for liver resection for initially unresectable hepatocellular carcinoma. *Surgery* 2021; **169**: 1044-1051 [PMID: 33648768 DOI: 10.1016/j.surg.2020.12.012]

31 **Klompenhouwer EG**, Dresen RC, Verslype C, Laenen A, De Hertogh G, Deroose CM, Bonne L, Vandevaveye V, Maleux G. Safety and Efficacy of Transarterial Radioembolisation in Patients with Intermediate or Advanced Stage Hepatocellular Carcinoma Refractory to Chemoembolisation. *Cardiovasc Intervent Radiol* 2017; **40**: 1882-1890 [PMID: 28685382 DOI: 10.1007/s00270-017-1739-5]

32 **Duan F**, Bai YH, Cui L, Li XH, Yan JY, Wang MQ. Simultaneous transarterial chemoembolization and radiofrequency ablation for large hepatocellular carcinoma. *World J Gastrointest Oncol* 2020; **12**: 92-100 [PMID: 31966917 DOI: 10.4251/wjgo.v12.i1.92]

33 **Wu J**, Li A, Yang J, Lu Y, Li J. Efficacy and safety of TACE in combination with sorafenib for the treatment of TACE-refractory advanced hepatocellular carcinoma in Chinese patients: a retrospective study. *Onco Targets Ther* 2017; **10**: 2761-2768 [PMID: 28603426 DOI: 10.2147/OTT.S131022]

34 **Forner A**, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018; **391**: 1301-1314 [PMID: 29307467 DOI: 10.1016/s0140-6736(18)30010-2]

35 **Kudo M**, Kubo S, Takayasu K, Sakamoto M, Tanaka M, Ikai I, Furuse J, Nakamura K, Makuuchi M; Liver Cancer Study Group of Japan (Committee for Response Evaluation Criteria in Cancer of the Liver, Liver Cancer Study Group of Japan). Response Evaluation Criteria in Cancer of the Liver (RECICL) proposed by the Liver Cancer Study Group of Japan (2009 Revised Version). *Hepatol Res* 2010; **40**: 686-692 [PMID: 20633194 DOI: 10.1111/j.1872-034X.2010.00674.x]

36 **Okusaka T**, Okada S, Ueno H, Ikeda M, Shimada K, Yamamoto J, Kosuge T, Yamasaki S, Fukushima N, Sakamoto M. Satellite lesions in patients with small hepatocellular carcinoma with reference to clinicopathologic features. *Cancer* 2002; **95**: 1931-1937 [PMID: 12404287 DOI: 10.1002/cncr.10892]

37 **Kudo M**. Multistep human hepatocarcinogenesis: correlation of imaging with pathology. *J Gastroenterol* 2009; **44** Suppl 19: 112-118 [PMID: 19148804 DOI: 10.1007/s00535-008-2274-6]

38 **Lauwers GY**, Terris B, Balis UJ, Batts KP, Regimbeau JM, Chang Y, Graeme-Cook F, Yamabe H, Ikai I, Cleary KR, Fujita S, Flejou JF, Zukerberg LR, Nagorney DM, Belghiti J, Yamaoka Y, Vauthey JN; International Cooperative Study Group on Hepatocellular Carcinoma. Prognostic histologic indicators of curatively resected hepatocellular carcinomas: a multi-institutional analysis of 425 patients with definition of a histologic prognostic index. *Am J Surg Pathol* 2002; **26**: 25-34 [PMID: 11756766 DOI: 10.1097/00000478-200201000-00003]

39 **Raoul JL**, Forner A, Bolondi L, Cheung TT, Kloeckner R, de Baere T. Updated use of TACE for hepatocellular carcinoma treatment: How and when to use it based on clinical evidence. *Cancer Treat Rev* 2019; **72**: 28-36 [PMID: 30447470 DOI: 10.1016/j.ctrv.2018.11.002]

40 **Miyayama S**. Ultraselective conventional transarterial chemoembolization: When and how? *Clin Mol Hepatol* 2019; **25**: 344-353 [PMID: 31022779 DOI: 10.3350/cmh.2019.0016]

41 **Park C**, Chu HH, Kim JH, Kim SY, Alrashidi I, Gwon DI, Yoon HK, Kim N. Clinical Significance of the Initial and Best Responses after Chemoembolization in the Treatment of Intermediate-Stage Hepatocellular Carcinoma with Preserved Liver Function. *J Vasc Interv Radiol* 2020; **31**: 1998-2006.e1 [PMID: 32988715 DOI: 10.1016/j.jvir.2020.04.017]

42 **Kudo M**, Cheng AL, Park JW, Park JH, Liang PC, Hidaka H, Izumi N, Heo J, Lee YJ, Sheen IS, Chiu CF, Arioka H, Morita S, Arai Y. Orantinib versus placebo combined with transcatheter arterial chemoembolisation in patients with unresectable hepatocellular carcinoma (ORIENTAL): a randomised, double-blind, placebo-controlled, multicentre, phase 3 study. *Lancet Gastroenterol Hepatol* 2018; **3**: 37-46 [PMID: 28988687 DOI: 10.1016/S2468-1253(17)30290-X]

43 **Kloeckner R**, Pitton MB, Dueber C, Schmidtmann I, Galle PR, Koch S, Wörns MA, Weinmann A. Validation of Clinical Scoring Systems ART and ABCR after Transarterial Chemoembolization of Hepatocellular Carcinoma. *J Vasc Interv Radiol* 2017; **28**: 94-102 [PMID: 27562621 DOI: 10.1016/j.jvir.2016.06.012]

44 **Nakazawa T**, Hidaka H, Takada J, Okuwaki Y, Tanaka Y, Watanabe M, Shibuya A, Minamino T, Kokubu S, Koizumi W. Early increase in α-fetoprotein for predicting unfavorable clinical outcomes in patients with advanced hepatocellular carcinoma treated with sorafenib. *Eur J Gastroenterol Hepatol* 2013; **25**: 683-689 [PMID: 23395995 DOI: 10.1097/MEG.0b013e32835d913b]

45 **Hiraoka A**, Ishimaru Y, Kawasaki H, Aibiki T, Okudaira T, Toshimori A, Kawamura T, Yamago H, Nakahara H, Suga Y, Azemoto N, Miyata H, Miyamoto Y, Ninomiya T, Hirooka M, Abe M, Matsuura B, Hiasa Y, Michitaka K. Tumor Markers AFP, AFP-L3, and DCP in Hepatocellular Carcinoma Refractory to Transcatheter Arterial Chemoembolization. *Oncology* 2015; **89**: 167-174 [PMID: 25999038 DOI: 10.1159/000381808]

46 **Arai T**, Kobayashi A, Ohya A, Takahashi M, Yokoyama T, Shimizu A, Motoyama H, Furusawa N, Notake T, Kitagawa N, Sakai H, Imamura H, Kadoya M, Miyagawa S. Assessment of treatment outcomes based on tumor marker trends in patients with recurrent hepatocellular carcinoma undergoing trans-catheter arterial chemo-embolization. *Int J Clin Oncol* 2014; **19**:

871-879 [PMID: 24218280 DOI: 10.1007/s10147-013-0634-6]
47 **Zhu AX**, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, Assenat E, Brandi G, Pracht M, Lim HY, Rau KM, Motomura K, Ohno I, Merle P, Daniele B, Shin DB, Gerken G, Borg C, Hiriart JB, Okusaka T, Morimoto M, Hsu Y, Abada PB, Kudo M; REACH-2 study investigators. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2019; **20**: 282-296 [PMID: 30665869 DOI: 10.1016/S1470-2045(18)30937-9]
48 **Lee JS**, Kim BK, Kim SU, Park JY, Ahn SH, Seong JS, Han KH, Kim DY. A survey on transarterial chemoembolization refractoriness and a real-world treatment pattern for hepatocellular carcinoma in Korea. *Clin Mol Hepatol* 2020; **26**: 24-32 [PMID: 31104456 DOI: 10.3350/cmh.2018.0065]
49 **Park JW**, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, Kudo M, Johnson P, Wagner S, Orsini LS, Sherman M. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. *Liver Int* 2015; **35**: 2155-2166 [PMID: 25752327 DOI: 10.1111/liv.12818]
50 **Cheng AL**, Guan Z, Chen Z, Tsao CJ, Qin S, Kim JS, Yang TS, Tak WY, Pan H, Yu S, Xu J, Fang F, Zou J, Lentini G, Voliotis D, Kang YK. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma according to baseline status: subset analyses of the phase III Sorafenib Asia-Pacific trial. *Eur J Cancer* 2012; **48**: 1452-1465 [PMID: 22240282 DOI: 10.1016/j.ejca.2011.12.006]
51 **Cheng AL**, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34 [PMID: 19095497 DOI: 10.1016/S1470-2045(08)70285-7]
52 **Bruix J**, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, Galle PR, Santoro A, Beaugrand M, Sangiovanni A, Porta C, Gerken G, Marrero JA, Nadel A, Shan M, Moscovici M, Voliotis D, Llovet JM. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. *J Hepatol* 2012; **57**: 821-829 [PMID: 22727733 DOI: 10.1016/j.jhep.2012.06.014]
53 **Kirstein MM**, Voigtländer T, Schweitzer N, Hinrichs JB, Marquardt J, Wörns MA, Kloeckner R, Fründt TW, Ittrich H, Wacker F, Rodt T, Manns MP, Wege H, Weinmann A, Vogel A. Transarterial chemoembolization versus sorafenib in patients with hepatocellular carcinoma and extrahepatic disease. *United European Gastroenterol J* 2018; **6**: 238-246 [PMID: 29511553 DOI: 10.1177/2050640617716597]
54 **Li QJ**, He MK, Chen HW, Fang WQ, Zhou YM, Xu L, Wei W, Zhang YJ, Guo Y, Guo RP, Chen MS, Shi M. Hepatic Arterial Infusion of Oxaliplatin, Fluorouracil, and Leucovorin Versus Transarterial Chemoembolization for Large Hepatocellular Carcinoma: A Randomized Phase III Trial. *J Clin Oncol* 2022; **40**: 150-160 [PMID: 34648352 DOI: 10.1200/JCO.21.00608]
55 **Choi GH**, Shim JH, Kim MJ, Ryu MH, Ryoo BY, Kang YK, Shin YM, Kim KM, Lim YS, Lee HC. Sorafenib alone versus sorafenib combined with transarterial chemoembolization for advanced-stage hepatocellular carcinoma: results of propensity score analyses. *Radiology* 2013; **269**: 603-611 [PMID: 23864102 DOI: 10.1148/radiol.13130150]
56 **Kim JH**, Shim JH, Yoon HK, Ko HK, Kim JW, Gwon DI. Chemoembolization related to good survival for selected patients with hepatocellular carcinoma invading segmental portal vein. *Liver Int* 2018; **38**: 1646-1654 [PMID: 29436101 DOI: 10.1111/liv.13719]
57 **Cheng S**, Chen M, Cai J, Sun J, Guo R, Bi X, Lau WY, Wu M. Chinese Expert Consensus on Multidisciplinary Diagnosis and Treatment of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus (2018 Edition). *Liver Cancer* 2020; **9**: 28-40 [PMID: 32071907 DOI: 10.1159/000503685]
58 **Xue TC**, Xie XY, Zhang L, Yin X, Zhang BH, Ren ZG. Transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombus: a meta-analysis. *BMC Gastroenterol* 2013; **13**: 60 [PMID: 23566041 DOI: 10.1186/1471-230X-13-60]
59 **Silva JP**, Berger NG, Tsai S, Christians KK, Clarke CN, Mogal H, White S, Rilling W, Gamblin TC. Transarterial chemoembolization in hepatocellular carcinoma with portal vein tumor thrombosis: a systematic review and meta-analysis. *HPB (Oxford)* 2017; **19**: 659-666 [PMID: 28552299 DOI: 10.1016/j.hpb.2017.04.016]
60 **Lu J**, Guo JH, Zhu HD, Zhu GY, Chen L, Teng GJ. Safety and Efficacy of Irradiation Stent Placement for Malignant Portal Vein Thrombus Combined with Transarterial Chemoembolization for Hepatocellular Carcinoma: A Single-Center Experience. *J Vasc Interv Radiol* 2017; **28**: 786-794.e3 [PMID: 28396192 DOI: 10.1016/j.jvir.2017.02.014]
61 **Wang W**, Wang C, Shen J, Ren B, Yin Y, Yang J, Tang H, Zhu X, Ni C. Integrated I-125 Seed Implantation Combined with Transarterial Chemoembolization for Treatment of Hepatocellular Carcinoma with Main Portal Vein Tumor Thrombus. *Cardiovasc Intervent Radiol* 2021; **44**: 1570-1578 [PMID: 34117503 DOI: 10.1007/s00270-021-02887-1]
62 **Ding X**, Sun W, Li W, Shen Y, Guo X, Teng Y, Liu X, Zheng L, Chen J. Transarterial chemoembolization plus lenvatinib versus transarterial chemoembolization plus sorafenib as first-line treatment for hepatocellular carcinoma with portal vein tumor thrombus: A prospective randomized study. *Cancer* 2021; **127**: 3782-3793 [PMID: 34237154 DOI: 10.1002/cncr.33677]
63 **Kok VC**, Chen YC, Chen YY, Su YC, Ku MC, Kuo JT, Yoshida GJ. Sorafenib with Transarterial Chemoembolization Achieves Improved Survival vs. Sorafenib Alone in Advanced Hepatocellular Carcinoma: A Nationwide Population-Based Cohort Study. *Cancers (Basel)* 2019; **11** [PMID: 31311148 DOI: 10.3390/cancers11070985]
64 **Wang W**, Shen J, Wang C, Ren B, Zhu X, Ni C. Safety and Feasibility of Helical I-125 Seed Implants Combined with Transcatheter Arterial Chemoembolization in Hepatocellular Carcinomas with Main Portal Vein Tumor Thrombus. *Cardiovasc Intervent Radiol* 2019; **42**: 1420-1428 [PMID: 31187228 DOI: 10.1007/s00270-019-02256-z]
65 **Galle PR**, Finn RS, Qin S, Ikeda M, Zhu AX, Kim TY, Kudo M, Breder V, Merle P, Kaseb A, Li D, Mulla S, Verret W, Xu DZ, Hernandez S, Ding B, Liu J, Huang C, Lim HY, Cheng AL, Ducreux M. Patient-reported outcomes with atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma (IMbrave150): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2021; **22**: 991-1001 [PMID: 34051880 DOI: 10.1016/S1470-2045(21)00151-0]
66 **Kim J**, Sinn DH, Choi MS, Kang W, Gwak GY, Paik YH, Lee JH, Koh KC, Paik SW. Hepatocellular carcinoma with

extrahepatic metastasis: Are there still candidates for transarterial chemoembolization as an initial treatment? *PLoS One* 2019; **14**: e0213547 [PMID: 30845192 DOI: 10.1371/journal.pone.0213547]

67 **Zhong BY**, Wang WS, Zhang S, Zhu HD, Zhang L, Shen J, Zhu XL, Teng GJ, Ni CF. Re-evaluating Transarterial Chemoembolization Failure/Refractoriness: A Survey by Chinese College of Interventionalists. *J Clin Transl Hepatol* 2021; **9**: 521-527 [PMID: 34447681 DOI: 10.14218/JCTH.2021.00049]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 June 27; 14(6): 538-543

DOI: 10.4240/wjgs.v14.i6.538

ISSN 1948-9366 (online)

*MINIREVIEWS*

# Indications for the surgical management of pancreatic trauma: An update

Efstathios Theodoros Pavlidis, Kyriakos Psarras, Nikolaos G Symeonidis, Georgios Geropoulos, Theodoros Efstathios Pavlidis

**Specialty type:** Surgery

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Fiori E, Italy; Iwao Y, Japan; Litvin A, Russia

**Received:** January 3, 2022
**Peer-review started:** January 3, 2022
**First decision:** March 12, 2022
**Revised:** March 17, 2022
**Accepted:** May 12, 2022
**Article in press:** May 12, 2022
**Published online:** June 27, 2022

**Efstathios Theodoros Pavlidis, Kyriakos Psarras, Nikolaos G Symeonidis, Theodoros Efstathios Pavlidis,** 2nd Propedeutic Department of Surgery, School of Medicine, Aristotle University, Thessaloniki 54642, Greece

**Georgios Geropoulos,** Department of General Surgery, University College London Hospitals, London NW1 2BU, United Kingdom

**Corresponding author:** Theodoros Efstathios Pavlidis, PhD, Chief Doctor, Director, Full Professor, Surgeon, 2nd Propedeutic Department of Surgery, School of Medicine, Aristotle University, Konstantinoupoleos 49, Thessaloniki 54642, Greece. pavlidth@auth.gr

## Abstract

Pancreatic trauma is rare compared to other abdominal solid organ injuries, accounting for 0.2%-0.3% of all trauma patients. Moreover, this type of injury may frequently be overlooked or not readily appreciated on initial clinical examinations and investigations. The organ injury scale determines the severity of the trauma. Nonetheless, there are conflicting recommendations for the best strategy in severe cases. Overall, conservative management of induced severe traumatic pancreatitis is adequate. Modern imaging modalities such as ultrasound scanning and computed tomography scanning can detect injuries in fewer than 60% of patients. However, magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography (ERCP) have diagnostic accuracies approaching 90%-100%. Thus, management options include ERCP and stent placement or distal pancreatectomy in cases of complete gland transection and wide drainage only for damage control surgery, which can prevent mortality but increases the risk of morbidity. In the majority of cases, surgical intervention is not required and should be reserved for only severe grade III to grade V injuries.

**Key Words:** Pancreas; Acute pancreatitis; Abdominal trauma; Pancreatic traumatic injury; Emergency surgery; Damage control surgery

**Core Tip:** Pancreatic trauma management should be individualized based on the exact grade of injury. Damage control surgery is the best approach for severe life-threatening cases. However, in such cases, the presence of severe acute pancreatitis makes safe resection impossible. Endoscopic stent placement into the ruptured pancreatic duct is the best alternative after the acute phase. In cases in which local conditions allow, pancreaticojejunostomy can be performed.

**Citation:** Pavlidis ET, Psarras K, Symeonidis NG, Geropoulos G, Pavlidis TE. Indications for the surgical management of pancreatic trauma: An update. *World J Gastrointest Surg* 2022; 14(6): 538-543
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i6/538.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i6.538

## INTRODUCTION

The location of the pancreas behind the posterior peritoneum contributes to the rarity of pancreatic trauma, which accounts for 0.2%-0.3% of all trauma patients[1,2]. This type of trauma usually occurs in conjunction with other organ injuries, mainly to the duodenum. In cases of blunt abdominal trauma, a reasonable mechanism of injury is crushing between the action force and the vertebral column. Less rare but more severe penetrating traumas (gunshot wounds, stab wounds) are common in North America and South Africa. Morbidity and mortality rates are high in cases of gunshot injuries to the pancreas[3,4].

It should be stressed that pancreatic trauma may frequently be overlooked in injured patients with multiple injuries, resulting in a delay in diagnosing severe traumatic pancreatitis[5].

Of the modern imaging techniques, magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography (ERCP) have superior diagnostic accuracy (90%-100%) compared to ultrasound scanning and computed tomography scanning (less than 60%)[6-8].

Elevated serum amylase levels (required time 4-6 h) and a high C-reactive protein level above 150 mg/dL contribute to the diagnosis of severe pancreatitis.

A recent large multicenter national cohort study from Japan showed that the Organ Injury Scaling of the American Association for Surgery for Trauma (grade III/IV severe), revised trauma scale score on arrival, age, and the coexistence of severe abdominal injury aside from pancreatic injury are prognostic factors of mortality after pancreatic trauma. Among 743 patients, 84.8% had blunt injuries, and 15% had penetrating injuries. The severity of the injuries was classified as follows: grade I: 45.4%; grade II: 8.9%; grade III: 24%; grade IV: 8.3%; and grade V: 13.5%[9].

The aim of this manuscript is to present an updated clinical analysis of the available knowledge on the detection, classification and optimal management of pancreatic trauma. For this minireview, we selected and focused on the most relevant recent articles from PubMed.

## STAGING SYSTEM

Optimal management depends on the exact staging of the injury. The organ injury scale by the American Association for Surgery of Trauma for pancreatic injury severity described in Moore *et al*[10] and Søreide *et al*[1] is shown in Table 1.

The revised trauma scale score to predict mortality on arrival used in Shibahaski *et al*[9] and Jeong *et al*[11] is shown in Table 2.

## CONSERVATIVE MANAGEMENT

Conservative management is adequate for grade I and grade II injuries, which represent the majority of cases, and includes proper conservative management of induced severe traumatic pancreatitis[1]. Close monitoring, no oral feeding to rest the pancreas, intravenous fluids and electrolytes, analgesics, antibiotics, total parenteral nutrition and, in the case of peripancreatic collections, percutaneous drainage are the basic proposed measures. The use of somatostatin in its original form or its chemical analog sandostatin is indicated for cases of persistent pancreatic fistula with an output above 500 mL per day. In the rare case in which the patient develops compartment syndrome and increased intraabdominal pressure, urgent lifesaving laparotomy and wide drainage are mandatory.

**Table 1 Pancreatic injury scale**

| Grade | Type of injury | Description of injury | Abbreviated injury score |
|---|---|---|---|
| I | Hematoma | Minor contusion without duct injury | 2 |
| | Laceration | Superficial laceration without duct injury | 2 |
| II | Hematoma | Major contusion without duct injury or tissue loss | 2 |
| | Laceration | Major laceration without duct injury or tissue loss | 3 |
| III | Laceration | Distal transection or parenchymal injury with duct injury | 3 |
| IV | Laceration | Proximal transection or parenchymal injury involving the ampulla | 4 |
| V | Laceration | Massive disruption of the pancreatic head | 5 |

**Table 2 Modification of the revised trauma score**

| Revised trauma score | | | | New trauma score | | |
|---|---|---|---|---|---|---|
| Glasgow coma scale | Systolic blood pressure (mmHg) | Respiratory rate | Coded value | Glasgow coma scale | Systolic blood pressure (mmHg) | Oxygen saturation (%) |
| 13-15 | > 89 | 10-29 | 4 | 3-15 | 110-149 | ≥ 94 |
| 9-12 | 76-89 | > 29 | 3 | | ≥ 150 | 80-93 |
| 6-8 | 50-75 | 6-9 | 2 | | 90-109 | 60-79 |
| 4-5 | 1-49 | 1-5 | 1 | | 70-89 | 40-59 |
| 3 | 0 | 0 | 0 | | < 70 | < 40 |

## INDICATIONS AND OPTIONS FOR SURGICAL MANAGEMENT

Much debate exists regarding the best strategy for severe grade III to grade V injuries. The management options include ERCP and stent placement into the major pancreatic duct, distal pancreatectomy in cases of complete gland transection, and wide drainage only for damage control surgery, which can prevent mortality but increases the risk of morbidity.

However, pancreatic trauma management should be individualized based on the exact grade of injury. Damage control surgery is the best alternative for severe life-threatening cases. In such cases, the presence of severe acute pancreatitis makes safe resection impossible. Endoscopic stent placement into the ruptured pancreatic duct is the best alternative after the acute phase. In cases in which local conditions allow, pancreaticojejunostomy can be performed[9].

Another study recommended resection surgery rather than drainage for grade IV pancreatic injuries, thus avoiding the need for reoperation[12].

A recent multicenter national survey in Japan showed that serum amylase levels and ERCP can more accurately indicate injury to the main pancreatic duct in hemodynamically stable patients. Poor outcomes were reported in patients with long-standing injuries who were initially managed nonoperatively[13].

Early pancreatic resection is recommended when possible for grade IV pancreatic duct injuries; otherwise, the development of peripancreatic fluid collections requires drainage[14].

In difficult cases, damage control surgery is the best alternative[4,15].

A recent multicenter trial showed that the updated management strategy should include earlier endoscopic evaluation and pancreatic duct stenting. However, a completely transected major pancreatic duct will likely require surgery, which can improve long-term outcomes[16].

Conservative management of pancreatic trauma is often feasible and effective. When surgical management is needed, the options should be resection or a more limited approach. A distal pancreatectomy with splenectomy can be performed safely, but proximal injuries require a stage-specific approach[17].

When possible, primary repair of the pancreatic duct can be attempted[18]. A comparison between blunt and penetrating trauma showed that the latter type of injury is worse[19].

The risk factors determined by regression analysis include other intraabdominal injury, hypovolemia, and penetrating injury[20,21].

The characteristics of pancreatic injuries among trauma patients have been studied in detail[22].

An analysis of immediate, intermediate and long-term outcomes of grade IV injuries showed that resection should be chosen when possible. The majority of patients who undergo drainage procedures

will require additional interventions[12].

In a systematic review and meta-analysis of pancreatic trauma occurring in children, most patients could initially be managed conservatively. In addition, ERCP was found to offer high diagnostic accuracy and to facilitate the repair of ductal injuries[23] in both children and adults[24].

Modern imaging techniques[25] as well as radiological and endoscopic interventions have changed the perception that surgery is mandatory for abdominal solid organ injuries; a more selective surgical strategy is now considered[26,27]. Multidisciplinary collaboration among surgeons, endoscopists, radiologists and intensivists is crucial for managing pancreatic trauma[28]. However, more complex conditions exist in severe hepatopancreatobiliary trauma[29,30].

For isolated grade III pancreatic duct injury, a Roux-en-Y pancreatojejunostomy is feasible[31].

According to the aforementioned, the anatomic location of the pancreas and its close relationship with major vascular structures such as mesenteric vessels, portal vein, and aorta, as well as the duodenum, predisposes for co-existing injuries. Therefore, the severe pancreatic trauma would be combined with major vascular injuries at 28% of the incidence[32]. Penetrating traumas more likely need emergency surgery compared with blunt traumas[33]. It should be emphasized that when pancreatic trauma is accompanied by hemorrhage due to major vascular injury or peritonitis caused by gastrointestinal tract perforation, urgent laparotomy is mandatory, regardless of the grade of pancreatic injury. For the latter, damage control surgery may be sufficient and related with improved outcomes [33], given the recent advancements in imaging modalities that make nonoperative management of pancreatic trauma possible at a later stage[4,5]; otherwise, a more detailed imaging modality is required after the acute phase to identify overlooked pancreatic injury. Thus, modern multidisciplinary management approaches have decreased mortality[34], and the majority of cases can be managed conservatively. ERCP, which determines the anatomical integrity of the main pancreatic duct and the possibility for stent placement, may be used to avoid surgical intervention in most cases[35-37]. Patients with severe traumatic pancreatitis in the subacute phase should be mainly managed nonoperatively[1].

## CONCLUSION

Pancreatic trauma is rare, and its management requires an individualized approach. Conservative management is sufficient for the majority of patients with low-grade injuries. In severe cases with pancreatic duct involvement, much controversy over the optimal patient management strategy still exists. Damage control surgery is the best option for such cases and should be used when indicated. Modern radiologic and endoscopic interventions have allowed select patients to avoid reoperation.

## FOOTNOTES

**Author contributions:** Pavlidis TE designed the research, contributed new analytic tools and analyzed the data; Pavlidis ET performed the research and wrote the paper; Psarras K, Symeonidis NG, Geropoulos G analyzed the data and reviewed the data.

**Conflict-of-interest statement:** There is no conflict of interest associated with any of the senior author or other coauthors contributed their efforts in this manuscript.



**Country/Territory of origin:** Greece

**ORCID number:** Efstathios Theodoros Pavlidis 0000-0002-7282-8101; Kyriakos Psarras 0000-0001-95079978; Nikolaos G Symeonidis 0000-0001-7703-7854; Georgios Geropoulos 0000-0002-2066-7975; Theodoros Efstathios Pavlidis 0000-0002-8141-1412.

**S-Editor:** Gong ZM
**L-Editor:** A
**P-Editor:** Gong ZM

## REFERENCES


1 **Søreide K**, Weiser TG, Parks RW. Clinical update on management of pancreatic trauma. *HPB (Oxford)* 2018; **20**: 1099-1108 [PMID: 30005994 DOI: 10.1016/j.hpb.2018.05.009]
2 **Johnsen NV**, Betzold RD, Guillamondegui OD, Dennis BM, Stassen NA, Bhullar I, Ibrahim JA. Surgical Management of Solid Organ Injuries. *Surg Clin North Am* 2017; **97**: 1077-1105 [PMID: 28958359 DOI: 10.1016/j.suc.2017.06.013]
3 **Chinnery GE**, Krige JE, Kotze UK, Navsaria P, Nicol A. Surgical management and outcome of civilian gunshot injuries to the pancreas. *Br J Surg* 2012; **99** Suppl 1: 140-148 [PMID: 22441869 DOI: 10.1002/bjs.7761]
4 **Roberts DJ**, Bobrovitz N, Zygun DA, Kirkpatrick AW, Ball CG, Faris PD, Stelfox HT; Indications for Trauma Damage Control Surgery International Study Group. Evidence for use of damage control surgery and damage control interventions in civilian trauma patients: a systematic review. *World J Emerg Surg* 2021; **16**: 10 [PMID: 33706763 DOI: 10.1186/s13017-021-00352-5]
5 **Torba M**, Gjata A, Rulli F, Kajo I, Ceka S, Asqeri T. Delayed diagnosis and treatment of high grade blunt pancreatic trauma. Case report and review of literature. *Ann Ital Chir* 2017; **88**: 539-545 [PMID: 29339584]
6 **Vasquez M**, Cardarelli C, Glaser J, Murthi S, Stein D, Scalea T. The ABC's of Pancreatic Trauma: Airway, Breathing, and Computerized Tomography Scan? *Mil Med* 2017; **182**: 66-71 [PMID: 28291454 DOI: 10.7205/MILMED-D-16-00084]
7 **Sharbidre KG**, Galgano SJ, Morgan DE. Traumatic pancreatitis. *Abdom Radiol (NY)* 2020; **45**: 1265-1276 [PMID: 31576413 DOI: 10.1007/s00261-019-02241-7]
8 **Ayoob AR**, Lee JT, Herr K, LeBedis CA, Jain A, Soto JA, Lim J, Joshi G, Graves J, Hoff C, Hanna TN. Pancreatic Trauma: Imaging Review and Management Update. *Radiographics* 2021; **41**: 58-74 [PMID: 33245670 DOI: 10.1148/rg.2021200077]
9 **Shibahashi K**, Sugiyama K, Kuwahara Y, Ishida T, Okura Y, Hamabe Y. Epidemiological state, predictive model for mortality, and optimal management strategy for pancreatic injury: A multicentre nationwide cohort study. *Injury* 2020; **51**: 59-65 [PMID: 31431334 DOI: 10.1016/j.injury.2019.08.009]
10 **Moore EE**, Cogbill TH, Malangoni MA, Jurkovich GJ, Champion HR, Gennarelli TA, McAninch JW, Pachter HL, Shackford SR, Trafton PG. Organ injury scaling, II: Pancreas, duodenum, small bowel, colon, and rectum. *J Trauma* 1990; **30**: 1427-1429 [PMID: 2231822 DOI: 10.1097/00005373-199011000-00035]
11 **Jeong JH**, Park YJ, Kim DH, Kim TY, Kang C, Lee SH, Lee SB, Kim SC, Lim D. The new trauma score (NTS): a modification of the revised trauma score for better trauma mortality prediction. *BMC Surg* 2017; **17**: 77 [PMID: 28673278 DOI: 10.1186/s12893-017-0272-4]
12 **Ball CG**, Biffl WL, Vogt K, Hameed SM, Parry NG, Kirkpatrick AW, Kaminsky M. Does drainage or resection predict subsequent interventions and long-term quality of life in patients with Grade IV pancreatic injuries: A population-based analysis. *J Trauma Acute Care Surg* 2021; **91**: 708-715 [PMID: 34559164 DOI: 10.1097/TA.0000000000003313]
13 **Ando Y**, Okano K, Yasumatsu H, Okada T, Mizunuma K, Takada M, Kobayashi S, Suzuki K, Kitamura N, Oshima M, Suto H, Nobuyuki M, Suzuki Y. Current status and management of pancreatic trauma with main pancreatic duct injury: A multicenter nationwide survey in Japan. *J Hepatobiliary Pancreat Sci* 2021; **28**: 183-191 [PMID: 33280257 DOI: 10.1002/jhbp.877]
14 **Lin BC**, Hwang TL. Resection versus drainage in the management of patients with AAST-OIS grade IV blunt pancreatic injury: A single trauma centre experience. *Injury* 2022; **53**: 129-136 [PMID: 34364681 DOI: 10.1016/j.injury.2021.07.033]
15 **Ordoñez CA**, Parra MW, Millán M, Caicedo Y, Padilla N, Guzmán-Rodríguez M, Miñan-Arana F, García A, González-Hadad A, Pino LF, Rodríguez-Holguin F, Serna JJ, Salcedo A, Ferrada R, Ivatury R. Pancreatic damage control: the pancreas is simple don't complicate it. *Colomb Med (Cali)* 2020; **51**: e4164361 [PMID: 33795904 DOI: 10.25100/cm.v51i4.4361]
16 **Biffl WL**, Zhao FZ, Morse B, McNutt M, Lees J, Byerly S, Weaver J, Callcut R, Ball CG, Nahmias J, West M, Jurkovich GJ, Todd SR, Bala M, Spalding C, Kornblith L, Castelo M, Schaffer KB, Moore EE; WTA Multicenter Trials Group on Pancreatic Injuries. A multicenter trial of current trends in the diagnosis and management of high-grade pancreatic injuries. *J Trauma Acute Care Surg* 2021; **90**: 776-786 [PMID: 33797499 DOI: 10.1097/TA.0000000000003080]
17 **Aldridge O**, Leang YJ, Soon DSC, Smith M, Fitzgerald M, Pilgrim C. Surgical management of pancreatic trauma in Australia. *ANZ J Surg* 2021; **91**: 89-94 [PMID: 33369826 DOI: 10.1111/ans.16498]
18 **Venianaki M**, Ierodiakonou D, Chryssou E, Chrysos E, Chalkiadakis G, Lasithiotakis K. Primary Repair of Traumatic Complete Pancreatic Rupture. *Am Surg* 2021; 31348211038566 [PMID: 34402676 DOI: 10.1177/00031348211038566]
19 **Buitendag JJP**, Kong VY, Laing GL, Bruce JL, Manchev V, Clarke DL. A comparison of blunt and penetrating pancreatic trauma. *S Afr J Surg* 2020; **58**: 218 [PMID: 34096212]
20 **Biffl WL**, Ball CG, Moore EE, Lees J, Todd SR, Wydo S, Privette A, Weaver JL, Koenig SM, Meagher A, Dultz L, Udekwu PO, Harrell K, Chen AK, Callcut R, Kornblith L, Jurkovich GJ, Castelo M, Schaffer KB; WTA Multicenter Trials Group on Pancreatic Injuries. Don't mess with the pancreas! *J Trauma Acute Care Surg* 2021; **91**: 820-828 [PMID: 34039927 DOI: 10.1097/TA.0000000000003293]
21 **Joos E**, de Jong N, Ball CG, Quigley S, Trottier V, Massé M, Engels PT, Rao J, Gillman LM, Visser R, Widder S, Hameed MS, Vogt KN; Canadian Collaborative on Urgent Care Surgery (CANUCS). Time to operating room matters in modern management of pancreatic injuries: A national review on the management of adult pancreatic injury at Canadian level 1 trauma centers. *J Trauma Acute Care Surg* 2021; **90**: 434-440 [PMID: 33617195 DOI: 10.1097/TA.0000000000003025]
22 **Wiik-Larsen J**, Thorsen K, Sandve KO, Søreide K. Incidence and characteristics of pancreatic injuries among trauma patients admitted to a Norwegian trauma centre: a population-based cohort study. *Scand J Gastroenterol* 2020; **55**: 1347-1353 [PMID: 33027601 DOI: 10.1080/00365521.2020.1829032]
23 **Kopljar M**, Ivandić S, Mesić M, Bakota B, Žiger T, Kondža G, Pavić R, Milan M, Čoklo M. Operative versus non-operative management of blunt pancreatic trauma in children: Systematic review and meta-analysis. *Injury* 2021; **52** Suppl 5: S49-S57 [PMID: 32089286 DOI: 10.1016/j.injury.2020.02.035]
24 **Sealock RJ**, Othman M, Das K. Endoscopic Diagnosis and Management of Gastrointestinal Trauma. *Clin Gastroenterol Hepatol* 2021; **19**: 14-23 [PMID: 31605872 DOI: 10.1016/j.cgh.2019.09.048]

25 **Odedra D**, Mellnick VM, Patlas MN. Imaging of Blunt Pancreatic Trauma: A Systematic Review. *Can Assoc Radiol J* 2020; **71**: 344-351 [PMID: 32063010 DOI: 10.1177/0846537119888383]

26 **Leppäniemi A**. Nonoperative management of solid abdominal organ injuries: From past to present. *Scand J Surg* 2019; **108**: 95-100 [PMID: 30832550 DOI: 10.1177/1457496919833220]

27 **Al-Thani H**, Ramzee AF, Al-Hassani A, Strandvik G, El-Menyar A. Traumatic Pancreatic Injury Presentation, Management, and Outcome: An Observational Retrospective Study From a Level 1 Trauma Center. *Front Surg* 2021; **8**: 771121 [PMID: 35155546 DOI: 10.3389/fsurg.2021.771121]

28 **Krige J**, Jonas E. Pancreatic trauma with main pancreatic duct injury. *J Hepatobiliary Pancreat Sci* 2021; **28**: e42-e43 [PMID: 34009750 DOI: 10.1002/jhbp.973]

29 **Streith L**, Silverberg J, Kirkpatrick AW, Hameed SM, Bathe OF, Ball CG. Optimal treatments for hepato-pancreato-biliary trauma in severely injured patients: a narrative scoping review. *Can J Surg* 2020; **63**: E431-E434 [PMID: 33009897 DOI: 10.1503/cjs.013919]

30 **Walker AE**. The Adult Pancreas in Trauma and Disease. *Acad Forensic Pathol* 2018; **8**: 192-218 [PMID: 31240039 DOI: 10.1177/1925362118781612]

31 **Naiem MEA**, Arabi NA. Isolated pancreatic injury in an adolescent treated with Roux-en-Y pancreatojejunostomy: a case report and review of the literature. *J Med Case Rep* 2021; **15**: 474 [PMID: 34526117 DOI: 10.1186/s13256-021-03042-7]

32 **Biffl WL**. Duodenum and pancreas. In Moore EE, Feliciano DV, Mattox KL. Trauma. 8th ed. New York: Mc-Graw-Hill, 2017: 621-638

33 **Kuza CM**, Hirji SA, Englum BR, Ganapathi AM, Speicher PJ, Scarborough JE. Pancreatic Injuries in Abdominal Trauma in US Adults: Analysis of the National Trauma Data Bank on Management, Outcomes, and Predictors of Mortality. *Scand J Surg* 2020; **109**: 193-204 [PMID: 31142209 DOI: 10.1177/1457496919851608]

34 **Velmahos GC**, Tabbara M, Gross R, Willette P, Hirsch E, Burke P, Emhoff T, Gupta R, Winchell RJ, Patterson LA, Manon-Matos Y, Alam HB, Rosenblatt M, Hurst J, Brotman S, Crookes B, Sartorelli K, Chang Y. Blunt pancreatoduodenal injury: a multicenter study of the Research Consortium of New England Centers for Trauma (ReCONECT). *Arch Surg* 2009; **144**: 413-9; discussion 419 [PMID: 19451482 DOI: 10.1001/archsurg.2009.52]

35 **Lin BC**, Liu NJ, Fang JF, Kao YC. Long-term results of endoscopic stent in the management of blunt major pancreatic duct injury. *Surg Endosc* 2006; **20**: 1551-1555 [PMID: 16897285 DOI: 10.1007/s00464-005-0807-0]

36 **Kim S**, Kim JW, Jung PY, Kwon HY, Shim H, Jang JY, Bae KS. Diagnostic and therapeutic role of endoscopic retrograde pancreatography in the management of traumatic pancreatic duct injury patients: Single center experience for 34 years. *Int J Surg* 2017; **42**: 152-157 [PMID: 28343030 DOI: 10.1016/j.ijsu.2017.03.054]

37 **Ito K**, Endo A, Kobayashi M, Otomo Y. Severe pancreatic injury with total disruption of main pancreatic duct successfully managed by multi-stage endoscopic therapy: a case report. *Acute Med Surg* 2022; **9**: e735 [PMID: 35169488 DOI: 10.1002/ams2.735]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 June 27; 14(6): 544-555

DOI: 10.4240/wjgs.v14.i6.544

ISSN 1948-9366 (online)

*MINIREVIEWS*

# Clinical application and research progress of extracellular slow wave recording in the gastrointestinal tract

Fan Ding, Run Guo, Zheng-Yu Cui, Hai Hu, Gang Zhao

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Jabbarpour Z, Iran; Perse M, Slovenia

**Received:** January 6, 2022
**Peer-review started:** January 6, 2022
**First decision:** March 12, 2022
**Revised:** March 21, 2022
**Accepted:** May 16, 2022
**Article in press:** May 16, 2022
**Published online:** June 27, 2022

**Fan Ding, Hai Hu, Gang Zhao,** Center of Gallbladder Disease, East Hospital of Tongji University, Shanghai 200120, China

**Fan Ding, Hai Hu, Gang Zhao,** Institute of Gallstone Disease, Tongji University School of Medicine, Shanghai 200331, China

**Run Guo,** Department of Ultrasonography, East Hospital of Tongji University, Shanghai 200120, China

**Zheng-Yu Cui,** Department of Internal Medicine of Traditional Chinese Medicine, East Hospital of Tongji University, Shanghai 200120, China

**Corresponding author:** Gang Zhao, PhD, Director, Center of Gallbladder Disease, East Hospital of Tongji University, No. 150 Jimo Road, Shanghai 200120, China. zhao_gang7@126.com

## Abstract

The physiological function of the gastrointestinal (GI) tract is based on the slow wave generated and transmitted by the interstitial cells of Cajal. Extracellular myoelectric recording techniques are often used to record the characteristics and propagation of slow wave and analyze the models of slow wave transmission under physiological and pathological conditions to further explore the mechanism of GI dysfunction. This article reviews the application and research progress of electromyography, bioelectromagnetic technology, and high-resolution mapping in animal and clinical experiments, summarizes the clinical application of GI electrical stimulation therapy, and reviews the electrophysiological research in the biliary system.

**Key Words:** Gastrointestinal tract; Slow wave; Electromyography; High-resolution mapping; Bioelectromagnetic technology

**Core Tip:** The motility pattern of the gastrointestinal (GI) tract is fundamental in studying functional GI disorders. Extracellular recording has been used to characterize the generation and propagation of slow waves and abnormalities that may lead to GI motility disorders. This review focuses on the application and progress of extracellular recording techniques in the physiological and pathological state of the alimentary system.

**Citation:** Ding F, Guo R, Cui ZY, Hu H, Zhao G. Clinical application and research progress of extracellular slow wave recording in the gastrointestinal tract. *World J Gastrointest Surg* 2022; 14(6): 544-555
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i6/544.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i6.544

## INTRODUCTION

The gastrointestinal (GI) tract is a complex organ that efficiently processes nutrients and waste. These tasks are facilitated by the phasic contractions resulting from a cyclical depolarization-repolarization cycle, known as electrical slow waves. The slow wave potential of the GI tract is generated by interstitial cells of Cajal (ICCs) distributed in the submucosa and smooth muscle layer of the GI wall and spreads to smooth muscle cells (SMCs), causing excitation-contraction coupling[1]. SMCs and ICCs are also electrically coupled with platelet-derived growth factor receptor alpha-positive (PDGFRα$^+$) cells, forming an integrated unit called the SMC-ICC-PDGFRα$^+$ cells (SIP) syncytium[2,3]. SIP cells provide pacemaker activity, propagation pathways for slow waves, transduction of inputs from motor neurons, and mechanosensitivity[4,5].

Alvarez *et al*[6] and Berkson *et al*[7] first recorded the extracellular slow wave potential of the stomach and small intestine, and proved the consistency between the frequency of slow wave and the rhythm of GI contraction. Over the past century, extracellular electrical recording technology has become one of the most critical methods to characterize the generation and propagation of slow wave and GI motility disorders[8]. The milestone research of GI extracellular slow wave recording is provided in Table 1. The limitation of electromyography (EMG) is the lack of temporal-spatial features of slow wave propagation, which has been proved to be an essential indicator of GI dysfunction[9]. In recent years, research on high-resolution (HR) mapping of GI mucosal slow wave using array matrix electrodes *in vivo* and a bioelectromagnetic technique for recording the magnetic field produced by GI electrical activity, has provided more accurate and reliable support for research on the role of GI dysrhythmia in digestive diseases.

This review explores the application and progress of extracellular recording techniques in the physiological and pathological states of the alimentary system.

## GI ELECTROPHYSIOLOGY

In the GI tract, SMCs form gap junctions with two types of interstitial cells, ICCs and PDGFRα$^+$ cells, creating a highly integrated electrical SIP syncytium. Electrical coupling makes it very difficult to deduce the specific functions of one component in intact tissues, so the functions of SIP cells have benefitted from studies of particular cell types[10]. ICCs are organized into networks in the pacemaker regions of the GI tract[11]. Spontaneous electrical activity is generated by ICCs, which are electrically coupled to the SMCs[12,13]. Once a slow wave is generated, it regenerates and propagates actively through the ICC network. Depolarization of SMCs by slow wave enhances the open probability of L-type voltage-dependent calcium ($Ca^{2+}$) channels, resulting in the generation of $Ca^{2+}$ action potentials, which are superimposed upon the peaks of slow waves. Slow waves are actively propagated in GI muscle tissues, enabling the recruitment of thousands of SMCs to contract together or in sequence to generate segmental and peristaltic contractions. In normal condition, the PDGFRα$^+$ cells network runs parallel or even intercalates with that formed by the ICC network. PDGFRα$^+$ cells express small conductance calcium-activated potassium channel 3 (SK3) channels and P2Y1 receptors[14,15]. These proteins are essential for the purinergic inhibitory regulation of GI motility[5,16,17]. GI motility patterns are highly integrated behaviors requiring coordination between SMCs and utilizing regulatory inputs from interstitial cells (ICCs and PDGFRα$^+$ cells), neurons, and endocrine and immune cells[11,18].

Disorders of gastroduodenal function without an apparent organic cause, defined by the Rome IV criteria, are common, including functional dyspepsia, chronic nausea and vomiting, belching, and rumination disorders[19]. The resultant inefficiencies contribute to vast health and economic burden, considering societal prevalence rates of > 10% for functional dyspepsia and > 2% for chronic nausea and vomiting[20-22]. Diagnosing GI functional disorders remains challenging. Slow waves are omnipresent in GI organs, and motor activity is controlled, in part, by modulation of the frequency, amplitude, and

**Table 1 Milestone research of extracellular gastrointestinal slow wave recording**

| Ref. | Year | Research type | Methods | Part of GI | Major advances |
|---|---|---|---|---|---|
| Alvarez *et al*[6] | 1922 | Rabbits | Monopolar electrode | Small intestine | First record the SW |
| Alvarez[32] | 1922 | Human | EGG | Abdominal wall | First electrogastrogram recording |
| Code and Marlett [89] | 1974 | Dogs | Multi-electrode | Stomach | First report gastric arrhythmia |
| Code *et al*[29] | 1975 | Dogs | Multi-electrode | Stomach and small intestine | Define the MMC |
| Hinder and Kell [54] | 1977 | Human | Multi-electrode | Stomach | First locate the gastric pacemaker |
| Di Luzio *et al*[90] | 1989 | Human | MGG | Stomach and small intestine | Noninvasively investigate the activity of the GI system |
| Miranda *et al*[91] | 1992 | Human | ACB | Stomach | Study stomach emptying model |
| Bradshaw *et al* [92] | 2003 | Rabbits | MGG | Stomach | Investigate gastric electrical activity under normal and vagotomized condition |
| Corá *et al*[76] | 2005 | Human | ACB | Stomach | Obtain a comprehensive knowledge of the behavior of pharmaceutical forms in the GI tract |
| Lammers *et al*[93] | 2008 | Dogs | HR mapping | Stomach | First observe the spatial origin and propagation patterns of SW arrhythmias |
| Bradshaw *et al* [68] | 2009 | Human | MGG | Stomach | Obtain spatiotemporal parameters of the gastric SW |
| Du *et al*[62] | 2009 | Pigs | HR mapping | Stomach | Design a new sterilized PCB electrode |
| O'Grady *et al*[66] | 2009 | Pigs and human | HR mapping | Stomach | Design a novel laparoscopic device for HR mapping |
| O'Grady *et al*[55] | 2010 | Human | HR mapping | Stomach | The most comprehensive study of the gastric conduction system |
| Farajidavar *et al* [52] | 2012 | Dogs | Multi-wireless modules | Stomach | Design a bidirectional wireless system for SW recording |
| Calabresi *et al*[72] | 2015 | Rats | ACB | Stomach | Assess gastric motility |
| Gharibans *et al* [94] | 2017 | Electrophysiology model | HR-EGG | Stomach | Address the spatial limitations of the EGG |
| Gharibans *et al* [95] | 2019 | Human | HR-EGG | Stomach | Achieve comprehensive spatial analytics of gastric far-field gastric potentials |

ACB: Alternate current biosusceptometry; EGG: Electrogastrogram; GI: Gastrointestinal tract; HR: High-resolution; MGG: Magnetogastrogram; MMC: Migrating motor complex; PCB: Printed circuit board; SW: Slow wave.

duration of slow waves[23,24]. ICC loss and injury are now a significant research focus, as it is recognized as a hallmark of several functional GI motility disorders[25]. Hence, coupling between slow waves and contractions is vital in understanding GI motility and developing concepts about what might lead to motility disorders. It requires techniques to record and model the patterns of slow wave generation and propagation.

## EMG

Since 1922, when Alvarez *et al*[6] first recorded the slow wave of an experimental animal using bioelectric recording devices, EMG has gradually developed into a technique for recording bioelectric signals produced by nerve-muscle activity, using electrical stimulation to detect nerve and muscle excitation conduction function, and has assisted in the diagnosis and treatment of diseases[26]. In the field of GI electrophysiology, the most commonly used electrodes are monopole electrodes and surface electrodes.

### *Monopolar electrode*

The monopole electrode records the action potential (AP) of the muscle fiber adjacent to the electrode so that the signal of AP amplitude is reliable and prominent[27]. Szurszewski *et al*[28] investigated the

myoelectric activity of the small intestine in conscious healthy dogs by implanting a monopolar electrode in the muscular layer of the small intestine and found that the periodic AP activity spreads slowly from the duodenum to the end of the ileum. This regular electrical activity only occurs during fasting. In follow-up research, Code *et al*[29] divided the periodic GI myoelectric activity, namely, the migrating motor complex (MMC), into four typical stages (I-IV). Phase I is the quiescent phase with no contractions, phase II is characterized by random contractions, phase III has a sudden onset and ends with a burst of contractions with maximal amplitude and duration, and phase IV is characterized by the rapid decrease of contractions. The human GI tract also has regular MMCs, and is regulated by circadian rhythms, hormones, nerves, and other factors[24].

As monopolar electrode implantation is an invasive operation, the main complications are pain, bleeding, infection, and perforation[27,30,31]. Moreover, the reference electrode is routinely placed on the surface of the skin near the tested tissue or organ, so the recorded myoelectric signal has many interferences and poor baseline stability. Therefore, the monopolar electrode is rarely used in the clinical diagnosis and treatment of diseases of the digestive system.

### Electrogastrography

Electrogastrography (EGG) is a non-invasive technique for recording GI myoelectric activity using a surface electrode placed on the abdominal wall[32]. Many early studies have shown a good correlation between EGG and EMG, which was recorded with a monopolar electrode[33,34]. Familonie *et al*[35] recorded the surface EGG and intragastric EMG of postoperative patients and healthy subjects, respectively. They found that EGG could not only detect normal slow wave and electrical rhythm but also successfully detected abnormal EGGs in patients with clinical GI symptoms.

EGG is currently regarded as an auxiliary diagnostic examination in the clinic, which is used to evaluate nausea, vomiting, and other GI rhythm disorders, eventually exploring the mechanism of functional GI disease[36,37]. Chen *et al*[38] found that approximately 75% of gastroparesis patients had preprandial or postprandial abnormal signal patterns following EGG examination of healthy subjects and gastroparesis patients. About 60% of patients with functional dyspepsia have an abnormal EGG, including delayed gastric emptying and slow wave reduction[39]. A prospective study that compared the EGG of mechanical, vascular, and paralytic intestinal obstruction, combined with inflammatory indices, indicated that EGG has a high sensitivity in evaluating vascular and paralytic intestinal obstruction, even though its specificity is low. However, the significant correlation between EGG and plasma levels of interleukin-6 and procalcitonin supports the role of inflammation in the pathogenesis of impaired gastric electrical activity in patients with intestinal obstruction[40].

EGG also shows potential in clinical pharmacological research, digestive system development, GI function evaluation, and treatment safety evaluation. A case-control study that studied the EGG changes in patients with esophageal variceal bleeding during treatment with octreotide found that octreotide could inhibit gastric electrical activity and was positively correlated with its hemostatic effect. Therefore, EGG can be used as a predictive index to evaluate the efficacy of octreotide in treating esophageal variceal bleeding[41]. Ortigoza *et al*[42] simultaneously used EGG, abdominal near-infrared spectroscopy, and intestinal tinnitus acoustics to monitor the development of the GI tract in premature infants, evaluate the safety of enteral feeding, and reduce the morbidity and mortality of premature infants.

Because the relative position of the electrode affixed to the body surface is easy to deviate from the stomach, it is difficult for the recording system to obtain stable and repeatable data. The main parameter of EGG analysis is the frequency of slow wave, which cannot fully reflect the function of the GI tract. Therefore, the value of EGG in clinical diagnosis is limited[43].

### GI electrical stimulation

The GI myoelectric abnormalities observed in the models of gastroparesis, intractable nausea and vomiting, and intestinal obstruction provide a theoretical basis for the development of GI electrical stimulation (GIES) therapy[38,44]. According to the location of electrical stimulation, GIES can be divided into inhibitory electrical stimulation and excitatory electrical stimulation[45]. Inhibitory electrical stimulation can inhibit the contractile movement of the normal GI tract by placing the electrode near the tail end of the GI tract to send stimulation signals, forcing GI myoelectric activity and movement to reverse propagation[46,47]. Excitatory electrical stimulation, also known as "electrical pacing," promotes GI peristalsis by implanting electrodes into the area near the physiological pacemaker to send electrical stimulation signals[48,49].

Recently, many clinical studies have shown that GIES can improve the physiological function of the GI tract and relieve clinical symptoms by setting different parameters and electrical stimulation sites (Table 2). However, as a treatment modality, GIES is still in the exploratory stage. A meta-analysis based on case-control studies found that GIES had a significant "placebo effect" in the treatment of gastroparesis. Therefore, GIES therapy requires further clinical studies to prove its safety and efficacy and related animal models to explore the pathogenic mechanism[50]. Although GIES is still controversial, it has great potential to improve and treat GI motility disorders[51,52].

**Table 2 Clinical research on gastrointestinal electrical stimulation**

| Ref. | Methods | Sample size | Indications | Location of GIES | Stimulation parameters | Duration | Results |
|---|---|---|---|---|---|---|---|
| Gastric electrical stimulation | | | | | | | |
| McCallum *et al*[96] | Multicenter, double-blind, RCT | 32 | Idiopathic gastroparesis | Stomach | 14 Hz, 5 mA, 330 μs | 3 mo | Significant decrease in vomiting and days of hospitalization |
| Teich *et al* [97] | Prospective study | 16 (children) | Chronic nausea andvomiting | Stomach | 14 Hz, 5 V, 330 μs | 0.5-23 mo | Significant improvement in severity and frequency of vomiting, frequency, and severity of nausea |
| Morales-Conde *et al* [98] | Randomized, multicenter trial | 47 | Obesity | Stomach | / | 24 mo | Limited weight regain with strong safety outcomes |
| Ducrotte *et al*[99] | RCT | 172 | Refractory vomiting | Stomach | 14 Hz, 5 mA, 330 μs | 8 mo | Effectively reduced the frequency of refractory vomiting in patients with and without diabetes, although it did not accelerate gastric emptying or increase the quality of life |
| Intestinal electrical stimulation | | | | | | | |
| Norton *et al* [100] | RCT | 90 | Fecal incontinence | Anus | 35 Hz, 300 ms | 8 wk | Improved bowel control to a modest extent |
| Daram *et al* [101] | Case report | 1 | Roux stasis syndrome | Jejunum | 14 Hz, 5 mA, 330 μs | 5 d | Effective relief of the symptom of stasis post-Roux-en-Y anastomosis |
| Cadeddu *et al*[102] | Randomized trial | 81 | Idiopathic constipation | Anus | 2 Hz, 30-35V, 360-960 μs | 6 times | Continuous improvement of constipation symptoms and anorectal function |
| Nerve electrical stimulation | | | | | | | |
| Fassov *et al* [103] | RCT | 20 | IBS | Sacral nerve | 14 Hz, 0.1-4.0 V, 210 μs | 3 wk | Reduced symptoms of diarrhea-predominant and mixed IBS |
| Stakenborg *et al*[104] | Pilot study | 18 | Post-colectomy surgery | Abdominal vagus nerve | 5, 20 Hz, 2.5 mA, 0.5, 1, 2 ms | 2 times (preparation, postoperation) | Inhibition of IL-6 and IL-8 induced by lipopolysaccharide to prevent postoperative intestinal obstruction |
| Zhang *et al* [105] | Pilot study | 42 | Major abdominal surgeries | Acupoints ST36 and PC6 | 25 Hz, 2-10 mA, 0.5 ms | 3 d | Improved major postoperative symptoms |
| Teckentrup *et al*[106] | RCT | 22 | Healthy subjects | Vagus nerve | 25 Hz, 0.3-0.9 mA | 2 d | Reduced the frequency of gastric myoelectricity and did not affect resting energy consumption |

GIES: Gastrointestinal electrical stimulation; IBS: Irritable bowel syndrome; IL: Interleukin; RCT: Randomized controlled trial.

## HR MAPPING

In clinical practice, the myoelectric signal obtained directly from the surface of the GI tract is still the most reliable method for analyzing GI myoelectricity. However, both EMG and EGG are highly dependent on equipment hardware, filtering technology, and the size and material of recording electrodes. They could only obtain low-resolution GI myoelectric recordings, which have limited value for analyzing slow wave propagation mode and speed of the GI tract. By placing multiple arrays of electrodes on the serous surface of the GI tract to record GI myoelectric signals, HR mapping can accurately analyze GI myoelectric signals and electrical rhythm disorders under pathological conditions [53].

### *Gastric pacing region*

Alvarez *et al*[6] first studied the pacing region of the human stomach and proposed the hypothesis that the "pacing region" may be located in the lesser curvature of the gastric cardia. Hinder *et al*[54] roughly located the "gastric pacing region" in the greater curvature of the middle gastric corpus by implanting multiple pairs of monopolar electrodes. Through HR mapping research of the stomach in patients with normal gastric function, O'Grady *et al*[55] found that the slow wave of the stomach originated from a "special region" in the middle and upper part of the great curvature of the stomach, which was consistent with the results of Hinder's work. They also found significant regional spread of slow waves from the pacing area to the distal gastric antrum. However, the pacing region lacked specialized

anatomical tissue or cellular structures and was labile in that if it was to be removed, a neighboring region would become the apparent site of initiation[56].

### Gastric conduction system

HR mapping studies in humans and large animal healthy stomach models have shown that slow waves arise from the defined pacemaker region and are quickly propagated in a circular waveform from the pacing area to the antrum[55,57-59]. In the human stomach, the annular slow waves are propagated longitudinally at a velocity of 3 $mm \cdot s^{-1}$ until the distal antrum is continuously moving at a higher velocity (almost > 7 $mm \cdot s^{-1}$) at the greater *vs* lesser curvature and eventually terminate in the pylorus [55]. Interestingly, slow waves do not normally excite the gastric fundus[60].

HR mapping technology has apparent advantages in diagnosing and treating GI motility disorders. In an HR mapping study, O'Grady *et al*[61] found that approximately 50% of experimental pigs with abnormal gastric function had abnormal rhythms, including incomplete and complete conduction block, escape rhythm competing, ectopic pacemakers, and functional re-entry. Subsequently, Du *et al*[62] designed and optimized a flexible printed circuit board that can be sterilized repeatedly, which can be used for HR mapping of the slow wave of the GI tract in an experimental animal model and shows excellent spatiotemporal accuracy, thus providing a low cost and stable alternative for clinical GI myoelectric detection. A recent clinical study comparing EGG and HR mapping showed that gastric slow waves exhibit pacing and conduction abnormalities in patients with gastroparesis, but their frequency is not significantly abnormal, resulting in the missed detection of abnormal gastric myoelectricity on the EGG, indicating that earlier studies likely underestimated both the prevalence and complexity of gastric dysrhythmia[63]. Berry *et al*[64] found that ectopic pacing of the remnant stomach after laparoscopic sleeve gastrectomy is one of the possible mechanisms leading to postoperative chronic gastric dyskinesia. Mapping studies also revealed how anisotropic propagation, re-entry, and conduction block contribute to motility disruption during dysrhythmia[61,63,65]. These works have enabled several novel clinically relevant insights into the features and mechanisms of gastric arrhythmias.

However, due to the limitations of invasive examination, HR mapping is rarely applied in the clinic. A clinical study attempted to detect and analyze the rhythm and propagation pattern of gastric slow wave reliably through trocars in the limited area of the gastric mucosa (limited by the number of trocars, usually less than four) during laparoscopic surgery[66]. Implanting temporary electrodes in the GI mucosa through the endoscope may be the direction of its future development.

## BIOELECTROMAGNETIC TECHNOLOGY

Compared with EMG and HR mapping technology, bioelectromagnetic technology has the advantages of non-invasiveness, non-ionizing radiation, and low risk, which provides a new direction for the research of GI tract dynamics. Until now, the bioelectromagnetic techniques used in GI research are mainly based on the alternate current biosusceptometry (ACB) of tracking the movement of magnetic tracers in the GI tract after ingestion and magnetogastrography (MGG) to detect the magnetic field produced by the electrical activity of GI smooth muscle[67,68].

### ACB

ACB is a bioelectromagnetic technique that records the changes in the magnetic flux of magnetic tracers ingested *in vivo* with the movement of the GI tract by placing induction coils and reference coils *in vitro*. This technique has the advantages of simplicity, easy operation, and low cost in investigating gastric emptying time and dynamic activity of the GI tract in humans or experimental animals[69]. An animal experiment studying the effect of triple immunosuppressive therapy on GI function found that both ACB and EGG can accurately monitor the contraction frequency and amplitude of the GI tract. Américo *et al*[70] implanted magnetic markers and monopole electrodes under the serosa of the distal stomach and proximal ascending colon in beagle dogs. Compared with EMG, these works proved that ACB could safely and effectively record the contractile activity of GI smooth muscle *in vitro*. The ACB image could visualize intrasegmental tracer distribution and the automated scan of the GI motility segments [71-73]. In two animal experiments, analysis of the relationship between ACB and the strain-gauge signal amplitude showed that ACB may serve as an accurate and sensitive technique for GI motility research[74,75].

In the field of pharmacological research, Corá *et al*[76] obtained a magnetic image of the disintegration of drug tablets in the human stomach using ACB, which shows that the ACB has sufficient sensitivity and spatial resolution in evaluating drug dosage forms *in vivo*. It provides a new research method for comprehensively understanding the metabolic model of drug dosage forms in the human GI tract and developing a new drug delivery system to improve and control the bioavailability and effectiveness of drugs. Another study developed a biomagnetic cellulose gel composed of polymeric nanocapsules containing ferrite nanoparticles, which can be substantially retained in the stomach walls, and consequently has the potential to be used as a traceable drug delivery system for gastric diseases

[77].

However, the measurement of ACB is easily affected by the magnetic tracer, the shape and position of the coils, and the spatial position of the tracer relative to the coils. Bruno *et al*[78] combined ultrasound and ACB to overcome its overdependence on the position and distribution of magnetic tracers in magnetic inductors. Above all, ACB has apparent advantages in recording gastric emptying, which reflects the unique superiority of ACB in GI function evaluation[79].

### MGG

MGG is a bioelectromagnetic technique based on a superconducting quantum interferometer to detect the extracellular magnetic field produced by the slow wave of the GI tract, which is highly related to EGG[69]. Several studies have shown that MGG is less affected by the difference in electrical conductivity of the tissue, so it is easier to reflect the physiological characteristics of slow waves in the GI tract[68,69,80]. Based on a study of the effect of erythromycin on gastric motility, Somarajan *et al*[81] compared the differences among MGG, EGG, and EMG, proving that MGG could objectively indicate gastric dysrhythmia and quantify the therapeutic effect in patients with functional gastropathy. In addition, MGG can reliably detect spatial parameters such as propagation velocity and mode of GI slow wave. Recently, Bradshaw *et al*[82] measured EGG and MGG in seven healthy subjects and seven patients with diabetic gastroparesis. The parameters such as dominant frequency, percentage of power distribution, and propagation characteristics were compared. They found that MGG could detect the pathological slow wave of gastroparesis. Above all, MGG shows unique advantages in detecting transmission speed and propagation mode, which provides a new method for studying the pathological myoelectric characteristics of digestive diseases.

## ELECTROPHYSIOLOGICAL RESEARCH ON THE GALLBLADDER AND BILIARY TRACT

Early studies on MMC have shown that rhythmic myoelectric activity also exists in the biliary system, which is regulated by many factors such as cholecystokinin, cholinergic receptor agonists, and intestinal peristalsis[83]. Romański *et al*[84] found that the minute rhythm occurs regularly in the entire ovine small intestine and gallbladder, which is controlled by nicotinic receptors and muscarinic receptor subtypes. In benign gallbladder diseases, research on biliary dysfunction, especially smooth muscle in the biliary tract and the sphincter of Oddi, is from animal experiments. Abell *et al*[85] designed an annular electrode to detect Oddi sphincter EMG without damaging the Oddi sphincter wall, which has the advantages of less trauma, convenient placement, accurate location, and high repeatability. In the guinea pig lithogenic model, EMG was used to detect the myoelectric difference in the Oddi sphincter at different stages under a high cholesterol diet, indicating that Oddi sphincter dysfunction caused by a high cholesterol diet may be one of the pathogenic mechanisms of cholesterol gallstones[86]. Liu *et al*[87] also found Oddi sphincter dysfunction in rabbits with chronic cholangitis and proved that the intracellular calcium mobilization pathway was involved in the relaxation of the sphincter under pathological conditions.

To date, there is still little research on gallbladder myoelectricity. It may be because of the weak gallbladder myoelectricity or signal close to the heart or respiration, making it difficult for researchers to obtain stable myoelectric signals. Therefore, the gallbladder myoelectric activity detection method needs to be continuously optimized and improved. Recently, we detected gallbladder EMG in guinea pigs with acute acalculous cholecystitis (AAC) using a bipolar electrode, which showed that the slow wave frequency in the control group was 10.66 ± 0.51 cpm, in the AAC 12 h group was 7.13 ± 0.20 cpm (mean ± standard deviation; $P < 0.001$), in the AAC 24 h group was 6.46 ± 0.16 cpm, and in the AAC 48 h group was 5.75 ± 0.43 cpm (unpublished data). There was no significant difference among the AAC 12 h, AAC 24 h, and AAC 48 h groups. This suggests that inflammation may first affect the function of gallbladder ICCs, then decrease gallbladder slow wave frequency, and eventually lead to a decline in gallbladder function.

With a deeper understanding of the electrophysiology of the biliary system, clinicians have begun to re-examine the necessity of gallbladder function evaluation for benign gallbladder diseases. Currently, the primary methods for evaluating gallbladder function are gallbladder angiography, three-dimensional ultrasonic detection, cholescintigraphy, and Oddi sphincter manometry, which indirectly evaluate gallbladder function through parameters such as gallbladder emptying and biliary pressure [88]. There is still a lack of direct methods to evaluate biliary function in the clinic. The advantages of EMG, bioelectromagnetic technology, and HR mapping in the study of the physiological function of the GI tract provide a new research direction for the evaluation of biliary system function, especially for gallbladder function. We believe that gallbladder EMG is the most concise, reliable, and direct method for evaluating gallbladder function. However, there is still a lack of research on gallbladder EMG under physiological and pathological conditions. Compared with EMG, HR mapping can directly detect the myoelectricity of the gallbladder and provide a spatiotemporal model of the origin and propagation pattern of gallbladder myoelectricity. This will enable a more comprehensive understanding of the origin and spread of myoelectric activity in gallbladder pathophysiology and may provide new

evaluation methods for the diagnosis and treatment of benign gallbladder diseases. Nevertheless, because EMG and HR mapping are invasive examinations, non-invasive low-risk bioelectromagnetic technology may be the best method for clinical gallbladder function evaluation in the future.

## CONCLUSION

The rhythmic slow wave in the GI tract is the basis for the realization of the physiological function of the digestive system. EMG detects the GI electrical signals by placing electrodes on the GI serosa or mucosal surface and has been widely used to study the normal physiological rhythm of the GI tract and the mode of dyskinesia under pathological conditions. Because EMG is an invasive technique, which limits its application in clinical diagnosis and treatment, it is mainly used in clinical scientific research and electrical stimulation therapy. Therefore, non-invasive detection technologies such as EGG and bioelectromagnetic technology are gaining more and more attention from scientific researchers and clinical workers. EGG collects GI electrical signals through the surface electrode of the abdominal wall, but it is easily affected by the difference in tissue conductivity. ACB and MGG, which are based on bioelectromagnetic technology, could not only accurately record the frequency and distribution of GI slow wave, but also provide their time-space variation parameters. HR mapping is also an invasive technique for detecting GI myoelectric signals. Unlike EMG, HR mapping uses array electrodes to obtain the myoelectric signal of the GI serosa surface, which can accurately obtain the spatial propagation model. Given the lack of electrophysiological research on the gallbladder, it will be an important research direction in the field of GI electrophysiology in the future.

## FOOTNOTES

**Author contributions:** Ding F and Cui ZY drafted the manuscript; Hu H and Zhao G conceived the review; Guo R provided critical feedback; all authors read and approved the final version to be submitted.

**Conflict-of-interest statement:** The authors have no conflicts of interest to declare.



**Country/Territory of origin:** China

**ORCID number:** Fan Ding 0000-0002-4624-3134; Run Guo 0000-0001-7036-0093; Zheng-Yu Cui 0000-0002-1041-5352; Hai Hu 0000-0001-6597-4375; Gang Zhao 0000-0003-4665-8492.

**S-Editor:** Gong ZM
**L-Editor:** Wang TQ
**P-Editor:** Gong ZM

## REFERENCES

1 **Sanders KM**, Koh SD, Ward SM. Interstitial cells of cajal as pacemakers in the gastrointestinal tract. *Annu Rev Physiol* 2006; **68**: 307-343 [PMID: 16460275 DOI: 10.1146/annurev.physiol.68.040504.094718]
2 **Sanders KM**, Koh SD, Ro S, Ward SM. Regulation of gastrointestinal motility--insights from smooth muscle biology. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 633-645 [PMID: 22965426 DOI: 10.1038/nrgastro.2012.168]
3 **Sanders KM**, Hwang SJ, Ward SM. Neuroeffector apparatus in gastrointestinal smooth muscle organs. *J Physiol* 2010; **588**: 4621-4639 [PMID: 20921202 DOI: 10.1113/jphysiol.2010.196030]
4 **Sanders KM**. Nerves, smooth muscle cells and interstitial cells in the GI tract: Molecular and cellular interactions. 2020
5 **Kurahashi M**, Zheng H, Dwyer L, Ward SM, Koh SD, Sanders KM. A functional role for the 'fibroblast-like cells' in gastrointestinal smooth muscles. *J Physiol* 2011; **589**: 697-710 [PMID: 21173079 DOI: 10.1113/jphysiol.2010.201129]
6 Alvarez WC. Action currents in stomach and intestine. *Am J Phys* 1922; **58**: 476-493 [DOI: 10.1152/ajplegacy.1922.58.3.476]
7 **Berkson J**, Baldes EJ, Alvarez WC. Electromyographic studies of the gastrointestinal tract. 1. The correlation between mechanical movement and changes in electrical potential during rhythmic contraction of the intestine. *Revista Brasileira De Coloproctologia* 1932; **27**: 423-431
8 **Liu JYH**, Du P, Chan WY, Rudd JA. Use of a microelectrode array to record extracellular pacemaker potentials from the gastrointestinal tracts of the ICR mouse and house musk shrew (Suncus murinus). *Cell Calcium* 2019; **80**: 175-188

[PMID: 31125825 DOI: 10.1016/j.ceca.2019.05.002]
9 **O'Grady G**, Abell TL. Gastric arrhythmias in gastroparesis: low- and high-resolution mapping of gastric electrical activity. *Gastroenterol Clin North Am* 2015; **44**: 169-184 [PMID: 25667031 DOI: 10.1016/j.gtc.2014.11.013]
10 **Sanders KM**, Ward SM, Koh SD. Interstitial cells: regulators of smooth muscle function. *Physiol Rev* 2014; **94**: 859-907 [PMID: 24987007 DOI: 10.1152/physrev.00037.2013]
11 **Huizinga JD**, Zarate N, Farrugia G. Physiology, injury, and recovery of interstitial cells of Cajal: basic and clinical science. *Gastroenterology* 2009; **137**: 1548-1556 [PMID: 19778538 DOI: 10.1053/j.gastro.2009.09.023]
12 **Huizinga JD**, Thuneberg L, Klüppel M, Malysz J, Mikkelsen HB, Bernstein A. W/kit gene required for interstitial cells of Cajal and for intestinal pacemaker activity. *Nature* 1995; **373**: 347-349 [PMID: 7530333 DOI: 10.1038/373347a0]
13 **Langton P**, Ward SM, Carl A, Norell MA, Sanders KM. Spontaneous electrical activity of interstitial cells of Cajal isolated from canine proximal colon. *Proc Natl Acad Sci USA* 1989; **86**: 7280-7284 [PMID: 2550938 DOI: 10.1073/pnas.86.18.7280]
14 **Iino S**, Nojyo Y. Immunohistochemical demonstration of c-Kit-negative fibroblast-like cells in murine gastrointestinal musculature. *Arch Histol Cytol* 2009; **72**: 107-115 [PMID: 20009347 DOI: 10.1679/aohc.72.107]
15 **Iino S**, Horiguchi K, Horiguchi S, Nojyo Y. c-Kit-negative fibroblast-like cells express platelet-derived growth factor receptor alpha in the murine gastrointestinal musculature. *Histochem Cell Biol* 2009; **131**: 691-702 [PMID: 19280210 DOI: 10.1007/s00418-009-0580-6]
16 **Hwang SJ**, Blair PJ, Durnin L, Mutafova-Yambolieva V, Sanders KM, Ward SM. P2Y1 purinoreceptors are fundamental to inhibitory motor control of murine colonic excitability and transit. *J Physiol* 2012; **590**: 1957-1972 [PMID: 22371476 DOI: 10.1113/jphysiol.2011.224634]
17 **Gallego D**, Gil V, Martínez-Cutillas M, Mañé N, Martín MT, Jiménez M. Purinergic neuromuscular transmission is absent in the colon of P2Y(1) knocked out mice. *J Physiol* 2012; **590**: 1943-1956 [PMID: 22371472 DOI: 10.1113/jphysiol.2011.224345]
18 **Maurer KJ**, Carey MC, Fox JG. Roles of infection, inflammation, and the immune system in cholesterol gallstone formation. *Gastroenterology* 2009; **136**: 425-440 [PMID: 19109959 DOI: 10.1053/j.gastro.2008.12.031]
19 **Stanghellini V**, Chan FK, Hasler WL, Malagelada JR, Suzuki H, Tack J, Talley NJ. Gastroduodenal Disorders. *Gastroenterology* 2016; **150**: 1380-1392 [PMID: 27147122 DOI: 10.1053/j.gastro.2016.02.011]
20 **Aziz I**, Palsson OS, Whitehead WE, Sperber AD, Simrén M, Törnblom H. Epidemiology, Clinical Characteristics, and Associations for Rome IV Functional Nausea and Vomiting Disorders in Adults. *Clin Gastroenterol Hepatol* 2019; **17**: 878-886 [PMID: 29857155 DOI: 10.1016/j.cgh.2018.05.020]
21 **Lacy BE**, Weiser KT, Kennedy AT, Crowell MD, Talley NJ. Functional dyspepsia: the economic impact to patients. *Aliment Pharmacol Ther* 2013; **38**: 170-177 [PMID: 23725230 DOI: 10.1111/apt.12355]
22 **Keller J**, Bassotti G, Clarke J, Dinning P, Fox M, Grover M, Hellström PM, Ke M, Layer P, Malagelada C, Parkman HP, Scott SM, Tack J, Simren M, Törnblom H, Camilleri M; International Working Group for Disorders of Gastrointestinal Motility and Function. Expert consensus document: Advances in the diagnosis and classification of gastric and intestinal motility disorders. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 291-308 [PMID: 29622808 DOI: 10.1038/nrgastro.2018.7]
23 **Szurszewski J**. Electrical basis of gastrointestinal motility. In: Johnson LR. Physiology of the Gastrointestinal Tract (2nd ed.). New York: Raven, 1987: 383-422
24 **Deloose E**, Janssen P, Depoortere I, Tack J. The migrating motor complex: control mechanisms and its role in health and disease. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 271-285 [PMID: 22450306 DOI: 10.1038/nrgastro.2012.57]
25 **Pasternak A**, Szura M, Gil K, Matyja A. Interstitial cells of Cajal - systematic review. *Folia Morphol (Warsz)* 2016; **75**: 281-286 [PMID: 26806433 DOI: 10.5603/FM.a2016.0002]
26 **Sanders KM**, Ward SM, Hennig GW. Problems with extracellular recording of electrical activity in gastrointestinal muscle. *Nat Rev Gastroenterol Hepatol* 2016; **13**: 731-741 [PMID: 27756919 DOI: 10.1038/nrgastro.2016.161]
27 **Rubin DI**. Needle electromyography: Basic concepts. *Handb Clin Neurol* 2019; **160**: 243-256 [PMID: 31277852 DOI: 10.1016/B978-0-444-64032-1.00016-3]
28 **Szurszewski JH**. A migrating electric complex of canine small intestine. *Am J Physiol* 1969; **217**: 1757-1763 [PMID: 5353053 DOI: 10.1152/ajplegacy.1969.217.6.1757]
29 **Code CF**, Marlett JA. The interdigestive myo-electric complex of the stomach and small bowel of dogs. *J Physiol* 1975; **246**: 289-309 [PMID: 1142245 DOI: 10.1113/jphysiol.1975.sp010891]
30 **Juel VC**. Single fiber electromyography. *Handb Clin Neurol* 2019; **160**: 303-310 [PMID: 31277856 DOI: 10.1016/B978-0-444-64032-1.00019-9]
31 **Merletti R**, Farina D. Analysis of intramuscular electromyogram signals. *Philos Trans A Math Phys Eng Sci* 2009; **367**: 357-368 [PMID: 19008187 DOI: 10.1098/rsta.2008.0235]
32 **Alvarez WC**. The electrogastrogram and what it shows. *JAMA* 1922; **78**: 1116-1119 [DOI: 10.1001/jama.1922.02640680020008]
33 **Smout AJ**, van der Schee EJ, Grashuis JL. What is measured in electrogastrography? *Dig Dis Sci* 1980; **25**: 179-187 [PMID: 7371462 DOI: 10.1007/bf01308136]
34 **Hamilton JW**, Bellahsene BE, Reichelderfer M, Webster JG, Bass P. Human electrogastrograms. Comparison of surface and mucosal recordings. *Dig Dis Sci* 1986; **31**: 33-39 [PMID: 2934238 DOI: 10.1007/bf01347907]
35 **Familoni BO**, Kingma YJ, Bowes KL. Study of transcutaneous and intraluminal measurement of gastric electrical activity in humans. *Med Biol Eng Comput* 1987; **25**: 397-402 [PMID: 3450990 DOI: 10.1007/BF02443360]
36 **Martinek R**, Ladrova M, Sidikova M, Jaros R, Behbehani K, Kahankova R, Kawala-Sterniuk A. Advanced Bioelectrical Signal Processing Methods: Past, Present, and Future Approach-Part III: Other Biosignals. *Sensors (Basel)* 2021; **21** [PMID: 34577270 DOI: 10.3390/s21186064]
37 **Chang FY**. Electrogastrography: basic knowledge, recording, processing and its clinical applications. *J Gastroenterol Hepatol* 2005; **20**: 502-516 [PMID: 15836697 DOI: 10.1111/j.1440-1746.2004.03751.x]
38 **Chen J**, McCallum RW. Gastric slow wave abnormalities in patients with gastroparesis. *Am J Gastroenterol* 1992; **87**:

477-482 [PMID: 1553934]
39 **Lin Z**, Eaker EY, Sarosiek I, McCallum RW. Gastric myoelectrical activity and gastric emptying in patients with functional dyspepsia. *Am J Gastroenterol* 1999; **94**: 2384-2389 [PMID: 10483996 DOI: 10.1111/j.1572-0241.1999.01362.x]
40 **Frasko R**, Maruna P, Gurlich R, Trca S. Transcutaneous electrogastrography in patients with ileus. Relations to interleukin-1beta, interleukin-6, procalcitonin and C-reactive protein. *Eur Surg Res* 2008; **41**: 197-202 [PMID: 18504369 DOI: 10.1159/000134918]
41 **Zhang Y**, Liu Z, Liu X, Han X, Zhou Y, Cao Y, Zhang X. Prediction of octreotide efficacy by electrogastrography in the treatment of patients with esophageal variceal hemorrhage. *Physiol Meas* 2013; **34**: 799-812 [PMID: 23780564 DOI: 10.1088/0967-3334/34/7/799]
42 **Ortigoza EB**, Cagle J, Chien JH, Oh S, Brown LS, Neu J. Electrogastrography, Near-infrared Spectroscopy, and Acoustics to Measure Gastrointestinal Development in Preterm Babies. *J Pediatr Gastroenterol Nutr* 2018; **66**: e146-e152 [PMID: 29287010 DOI: 10.1097/MPG.0000000000001867]
43 **Farajidavar A**. Bioelectronics for mapping gut activity. *Brain Res* 2018; **1693**: 169-173 [PMID: 29903619 DOI: 10.1016/j.brainres.2018.03.004]
44 **Sullivan MA**, Snape WJ Jr, Matarazzo SA, Petrokubi RJ, Jeffries G, Cohen S. Gastrointestinal myoelectrical activity in idiopathic intestinal pseudo-obstruction. *N Engl J Med* 1977; **297**: 233-238 [PMID: 876299 DOI: 10.1056/nejm197708042970501]
45 **Cheng LK**, Nagahawatte ND, Avci R, Du P, Liu Z, Paskaranandavadivel N. Strategies to Refine Gastric Stimulation and Pacing Protocols: Experimental and Modeling Approaches. *Front Neurosci* 2021; **15**: 645472 [PMID: 33967679 DOI: 10.3389/fnins.2021.645472]
46 **Zhao X**, Yin J, Wang L, Chen JD. Diffused and sustained inhibitory effects of intestinal electrical stimulation on intestinal motility mediated *via* sympathetic pathway. *Neuromodulation* 2014; **17**: 373-79; discussion 380 [PMID: 23924055 DOI: 10.1111/ner.12099]
47 **Zaw TS**, Khin PP, Sohn UD. The signaling of amitriptyline-induced inhibitory effect on electrical field stimulation response in colon smooth muscle. *Naunyn Schmiedebergs Arch Pharmacol* 2016; **389**: 961-970 [PMID: 27234925 DOI: 10.1007/s00210-016-1259-x]
48 **Penfold JA**, Wells CI, Du P, Bissett IP, O'Grady G. Electrical Stimulation and Recovery of Gastrointestinal Function Following Surgery: A Systematic Review. *Neuromodulation* 2019; **22**: 669-679 [PMID: 30451336 DOI: 10.1111/ner.12878]
49 **McKenzie P**, Stocker A, Du P, Lahr C, Cheng LK, McElmurray L, Kedar A, Boatright B, Hassan H, Hughes M, Omer E, Bhandari B, Abell TL. The Effect of Gastric Electrical Stimulation on Small Bowel Motility in Patients With Gastroparesis and Concomitant Pancreatic and Small Bowel Dysfunction: From Animal Model to Human Application. *Neuromodulation* 2019; **22**: 723-729 [PMID: 30525253 DOI: 10.1111/ner.12888]
50 **Levinthal DJ**, Bielefeldt K. Systematic review and meta-analysis: Gastric electrical stimulation for gastroparesis. *Auton Neurosci* 2017; **202**: 45-55 [PMID: 27085627 DOI: 10.1016/j.autneu.2016.03.004]
51 **Deb S**, Tang SJ, Abell TL, McLawhorn T, Huang WD, Lahr C, To SD, Easter J, Chiao JC. Development of innovative techniques for the endoscopic implantation and securing of a novel, wireless, miniature gastrostimulator (with videos). *Gastrointest Endosc* 2012; **76**: 179-184 [PMID: 22726478 DOI: 10.1016/j.gie.2012.03.177]
52 **Farajidavar A**, O'Grady G, Rao SM, Cheng LK, Abell T, Chiao JC. A miniature bidirectional telemetry system for in vivo gastric slow wave recordings. *Physiol Meas* 2012; **33**: N29-N37 [PMID: 22635054 DOI: 10.1088/0967-3334/33/6/N29]
53 **Lammers WJ**, Ver Donck L, Schuurkes JA, Stephen B. Peripheral pacemakers and patterns of slow wave propagation in the canine small intestine in vivo. *Can J Physiol Pharmacol* 2005; **83**: 1031-1043 [PMID: 16391712 DOI: 10.1139/y05-084]
54 **Hinder RA**, Kelly KA. Human gastric pacesetter potential. Site of origin, spread, and response to gastric transection and proximal gastric vagotomy. *Am J Surg* 1977; **133**: 29-33 [PMID: 835775 DOI: 10.1016/0002-9610(77)90187-8]
55 **O'Grady G**, Du P, Cheng LK, Egbuji JU, Lammers WJ, Windsor JA, Pullan AJ. Origin and propagation of human gastric slow-wave activity defined by high-resolution mapping. *Am J Physiol Gastrointest Liver Physiol* 2010; **299**: G585-G592 [PMID: 20595620 DOI: 10.1152/ajpgi.00125.2010]
56 **O'Grady G**, Gharibans AA, Du P, Huizinga JD. The gastric conduction system in health and disease: a translational review. *Am J Physiol Gastrointest Liver Physiol* 2021; **321**: G527-G542 [PMID: 34549598 DOI: 10.1152/ajpgi.00065.2021]
57 **Du P**, Grady GO, Paskaranandavadivel N, Tang SJ, Abell T, Cheng LK. High-resolution Mapping of Hyperglycemia-induced Gastric Slow Wave Dysrhythmias. *J Neurogastroenterol Motil* 2019; **25**: 276-285 [PMID: 30870879 DOI: 10.5056/jnm18192]
58 **Lammers WJ**, Ver Donck L, Stephen B, Smets D, Schuurkes JA. Origin and propagation of the slow wave in the canine stomach: the outlines of a gastric conduction system. *Am J Physiol Gastrointest Liver Physiol* 2009; **296**: G1200-G1210 [PMID: 19359425 DOI: 10.1152/ajpgi.90581.2008]
59 **Berry R**, Miyagawa T, Paskaranandavadivel N, Du P, Angeli TR, Trew ML, Windsor JA, Imai Y, O'Grady G, Cheng LK. Functional physiology of the human terminal antrum defined by high-resolution electrical mapping and computational modeling. *Am J Physiol Gastrointest Liver Physiol* 2016; **311**: G895-G902 [PMID: 27659422 DOI: 10.1152/ajpgi.00255.2016]
60 **Rhee PL**, Lee JY, Son HJ, Kim JJ, Rhee JC, Kim S, Koh SD, Hwang SJ, Sanders KM, Ward SM. Analysis of pacemaker activity in the human stomach. *J Physiol* 2011; **589**: 6105-6118 [PMID: 22005683 DOI: 10.1113/jphysiol.2011.217497]
61 **O'Grady G**, Egbuji JU, Du P, Lammers WJ, Cheng LK, Windsor JA, Pullan AJ. High-resolution spatial analysis of slow wave initiation and conduction in porcine gastric dysrhythmia. *Neurogastroenterol Motil* 2011; **23**: e345-e355 [PMID: 21714831 DOI: 10.1111/j.1365-2982.2011.01739.x]
62 **Du P**, O'Grady G, Egbuji JU, Lammers WJ, Budgett D, Nielsen P, Windsor JA, Pullan AJ, Cheng LK. High-resolution

mapping of in vivo gastrointestinal slow wave activity using flexible printed circuit board electrodes: methodology and validation. *Ann Biomed Eng* 2009; **37**: 839-846 [PMID: 19224368 DOI: 10.1007/s10439-009-9654-9]

63 **O'Grady G**, Angeli TR, Du P, Lahr C, Lammers WJEP, Windsor JA, Abell TL, Farrugia G, Pullan AJ, Cheng LK. Abnormal initiation and conduction of slow-wave activity in gastroparesis, defined by high-resolution electrical mapping. *Gastroenterology* 2012; **143**: 589-598.e3 [PMID: 22643349 DOI: 10.1053/j.gastro.2012.05.036]

64 **Berry R**, Cheng LK, Du P, Paskaranandavadivel N, Angeli TR, Mayne T, Beban G, O'Grady G. Patterns of Abnormal Gastric Pacemaking After Sleeve Gastrectomy Defined by Laparoscopic High-Resolution Electrical Mapping. *Obes Surg* 2017; **27**: 1929-1937 [PMID: 28213666 DOI: 10.1007/s11695-017-2597-6]

65 **Angeli TR**, Cheng LK, Du P, Wang TH, Bernard CE, Vannucchi MG, Faussone-Pellegrini MS, Lahr C, Vather R, Windsor JA, Farrugia G, Abell TL, O'Grady G. Loss of Interstitial Cells of Cajal and Patterns of Gastric Dysrhythmia in Patients With Chronic Unexplained Nausea and Vomiting. *Gastroenterology* 2015; **149**: 56-66.e5 [PMID: 25863217 DOI: 10.1053/j.gastro.2015.04.003]

66 **O'Grady G**, Du P, Egbuji JU, Lammers WJ, Wahab A, Pullan AJ, Cheng LK, Windsor JA. A novel laparoscopic device for measuring gastrointestinal slow-wave activity. *Surg Endosc* 2009; **23**: 2842-2848 [PMID: 19466491 DOI: 10.1007/s00464-009-0515-2]

67 **O'Mahony GD**, Gallucci MR, Córdova-Fraga T, Berch B, Richards WO, Bradshaw LA. Biomagnetic investigation of injury currents in rabbit intestinal smooth muscle during mesenteric ischemia and reperfusion. *Dig Dis Sci* 2007; **52**: 292-301 [PMID: 17160467 DOI: 10.1007/s10620-006-9559-5]

68 **Bradshaw LA**, Cheng LK, Richards WO, Pullan AJ. Surface current density mapping for identification of gastric slow wave propagation. *IEEE Trans Biomed Eng* 2009; **56**: 2131-2139 [PMID: 19403355 DOI: 10.1109/TBME.2009.2021576]

69 **Irimia A**, Cheng LK, Buist ML, Pullan AJ, Bradshaw LA. An integrative software package for gastrointestinal biomagnetic data acquisition and analysis using SQUID magnetometers. *Comput Methods Programs Biomed* 2006; **83**: 83-94 [PMID: 16857291 DOI: 10.1016/j.cmpb.2006.03.006]

70 **Américo MF**, Oliveira RB, Corá LA, Marques RG, Romeiro FG, Andreis U, Miranda JR. The ACB technique: a biomagentic tool for monitoring gastrointestinal contraction directly from smooth muscle in dogs. *Physiol Meas* 2010; **31**: 159-169 [PMID: 20009185 DOI: 10.1088/0967-3334/31/2/003]

71 **Pinto L**, Soares G, Próspero A, Stoppa E, Biasotti G, Paixão F, Santos A, Oliveira R, Miranda J. An easy and low-cost biomagnetic methodology to study regional gastrointestinal transit in rats. *Biomed Tech (Berl)* 2021; **66**: 405-412 [PMID: 33544465 DOI: 10.1515/bmt-2020-0202]

72 **Calabresi MF**, Quini CC, Matos JF, Moretto GM, Americo MF, Graça JR, Santos AA, Oliveira RB, Pina DR, Miranda JR. Alternate current biosusceptometry for the assessment of gastric motility after proximal gastrectomy in rats: a feasibility study. *Neurogastroenterol Motil* 2015; **27**: 1613-1620 [PMID: 26303680 DOI: 10.1111/nmo.12660]

73 **Teixeira MC**, Magalhães I, Galvão PV, Souza GS, Miranda JR, Oliveira RB, Corá LA. Assessment of gastrointestinal motility in renal transplant recipients by alternate current biosusceptometry. *Transplant Proc* 2012; **44**: 2384-2387 [PMID: 23026600 DOI: 10.1016/j.transproceed.2012.07.048]

74 **Américo MF**, Marques RG, Zandoná EA, Andreis U, Stelzer M, Corá LA, Oliveira RB, Miranda JR. Validation of ACB in vitro and in vivo as a biomagnetic method for measuring stomach contraction. *Neurogastroenterol Motil* 2010; **22**: 1340-1344, e374 [PMID: 20874731 DOI: 10.1111/j.1365-2982.2010.01582.x]

75 **Agostinho M**, Américo MF, Marques RG, Zandoná EA, Stelzer M, Corá LA, Andreis U, Oliveira RB, Miranda JR. AC Biosusceptometry as a method for measuring gastric contraction. *Annu Int Conf IEEE Eng Med Biol Soc* 2010; **2010**: 5740-5743 [PMID: 21097331 DOI: 10.1109/IEMBS.2010.5627855]

76 **Corá LA**, Andreis U, Romeiro FG, Américo MF, Oliveira RB, Baffa O, Miranda JR. Magnetic images of the disintegration process of tablets in the human stomach by ac biosusceptometry. *Phys Med Biol* 2005; **50**: 5523-5534 [PMID: 16306649 DOI: 10.1088/0031-9155/50/23/007]

77 **Martins ML**, Calabresi MF, Quini C, Matos JF, Miranda JR, Saeki MJ, Bordallo HN. Enhancing the versatility of alternate current biosusceptometry (ACB) through the synthesis of a dextrose-modified tracer and a magnetic muco-adhesive cellulose gel. *Mater Sci Eng C Mater Biol Appl* 2015; **48**: 80-85 [PMID: 25579899 DOI: 10.1016/j.msec.2014.11.059]

78 **Bruno AC**, Pavan TZ, Baffa O, Carneiro AA. A hybrid transducer to magnetically and ultrasonically evaluate magnetic fluids. *IEEE Trans Ultrason Ferroelectr Freq Control* 2013; **60**: 2004-2012 [PMID: 24658731 DOI: 10.1109/TUFFC.2013.2785]

79 **Dallagnol DJR**, Corá LA, Gama LA, Caló RS, Miranda JRA, Américo MF. Gastrointestinal Side Effects of Triple Immunosuppressive Therapy Evaluated by AC Biosusceptometry and Electrogastrography in Rats. *Endocr Metab Immune Disord Drug Targets* 2020; **20**: 1494-1503 [PMID: 32368985 DOI: 10.2174/1871530320666200505111456]

80 **Somarajan S**, Cassilly S, Obioha C, Richards WO, Bradshaw LA. Effects of body mass index on gastric slow wave: a magnetogastrographic study. *Physiol Meas* 2014; **35**: 205-215 [PMID: 24398454 DOI: 10.1088/0967-3334/35/2/205]

81 **Somarajan S**, Muszynski ND, Hawrami D, Olson JD, Cheng LK, Bradshaw LA. Noninvasive Magnetogastrography Detects Erythromycin-Induced Effects on the Gastric Slow Wave. *IEEE Trans Biomed Eng* 2019; **66**: 327-334 [PMID: 29993499 DOI: 10.1109/TBME.2018.2837647]

82 **Bradshaw LA**, Cheng LK, Chung E, Obioha CB, Erickson JC, Gorman BL, Somarajan S, Richards WO. Diabetic gastroparesis alters the biomagnetic signature of the gastric slow wave. *Neurogastroenterol Motil* 2016; **28**: 837-848 [PMID: 26839980 DOI: 10.1111/nmo.12780]

83 **Pozo MJ**, Camello PJ, Mawe GM. Chemical mediators of gallbladder dysmotility. *Curr Med Chem* 2004; **11**: 1801-1812 [PMID: 15279583 DOI: 10.2174/0929867043364955]

84 **Romański KW**. Characteristics and cholinergic control of the 'minute rhythm' in ovine antrum, small bowel and gallbladder. *J Vet Med A Physiol Pathol Clin Med* 2002; **49**: 313-320 [PMID: 12227475 DOI: 10.1046/j.1439-0442.2002.00399.x]

85 **Abell TL**, Werkman RF, Familoni BO, Baggous W, Massie D, Vera S. Biliary, pancreatic, and sphincter of Oddi electrical and mechanical signals recorded during ERCP. *Dig Dis Sci* 1998; **43**: 540-546 [PMID: 9539649 DOI:

10.1023/a:1018859007353]
86 **Rong ZH**, Chen HY, Wang XX, Wang ZY, Xian GZ, Ma BZ, Qin CK, Zhang ZH. Effects of sphincter of Oddi motility on the formation of cholesterol gallstones. *World J Gastroenterol* 2016; **22**: 5540-5547 [PMID: 27350732 DOI: 10.3748/wjg.v22.i24.5540]
87 **Liu YK**, Li ZH, Liu NZ, He Q, Lin H, Wang XJ, Li XW, Dong JH. Reduced myoelectric activity in the sphincter of Oddi in a new model of chronic cholangitis in rabbits: an in vivo and in vitro study. *Neurogastroenterol Motil* 2010; **22**: 927-934, e238 [PMID: 20426800 DOI: 10.1111/j.1365-2982.2010.01500.x]
88 **Fotos JS**, Tulchinsky M. Oral Cholecystagogue Cholescintigraphy: A Systematic Review of Fatty Meal Options. *Clin Nucl Med* 2015; **40**: 796-798 [PMID: 26222535 DOI: 10.1097/RLU.0000000000000913]
89 **Code CF**, Marlett JA. Canine tachygastria. *Mayo Clin Proc* 1974; **49**: 325-332 [PMID: 4829263]
90 **Di Luzio S**, Comani S, Romani GL, Basile M, Del Gratta C, Pizzella V. A biomagnetic method for studying gastrointestinal activity. *Nouv Cim D* 1989; **11**: 1853-1859 [DOI: 10.1007/BF02459126]
91 **Miranda JR**, Baffa O, de Oliveira RB, Matsuda NM. An AC biosusceptometer to study gastric emptying. *Med Phys* 1992; **19**: 445-448 [PMID: 1584144 DOI: 10.1118/1.596832]
92 **Bradshaw LA**, Myers AG, Redmond A, Wikswo JP, Richards WO. Biomagnetic detection of gastric electrical activity in normal and vagotomized rabbits. *Neurogastroenterol Motil* 2003; **15**: 475-482 [PMID: 14507349 DOI: 10.1046/j.1365-2982.2003.00432.x]
93 **Lammers WJ**, Ver Donck L, Stephen B, Smets D, Schuurkes JA. Focal activities and re-entrant propagations as mechanisms of gastric tachyarrhythmias. *Gastroenterology* 2008; **135**: 1601-1611 [PMID: 18713627 DOI: 10.1053/j.gastro.2008.07.020]
94 **Gharibans AA**, Kim S, Kunkel D, Coleman TP. High-Resolution Electrogastrogram: A Novel, Noninvasive Method for Determining Gastric Slow-Wave Direction and Speed. *IEEE Trans Biomed Eng* 2017; **64**: 807-815 [PMID: 27305668 DOI: 10.1109/tbme.2016.2579310]
95 **Gharibans AA**, Coleman TP, Mousa H, Kunkel DC. Spatial Patterns From High-Resolution Electrogastrography Correlate With Severity of Symptoms in Patients With Functional Dyspepsia and Gastroparesis. *Clin Gastroenterol Hepatol* 2019; **17**: 2668-2677 [PMID: 31009794 DOI: 10.1016/j.cgh.2019.04.039]
96 **McCallum RW**, Sarosiek I, Parkman HP, Snape W, Brody F, Wo J, Nowak T. Gastric electrical stimulation with Enterra therapy improves symptoms of idiopathic gastroparesis. *Neurogastroenterol Motil* 2013; **25**: 815-e636 [PMID: 23895180 DOI: 10.1111/nmo.12185]
97 **Teich S**, Mousa HM, Punati J, Di Lorenzo C. Efficacy of permanent gastric electrical stimulation for the treatment of gastroparesis and functional dyspepsia in children and adolescents. *J Pediatr Surg* 2013; **48**: 178-183 [PMID: 23331812 DOI: 10.1016/j.jpedsurg.2012.10.038]
98 **Morales-Conde S**, Alarcón Del Agua I, Busetto L, Favretti F, Anselmino M, Rovera GM, Socas-Macias M, Barranco-Moreno A, Province-Azalde R, Torres AJ. Implanted Closed-Loop Gastric Electrical Stimulation (CLGES) System with Sensor-Based Feedback Safely Limits Weight Regain at 24 Months. *Obes Surg* 2018; **28**: 1766-1774 [PMID: 29333595 DOI: 10.1007/s11695-017-3093-8]
99 **Ducrotte P**, Coffin B, Bonaz B, Fontaine S, Bruley Des Varannes S, Zerbib F, Caiazzo R, Grimaud JC, Mion F, Hadjadj S, Valensi PE, Vuitton L, Charpentier G, Ropert A, Altwegg R, Pouderoux P, Dorval E, Dapoigny M, Duboc H, Benhamou PY, Schmidt A, Donnadieu N, Gourcerol G, Guerci B; ENTERRA Research Group. Gastric Electrical Stimulation Reduces Refractory Vomiting in a Randomized Crossover Trial. *Gastroenterology* 2020; **158**: 506-514.e2 [PMID: 31647902 DOI: 10.1053/j.gastro.2019.10.018]
100 **Norton C**, Gibbs A, Kamm MA. Randomized, controlled trial of anal electrical stimulation for fecal incontinence. *Dis Colon Rectum* 2006; **49**: 190-196 [PMID: 16362803 DOI: 10.1007/s10350-005-0251-1]
101 **Daram SR**, Tang SJ, Vick K, Aru G, Lahr C, Amin O, Taylor M, Sheehan JJ, Abell TL. Novel application of GI electrical stimulation in Roux stasis syndrome (with video). *Gastrointest Endosc* 2011; **74**: 683-686 [PMID: 21872718 DOI: 10.1016/j.gie.2011.05.023]
102 **Cadeddu F**, Salis F, De Luca E, Ciangola I, Milito G. Efficacy of biofeedback plus transanal stimulation in the management of pelvic floor dyssynergia: a randomized trial. *Tech Coloproctol* 2015; **19**: 333-338 [PMID: 25744688 DOI: 10.1007/s10151-015-1292-7]
103 **Fassov J**, Lundby L, Worsøe J, Buntzen S, Laurberg S, Krogh K. A randomised, controlled study of small intestinal motility in patients treated with sacral nerve stimulation for irritable bowel syndrome. *BMC Gastroenterol* 2014; **14**: 111 [PMID: 24965754 DOI: 10.1186/1471-230X-14-111]
104 **Stakenborg N**, Wolthuis AM, Gomez-Pinilla PJ, Farro G, Di Giovangiulio M, Bosmans G, Labeeuw E, Verhaegen M, Depoortere I, D'Hoore A, Matteoli G, Boeckxstaens GE. Abdominal vagus nerve stimulation as a new therapeutic approach to prevent postoperative ileus. *Neurogastroenterol Motil* 2017; **29** [PMID: 28429863 DOI: 10.1111/nmo.13075]
105 **Zhang B**, Xu F, Hu P, Zhang M, Tong K, Ma G, Xu Y, Zhu L, Chen JDZ. Needleless Transcutaneous Electrical Acustimulation: A Pilot Study Evaluating Improvement in Post-Operative Recovery. *Am J Gastroenterol* 2018; **113**: 1026-1035 [PMID: 29925916 DOI: 10.1038/s41395-018-0156-y]
106 **Teckentrup V**, Neubert S, Santiago JCP, Hallschmid M, Walter M, Kroemer NB. Non-invasive stimulation of vagal afferents reduces gastric frequency. *Brain Stimul* 2020; **13**: 470-473 [PMID: 31884186 DOI: 10.1016/j.brs.2019.12.018]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 June 27; 14(6): 556-566

DOI: 10.4240/wjgs.v14.i6.556

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

# Predicting the outcome of closed-loop small bowel obstruction by preoperative characteristics

Masja K Toneman, Bente M de Kok, Frank M Zijta, Stanley Oei, Gijs J D van Acker, Marinke Westerterp, Anne E M van der Pool

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

**P-Reviewer:** Chisthi MM, India; Sánchez JIA, Colombia

**Received:** July 28, 2021
**Peer-review started:** July 28, 2021
**First decision:** September 5, 2021
**Revised:** September 24, 2021
**Accepted:** June 17, 2022
**Article in press:** June 17, 2022
**Published online:** June 27, 2022

**Masja K Toneman, Gijs J D van Acker, Marinke Westerterp, Anne E M van der Pool,** Department of Surgery, Haaglanden Medical Centre, The Hague 2512 VA, Netherlands

**Bente M de Kok, Frank M Zijta, Stanley Oei,** Department of Radiology, Haaglanden Medical Centre, The Hague 2512 VA, Netherlands

**Corresponding author:** Masja K Toneman, Doctor, Department of Surgery, Haaglanden Medical Centre, Lijnbaan 32, The Hague 2512 VA, Netherlands. mktoneman@gmail.com

## Abstract

***BACKGROUND***

Closed-loop small bowel obstruction (CL-SBO) can threaten the viability of the intestine by obstructing a bowel segment at two adjacent points. Prompt recognition and surgery are crucial.

***AIM***

To analyze the outcomes of patients who underwent surgery for CL-SBO and to evaluate clinical predictors.

***METHODS***

Patients who underwent surgery for suspected CL-BSO on computed tomography (CT) at a single center between 2013 and 2019 were evaluated retrospectively. Patients were divided into three groups by perioperative outcome, including viable bowel, reversible ischemia, and irreversible ischemia. Clinical and laboratorial variables at presentation were compared and postoperative outcomes were analyzed.

***RESULTS***

Of 148 patients with CL-SBO, 28 (19%) had a perioperative viable small bowel, 86 (58%) had reversible ischemia, and 34 (23%) had irreversible ischemia. Patients with a higher age had higher risk for perioperative irreversible ischemia [odds ratio (OR): 1.03, 95% confidence interval (CI): 0.99-1.06]. Patients with American Society of Anaesthesiologists (ASA) classification ≥ 3 had higher risk of perioperative irreversible ischemia compared to lower ASA classifications (OR: 3.76, 95%CI: 1.31-10.81). Eighty-six patients (58%) did not have elevated C-reactive protein (> 10 mg/L), and between-group differences were insignificant. Postoperative in-hospital stay was significantly longer for patients with irre-

versible ischemia (median 8 d, $P$ = 0.001) than for those with reversible ischemia (median 6 d) or a viable bowel (median 5 d). Postoperative morbidity was significantly higher in patients with perioperative irreversible ischemia (45%, $P$ = 0.043) compared with reversible ischemia (20%) and viable bowel (4%).

*CONCLUSION*

Older patients or those with higher ASA classification had an increased risk of irreversible ischemia in case of CL-SBO. After irreversible ischemia, postoperative morbidity was increased.

**Key Words:** General surgery; Laparoscopy; Laparotomy; Critical care; Intestinal obstruction; Morbidity



**Core Tip:** We studied the preoperative characteristics and postoperative outcomes of 148 patients with closed-loop small bowel obstruction, based on the perioperative small bowel viability (viable, reversible ischemia, or irreversible ischemia). Retrospective evaluation found that older age or an American Society of Anesthesiologists classification of 3 or higher increased the risk of perioperative irreversible ischemia. C-reactive protein (CRP) that is not increased above normal levels does not assure the presence of a viable bowel, and 55.83% of patients with ischemia had normal CRP levels. Perioperative irreversible ischemia significantly increased postoperative morbidity. These risks should be mentioned in preoperative consultations.

**Citation:** Toneman MK, de Kok BM, Zijta FM, Oei S, van Acker GJD, Westerterp M, van der Pool AEM. Predicting the outcome of closed-loop small bowel obstruction by preoperative characteristics. *World J Gastrointest Surg* 2022; 14(6): 556-566

**URL:** https://www.wjgnet.com/1948-9366/full/v14/i6/556.htm

**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i6.556

## INTRODUCTION

Small bowel obstructions (SBOs) are a common cause of (sub)acute abdominal pain in patients presenting to the emergency department, and account for approximately 300000 hospitalizations in the United States annually[1]. Simple SBOs that occur at one site because of a single adhesion may allow conservative treatment without surgery[2-4]. However, in about 10% of SBOs, the intestine is occluded at two separate sites at one anatomic location because of adhesions, internal herniation, or torsion of the small bowel[5-7]. Such closed-loop SBOs (CL-SBOs) present with (sub)acute abdominal pain, vomiting, abdominal distension, and sometimes obstipation[6,8,9].

In cases of CL-SBO, viability of the small bowel is threatened by the possibility of strangulation. Three factors increase the risk of strangulation and indicate emergency surgery, external compression of the vascular pedicle of the closed loop at the obstruction site, distension of the closed loop, and/or volvulus of the closed loop with twisting of its mesentery[5]. If a strangulated small bowel is not surgically released, bowel wall ischemia and necrosis can occur, which increase the risk of septic shock and other complications[10]. Prompt recognition and surgery are crucial to achieve a good patient outcome and to preserve the involved bowel.

To date, most studies have evaluated patients with SBOs by comparing surgical *vs* conservative treatments[2]. Studies for CL-SBOs have mostly focused on aspects of computed tomography (CT) imaging[5,11-13]. The perioperative findings of previous studies vary and there is often a lack information on the postoperative outcomes. The aim of this single-center study was to analyze the perioperative and postoperative outcomes of patients with CT imaging consistent with CL-SBOs, and to evaluate clinical predictors.

## MATERIALS AND METHODS

### *Patients and study design*

A series of Dutch patients who underwent surgery for suspected CL-SBOs between September 2013 and September 2019 were included. Potential patients were retrieved from a medical records database that included all abdominal surgeries involving the small bowel. Patients with a preoperative CT scan that diagnosed CL-SBO, defined as an SBO with two contiguous caliber changes at a single anatomic

location, were eligible for inclusion. Patients with bowel obstructions caused by external abdominal herniation (*e.g.*, inguinal or umbilical hernia) or malignancy, or with a history of bariatric surgery or surgery with Roux-and-Y reconstruction were excluded. Patients with Roux-and-Y surgery were excluded because of the difference in clinical presentation with intermittent and subacute pain, and difference in perioperative aetiology, *i.e.* small bowel herniation through an iatrogenic defect created in the mesentery[14,15].

The regional Medical Ethical Testing Committee evaluated the study protocol and declared that the law on medical scientific research concerning humans was not applicable because of the non-invasive and retrospective nature of the study. The scientific board of our hospital approved the study, and the need for written informed consent was waived. However, every patient file was checked for notes of refusal to participate in scientific research. No patients were excluded on that basis.

### Patient characteristics

Age, sex, American Society of Anesthesiologists (ASA) classification[16], body mass index and history of abdominal surgery were obtained from medical records. The presence of abdominal pain, vomiting, obstipation (no stool for > 24 h), and abdominal guarding, as well as vital signs, including tachycardia (> 100 beats/min), tachypnoea (> 20 breaths/min), and fever (body temperature > 38.5 °C) had been recorded at the initial evaluation. Blood and laboratory tests at presentation included measures of hematocrit, thrombocyte and white blood cell (WBC) count, C-reactive protein (CRP), creatinine, urea, lactate dehydrogenase, creatine kinase, albumin, and glucose.

Patients were divided into three groups based on the perioperative findings, including viable bowel, reversible bowel wall ischemia, and irreversible bowel wall ischemia. The small bowel was considered viable when the affected region between the two sites of obstruction did not show signs of discoloration before the obstruction was released. Reversible ischemia required that a discolored portion of the small bowel regained normal color within 5 min after surgical release and repositioning of the bowel. If there was no evident return to viable bowel in 5 min, but a clear increase in color did occur, we waited a maximum of 20 min, as previously described[17]. If recoloration did not occur after release of the obstruction, the ischemia was considered irreversible and the affected bowel was resected. The type of surgery (laparoscopy/laparotomy), whether a resection was performed, and type of anastomosis (hand sutured/stapled) was recorded. The intervals between the onset of symptoms and CT imaging and between CT imaging and the start of surgery were recorded in hours of time. Postoperative data collected were length of hospital stay (days) and postoperative complications, which were recorded following the Clavien–Dindo classification[18].

### Imaging

For all included patients, CT imaging was performed with or without contrast and including the arterial and/or portal venous phase. The original radiology reports were scored for suspicion of small bowel ischemia because of CL-SBO and graded as no suspicion of ischemia, inconclusive, or strong suspicion of ischemia. Grades were based on suspicion of ischemia in the original radiology report. Imaging features reported in the original radiology report, such as decreased enhancement of mesenterial vessels and the bowel wall and the presence of peritoneal fluid or pneumatosis intestinalis, were taken into account.

### Statistical analysis

The statistical analysis was performed with SPSS version 22 (IBM Corp., Armonk, NY, United States). Categorical data were reported as numbers and percentages. Differences between proportions were compared with chi-square or Fisher's exact tests, as appropriate. Continuous data with a significantly skewed distribution were reported as medians and were compared using Kruskal–Wallis test. Univariate analysis was performed to identify whether any clinical characteristics were associated with specific perioperative outcomes. For characteristics with significant between-group differences, odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated trough logistic regression. The significance level was set at $P < 0.05$.

## RESULTS

### Patients

A series of 148 patients included in a database of 763 patients (19.40%) with abdominal surgery of the small bowel between September 2013 and September 2019 met the inclusion criteria. In total, 28 patients (18.92%) had perioperative viable small bowel, 86 patients (58.11%) had reversible ischemia, and 34 patients (22.97%) had irreversible ischemia and resection. The baseline characteristics are shown in Table 1. Fifty-eight percent of patients (86/148) had previous abdominal surgery. Between-group differences were not significant. The median ages of the groups were significantly different, and the patients with irreversible ischemia were the oldest. Patients with irreversible ischemia were significantly

**Table 1 Baseline characteristics of patients in the three study groups**

| Baseline characteristics | Total, *n* = 148 | Viable bowel, *n* = 28 | Reversible ischemia, *n* = 86 | Irreversible ischemia, *n* = 34 | *P* value |
|---|---|---|---|---|---|
| Male, *n* (%) | 64 (43.24) | 13 (46.43) | 41 (47.67) | 10 (29.41) | 0.18 |
| Age in yr, median (range) | 68 (15–98) | 57 (35–98) | 68 (15–93) | 76 (23–92) | 0.04 |
| ASA classification (%) | | | | | 0.01 |
| 1–2 | 82 (55.41) | 18 (64.29) | 53 (61.63) | 11 (32.35) | |
| ≥ 3 | 66 (44.59) | 10 (35.71) | 33 (38.37) | 23 (67.65) | |
| BMI in kg/m$^2$, median (range) | 24 (16–35) | 23 (17–31) | 24 (16–35) | 23 (18–30) | 0.89 |
| Previous abdominal surgery, median (%) | 86 (58.11) | 19 (67.86) | 45 (52.33) | 22 (64.71) | 0.24 |

ASA: American Society of Anaesthesiologists; BMI: Body mass index.

more frequently classified as ASA ≥ 3. The ORs of these two characteristics are shown in Table 2.

All 148 patients presenting to the emergency department with CL-SBO had abdominal pain that was accompanied by vomiting in 112 (75.68%) and obstipation in 43 (29.05%). Fifteen patients (10.14%) presented with abdominal guarding and four (2.82%) presented with fever (body temperature > 38.5 $^{o}$C); between-group differences were not significant (Table 3). Tachycardia was reported in 26 patients (17.67%) and tachypnoea in 30 of the 75 patients with that information (40.00%). The occurrence of tachycardia and tachypnoea on admission did not differ significantly in the three study groups (Table 3).

### Blood and laboratory results

One hundred patients (67.57%) had elevated WBC counts and sixty-six patients (44.90%) had an elevated CRP, but between-group differences were not significant (Table 4). The median values of the other laboratory results (Table 5) were within the normal ranges and no significant between-group differences were observed. Arterial blood gases were analyzed in only 9 patients; hence, no conclusions could be drawn.

### CT imaging

The baseline evaluation of the CT scans included no suspicion of ischemia in 18 of the 28 patients (64.29%) with a perioperative viable bowel. The reports for the other 10 patients were inconclusive (Table 6). When ischemia was found during surgery, more than half of the radiology reports had been inconclusive for the suspicion of ischemia (78/148, 52.70%). Strong suspicion of ischemia was reported in only 13.96% of the patients with reversible ischemia (12/86) and 38.24% of patients with irreversible ischemia (13/34).

### Timing

Although the interval between the onset of symptoms and surgery was very variable (2–264 h), the differences in the median hours for the three groups were not significant (Table 7).

### Surgery

In all 34 patients with irreversible ischemia, the affected bowel was resected. The median length of the resected bowel was 45 (range: 30-100) cm. In 30 patients (88.24%), bowel continuity was restored with either a hand-sutured (53.33%) or stapled (46.67%) anastomosis. In 3 patients (9.00%), a temporary ileostomy was constructed. A laparotomy was performed in 128 of the 148 patients (86.49%). In 5 of the patients with viable bowel (17.86%), the obstruction was relieved laparoscopically. Laparoscopic procedures were performed in 13 patients (15.11%) with reversible ischemia and in 2 (5.88%) with irreversible ischemia.

### Postoperative course

The median postoperative hospital stay was 5 (range: 2–13) d for patients with a viable bowel, 6 (range: 2–45) d for those with reversible ischemia, and 8 (range: 3–45) d for those with irreversible ischemia ($P$ = 0.001). Only 32 of 148 patients (21.62%) had postoperative complications (Table 8). Only 1 of those patients was in the viable bowel group. Postoperative morbidity was reported in 44.11% (15/34) of patients with irreversible ischemia and resection, which was significantly higher ($P$ = 0.043) than the frequency in those with reversible ischemia (19.77%, 17/86) and viable bowel (3.57%, 1/28). With reference to the patients with preoperative viable bowel, the ORs for postoperative complications was

**Table 2 Logistic regression of predictors of perioperative ischemia**

| Patient characteristics | Viable bowel, OR (95%CI) | Reversible ischemia, OR (95%CI) | Irreversible ischemia, OR (95%CI) |
|---|---|---|---|
| Age | Ref. | 1.01 (0.98-1.03) | 1.03 (0.99-1.06) |
| ASA classification | | | |
| 1-2 | Ref. | Ref. | Ref. |
| ≥ 3 | Ref. | 1.12 (0.46–2.72) | 3.76 (1.31-10.81) |

ASA: American Society of Anaesthesiologists; CI: Confidence interval; OR: Odds ratio.

**Table 3 Clinical symptoms and vital signs at presentation**

| Signs at presentation | Overall, *n* = 148 | Viable bowel, *n* = 28 | Reversible ischemia, *n* = 82 | Irreversible ischemia, *n* = 34 | *P* value |
|---|---|---|---|---|---|
| Vomiting, *n* (%) | | | | | 0.07 |
| No | 36 (24.32) | 9 (32.14) | 15 (17.44) | 12 (35.29) | |
| Yes | 112 (75.68) | 19 (67.86) | 71 (82.56) | 22 (64.71) | |
| Obstipation[1], *n* (%) | | | | | 0.60 |
| No | 105 (70.95) | 22 (78.57) | 60 (69.77) | 23 (67.65) | |
| Yes | 43 (29.05) | 6 (21.43) | 26 (30.23) | 11 (32.35) | |
| Abdominal guarding, *n* (%) | | | | | 0.35 |
| No | 133 (89.86) | 27 (96.43) | 77 (89.53) | 29 (85.29) | |
| Yes | 15 (10.14) | 1 (3.57) | 9 (10.47) | 5 (14.71) | |
| Heart rate[2], *n* (%) | | | | | 0.42 |
| Bradycardia | 2 (1.35) | 0 (0.00) | 1 (1.16) | 1 (2.94) | |
| Normocardia | 120 (81.08) | 26 (92.86) | 67 (77.91) | 27 (79.41) | |
| Tachycardia | 26 (17.67) | 2 (7.14) | 18 (20.93) | 6 (17.65) | |
| Respiratory rate[3,4], *n* (%) | | | | | 0.50 |
| Normopnoea | 45 (60.00) | 9 (69.23) | 27 (64.29) | 9 (45.00) | |
| Tachypnea | 30 (40.00) | 4 (30.77) | 15 (35.71) | 11 (55.00) | |
| Fever[5], *n* (%) | | | | | 0.52 |
| No | 138 (97.18) | 25 (96.15) | 79 (96.34) | 34 (100.00) | |
| Yes | 4 (2.82) | 1 (3.85) | 3 (3.66) | 0 (0.00) | |

[1]Obstipation: No defecation > 24 h.
[2]Bradycardia: ≤ 50 beats/min; Normocardia: 50-100 beats/min; Tachycardia: > 100 beats/min.
[3]Normopnoea: < 20 breaths/min; Tachypnoea: > 20 breaths/min.
[4]11 patients missing, *n* = 137.
[5]Fever: > 38.5 °C body temperature.

6.65 (95%CI: 0.84-52.47) in patients with reversible ischemia and 19.89 (95%CI: 2.40-164.42) in those with irreversible ischemia.

Severe Clavien–Dindo classification ≥ IIIa complications occurred in 12 patients (14%) with reversible ischemia and in 10 (30%) with irreversible ischemia. Twelve re-exploration procedures were performed during postoperative recovery; one was for an intra-abdominal abscess with ileus in a patient in the viable bowel group. Three patients with reversible ischemia required re-exploration for a suspected perforation, which was not confirmed. Hence, no additional small bowel resection was performed. Two re-exploration procedures resulted in small bowel resection after initial surgery with irreversible ischemia; one was performed because of intra-abdominal bleeding and the other because of an ischemic colostomy that required reversion. In addition, 2 patients developed respiratory insufficiency and 1 patient was septic; no explanation was found during re-exploration.

**Table 4 Patient characteristics and findings of perioperative ischemia**

| Infection parameters at presentation | Overall, *n* = 148 | Viable bowel, *n* = 28 | Reversible ischemia, *n* = 86 | Irreversible ischemia, *n* = 34 | *P* value |
|---|---|---|---|---|---|
| WBC, median (%) | | | | | |
| 4.5-11 × $10^9$/L | 48 (32.43) | 9 (32.14) | 31 (36.05) | 8 (23.53) | 0.42 |
| > 11 × $10^9$/L | 100 (67.57) | 19 (67.86) | 55 (63.95) | 26 (76.47) | |
| CRP, median (%) | | | | | 0.92 |
| 1–10 mg/L | 82 (55.10) | 15 (53.57) | 49 (56.47) | 18 (52.94) | |
| 11–74 mg/L | 38 (25.85) | 7 (25.00) | 23 (27.06) | 8 (23.53) | |
| > 75 mg/L | 28 (19.05) | 6 (21.43) | 14 (16.47) | 8 (23.53) | |

CRP: C-reactive protein; WBC: White blood cell.

**Table 5 Blood and laboratory results in the three study groups**

| Laboratory results at presentation | Overall, median (range) | Viable bowel, median (range) | Reversible ischemia, median (range) | Irreversible ischemia, median (range) | *P* value |
|---|---|---|---|---|---|
| Haematocrit, L/L | 0.43 (0.31-0.59) | 0.43 (0.37-0.52) | 0.44 (0.34-0.59) | 0.42 (0.31-0.53) | 0.34 |
| Thrombocytes × $10^9$/L | 263.00 (145.00-687.00) | 280.50 (161.00-687.00) | 266.00 (145.00-650.00) | 235.50 (148.00-511.00) | 0.20 |
| WBCs × $10^9$/L | 11.80 (4.0-27.2) | 12.40 (4.80-21.30) | 11.55 (4.00-25.00) | 12.00 (5.50-27.20) | 0.33 |
| CRP, mg/L | 6.00 (1.00-630.00) | 6.00 (1.00-216.00) | 5.50 (1.00-630.00) | 5.00 (1.00-434.00) | 0.84 |
| Creatinine, μmol/L | 80.00 (38.00-785.00) | 81.00 (53.00-141.00) | 80.00 (38.00-785.00) | 81.00 (45.00-258.00) | 0.97 |
| Urea, mmol/L | 6.60 (2.30-30.60) | 5.95 (2.70-23.10) | 6.40 (2.30-30.60) | 7.60 (3.00-20.70) | 0.33 |
| LDH, U/L | 208.00 (109.00-333.00) | 184.00 (142.00-309.00) | 210.00 (109.00-309.00) | 208.00 (151.00-333.00) | 0.15 |
| CK, U/L | 112.00 (24.00-472.00) | 107.50 (30.00-207.00) | 127.50 (51.00-472.00) | 95.00 (24.00-192.00) | 0.47 |
| Albumin, g/L | 44.00 (36.00-52.00) | 43.00 (36.00-50.00) | 44.00 (37.00-52.00) | 40.50 (37.00-51.00) | 0.10 |
| Glucose, mmol/L | 8.00 (5.00-15.60) | 7.40 (5.40-12.20) | 8.00 (5.00-15.60) | 8.20 (5.10-15.00) | 0.19 |

CK: Creatine kinase; CRP: C-reactive protein; LDH: Lactate dehydrogenase; WBC: White blood cell.

**Table 6 Suspicion of ischemia on computed tomography imaging in the three study groups**

| Grading of initial radiology reports | Viable bowel, *n* = 28 | Reversible ischemia, *n* = 86 | Irreversible ischemia, *n* = 34 |
|---|---|---|---|
| No suspicion of ischemia, *n* (%) | 18 (64.29) | 23 (26.74) | 4 (11.76) |
| Inconclusive, *n* (%) | 10 (36.71) | 51 (59.30) | 17 (50.00) |
| Strong suspicion of ischemia, *n* (%) | 0 | 12 (13.96) | 13 (38.24) |

Ten patients (6.76%) died during their hospital stay following surgery, including seven of eight-six with reversible ischemia (8.14%) and three of thirty-four with irreversible ischemia (8.82%). None of the patients with perioperative viable small bowel died after surgery. The causes of death were multiorgan failure because of postoperative systemic inflammatory response syndrome, aspiration, and pneumonia with congestive heart failure.

**Table 7 Intervals between onset of symptoms and computed tomography and surgery in the three study groups**

| Intervals | Viable bowel, *n* = 28 | Reversible ischemia, *n* = 86 | Irreversible ischemia, *n* = 34 | *P* value |
|---|---|---|---|---|
| Onset of symptoms to CT, median (range) | 16.50 h (2.00–120.00 h) | 20.50 h (1.00–260.00 h) | 18.00 h (2.00–120.00 h) | 0.79 |
| CT to surgery, median (range) | 4.00 h (1.00–65.00 h) | 4.00 h (1.00–51.00 h) | 4.00 h (1.00–71.00 h) | 0.98 |
| Onset of symptoms to surgery, median (range) | 23.00 h (3.00–124.00 h) | 26.00 h (2.00–264.00 h) | 25.50 h (5.00–126.00 h) | 0.91 |

CT: Computed tomography.

**Table 8 Clavien–Dindo classification of complications and perioperative findings**

| Clavien–Dindo | Overall, *n* = 148 | Viable bowel, *n* = 28 | Reversible ischaemia, *n* = 86 | Irreversible ischaemia, *n* = 34 |
|---|---|---|---|---|
| No complications, *n* (%) | 115 (77.70) | 27 (96.43) | 69 (80.23) | 19 (55.88) |
| Grade I, *n* (%) | 3 (2.03) | 0 (0.00) | 2 (2.33) | 1 (2.94) |
| Grade II, *n* (%) | 7 (4.73) | 0 (0.00) | 3 (3.49) | 4 (11.76) |
| Grade III, *n* (%) | | | | |
| a | 1 (0.68) | 0 (0.00) | 1 (1.16) | 0 (0.00) |
| b | 10 (6.76) | 1 (3.57) | 3 (3.49) | 6 (17.65) |
| Grade IV, *n* (%) | | | | |
| a | 1 (0.68) | 0 (0.00) | 1 (1.16) | 0 (0.00) |
| b | 1 (0.68) | 0 (0.00) | 0 (0.00) | 1 (2.94) |
| Grade V, *n* (%) | 10 (6.76) | 0 (0.00) | 7 (8.14) | 3 (8.82) |

Grade I: Complication without pharmacological, surgical, endoscopic, or radiologic treatment (anti-emetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy were acceptable); Grade II: Complication requiring pharmacological management including blood transfusion or total parenteral nutrition; Grade IIIa: Complication requiring intervention under local anaesthesia; Grade IIIb: Complication requiring general or epidural anaesthesia; Grade IVa: Single organ dysfunction (including dialysis); Grade IVb: Multiorgan dysfunction; Grade V: Patient death.

## DISCUSSION

CL-SBO is a serious clinical diagnosis that can be fatal if left untreated or undiagnosed. Despite the significance of the condition, diagnosis remains a challenge. In this study, a large cohort of patients with surgery for CL-BSO was retrospectively analyzed. Most patients in our cohort presented with abdominal pain that was accompanied with vomiting in 76% of cases, consistent with the 66% to 81% of cases in other studies[19,20]. We believe that obstipation does not often accompany CL-SBO because colon movements usually continue during an obstruction of the small bowel and because CL-SBO is considered a (sub)acute entity. In this cohort, 29% of the patients reported obstipation, as did 22% of the patients in another study[20]. Possibly the definition of obstipation, *i.e.* no stool for > 24 h, was not sufficiently specific, as not all patients have bowel movements every 24 h, and a change in their bowel movement pattern was not noted. With regard to patient characteristics, 42% had no history of abdominal surgery, which is noteworthy and more than reported in previous studies that included smaller cohorts[2,21]. Even in patients without a history of abdominal surgery presenting with abdominal pain and vomiting without fever, a CT should be performed to rule out CL-BSO.

Patients with CL-SBO and irreversible ischemia were significantly older and had higher ASA classifications than those in the other study groups. Older patients also had an increased risk of 3% *per* year for perioperative irreversible ischemia. Patients with an ASA classification of > 3 had an increased risk (OR of 3.76) of perioperative irreversible ischemia. Other studies have not reported a correlation between age or ASA classification and intraoperative outcome in CL-SBO patients[11,12]. To the best of our knowledge, this is the first study to report an association of comorbidities and ASA classification in patients with surgery for CL-BSO. The finding is very important for guiding the surgical approach and expectations of treatment for such high-risk patients.

Some studies reported that a WBC count of > $10 \times 10^9$ cells/L was predictive of perioperative bowel ischemia[2,19]. In our CL-BSO series, the WBC count was increased in most patients and was highest in patients with irreversible ischemia (77%), but the differences in WBC count were not significant. Another study reported a WBC count of > $10 \times 10^9$ and a CRP concentration of > 75 mg/L as two out of

six variables indicating the need for surgery with resection for ischemia. The reported sensitivity was 67.7% and the specificity was 90.8%[11]. CRP is an acute-phase reactant and considered a predictor of vascular compromise and bacterial translocation severity[22]. Contrary to a study by Schwenter *et al* [11], only 43% of the patients in our cohort with reversible ischemia and 48% with irreversible ischemia had an elevated CRP. That might have been a result of the short interval between the onset of symptoms and presentation. However, the results in our large patient cohort indicate that a CRP concentration within the normal range does not ensure the absence of ischemia in patients who present with signs of CL-SBO.

CT imaging is reported to have high interobserver agreement for the diagnosis of CL-SBO. However, small bowel ischemia can be much more difficult to predict, and has poor-to-moderate interobserver agreement[23,24]. Radiologists have a significant role in recognizing signs that require immediate surgical exploration. In studies of small cohorts, increased unenhanced bowel wall attenuation was reported to be predictive of (irreversible) ischemia[12,13,25,26].

When the need for surgery is determined, the choice between a laparotomy or laparoscopic procedure is made by the surgeon. In most of the literature on CL-SBOs, the type of surgical procedure is not discussed[2,19,21]. Most comparisons have found that recovery and in-hospital stays are longer after a laparotomy than after laparoscopic surgery and with less postoperative morbidity after laparoscopic surgeries[27]. Therefore, the type of surgical approach was taken into account in our dataset. Laparoscopic procedures comprised only 13% (20/148) of the procedures performed in this study. The percentage of laparoscopic procedures was the highest in patients with a perioperative viable bowel (17%, 5/28). This type of abdominal surgery will be performed more and more frequently by specialized gastrointestinal surgeons in the acute setting, which may lead to more laparoscopic procedures, with better postoperative morbidity and shorter in-hospital stay.

During surgery, 120 patients (81%) were found to have ischemia, which was reversible in 86 (58%). Although resection was not necessary in that group, 30-d morbidity was 20% and mortality was 8%. After surgery for irreversible ischemia, morbidity increased to 45% and mortality was 9%, consistent with the 39% and 9% rates reported in other study populations[5,21]. High morbidity and mortality in patients with CL-SBO and ischemia show that we have to pay close attention to patients who present with CL-SBO that requires emergent surgery. In this cohort, 2 of 86 patients (2.33%) with perioperative reversible ischemia required re-exploration and additional small bowel resection, suggestive of more advanced ischemia than initially expected. We have to pay close postoperative attention to patients with reversible ischemia.

Although surgery *vs* conservative treatment of complicated SBOs has been widely studied, to the best of our knowledge this is the first study to compare patients with absent, reversible, and irreversible ischemia, and the largest patient cohort to include only CL-SBO cases. We assessed patient characteristics, clinical presentation, blood values, and initial radiology reports as predictors of ischemia. Postoperative outcomes were taken into account. This relatively large cohort of 148 patients in a single center was analyzed retrospectively, with a focus on the clinical characteristics and blood results that were able to predict perioperative ischemia and postoperative outcomes.

## CONCLUSION

In conclusion, a diagnosis of CL-SBO should not be ignored in patients with no history of abdominal symptoms. In patients with CL-SBO, older age and an ASA classification ≥ 3 were predictive of irreversible ischemia, and urgent surgery is indicated. Patients should be informed of the relatively high chance of morbidity, longer in-hospital stay, and mortality after resection. Lastly, a CRP concentration within the normal range in patients with suspected CL-SBO does not ensure that ischemia is not present.

## ARTICLE HIGHLIGHTS

### *Research background*

Closed-loop small bowel obstruction (CL-SBO) can threaten the viability of the intestine by obstruction of a bowel segment at two adjacent points. Prompt recognition of CL-SBO, followed by surgery, is crucial. Clinical predictors of perioperative ischemia and postoperative outcome have not been previously analyzed in a cohort as large as this one.

### *Research motivation*

To date, most studies have evaluated patients with SBOs by comparing surgical *vs* conservative treatments. Studies for CL-SBOs have mostly focused on aspects of computed tomography imaging. The perioperative findings of previous studies vary and there is often a lack information on the postoperative outcomes.

### *Research objectives*

The aim of this study was to analyze perioperative characteristics and postoperative outcomes of patients with surgery for CL-SBO and to evaluate clinical predictors.

### *Research methods*

The medical records of a cohort of 148 patients who underwent surgery for CL-SBO were analyzed retrospectively. Univariate analysis was performed to identify clinical characteristics that were associated with specific perioperative outcomes. The odds ratios for those that were significantly associated with outcomes were analyzed by logistic regression.

### *Research results*

Of 148 patients with CL-SBO, 28 (19%) had a perioperative viable small bowel, 86 (58%) had reversible ischemia and 34 (23%) had irreversible ischemia. Median age and American Society of Anesthesiologists (ASA) classification were significantly higher in patients with irreversible ischemia ($P$ = 0.042 and 0.008, respectively). Postoperative morbidity was significantly higher in patients with perioperative irreversible ischemia (45%, $P$ = 0.043) than in those with reversible ischemia (20%) and a viable bowel (4%).

### *Research conclusions*

Older patients and those with an ASA classification ≥ 3 had an increased risk of irreversible ischemia. C-reactive protein within the normal range did not ensure the absence of ischemia. After irreversible ischemia, postoperative morbidity was increased.

### *Research perspectives*

The study results are relevant to preoperative informed consent procedures in patients with CL-SBO. Close attention should be paid to patients with perioperative ischemia for the prompt detection of postoperative complications.


## FOOTNOTES


**Author contributions:** Toneman MK, de Kok BM, Zijta FM, Oei S, van Acker GJD, Westerterp M and van der Pool AEM designed the report; Toneman MK collected the patient's clinical data, analyzed the data and wrote the paper; de Kok BM, Zijta FM, Oie S, van Acker GJD, Westerterp M and van der Pool AEM revised the paper for important intellectual content; van der Pool AE supervised the report.

**Institutional review board statement:** The Institutional Review Board of Haaglanden Medical center provided approval for this study, No. 2018-105.

**Informed consent statement:** The scientific board of our hospital approved the study. Because the law on medical scientific research concerning humans was not applicable due of the non-invasive and retrospective nature of the study, the need for written informed consent was waived. However, it was required that every patient file was checked for notes of refusal to participate in scientific research.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Data sharing statement:** The corresponding author (Masja K Toneman, mktoneman@gmail.com) of this article is available for contact about the dataset, which is anonymized. The keyfile to translate to patients is available.

**STROBE statement:** The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.





**Country/Territory of origin:** Netherlands



**ORCID number:** Masja K Toneman 0000-0002-2674-0635; Bente M de Kok 0000-0002-2020-5797; Frank M Zijta 0000-0001-9813-5226; Stanley Oei 0000-0002-4859-1044; Gijs J D van Acker 0000-0002-6131-7656; Marinke Westerterp 0000-0003-2698-0329; Anne E M van der Pool 0000-0002-1426-6649.



**S-Editor:** Fan JR

**L-Editor:** A
**P-Editor:** Fan JR

## REFERENCES

1 **Frasure SE**, Hildreth A, Takhar S, Stone MB. Emergency department patients with small bowel obstruction: What is the anticipated clinical course? *World J Emerg Med* 2016; **7**: 35-39 [PMID: 27006736 DOI: 10.5847/wjem.j.1920-8642.2016.01.006]
2 **Zielinski MD**, Eiken PW, Bannon MP, Heller SF, Lohse CM, Huebner M, Sarr MG. Small bowel obstruction-who needs an operation? *World J Surg* 2010; **34**: 910-919 [PMID: 20217412 DOI: 10.1007/s00268-010-0479-3]
3 **Taghavifar S**, Joyce P, Salehi S, Khosa F, Shin H, Gholamrezanezhad A, Shah S. Computed Tomography in Emergency Diagnosis and Management Considerations of Small Bowel Obstruction for Surgical vs. Non-surgical Approach. *Curr Med Imaging* 2022; **18**: 275-284 [PMID: 34182911 DOI: 10.2174/1573405617666210628154218]
4 **Kim J**, Lee Y, Yoon JH, Lee HJ, Lim YJ, Yi J, Jung WB. Non-strangulated adhesive small bowel obstruction: CT findings predicting outcome of conservative treatment. *Eur Radiol* 2021; **31**: 1597-1607 [PMID: 33128599 DOI: 10.1007/s00330-020-07406-3]
5 **Millet I**, Taourel P, Ruyer A, Molinari N. Value of CT findings to predict surgical ischemia in small bowel obstruction: A systematic review and meta-analysis. *Eur Radiol* 2015; **25**: 1823-1835 [PMID: 25850889 DOI: 10.1007/s00330-014-3440-2]
6 **Paulson EK**, Thompson WM. Review of small-bowel obstruction: the diagnosis and when to worry. *Radiology* 2015; **275**: 332-342 [PMID: 25906301 DOI: 10.1148/radiol.15131519]
7 **Tong JWV**, Lingam P, Shelat VG. Adhesive small bowel obstruction - an update. *Acute Med Surg* 2020; **7**: e587 [PMID: 33173587 DOI: 10.1002/ams2.587]
8 **Ten Broek RPG**, Krielen P, Di Saverio S, Coccolini F, Biffl WL, Ansaloni L, Velmahos GC, Sartelli M, Fraga GP, Kelly MD, Moore FA, Peitzman AB, Leppaniemi A, Moore EE, Jeekel J, Kluger Y, Sugrue M, Balogh ZJ, Bendinelli C, Civil I, Coimbra R, De Moya M, Ferrada P, Inaba K, Ivatury R, Latifi R, Kashuk JL, Kirkpatrick AW, Maier R, Rizoli S, Sakakushev B, Scalea T, Søreide K, Weber D, Wani I, Abu-Zidan FM, De'Angelis N, Piscioneri F, Galante JM, Catena F, van Goor H. Bologna guidelines for diagnosis and management of adhesive small bowel obstruction (ASBO): 2017 update of the evidence-based guidelines from the world society of emergency surgery ASBO working group. *World J Emerg Surg* 2018; **13**: 24 [PMID: 29946347 DOI: 10.1186/s13017-018-0185-2]
9 **Jancelewicz T**, Vu LT, Shawo AE, Yeh B, Gasper WJ, Harris HW. Predicting strangulated small bowel obstruction: an old problem revisited. *J Gastrointest Surg* 2009; **13**: 93-99 [PMID: 18685902 DOI: 10.1007/s11605-008-0610-z]
10 **Diamond M**, Lee J, LeBedis CA. Small Bowel Obstruction and Ischemia. *Radiol Clin North Am* 2019; **57**: 689-703 [PMID: 31076026 DOI: 10.1016/j.rcl.2019.02.002]
11 **Schwenter F**, Poletti PA, Platon A, Perneger T, Morel P, Gervaz P. Clinicoradiological score for predicting the risk of strangulated small bowel obstruction. *Br J Surg* 2010; **97**: 1119-1125 [PMID: 20632281 DOI: 10.1002/bjs.7037]
12 **Rondenet C**, Millet I, Corno L, Boulay-Coletta I, Taourel P, Zins M. Increased unenhanced bowel-wall attenuation: a specific sign of bowel necrosis in closed-loop small-bowel obstruction. *Eur Radiol* 2018; **28**: 4225-4233 [PMID: 29679213 DOI: 10.1007/s00330-018-5402-6]
13 **Millet I**, Boutot D, Faget C, Pages-Bouic E, Molinari N, Zins M, Taourel P. Assessment of Strangulation in Adhesive Small Bowel Obstruction on the Basis of Combined CT Findings: Implications for Clinical Care. *Radiology* 2017; **285**: 798-808 [PMID: 28759326 DOI: 10.1148/radiol.2017162352]
14 **Zaigham H**, Ekelund M, Regnér S, Olsson Å. Abdominal pain after gastric bypass in the acute general surgical care setting. *Surg Obes Relat Dis* 2020; **16**: 2058-2067 [PMID: 32839123 DOI: 10.1016/j.soard.2020.07.008]
15 **Geubbels N**, Lijftogt N, Fiocco M, van Leersum NJ, Wouters MW, de Brauw LM. Meta-analysis of internal herniation after gastric bypass surgery. *Br J Surg* 2015; **102**: 451-460 [PMID: 25708572 DOI: 10.1002/bjs.9738]
16 **Comittee AHoDE**. ASA Physical Status Classification System. [citation 10 June 2021]. Available from: https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system
17 **Vallicelli C**, Coccolini F, Catena F, Ansaloni L, Montori G, Di Saverio S, Pinna AD. Small bowel emergency surgery: literature's review. *World J Emerg Surg* 2011; **6**: 1 [PMID: 21214933 DOI: 10.1186/1749-7922-6-1]
18 **Dindo D**, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205-213 [PMID: 15273542 DOI: 10.1097/01.sla.0000133083.54934.ae]
19 **Huang X**, Fang G, Lin J, Xu K, Shi H, Zhuang L. A Prediction Model for Recognizing Strangulated Small Bowel Obstruction. *Gastroenterol Res Pract* 2018; **2018**: 7164648 [PMID: 29780412 DOI: 10.1155/2018/7164648]
20 **Zielinski MD**, Eiken PW, Heller SF, Lohse CM, Huebner M, Sarr MG, Bannon MP. Prospective, observational validation of a multivariate small-bowel obstruction model to predict the need for operative intervention. *J Am Coll Surg* 2011; **212**: 1068-1076 [PMID: 21458305 DOI: 10.1016/j.jamcollsurg.2011.02.023]
21 **Hashimoto D**, Hirota M, Matsukawa T, Yagi Y, Baba H. Clinical features of strangulated small bowel obstruction. *Surg Today* 2012; **42**: 1061-1065 [PMID: 22661266 DOI: 10.1007/s00595-012-0207-8]
22 **El-Awady SI**, El-Nagar M, El-Dakar M, Ragab M, Elnady G. Bacterial translocation in an experimental intestinal obstruction model. C-reactive protein reliability? *Acta Cir Bras* 2009; **24**: 98-106 [PMID: 19377777 DOI: 10.1590/s0102-86502009000200005]
23 **Kato K**, Mizunuma K, Sugiyama M, Sugawara S, Suzuki T, Tomabechi M, Kariyasu T, Fukuda T. Interobserver agreement on the diagnosis of bowel ischemia: assessment using dynamic computed tomography of small bowel obstruction. *Jpn J Radiol* 2010; **28**: 727-732 [PMID: 21191737 DOI: 10.1007/s11604-010-0500-7]

24 **Makar RA**, Bashir MR, Haystead CM, Iseman C, Mayes N, Hebert S, Allen BC, Bhattacharya SD, Choudhury KR, Jaffe TA. Diagnostic performance of MDCT in identifying closed loop small bowel obstruction. *Abdom Radiol (NY)* 2016; **41**: 1253-1260 [PMID: 26830421 DOI: 10.1007/s00261-016-0656-4]

25 **Kohga A**, Kawabe A, Yajima K, Okumura T, Yamashita K, Isogaki J, Suzuki K, Muramatsu K. CT value of the intestine is useful predictor for differentiate irreversible ischaemic changes in strangulated ileus. *Abdom Radiol (NY)* 2017; **42**: 2816-2821 [PMID: 28647770 DOI: 10.1007/s00261-017-1227-z]

26 **Geffroy Y**, Boulay-Coletta I, Jullès MC, Nakache S, Taourel P, Zins M. Increased unenhanced bowel-wall attenuation at multidetector CT is highly specific of ischemia complicating small-bowel obstruction. *Radiology* 2014; **270**: 159-167 [PMID: 24029649 DOI: 10.1148/radiol.13122654]

27 **Sajid MS**, Khawaja AH, Sains P, Singh KK, Baig MK. A systematic review comparing laparoscopic *vs* open adhesiolysis in patients with adhesional small bowel obstruction. *Am J Surg* 2016; **212**: 138-150 [PMID: 27162071 DOI: 10.1016/j.amjsurg.2016.01.030]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 June 27; 14(6): 567-579

DOI: 10.4240/wjgs.v14.i6.567

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

# Transjugular intrahepatic portosystemic shunt with radioactive seed strand for main portal vein tumor thrombosis with cirrhotic portal hypertension

Xuan-Hui Yan, Zhen-Dong Yue, Hong-Wei Zhao, Lei Wang, Zhen-Hua Fan, Yi-Fan Wu, Ming-Ming Meng, Ke Zhang, Li Jiang, Hui-Guo Ding, Yue-Ning Zhang, Yong-Ping Yang, Fu-Quan Liu

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Lidofsky S, United States; Maslennikov R, Russia
**A-Editor:** Yao QG, China

**Received:** December 1, 2021
**Peer-review started:** December 1, 2021
**First decision:** April 16, 2022
**Revised:** April 21, 2022
**Accepted:** May 21, 2022
**Article in press:** May 21, 2022
**Published online:** June 27, 2022

**Xuan-Hui Yan, Fu-Quan Liu,** Department of Interventional Therapy, Peking University Ninth School of Clinical Medicine, Beijing Shijitan Hospital, Beijing 100038, China

**Zhen-Dong Yue, Lei Wang, Zhen-Hua Fan, Yi-Fan Wu, Fu-Quan Liu,** Department of Interventional Therapy, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, China

**Hong-Wei Zhao,** Department of Interventional Therapy, Beijing Tongren Hospital, Capital Medical University, Beijing 100005, China

**Ming-Ming Meng,** Department of Gastroenterology, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, China

**Ke Zhang, Li Jiang,** Department of General Surgery, Beijing Ditan Hospital, Capital Medical University, Beijing 100102, China

**Hui-Guo Ding,** Department of Gastroenterology, Beijing You'an Hospital, Capital Medical University, Beijing 100069, China

**Yue-Ning Zhang,** Department of Liver Disease Digestion Center, Beijing You'an Hospital, Capital Medical University, Beijing 100069, China

**Yong-Ping Yang,** Department of Liver Disease, The Fifth Medical Center of Chinese PLA General Hospital, Beijing 100039, China

**Corresponding author:** Fu-Quan Liu, BCPS, MD, Director, Professor, Department of Interventional Therapy, Peking University Ninth School of Clinical Medicine, Beijing Shijitan Hospital, No. 10 Tie Yi Road, Yangfangdian, Haidian District, Beijing 100038, China.
lfuquan@aliyun.com

## Abstract

*BACKGROUND*

Patients with hepatocellular carcinoma complicated with main portal vein tumor thrombosis (mPVTT) and cirrhotic portal hypertension (CPH) have an extremely poor prognosis, and there is a lack of a clinically effective treatment paradigm.

*AIM*

To evaluate the efficacy and safety of transjugular intrahepatic portosystemic shunt (TIPS) combined with radioactive seed strand for the treatment of mPVTT patients with CPH.

***METHODS***

The clinical data of 83 consecutive patients who underwent TIPS combined with $^{125}$I seed strand placement for mPVTT and CPH from January 2015 to December 2018 were retrospectively reviewed. Procedure-related data (success rate, relief of portal vein pressure and CPH symptoms, and adverse events), PVTT response, and patient survival were assessed through a 2-year follow-up.

***RESULTS***

The success rate was 100.0% without perioperative death or procedure-related severe adverse events. The mean portal vein pressure was significantly decreased after the procedure (22.25 ± 7.33 mmHg *vs* 35.12 ± 7.94 mmHg, $t$ = 20.61, $P$ < 0.001). The symptoms of CPH were all effectively relieved within 1 mo. The objective response rate of PVTT was 67.5%. During a mean follow-up of 14.5 ± 9.4 mo (range 1-37 mo), the cumulative survival rates at 6, 12 and 24 mo were 83.1%, 49.7%, and 21.8%, respectively. The median survival time was 12.0 ± 1.3 mo (95% confidence interval: 9.5-14.5). In multivariate Cox regression analysis, body mass index, Child-Pugh grade, cTNM stage, and PVTT response were independent prognostic factors ($P$ < 0.05).

***CONCLUSION***

TIPS combined with radioactive seed strand might be effective and safe in treating mPVTT patients with CPH.

**Key Words:** Transjugular intrahepatic portosystemic shunt; Radioactive seed strand; Portal vein tumor thrombosis; Hepatocellular carcinoma; Cirrhotic portal hypertension; Cirrhosis



**Core Tip:** We adequately evaluated whether transjugular intrahepatic portosystemic shunt combined with radioactive seed strand placement was safe in adverse events and effective in portal vein tumor thrombosis response and prolonging survival time for the treatment of patients with main portal vein tumor thrombosis and cirrhotic portal hypertension through a retrospective cohort study with 2 years of follow-up.

**Citation:** Yan XH, Yue ZD, Zhao HW, Wang L, Fan ZH, Wu YF, Meng MM, Zhang K, Jiang L, Ding HG, Zhang YN, Yang YP, Liu FQ. Transjugular intrahepatic portosystemic shunt with radioactive seed strand for main portal vein tumor thrombosis with cirrhotic portal hypertension. *World J Gastrointest Surg* 2022; 14(6): 567-579
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i6/567.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i6.567

## INTRODUCTION

Portal vein tumor thrombosis (PVTT) is common in patients with hepatocellular carcinoma (HCC), with an incidence of 44.0%-62.2%[1]. Main PVTT (mPVTT) is defined as PVTT invading the main trunk of the portal vein, accounting for approximately 19.5%-35.2% of PVTT[2-4]. The prognosis of patients with PVTT is poor and the median overall survival is only 2.7-4.0 mo without treatment[5].

HCC is mostly based on cirrhosis, and is usually complicated with cirrhotic portal hypertension (CPH). The decompensated stage of CPH is often accompanied by high-mortality events, *e.g.*, esophagogastric variceal bleeding (EGVB) and refractory ascites/hydrothorax. EGVB is associated with a mortality of 10%-20% at 6 wk[6], and refractory ascites is associated with a reduction in the survival rate to 50% at 6 mo[7]. Once PVTT is combined with cirrhosis-related decompensated events, it would worsen the disease and accelerate the death of patients.

The treatment strategies for PVTT include palliative surgical resection, transarterial chemoembolization (TACE), external radiotherapy, chemotherapy, and targeted therapy[2,8,9], but these treatments are usually infeasible and unsatisfactory in patients with decompensated CPH. Transjugular intrahepatic portosystemic shunt (TIPS) is an effective treatment for CPH[10,11] and eliminates pylemphraxis with the covered stent, but the stent has no substantial therapeutic effect on mPVTT and results in PVTT progression and stent stenosis.

In recent years, the application of radioactive seed placement, such as the low-energy radionuclide $^{125}$I [12-14], has attracted attention and achieved promising efficacy when combined with portal vein stents. Radioactive seed strand placement is one method of endovascular brachytherapy. The purpose of this study was to retrospectively analyze the clinical efficacy of TIPS combined with radioactive seed strand placement for mPVTT patients with CPH from January 2015 to December 2018.

## MATERIALS AND METHODS

### Participants

The study was approved by the Ethics Committee and Institutional Review Board of Peking University Ninth School of Clinical Medicine. A consecutive cohort of 83 patients with HCC who underwent TIPS combined with $^{125}$I seed strand placement for mPVTT and CPH from January 2015 to December 2018 was retrospectively reviewed. Patients with incomplete clinical data or loss to follow-up were excluded from the analysis. Among 81 patients, 70 (84.3%) were males and 13 (15.7%) were females, aged 35-79 years (mean 56.46 years). There were 62 (74.7%) cases of EGVB, 14 (16.9%) cases of refractory ascites/hydrothorax, and 7 (8.4%) cases of both. Child–Pugh grading included 23 (27.7%) cases with grade A, 52 (62.7%) cases with grade B, and 8 (9.6%) cases with grade C. According to cTNM staging, 55 (66.3%) cases were stage IIIB, 19 (22.9%) cases were stage IVA, and 9 (10.8%) cases were stage IVB. The baseline characteristics of the patients are presented in Table 1.

### Study design

Procedure-related data [success rate, relief of portal vein pressure (PVP) and CPH symptoms, and adverse events], mPVTT response, and patient survival were assessed through a 2-year follow-up. The success rate was defined by the planned stent and seed successfully placed. PVTT response was determined according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST)[15] by experienced radiologists: (1) Complete response (CR) was defined as disappearance of PVTT; (2) Partial response (PR) was a ≥ 30% reduction of the PVTT lesion compared with baseline; (3) Progressive disease (PD) was defined as ≥ 20% enlargement of the PVTT lesion than baseline; (4) Stable disease (SD) referred to the PVTT lesion that did not reach the standard of PR and PD. The objective response rate (ORR) of PVTT was the sum of CR and PR. Patient survival was defined as the period from the day of operation to patient death from any cause or to the last follow-up time point.

Adverse events were classified as shunt-related adverse events and radiation-related adverse events. Shunt-related adverse events consisted of post-TIPS hepatic encephalopathy (HE), the recurrence of CPH, shunt stenosis, and shunt-induced potential distant metastasis. The recurrence of CPH was determined as recurrent EGVB or hepatic ascites/hydrothorax, which principally resulted from shunt or intra-stent stenosis. Shunt stenosis was indicated by the recurrence of CPH events and confirmed by imaging [*e.g.*, enhanced computed tomography (CT) or portal venography]. Shunt-induced potential distant metastasis was defined as new-onset hematogenous metastasis after shunt opening of TIPS, which was diagnosed by systemic imaging or pathology. Radiation-related adverse events included radiation injury and seed strand or $^{125}$I seed translocation.

### TIPS combined with transcatheter radioactive seed strand placement

All patients were fully evaluated before the procedure: (1) The severity of esophagogastric varices (EGV) was graded by gastroscopy; (2) The degree of ascites was graded by ultrasound examination[16]; (3) Child-Pugh was used for evaluation of liver function; (4) Tumors were staged according to both the international Barcelona Clinic Liver Cancer (BCLC) staging system[17] and cTNM staging system[18]; and (5) intrahepatic tumor size was determined as the sum of the longest viable tumor diameters of typical intrahepatic target lesions according to mRECIST[15], measured by experienced radiologists.

The indications for the procedure were as follows: (1) mPVTT secondary to HCC, as confirmed by percutaneous biopsy or enhanced CT/magnetic resonance imaging /positron emission tomography imaging; (2) Intrahepatic CPH confirmed by imaging examinations and hepatic venous pressure gradient (HVPG) measurement; (3) Failure of prior conservative treatment for cirrhosis-related decompensated events such as EGVB or refractory ascites/hydrothorax; and (4) Life expectancy > 2 mo. The contraindications were any one of the following: (1) Uncomplicated prehepatic portal hypertension; (2) Severe cardiac, cerebral, respiratory, renal insufficiency or other systemic malignancy; (3) Rapid progression in hepatic insufficiency; (4) Intrahepatic tumor hampering the procedure; (5) Allergy to contrast agent; and (6) Pregnancy or lactation. The operation was performed by interventional physicians with more than 15 years of experience. The benefits and potential risks of the procedure were explained thoroughly to all patients and their families, and then, written informed consent was signed.

During the procedure, the right internal jugular vein was punctured routinely under local anesthesia. After intubation to the inferior vena cava and hepatic vein, HVPG was measured, and then RUPS-100 (Cook Inc., United States) was inserted. According to preoperative imaging and angiography, the appropriate position and angle were determined to puncture the intrahepatic portal vein from the hepatic vein or inferior vena cava of the hepatic segment. After successful puncture, an angiographic

**Table 1 Baseline characteristics of patients**

| Characteristics | *n* (%)/mean ± SD/M ($P_{25}$-$P_{75}$) |
|---|---|
| Gender (male/female) | 70/13 (84.3/15.7) |
| Age (yr) | 56.46 ± 8.97 |
| BMI | 22.83 ± 2.99 |
| Etiology of cirrhosis (HBV/HCV/alcoholic/other) | 66/8/4/5 (79.5/9.6/4.8/6.0) |
| Cirrhosis-related decompensated events (EGVB/Refractory ascites or hydrothorax/Both) | 62/14/7 (74.7/16.9/8.4) |
| EGV degree (mild/moderate/severe) | 7/36/40 (8.4/43.4/48.2) |
| Ascites degree (no/mild/moderate-severe) | 8/24/51 (9.6/28.9/61.4) |
| Preoperative HVPG (mmHg) | 19.96 ± 9.01 |
| Child–Pugh grade (A/B/C) | 23/52/8 (27.7/62.7/9.6) |
| Intrahepatic HCC morphology (unifocal/multifocal) | 47/36 (56.6/43.4) |
| Sum of longest viable tumor diameters (cm) | 6.62 ± 2.77 |
| ≤ 5/5-8/> 8 | 23/44/16 (27.7/53.0/19.3) |
| BCLC stage (C/D) | 75/8 (90.4/9.6) |
| cTNM stage (IIIB/IVA/IVB) | 55/19/9 (66.3/22.9/10.8) |
| PLT ($10^9$/L) | 108.24 ± 86.09 |
| PT (s) | 14.89 ± 3.89 |
| ALT (U/L) | 31.40 ± 29.29 |
| AST (U/L) | 49.63 ± 45.00 |
| TBil (μmol/L) | 31.74 ± 17.68 |
| Albumin (g/L) | 35.08 ± 4.85 |
| AFP (ng/mL)[1] | 769.49 (16.69-2345.11) |
| $Log_{10}$(AFP) | 2.40 ± 1.26 |
| Combined TACE/RFA/targeted therapy | 83/52/41 (100/62.7/49.4) |

[1]Skewness distribution. The upper limit of AFP detection is 20000 ng/mL. BMI: Body mass index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; EGVB: Esophagogastric variceal bleeding; EGV: Esophagogastric varices; HVPG: Hepatic venous pressure gradient; HCC: Hepatocellular carcinoma; PLT: Platelet; PT: Prothrombin time; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBil: Total bilirubin; AFP: Alpha-fetoprotein; TACE: Transarterial chemoembolization; RFA: Radiofrequency ablation.

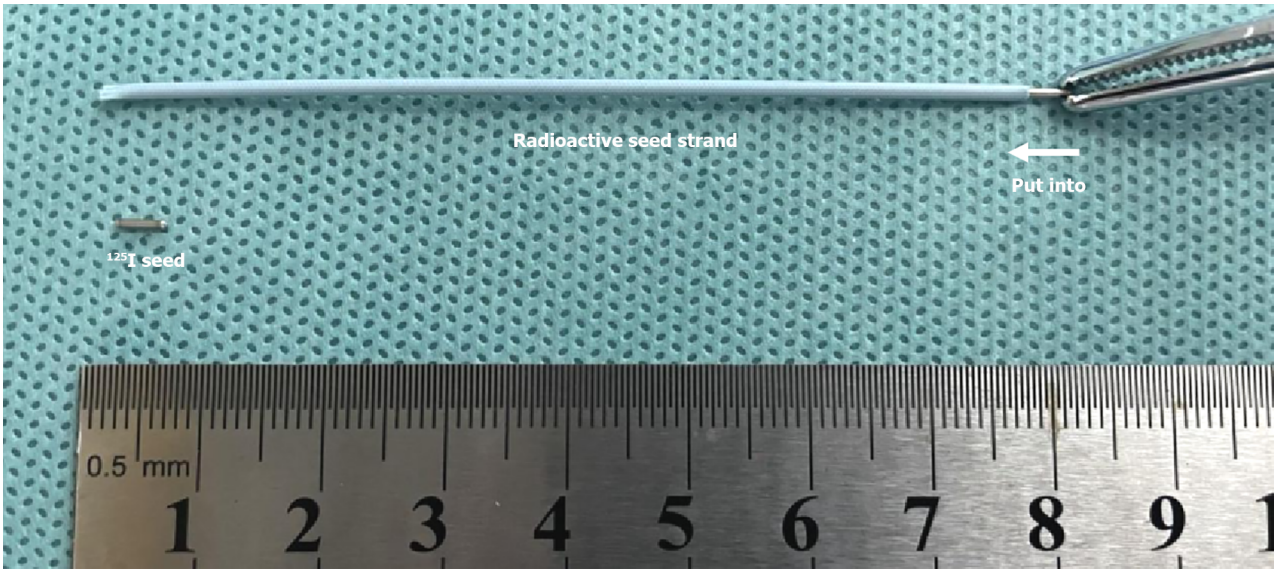
catheter was inserted for portal venography, and the puncture set was placed into the intrahepatic portal vein.

Before shunting, PVP was measured, and then PVTT was grabbed and aspirated as much as possible. Two ultrasmooth guidewires were inserted through the outer sheath of RUPS-100, one of which was retained in the splenic vein, and the other introduced a 4-5F single-bend or cobra catheter that was selected to the distal end of branch PVTT. Then, a 6F guiding catheter was replaced, and a radioactive seed strand was implanted *via* the guiding catheter. Next, a 6-8 mm balloon was introduced through the outer sheath to dilate the shunt, and then a 7-8 mm Fluency covered stent (Bard Inc., United States) was placed. According to the extent of mPVTT, a distal 10-12 mm covered stent was placed for the entire coverage of mPVTT.

The radioactive seed (Isotope & Radiation Corp., China) was fully loaded into a 4F catheter in vitro, creating the radioactive seed strand (Figure 1). Then, the radioactive seed strand was placed outside the stents *via* a 6F guiding catheter (by the guidewire retained in the splenic vein). The radioactive seed strand was compressed and fixed to the portal vein by the stents. The length of the radioactive seed strand was usually more than 10 mm at both ends of the PVTT. Finally, PVP after shunting was measured, and portal venography was performed again (Figure 2).

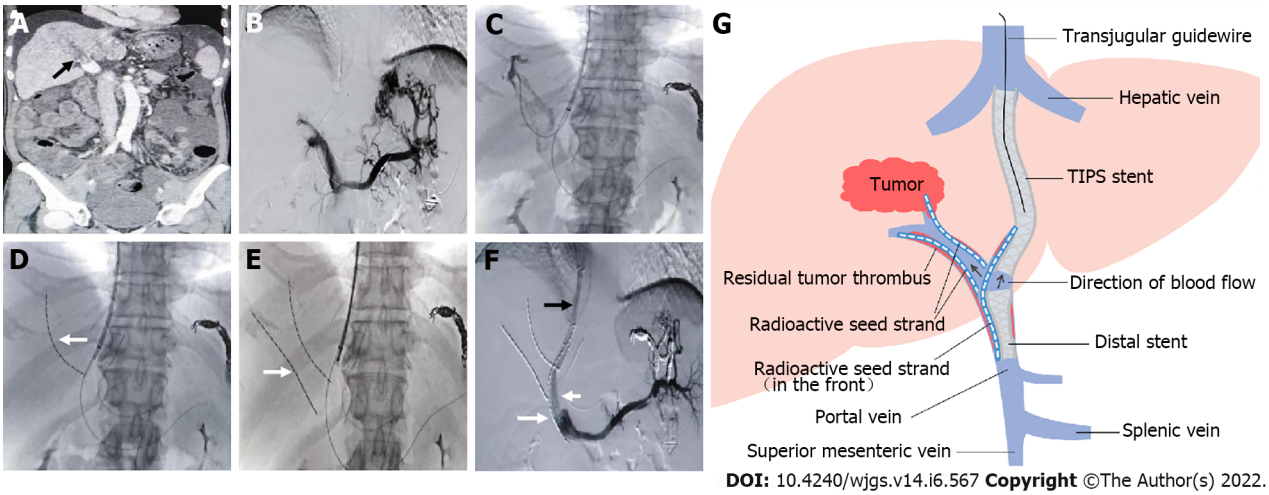
### *Treatment for HCC*

TACE was used for intrahepatic tumors and PVTT lesions every 1-3 mo by using an embolic agent (lipiodol 3-30 mL) and chemotherapy drugs (epirubicin 10-20 mg and hydroxycamptothecine 5-15 mg).




**DOI:** 10.4240/wjgs.v14.i6.567 **Copyright** ©The Author(s) 2022.

**Figure 1 Assembly of a radioactive seed strand *in vitro*.**




**DOI:** 10.4240/wjgs.v14.i6.567 **Copyright** ©The Author(s) 2022.

**Figure 2 Representative case.** A: Filling defect in the main portal vein (black arrow), suggesting main portal vein tumor thrombosis; B: Most of the intrahepatic branches did not develop under contrast, and several short gastric veins were obviously varicose; C and D: A guidewire was retained in the splenic vein, a catheter was directed into the secondary branch of the right portal vein, and then a radioactive seed strand (white arrow) was implanted; E: Another radioactive seed strand (white arrow) was implanted into another secondary branch of the right portal vein; F: A shunt of transjugular intrahepatic portosystemic shunt (black arrow) was established, a distal stent (short white arrow) was placed, and then a radioactive seed strand (long white arrow) was implanted. Portal venography showed unobstructed blood flow in the shunt and obvious reduction in the varicose veins; G: Schematic diagram. TIPS: Transjugular intrahepatic portosystemic shunt.

TACE was performed in all patients (ranging from 1-12 times per patient and an average of 4.2 times).

Radiofrequency ablation (RFA) was also carried out for intrahepatic tumors in patients with good coagulation function and platelet count and the inability to sequentially undergo TACE due to arterial occlusion after repeated arterial intervention. The RFA equipment was WHK-IB, Beijing Welfare Electronics Co., China. 52 of 83 patients underwent RFA (ranging from 1-3 times per patient and an average of 1.6 times).

According to patients' specific conditions and wishes, 41 patients received targeted therapy such as sorafenib or lenvatinib.

### *Follow-up*

All patients were followed up by telephone at a 4-6-wk interval postoperatively until death or their last follow-up. At 3, 6, 12, and 24 mo after the operation, patients were required to undergo a hospital revisit to assess PVTT response and adverse events. Sequential TACE or RFA was performed on the intrahepatic primary lesions. In addition, positive and timely management was given for adverse events such as post-TIPS HE, shunt stenosis, and recurrence of CPH.

### Statistical analysis

Continuous variables conforming to a normal distribution are presented as the mean ± SD and median (interquartile range) [M ($P_{25}$-$P_{75}$)] for those with a nonnormal distribution. Categorical variables are presented as percentages (%). The mean values of two related samples were compared by using the paired samples *t* test. In survival analysis, the Kaplan-Meier curve was performed for description, the log-rank test was utilized for comparison, and Cox regression was carried out for correlated factor analysis. Variables satisfying the proportional hazards assumption were included in the multivariate analysis using Cox regression. $P < 0.05$ was considered a statistically significant difference. IBM SPSS software version 26.0 was used for statistical analysis.

## RESULTS

### Procedure-related data

The success rate of the procedure was 100.0% (83/83), without perioperative death or procedure-related serious adverse events. The number of implanted seeds ranged from 29 to 95, with an average of 47 per patient. The mean PVP was significantly decreased after the procedure (22.25 ± 7.33 mmHg *vs* 35.12 ± 7.94 mmHg, $t = 20.61$, $P < 0.001$). The symptoms of CPH, including EGVB and/or refractory ascites/hydrothorax, were all effectively relieved within 1 mo.

The mean follow-up period was 14.5 ± 9.4 mo (range 1-37 mo). HE developed in a total of 16 patients (19.3%) after the procedure, most of whom had mild HE in clinical stages 1-2. The cumulative recurrence rates of CPH at 6, 12, and 24 mo were 9.6% (8/83), 22.9% (19/83), and 33.7% (28/83), respectively. The cumulative rates of shunt stenosis at 6, 12, and 24 mo were 13.3% (11/83), 28.9% (24/83), and 38.6% (32/83), respectively (Table 2). During follow-up, no seed strand shift or $^{125}$I seed fall-off and translocation occurred, and no radiation injury (such as radiation-induced liver disease or gastrointestinal ulceration) was observed.

### PVTT response

Four patients failed to be assessed on account of death within 2 mo. The ORR of PVTT was 67.5% (Table 3). Among patients who presented PD, all 6 cases related to PVTT exceeded the distal portal system, *e.g.*, the mesenteric vein or splenic vein.

### Patient survival

The Kaplan-Meier survival curve is shown in Figure 3. The median survival time was 12.0 ± 1.3 mo [95% confidence interval (CI): 9.5-14.5]. The cumulative survival rates at 6, 12, and 24 mo were 83.1%, 49.7%, and 21.8%, respectively.

In the stratification analysis using the survival curves and log-rank test, patients with age < 60, Child-Pugh grade A or B, BCLC stage C, cTNM stage IIIB or IVA, and PVTT response had significant survival benefits ($P < 0.05$) in the comparison of their respective groups (Figure 4 and Table 4). Notably, cTNM staging showed a more detailed stratification capability than BCLC staging.

In Cox regression analysis, the relevant parameters including body mass index (BMI), Child-Pugh grade, cTNM stage, and PVTT response, were independent prognostic factors as indicated in the multivariate Cox regression model (Table 5).

## DISCUSSION

With the development of multidisciplinary teamwork, HCC complicated with PVTT has attracted increasing interest and research. Owing to the biological characteristics of HCC and anatomical features of the liver, HCC cells tend to invade the intrahepatic vasculature, especially the portal venous system [19]. In the past few years, the application of $^{125}$I seeds[12-14] has provided a new therapy for advanced HCC. In our study, the ORR of PVTT reached 67.5% after $^{125}$I seed strand placement. In multivariate survival analysis, PVTT response had a significant effect on patient survival, which could reduce the risk of death [hazard ratio (HR) = 0.472]. Additionally, no radiation injury was observed during postoperative follow-up. In short, radioactive seed strand placement may be an effective approach for the local treatment of PVTT.

It is a biological effect of ionizing radiation that $^{125}$I relies on by continuously releasing low-energy γ rays to kill tumor cells and then achieve the purpose of treatment. With a half-value layer of only 17 mm in equivalent tissue, $^{125}$I rarely involves adjacent tissues or organs. Thus, radioactive seed strand placement has the advantages of a high local dose to the tumor thrombus and less damage to normal tissues.

In addition, radioactive seed strands also have the following advantages: first, the length of the seed strand can be determined according to the length of the tumor thrombus, and the seeds in the catheter are arranged neatly; second, the seed strand implanted in the portal vein branch does not shift, nor does

**Table 2 Summary of long-term efficacy and safety**

| Items | 6 mo | 12 mo | 24 mo |
|---|---|---|---|
| Cumulative survival rate (%) | 83.1 | 49.7 | 21.8 |
| Cumulative rate of shunt stenosis (%) | 13.3 | 28.9 | 38.6 |
| Cumulative recurrence rate of CPH (%) | 9.6 | 22.9 | 33.7 |

CPH: Cirrhotic portal hypertension.

**Table 3 Summary of portal vein tumor thrombosis response in short-term efficacy**

| PVTT response | CR | PR | SD | PD | Response (ORR) |
|---|---|---|---|---|---|
| Number (%) | 15 (18.1) | 41 (49.4) | 17 (20.5) | 6 (7.2) | 56 (67.5) |

PVTT: Portal vein tumor thrombosis; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; ORR: Objective response rate.

**Table 4 Summary of survival comparison of different stratification factors**

| Stratification indicator | Log-rank $\chi^2$ | *P* value |
|---|---|---|
| Gender | 0.448 | 0.503 |
| Age group | 5.311 | 0.021 |
| EGV degree | 0.448 | 0.600 |
| Ascites degree | 1.308 | 0.520 |
| Child-Pugh grade | 15.810 | < 0.001 |
| Intrahepatic HCC morphology | 0.174 | 0.677 |
| Group of tumor diameters | 1.685 | 0.431 |
| BCLC stage | 10.883 | < 0.001 |
| cTNM stage | 51.774 | < 0.001 |
| Combined with RFA | 0.275 | 0.600 |
| Combined with targeted therapy | 0.001 | 0.978 |
| PVTT response | 22.617 | < 0.001 |
| Post-TIPS HE | 0.255 | 0.613 |
| Shunt stenosis | 0.027 | 0.868 |
| Recurrence of CPH | 0.235 | 0.628 |

EGV: Esophagogastric varices; HCC: Hepatocellular carcinoma; BCLC: Barcelona Clinic Liver Cancer; RFA: Radiofrequency ablation; PVTT: Portal vein tumor thrombosis; TIPS: Transjugular intrahepatic portosystemic shunt; HE: Hepatic encephalopathy; CPH: Cirrhotic portal hypertension.

the seed strand that is fixed in the main portal vein by stents; and finally, radioactive seed have antitumor and anti-intimal hyperplasia effects, which can prevent stent stenosis. However, as a drawback of this approach, when the diameter of the tumor thrombus is large, the effective radiation dose may not be achieved.

In clinical practice, the management of HCC patients with PVTT often neglects the effective diagnosis and treatment of CPH. PVTT patients complicated with CPH usually have an extremely poor prognosis. TIPS is an established treatment for CPH and its decompensated events by establishing a shunt between the intrahepatic portal vein and the hepatic vein or inferior vena cava. In our study, PVP was significantly reduced, and the symptoms of CPH were efficaciously relieved in mPVTT patients with CPH after combined TIPS. Moreover, survival analysis showed that the severity of EGV and the degree of ascites had no significant impact on survival, which indirectly indicated the therapeutic effect of TIPS on decompensated CPH.

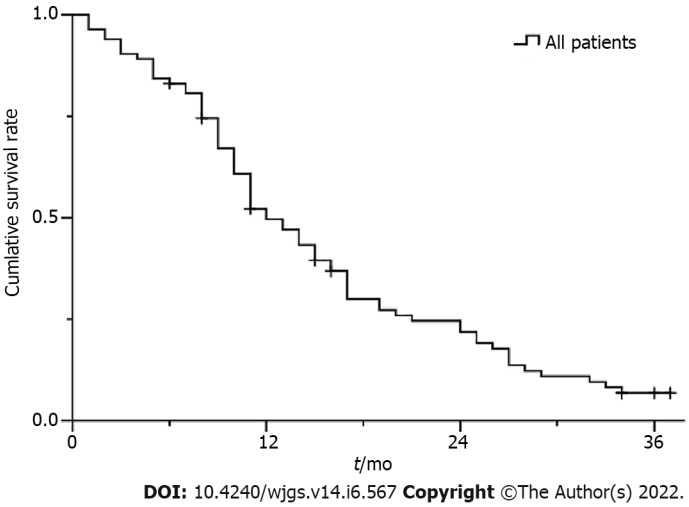
**Table 5 Correlative factors for survival in univariate and multivariate analyses**

| Variable | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95%CI | *P* value | HR | 95%CI | *P* value |
| Gender (female/male) | 1.237 | 0.650-2.355 | 0.518 | | | |
| Age (years) | 1.039 | 1.011-1.068 | 0.006 | | | |
| BMI | 0.781 | 0.701-0.871 | < 0.001 | 0.861 | 0.768-0.965 | 0.010 |
| EGV degree (mild/moderate/severe) | 1.130 | 0.796-1.605 | 0.493 | | | |
| Ascites degree (no/mild/moderate-severe) | 1.055 | 0.760-1.464 | 0.748 | | | |
| Preoperative HVPG (mmHg) | 1.006 | 0.979-1.034 | 0.668 | | | |
| Child-Pugh grade | | | < 0.001 | | | |
| A/B | 1.856 | 1.068-3.225 | 0.028 | 2.243 | 1.270-3.961 | 0.005 |
| A/C | 4.999 | 2.099-11.907 | < 0.001 | 7.308 | 2.898-18.425 | < 0.001 |
| Intrahepatic HCC morphology (unifocal/multifocal) | 0.909 | 0.570-1.447 | 0.687 | | | |
| Sum of longest viable tumor diameters (cm) | 1.070 | 0.988-1.158 | 0.097 | | | |
| BCLC stage (C/D) | 3.216 | 1.509-6.851 | 0.002 | | | |
| cTNM stage (IIIB/IVA/IVB) | 3.269 | 2.228-4.795 | < 0.001 | 2.745 | 1.726-4.366 | < 0.001 |
| PLT ($10^9$/L) | 1.000 | 0.997-1.003 | 0.917 | | | |
| PT (s) | 1.006 | 0.959-1.056 | 0.802 | | | |
| ALT (U/L) | 1.004 | 0.994-1.013 | 0.465 | | | |
| AST (U/L) | 1.003 | 0.998-1.008 | 0.173 | | | |
| TBil (μmol/L) | 1.022 | 1.008-1.035 | 0.001 | | | |
| Albumin (g/L) | 0.929 | 0.886-0.974 | 0.002 | | | |
| $Log_{10}$(AFP) (ng/mL) | 1.341 | 1.097-1.639 | 0.004 | | | |
| Combined RFA (no/yes) | 0.885 | 0.552-1.419 | 0.612 | | | |
| Combined targeted therapy (no/yes) | 0.994 | 0.627-1.574 | 0.978 | | | |
| Reduction of PVP (mmHg) | 1.025 | 0.983-1.069 | 0.247 | | | |
| PVTT response (nonresponse/response) | 0.302 | 0.176-0.516 | < 0.001 | 0.472 | 0.259-0.859 | 0.014 |
| Post-TIPS HE (no/yes) | 0.864 | 0.482-1.551 | 0.625 | | | |
| Shunt stenosis (no/yes) | 1.039 | 0.650-1.662 | 0.873 | | | |
| Recurrence of CPH (no/yes) | 1.122 | 0.694-1.814 | 0.639 | | | |

BMI: Body mass index; EGV: Esophagogastric varices; HVPG: Hepatic venous pressure gradient; HCC: Hepatocellular carcinoma; PLT: Platelet; PT: Prothrombin time; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBil: Total bilirubin; AFP: Alpha-fetoprotein; RFA: Radiofrequency ablation; PVP: Portal vein pressure; PVTT: Portal vein tumor thrombosis; TIPS: Transjugular intrahepatic portosystemic shunt; HE: Hepatic encephalopathy; CPH: Cirrhotic portal hypertension.

In addition, TIPS still has the following effects: first, it can improve liver functional reserve by improving portal blood supply to normal liver tissue and then prevent fatal liver failure caused by PVTT and provide favorable conditions for the subsequent treatment of intrahepatic primary lesions; next, the covered stent of TIPS plays a part in covering and compressing PVTT; and last, TIPS is able to resolve portal hypertension not only caused by cirrhosis but also due to the combination of intrahepatic cirrhosis and prehepatic PVTT[20,21].

TIPS combined with radioactive seed strand placement and sequential TACE/RFA for mPVTT with CPH may reduce the mortality risk from decompensated events of CPH (*i.e.*, nonneoplastic mortality risk) as well as reduce neoplastic mortality risk by controlling PVTT and primary lesions, prolonging survival. In our study, the median survival time of patients was 12.0 ± 1.3 mo (95%CI: 9.5-14.5), and the cumulative survival rates at 6, 12 and 24 mo were 83.1%, 49.7% and 21.8%, respectively. In a systematic




**DOI:** 10.4240/wjgs.v14.i6.567 

**Figure 3 Kaplan-Meier survival curve for all patients.**

review[13] of 6 retrospective studies involving mPVTT patients whose CPH was unclear, after percutaneous transhepatic $^{125}$I seed strand with stent placement combined with TACE, the median survival time was 10.3 mo (range 4.9-12.5 mo), and the cumulative survival rates at 6, 12 and 24 mo were 74.5% (range 61.8%-88.9%), 48.7% (range 32.4%-54.5%) and 20.1% (range 14.1%-26.1%), respectively. Huo *et al*[22] reported that in mPVTT patients partly mixed with CPH, the 2-year cumulative survival rate after palliative resection was 17.1%. Our results were similar to theirs. Despite similar survival results, it is necessary to differentiate and treat CPH in the management of PVTT or mPVTT patients.

In regard to postoperative long-term complications, our results showed that the cumulative rates of shunt stenosis at 6, 12 and 24 mo were 13.3%, 28.9% and 38.6%, respectively. Luo *et al*[23] and Yu *et al*[24] reported that after $^{125}$I seed strand with stent placement combined with TACE, the cumulative stent patency rates were 43.2% and 46.5% at 12 mo and 26.1% and 25.7% at 24 mo, respectively. Our results were clearly superior to theirs, which might be related to the following reasons: TIPS dredging the blood flow of the portal vein, full use of covered stents, and our postoperative anticoagulation treatment.

Furthermore, by survival analysis, shunt-related adverse events, including post-TIPS HE, shunt stenosis and recurrence of CPH, had no significant influence on survival, which might be related to the timely management of these complications, such as removal of HE inducements, balloon dilatation and/or stent reimplantation for shunt stenosis.

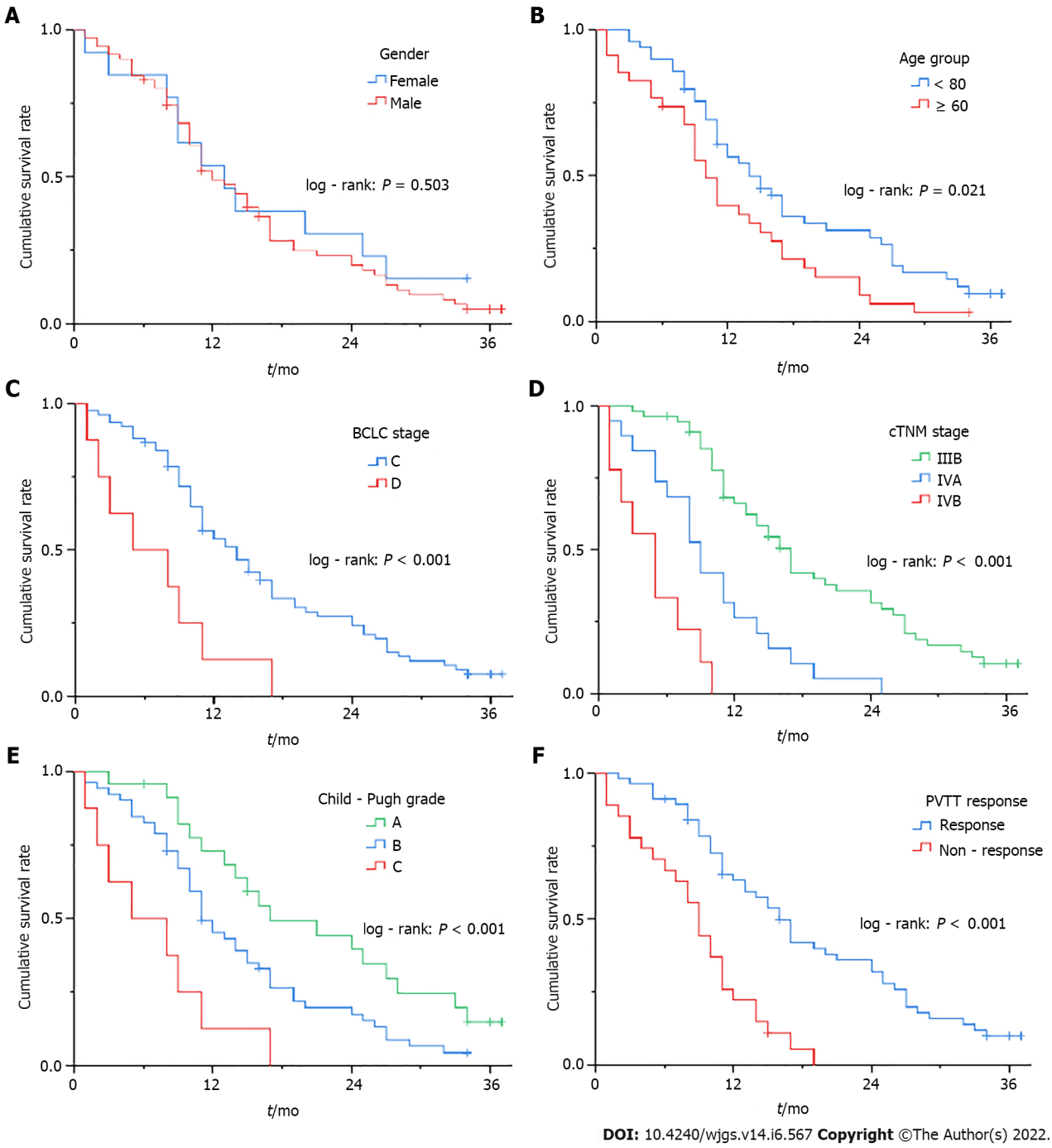
Regarding shunt-induced potential distant metastasis, 5 new cases of pulmonary metastasis and 1 new case of adrenal metastasis were observed. This small number of cases observed might be related to the censoring of death and the nonadherence of patients to the revisit and systematic examination. Further study is needed to expand the sample. However, it cannot be ignored that distant metastasis may be reduced to some extent by PVTT grab and aspiration before shunting, the entire coverage of mPVTT using covered stents, the PVTT response obtained by radioactive seed strand, and active intervention for intrahepatic lesions.

Among other factors that affected survival, cTNM staging showed a more detailed stratification capability than BCLC staging and showed an independent significant association with survival, with an increased risk of death for each increase in cTNM stage (HR = 2.745). Child-Pugh grade was an important factor affecting survival throughout, and the mortality risk in patients with grade C (HR = 7.308) and grade B (HR = 2.243) was much higher than those with grade A. Combining the Child-Pugh liver function grade and the cTNM tumor stage may be of great significance for the assessment of prognosis and survival.

Concerning other tumor-related factors, intrahepatic HCC morphology had no significant effect on survival, and the sum of longest viable tumor diameters approached significance, which might be related to active interventional treatment for intrahepatic primary lesions. Combined RFA was not significant, which might be related to RFA as an additional therapy after TACE for intrahepatic lesions. Combined targeted therapy was also not significant, and some high-quality studies[25,26] showed that targeted therapy did not achieve satisfactory outcomes in the treatment of HCC with PVTT.

BMI exerted a significant influence on survival (HR = 0.861). Patients with advanced HCC and decompensated cirrhosis often present malnutrition, so attention should be given to improving nutrition.

In addition, radioembolizaton was not used in combination therapy because it was not approved during the time of the study, but it could be considered for treatment in the future.




**DOI:** 10.4240/wjgs.v14.i6.567 

**Figure 4 Kaplan-Meier survival curve for different stratification factors.** A: Gender group; B: Age group; C: Barcelona Clinic Liver Cancer stage; D: cTNM stage; E: Child-Pugh grade; F: Portal vein tumor thrombosis response). BCLC: Barcelona Clinic Liver Cancer; PVTT: Portal vein tumor thrombosis.

This single-arm retrospective cohort study has inherent limitations. Further relevant studies are warranted to follow and expand on the findings.

## CONCLUSION

In conclusion, the key points of this initial study may be summarized as follows: (1) TIPS combined with radioactive seed strand placement might be effective and safe in treating mPVTT with CPH, which could effectively alleviate symptoms of portal hypertension and prolong patient survival time; (2) In the management of PVTT or mPVTT patients, it is necessary to differentiate and effectively treat CPH; (3) Combining Child-Pugh liver function grade and cTNM tumor stage may be of guiding significance for the assessment of prognosis and survival.

## ARTICLE HIGHLIGHTS

### *Research background*

Main portal vein tumor thrombosis (mPVTT) is common in patients with hepatocellular carcinoma (HCC). Mostly based on cirrhosis, HCC is usually complicated with cirrhotic portal hypertension (CPH), which is often accompanied by high-mortality decompensated events such as esophagogastric variceal bleeding and refractory ascites/hydrothorax.

### *Research motivation*

HCC patients with PVTT have a poor prognosis with median survival of only 2.7-4.0 mo. Once mPVTT is combined with cirrhotic decompensated events, it would deteriorate the disease and accelerate the death of patients. However, there is a lack of a clinical treatment paradigm for mPVTT patients with CPH.

### *Research objectives*

This cohort study is to evaluate the efficacy and safety of transjugular intrahepatic portosystemic shunt (TIPS) combined with radioactive seed strand for the treatment of mPVTT complicated with CPH. It might contribute new perspectives into clinical treatment management.

### *Research methods*

The clinical data of 83 consecutive patients who underwent TIPS combined with $^{125}$I seed strand placement for mPVTT and CPH from January 2015 to December 2018 were retrospectively reviewed, and the efficacy and safety were adequately evaluated by a 2-year follow-up.

### *Research results*

There was universal improvement in CPH and apparent relief of its decompensated complications after operation. The majority of patients had at least a decrease in the extent of PVTT and the objective response rate of PVTT was 67.5%. The cumulative rate of shunt stenosis and recurrence rate of CPH were low within the first year. The median survival time was 12.0 ± 1.3 mo (95% confidence interval: 9.5-14.5).

### *Research conclusions*

TIPS combined with radioactive seed strand might be effective and safe in the treatment of mPVTT with CPH, which could effectively alleviate symptoms of portal hypertension and prolong patient survival time.

### *Research perspectives*

In the management of HCC patients with PVTT or mPVTT, it is necessary to differentiate and effectively treat CPH. The treatment of mPVTT with CPH is still a clinical difficulty and requires multidisciplinary teamwork. Future studies may require randomized controlled trials to verify our results.

## FOOTNOTES

**Author contributions:** Liu FQ designed the research; Yue ZD, Zhao HW, Wang L, Fan ZH, Wu YF, Meng MM, Zhang K, Jiang L, Ding HG, Zhang YN and Yang YP performed the research; Yan XH analyzed the data and wrote the paper; Liu FQ reviewed and edited the manuscript; all authors read and approved the manuscript.

**Supported by** Beijing Municipal Science and Technology Commission project, The Capital of The Public Health Cultivation, No. Z171100000417031; The Capital Health Research and Development of Special, Beijing Municipal Health Commission, No. 2018-1-2081; and Scientific Research Common Program of Beijing Municipal Commission of Education, No. KM201810025028 (to Liu FQ).

**Institutional review board statement:** The study was reviewed and approved by the Ethics Committee and Institutional Review Board of Peking University Ninth School of Clinical Medicine.

**Informed consent statement:** All study participants or their legal guardians signed written informed consent forms.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Data sharing statement:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**STROBE statement:** The authors have read the STROBE Statement-checklist of items, and the manuscript was

prepared and revised according to the STROBE Statement-checklist of items.



**Country/Territory of origin:** China

**ORCID number:** Xuan-Hui Yan 0000-0003-1706-4847; Zhen-Dong Yue 0000-0001-5403-8336; Hong-Wei Zhao 0000-0001-6409-5537; Lei Wang 0000-0003-4080-1630; Zhen-Hua Fan 0000-0001-5417-1997; Yi-Fan Wu 0000-0003-2709-2729; Ming-Ming Meng 0000-0003-3560-1052; Ke Zhang 0000-0001-9803-138X; Li Jiang 0000-0001-6632-9229; Hui-Guo Ding 0000-0002-8716-4926; Yue-Ning Zhang 0000-0003-2205-3413; Yong-Ping Yang 0000-0002-8307-1095; Fu-Quan Liu 0000-0003-1972-7712.

**S-Editor:** Gao CC
**L-Editor:** A
**P-Editor:** Cai YX

## REFERENCES

1 **Zhang ZM**, Lai EC, Zhang C, Yu HW, Liu Z, Wan BJ, Liu LM, Tian ZH, Deng H, Sun QH, Chen XP. The strategies for treating primary hepatocellular carcinoma with portal vein tumor thrombus. *Int J Surg* 2015; **20**: 8-16 [PMID: 26026424 DOI: 10.1016/j.ijsu.2015.05.009]
2 **Chan SL**, Chong CC, Chan AW, Poon DM, Chok KS. Management of hepatocellular carcinoma with portal vein tumor thrombosis: Review and update at 2016. *World J Gastroenterol* 2016; **22**: 7289-7300 [PMID: 27621575 DOI: 10.3748/wjg.v22.i32.7289]
3 **Shi J**, Lai EC, Li N, Guo WX, Xue J, Lau WY, Wu MC, Cheng SQ. Surgical treatment of hepatocellular carcinoma with portal vein tumor thrombus. *Ann Surg Oncol* 2010; **17**: 2073-2080 [PMID: 20131013 DOI: 10.1245/s10434-010-0940-4]
4 **Wang K**, Guo WX, Chen MS, Mao YL, Sun BC, Shi J, Zhang YJ, Meng Y, Yang YF, Cong WM, Wu MC, Lau WY, Cheng SQ. Multimodality Treatment for Hepatocellular Carcinoma With Portal Vein Tumor Thrombus: A Large-Scale, Multicenter, Propensity Mathching Score Analysis. *Medicine (Baltimore)* 2016; **95**: e3015 [PMID: 26986115 DOI: 10.1097/MD.0000000000003015]
5 **Kaneko S**, Tsuchiya K, Yasui Y, Inada K, Kirino S, Yamashita K, Osawa L, Hayakawa Y, Sekiguchi S, Higuchi M, Takaura K, Maeyashiki C, Tamaki N, Takeguchi T, Takeguchi Y, Nagano T, Nakanishi H, Itakura J, Takahashi Y, Himeno Y, Hoshi A, Kurosaki M, Izumi N. Strategy for advanced hepatocellular carcinoma based on liver function and portal vein tumor thrombosis. *Hepatol Res* 2020; **50**: 1375-1385 [PMID: 32924266 DOI: 10.1111/hepr.13567]
6 **de Franchis R**; Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015; **63**: 743-752 [PMID: 26047908 DOI: 10.1016/j.jhep.2015.05.022]
7 **Adebayo D**, Neong SF, Wong F. Refractory Ascites in Liver Cirrhosis. *Am J Gastroenterol* 2019; **114**: 40-47 [PMID: 29973706 DOI: 10.1038/s41395-018-0185-6]
8 **Liu PH**, Huo TI, Miksad RA. Hepatocellular Carcinoma with Portal Vein Tumor Involvement: Best Management Strategies. *Semin Liver Dis* 2018; **38**: 242-251 [PMID: 30041276 DOI: 10.1055/s-0038-1666805]
9 **Cerrito L**, Annicchiarico BE, Iezzi R, Gasbarrini A, Pompili M, Ponziani FR. Treatment of hepatocellular carcinoma in patients with portal vein tumor thrombosis: Beyond the known frontiers. *World J Gastroenterol* 2019; **25**: 4360-4382 [PMID: 31496618 DOI: 10.3748/wjg.v25.i31.4360]
10 **Sankar K**, Moore CM. Transjugular Intrahepatic Portosystemic Shunts. *JAMA* 2017; **317**: 880 [PMID: 28245324 DOI: 10.1001/jama.2016.20899]
11 **Tripathi D**, Stanley AJ, Hayes PC, Travis S, Armstrong MJ, Tsochatzis EA, Rowe IA, Roslund N, Ireland H, Lomax M, Leithead JA, Mehrzad H, Aspinall RJ, McDonagh J, Patch D. Transjugular intrahepatic portosystemic stent-shunt in the management of portal hypertension. *Gut* 2020; **69**: 1173-1192 [PMID: 32114503 DOI: 10.1136/gutjnl-2019-320221]
12 **Yuan D**, Gao Z, Zhao J, Zhang H, Wang J. $^{125}$I seed implantation for hepatocellular carcinoma with portal vein tumor thrombus: A systematic review and meta-analysis. *Brachytherapy* 2019; **18**: 521-529 [PMID: 30954398 DOI: 10.1016/j.brachy.2019.01.014]
13 **Zhang L**, Hu B, Li W, Huang P, Zhang S, Zhong BY, Ni CF. $^{125}$I Irradiation Stent for Hepatocellular Carcinoma with Main Portal Vein Tumor Thrombosis: A Systematic Review. *Cardiovasc Intervent Radiol* 2020; **43**: 196-203 [PMID: 31602496 DOI: 10.1007/s00270-019-02346-y]
14 **Li S**, Guo JH, Lu J, Wang C, Wu H, Wang H, Zha J, Fan R. $I^{125}$ irradiation stent for treatment of hepatocellular carcinoma with portal vein thrombosis: A meta-analysis. *Cancer Radiother* 2021; **25**: 340-349 [PMID: 33455874 DOI: 10.1016/j.canrad.2020.12.003]
15 **Lencioni R**, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010; **30**: 52-60 [PMID: 20175033 DOI: 10.1055/s-0030-1247132]
16 **Moore KP**, Wong F, Gines P, Bernardi M, Ochs A, Salerno F, Angeli P, Porayko M, Moreau R, Garcia-Tsao G, Jimenez W, Planas R, Arroyo V. The management of ascites in cirrhosis: report on the consensus conference of the International

Ascites Club. *Hepatology* 2003; **38**: 258-266 [PMID: 12830009 DOI: 10.1053/jhep.2003.50315]
17 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018; **69**: 182-236 [PMID: 29628281 DOI: 10.1016/j.jhep.2018.03.019]
18 **Chun YS**, Pawlik TM, Vauthey JN. 8th Edition of the AJCC Cancer Staging Manual: Pancreas and Hepatobiliary Cancers. *Ann Surg Oncol* 2018; **25**: 845-847 [PMID: 28752469 DOI: 10.1245/s10434-017-6025-x]
19 **Cheng S**, Chen M, Cai J, Sun J, Guo R, Bi X, Lau WY, Wu M. Chinese Expert Consensus on Multidisciplinary Diagnosis and Treatment of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus (2018 Edition). *Liver Cancer* 2020; **9**: 28-40 [PMID: 32071907 DOI: 10.1159/000503685]
20 **Liu L**, Zhao Y, Qi X, Cai G, He C, Guo W, Yin Z, Chen H, Chen X, Fan D, Han G. Transjugular intrahepatic portosystemic shunt for symptomatic portal hypertension in hepatocellular carcinoma with portal vein tumor thrombosis. *Hepatol Res* 2014; **44**: 621-630 [PMID: 23679937 DOI: 10.1111/hepr.12162]
21 **Qiu B**, Li K, Dong X, Liu FQ. Transjugular Intrahepatic Portosystemic Shunt for Portal Hypertension in Hepatocellular Carcinoma with Portal Vein Tumor Thrombus. *Cardiovasc Intervent Radiol* 2017; **40**: 1372-1382 [PMID: 28488102 DOI: 10.1007/s00270-017-1655-8]
22 **Huo L**, Wei W, Yan Z, Lei Z, Xie Y, Gong R, Huang S, Jia N, Xia Y. Short-term and long-term outcomes of liver resection for HCC patients with portal vein tumor thrombus. *Cell Biosci* 2019; **9**: 23 [PMID: 30886700 DOI: 10.1186/s13578-019-0285-z]
23 **Luo JJ**, Zhang ZH, Liu QX, Zhang W, Wang JH, Yan ZP. Endovascular brachytherapy combined with stent placement and TACE for treatment of HCC with main portal vein tumor thrombus. *Hepatol Int* 2016; **10**: 185-195 [PMID: 26341514 DOI: 10.1007/s12072-015-9663-8]
24 **Yu TZ**, Zhang W, Liu QX, Li WH, Ma JQ, Zhang ZH, Yang MJ, Wang JH, Chen B, Zeng SC, Luo JJ, Liu LX, Yan ZP. Endovascular brachytherapy combined with portal vein stenting and transarterial chemoembolization improves overall survival of hepatocellular carcinoma patients with main portal vein tumor thrombus. *Oncotarget* 2017; **8**: 12108-12119 [PMID: 28076848 DOI: 10.18632/oncotarget.14520]
25 **Cheng AL**, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34 [PMID: 19095497 DOI: 10.1016/S1470-2045(08)70285-7]
26 **Zhu K**, Chen J, Lai L, Meng X, Zhou B, Huang W, Cai M, Shan H. Hepatocellular carcinoma with portal vein tumor thrombus: treatment with transarterial chemoembolization combined with sorafenib--a retrospective controlled study. *Radiology* 2014; **272**: 284-293 [PMID: 24708192 DOI: 10.1148/radiol.14131946]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 June 27; 14(6): 580-593

DOI: 10.4240/wjgs.v14.i6.580

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

# Prognostic significance of the preoperative hemoglobin to albumin ratio for the short-term survival of gastric cancer patients

Ce-Gui Hu, Bai-E Hu, Jin-Feng Zhu, Zheng-Ming Zhu, Chao Huang

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

**P-Reviewer:** Silano F, Brazil; Xi Y, China
**A-Editor:** Garg P, India

**Received:** January 11, 2022
**Peer-review started:** January 11, 2022
**First decision:** March 12, 2022
**Revised:** March 20, 2022
**Accepted:** May 28, 2022
**Article in press:** May 28, 2022
**Published online:** June 27, 2022

**Ce-Gui Hu, Bai-E Hu, Jin-Feng Zhu, Zheng-Ming Zhu, Chao Huang,** Department of Gastrointestinal Surgery, The Second Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, China

**Corresponding author:** Chao Huang, PhD, Doctor, Department of Gastrointestinal Surgery, The Second Affiliated Hospital of Nanchang University, No. 1 Minde Road, Nanchang 330006, Jiangxi Province, China. huangchao8041@163.com

## Abstract

***BACKGROUND***

Hemoglobin and albumin are associated with the prognosis of gastric cancer (GC) patients. However, the prognostic value of the hemoglobin to albumin ratio (HAR) for the short-term survival of GC patients with D2 radical resection has not been studied.

***AIM***

To investigate the significance of the HAR in evaluating the short-term survival of GC patients after D2 radical resection and to construct a nomogram to predict the prognosis in GC patients after surgery, thus providing a reference for the development of postoperative individualized treatment and follow-up plans.

***METHODS***

Cox regression and Kaplan-Meier analysis was used for prognostic analysis. Logistic regression was used to analyze the relationships between HAR and the clinicopathological characteristics of the GC patients. A prognostic nomogram model for the short-term survival of GC patients was constructed by R software.

***RESULTS***

HAR was an independent risk factor for the short-term survival of GC patients. GC patients with a low HAR had a poor prognosis ($P < 0.001$). Low HAR was markedly related to high stage [odds ratio (OR) = 0.45 for II *vs* I; OR = 0.48 for III *vs* I], T classification (OR = 0.52 for T4 *vs* T1) and large tumor size (OR = 0.51 for ≥ 4 cm *vs* < 4 cm) (all $P < 0.05$). The nomogram model was based on HAR, age, CA19-9, CA125 and stage, and the C-index was 0.820.

***CONCLUSION***

Preoperative low HAR was associated with short-term survival in GC patients. The prognostic nomogram model can accurately predict the short-term survival of

GC patients with D2 radical resection.

**Key Words:** Gastric cancer; Hemoglobin to albumin ratio; Short-term survival; Prognosis; Nomogram



**Core Tip:** Hemoglobin and albumin are associated with the prognosis of gastric cancer (GC) patients. However, the prognostic value of the hemoglobin to albumin ratio (HAR) for the short-term survival of GC patients with D2 radical resection has not been studied. HAR was an independent risk factor for the short-term survival of GC patients. GC patients with a low HAR had a poor prognosis. Low HAR was markedly related to high stage, T classification and tumor size. The nomogram model was based on HAR, age, CA19-9, CA125 and stage and can accurately predict the short-term survival of D2 radical resection GC patients.

**Citation:** Hu CG, Hu BE, Zhu JF, Zhu ZM, Huang C. Prognostic significance of the preoperative hemoglobin to albumin ratio for the short-term survival of gastric cancer patients. *World J Gastrointest Surg* 2022; 14(6): 580-593
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i6/580.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i6.580

## INTRODUCTION

For resectable gastric cancer (GC), radical surgery and adjuvant therapy are the standard therapies[1,2]. Postoperative prognosis is evaluated by the American Joint Committee on Cancer TNM classification system[3,4]. However, prognostic factors such as age, tumor size and tumor location are not considered in the prediction of individual survival. Moreover, the prognosis of patients in the same stage with similar treatment regimens varies greatly[5,6]. Therefore, it is necessary to develop a comprehensive and accurate prognostic evaluation system to predict the prognosis of GC patients, which is of great significance in selecting individualized treatment plans for these patients.

In addition, studies have shown that the prognosis of cancer is not only correlated with tumor characteristics but also to the nutritional status and systemic inflammation of patients[7,8]. The systemic inflammatory response can affect the progression and metastasis of tumors[9]. Recently, studies also found that malnutrition is associated with decreased immunity, which increases the incidence of complications and mortality postoperatively, leading to poor postoperative prognosis in cancer patients [10,11].

Hemoglobin and albumin are used as the two most common indicators of nutritional status. Various perioperative nutritional parameters have been confirmed as independent prognostic factors in GC patients who underwent D2 radical resection[12]. Low hemoglobin levels can lead to tumor hypoxia, which can accelerate tumor growth and promote the angiogenesis of tumor cells[13]. Low serum albumin concentration was an independent risk factor affecting the survival of GC patients[14]. In addition, low serum albumin levels can impair cellular immune function, leading to poor prognosis in cancer patients[15]. Studies have demonstrated that preoperative low serum albumin and hemoglobin levels are closely associated with the poor prognosis of malignant tumors[16,17]; the high preoperative C-reactive protein to albumin ratio was related to poor outcome in patients with GC[18,19].

However, the clinical value of the hemoglobin to albumin ratio (HAR) in the prognosis of GC patients with D2 radical resection has not been reported. Nomogram can provide the overall probability of specific outcomes for individual patients and provide more accurate predictions than the traditional TNM staging system, thereby improving personalized treatment decisions[20,21]. Therefore, the aim of this study was to investigate the significance of the HAR in evaluating the short-term survival of GC patients after D2 radical resection and to construct a nomogram to predict the prognosis in GC patients after surgery, thus providing a reference for the development of postoperative individualized treatment and follow-up plans.

## MATERIALS AND METHODS

### *Patient characteristics*

The clinical and follow-up data of 312 GC patients who underwent D2 radical resection in our hospital were collected from January 2017 to January 2019. Tumor markers, serum albumin and fibrinogen levels and blood cell counts, including hemoglobin, neutrophils, platelets and lymphocytes, were extracted at

the first admission. The HAR, platelet to hemoglobin ratio, platelet to lymphocyte ratio (PLR), platelet to albumin ratio (PAR), fibrinogen to lymphocyte ratio (FLR), albumin to fibrinogen ratio, hemoglobin to fibrinogen ratio (HFR), platelet to fibrinogen ratio, neutrophil to lymphocyte ratio (NLR) and albumin to lymphocyte ratio were calculated. According to the median HAR value, GC patients were divided into a high HAR group and a low HAR group. The stage of postoperative patients was based on the American Joint Committee on Cancer TNM classification system. Survival time was calculated from the day of surgery to the last follow-up. After surgery, all patients were followed up every 3 mo for the first 2 years and then every 6 mo until 5 years. The last follow-up date was March 1, 2020.

### Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Patients with GC were diagnosed by pathology after surgery; and (2) Neoadjuvant chemoradiotherapy was not performed before surgery. The exclusion criteria were as follows: (1) Patients with a history of surgery 2 mo before admission; (2) Patients with a history of blood transfusion; (3) Patients using hemostatic and anticoagulant drugs; (4) Patients with bleeding, thrombotic disease or splenectomy; and (5) Patients with pregnancy, chronic disease, acute infection, relapse or other distant organ metastases and those who were lost to follow-up or had incomplete information.

### Statistical analysis

Prognostic analysis was performed using Kaplan-Meier and Cox regression analyses. The Mann-Whitney *U* test was used for comparisons between two groups. The relationships between HAR and clinicopathological characteristics were determined by logistic regression. The receiver operating characteristic curve was used to evaluate the ability of a single factor or combined factors to predict the short-term survival of GC patients. The RMS package of R software was used to construct a prognostic nomogram model for the short-term survival of GC patients, and the scores of various indicators were obtained. In addition, Harrell's concordance index (C-index) was calculated to evaluate the performance of the model's prediction results[22]. A *P* value less than 0.05 was considered to indicate a statistically significant result. Analyses were performed by SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, United States) and R (version x64 3.6.1).

## RESULTS

### Prognostic analysis of GC patients with D2 radical resection

The factors associated with prognosis were as follows: age, CEA, CA19-9, CA125, HAR, platelet to hemoglobin ratio, PLR, PAR, FLR, HFR, tumor size, vascular infiltration, nerve infiltration and stage (all $P < 0.05$). Multivariate Cox regression analysis found that age, HAR and stage were independent risk factors affecting prognosis (all $P < 0.05$) (Table 1). Kaplan-Meier analysis found that the difference in the survival time of GC patients with a low HAR and high HAR was statistically significant ($P = 0.003$), indicating that GC patients with low HAR had a poor prognosis (Figure 1).

### Association between HAR and clinicopathological characteristics

To analyze the association between HAR and clinicopathological characteristics, we performed logistic regression analysis. HAR was associated with stage, T classification and large tumor size (all $P < 0.05$) (Figure 2). Logistic regression analysis showed that a low HAR was effectively related to high stage [odds ratio (OR) = 0.45 for II *vs* I; OR = 0.48 for III *vs* I], T classification (OR = 0.52 for T4 *vs* T1) and large tumor size (OR = 0.51 for ≥ 4 cm *vs* < 4 cm) (all $P < 0.05$) in GC patients (Table 2). These results indicate that GC patients with a low HAR were more likely to have advanced GC.

### Comparison between the low HAR group and the high HAR group

To further analyze the relationships between HAR and prognostic factors, we divided the GC patients into a low HAR group and a high HAR group according to the median HAR value. The factors with statistically significant differences between the two groups were sex, CA125, platelet to hemoglobin ratio, PLR, PAR, FLR, HFR, platelet to fibrinogen ratio, NLR, albumin to lymphocyte ratio, large tumor size, stage and T classification (all $P < 0.05$), suggesting that patients with a low HAR had high stage, T classification, CA125, FLR, PAR, PLR, large tumor sizes and low HFR (Table 3 and Figure 3).

### Receiver operating characteristic curve analysis

To evaluate the ability of HAR or combined factors to predict the short-term survival of GC patients, we performed receiver operating characteristic curve analysis. The area under the curve (AUC) of HAR alone in predicting the 1-year survival of GC patients was 0.656, the sensitivity was 78.19%, and the specificity was 52.94%, while the AUC of predicting the 2.5-year survival was 0.804, the sensitivity was 85.29%, and the specificity was 74.95%. The AUC of HAR combined with age, CA19-9, CA125 and stage to predict the 1-year survival of GC patients was 0.833, the sensitivity was 86.83%, and the specificity

**Table 1 Prognostic analysis of clinical characteristics in patients with gastric cancer**

| Clinical variable | *n* | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|
| | 312 | HR (95%CI) | *P* value | HR (95%CI) | *P* value |
| Age (yr) | 62 (54-68) | 1.046 (1.015-1.077) | 0.003 | 1.049(1.017-1.081) | 0.002 |
| Sex (male/female) | 225/87 | 0.715 (0.400-1.280) | 0.259 | | |
| BMI (kg/m$^2$) | 21.55 (19.53-23.55) | 0.983 (0.911-1.062) | 0.670 | | |
| Smoking (yes/no) | 64/248 | 0.442 (0.189-1.034) | 0.060 | | |
| Drinking (yes/no) | 49/263 | 1.316 (0.641-2.701) | 0.454 | | |
| CEA (ng/mL) | 2.94 (1.85-5.29) | 1.006 (1.003-1.009) | 0.000 | | |
| CA19-9 (U/mL) | 13.26 (7.36-23.70) | 1.001 (1.000-1.002) | 0.003 | | |
| CA125 (U/mL) | 8.50 (5.90-13.80) | 1.008 (1.000-1.016) | 0.049 | | |
| CA72-4 (IU/mL) | 1.81 (1.17-4.46) | 1.004 (0.990-1.018) | 0.57 | | |
| HAR | 3.18 (2.68-3.44) | 0.425 (0.278-0.650) | 0.000 | 0.466 (0.301-0.720) | 0.001 |
| PHR | 1.86 (1.40-2.58) | 1.371 (1.194-1.575) | 0.000 | | |
| PLR | 157.74 (114.06-211.23) | 1.003 (1.001-1.006) | 0.004 | | |
| PAR | 5.75 (4.51-7.48) | 1.184 (1.088-1.288) | 0.000 | | |
| FLR | 2.05 (1.49-2.89) | 1.171 (1.018-1.347) | 0.028 | | |
| AFR | 13.16 (10.36-16.85) | 0.970 (0.912-1.033) | 0.344 | | |
| HFR | 42.52 ± 17.83 | 0.974 (0.955-0.993) | 0.007 | | |
| PFR | 77.41 (57.84-101.46) | 1.005 (0.998-1.012) | 0.135 | | |
| NLR | 2.47 (1.76-3.59) | 1.100 (0.974-1.242) | 0.124 | | |
| ALR | 26.25 (22.16-35.08) | 1.008 (0.986-1.030) | 0.489 | | |
| Tumor size (cm) | 4.0 (2.5-5.5) | 1.167 (1.079-1.262) | 0.000 | | |
| Vascular infiltration (present/absent) | 168/144 | 3.230 (1.695-6.153) | 0.000 | | |
| Nerve infiltration (present/absent) | 149/163 | 2.974 (1.651-5.359) | 0.000 | | |
| Histological grade (G1/G2/G3) | 6/120/186 | 0.920 (0.553-1.530) | 0.748 | | |
| Stage (I/II/III) | 88/75/149 | 4.154 (2.291-7.531) | 0.000 | 4.112 (2.225-7.602) | 0.000 |
| Survival status (death/survival) | 53/259 | | | | |
| Follow-up time (d) | 531 (440-691) | | | | |

BMI: Body mass index; PHR: Platelet to hemoglobin ratio; PLR: Platelet to lymphocyte ratio; PAR: Platelet to albumin ratio; FLR: Fibrinogen to lymphocyte ratio; AFR: Albumin to fibrinogen ratio; HFR: Hemoglobin to fibrinogen ratio; PFR: Platelet to fibrinogen ratio; NLR: Neutrophil to lymphocyte ratio; ALR: Albumin to lymphocyte ratio. HR: Hazard ratio; CI: Confidence interval; HAR: Hemoglobin to albumin ratio.

was 84.77%, while the AUC of predicting the 2.5-year survival was 0.832, the sensitivity was 87.87%, and the specificity was 72.18% (Figure 4). These results indicate that HAR combined with prognostic factors can accurately predict the short-term survival of patients with GC.

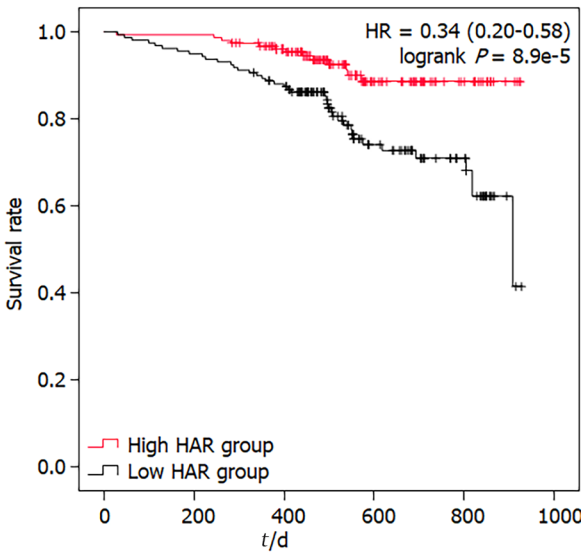
### *Construction of the prognostic nomogram*

To predict the short-term survival probability of GC patients after surgery, we used the rms package to construct a logistic regression model of HAR combined with age, CA19-9, CA125 and stage, and the C-index evaluated by this model was 0.820, indicating that this prediction model had certain accuracy. Then, the plotting function was employed, and the nomogram was plotted (Figure 5). A score of HAR ≥ 3.18 was 0 points, while a score of HAR < 3.18 was 37 points. A score of age ≥ 62 years was 13 points, while a score of age < 62 years was 0 points. A score of CA19-9 ≥ 13.255 U/mL was 26 points, while a score of CA19-9 < 13.255 U/mL was 0 points. A score of CA125 ≥ 8.5 U/mL was 18 points, while a score of CA125 < 8.5 U/mL was 0 points. A score of stage I was 0 points, a score of stage II was 63 points, and a score of stage III was 100 points. The highest score was 194 points, indicating that the 1-year survival

**Table 2 Hemoglobin to albumin ratio value associated with clinical pathological characteristics**

| Clinical characteristics | Total (*n*) | Odds ratio in HAR value | *P* value |
|---|---|---|---|
| Age (≥ 62 yr *vs* < 62 yr) | 312 | 0.78 (0.50-1.21) | 0.264 |
| Size (≥ 4 cm *vs* < 4 cm) | 312 | 0.51 (0.32-0.80) | 0.004 |
| Histological grade | | | |
| (G2 *vs* G1) | 126 | 0.91 (0.16-5.06) | 0.905 |
| (G3 *vs* G1) | 192 | 1.00 (0.18-5.52) | 1.000 |
| Vascular infiltration (yes *vs* no) | 312 | 1.14 (0.73-1.79) | 0.552 |
| Nerve infiltration (yes *vs* no) | 312 | 1.00 (0.64-1.56) | 0.988 |
| Stage | | | |
| (II *vs* I) | 163 | 0.45 (0.24-0.83) | 0.012 |
| (III *vs* I) | 237 | 0.48 (0.28-0.81) | 0.007 |
| T classification | | | |
| (T2 *vs* T1) | 106 | 0.61 (0.27-1.39) | 0.243 |
| (T3 *vs* T1) | 112 | 0.62 (0.28-1.35) | 0.227 |
| (T4 *vs* T1) | 236 | 0.52 (0.29-0.91) | 0.022 |
| N classification | | | |
| (N1 *vs* N0) | 169 | 0.76 (0.33-1.74) | 0.518 |
| (N2 *vs* N0) | 201 | 0.56 (0.30-1.04) | 0.067 |
| (N3 *vs* N0) | 226 | 0.68 (0.39-1.16) | 0.160 |

HAR: Hemoglobin to albumin ratio.




**DOI:** 10.4240/wjgs.v14.i6.580 

**Figure 1 Survival curve of gastric cancer patients with low hemoglobin to albumin ratio and high hemoglobin to albumin ratio.** HAR: Hemoglobin to albumin ratio; HR: Hazard ratio.

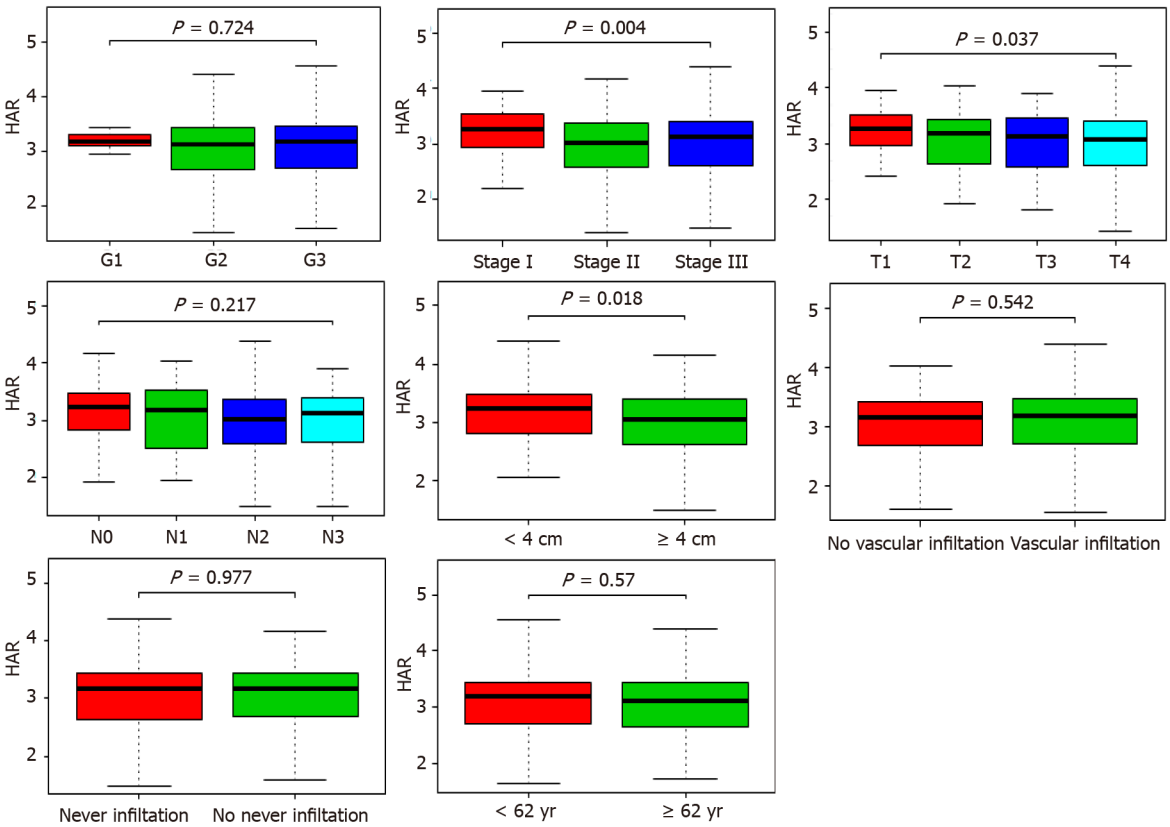
probability of GC patients was 60%-65% and that the 5-year survival probability was < 10%. According to the total points, the probability of the short-term survival of GC patients can be predicted.

**Table 3 Comparison of the relevant factors between the high hemoglobin to albumin ratio group and low hemoglobin to albumin ratio group**

| Factors | High HAR group (*n* = 158) | Low HAR group (*n* = 154) | *P* value |
|---|---|---|---|
| Age (yr) | 61 (53-67) | 63 (54-69) | 0.266 |
| Sex (*n*) | | | 0.000 |
| Male | 132 | 93 | |
| Female | 26 | 61 | |
| BMI (kg/m$^2$) | 21.81 (19.90-23.82) | 21.30 (19.32-23.33) | 0.154 |
| Smoking (*n*) | | | 0.468 |
| Yes | 35 | 29 | |
| No | 123 | 125 | |
| Drinking (*n*) | | | 0.322 |
| Yes | 28 | 21 | |
| No | 130 | 133 | |
| CEA (ng/mL) | 2.89 (1.87-5.23) | 2.97 (1.83-5.44) | 0.581 |
| CA19-9 (U/mL) | 12.63 (7.43-21.52) | 13.38 (7.23-24.20) | 0.658 |
| CA125 (U/mL) | 8.30 (5.68-11.30) | 9.15 (6.08-16.80) | 0.034 |
| CA72-4 (IU/mL) | 1.91 (1.19-4.46) | 1.73 (1.14-4.46) | 0.396 |
| PHR | 1.55 (1.25-1.95) | 2.29 (1.71-3.36) | 0.000 |
| PLR | 138.71 (98.29-188.22) | 177.27 (134.34-252.12) | 0.000 |
| PAR | 5.49 (4.36-6.86) | 6.04 (4.70-8.20) | 0.002 |
| FLR | 1.83 (1.39-2.62) | 2.26 (1.57-3.11) | 0.001 |
| AFR | 13.73 (10.92-16.83) | 12.62 (9.69-16.93) | 0.162 |
| HFR | 48.46 ± 14.63 | 36.42 ± 18.78 | 0.000 |
| PFR | 73.48 (57.12-92.62) | 79.78 (60.16-112.23) | 0.040 |
| NLR | 2.32 (1.74-3.36) | 2.89 (1.92-3.78) | 0.024 |
| ALR | 24.40 (19.05-32.52) | 27.87 (23.08-35.77) | 0.000 |
| Tumor size (cm) | 3.5 (2.4-5.0) | 4.5 (3.0-6.1) | 0.009 |
| Vascular infiltration (*n*) | | | 0.507 |
| present | 88 | 80 | |
| absent | 70 | 74 | |
| Nerve infiltration (*n*) | | | 0.918 |
| present | 75 | 74 | |
| absent | 83 | 80 | |
| Histological grade (*n*) | | | 0.682 |
| G1 | 3 | 3 | |
| G2 | 59 | 61 | |
| G3 | 96 | 90 | |
| Stage (*n*) | | | 0.036 |
| I | 56 | 32 | |
| II | 32 | 43 | |
| III | 70 | 79 | |
| T classification (*n*) | | | 0.037 |

| | | | |
|---|---|---|---|
| T1 | 44 | 27 | |
| T2 | 18 | 17 | |
| T3 | 20 | 21 | |
| T4 | 76 | 89 | |
| N classification (*n*) | | | 0.141 |
| N0 | 79 | 63 | |
| N1 | 14 | 13 | |
| N2 | 25 | 34 | |
| N3 | 40 | 44 | |

HAR: Hemoglobin to albumin ratio; BMI: Body mass index; PHR: Platelet to hemoglobin ratio; PLR: Platelet to lymphocyte ratio; PAR: Platelet to albumin ratio; FLR: Fibrinogen to lymphocyte ratio; AFR: Albumin to fibrinogen ratio; HFR: Hemoglobin to fibrinogen ratio; PFR: Platelet to fibrinogen ratio; NLR: Neutrophil to lymphocyte ratio; ALR: Albumin to lymphocyte ratio.

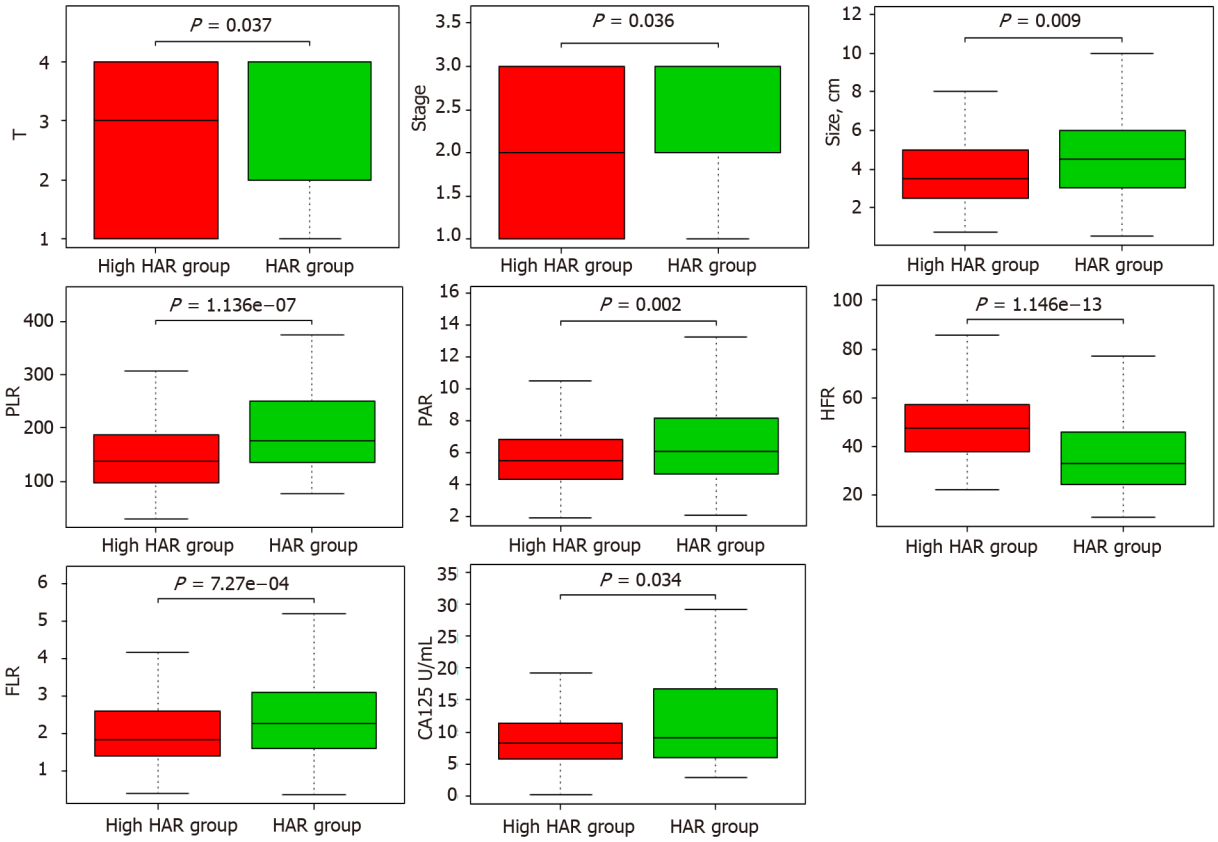



**DOI:** 10.4240/wjgs.v14.i6.580 

**Figure 2 Association between hemoglobin to albumin ratio and clinicopathological characteristics, including grade, stage, T classification, N classification, tumor size, vascular infiltration, nerve infiltration and age.** HAR: Hemoglobin to albumin ratio.

## DISCUSSION

The systemic inflammatory response and malnutrition are markedly related to the prognosis of cancer [10,11,13]. Neutrophils, lymphocytes, platelets and fibrinogen may play important roles in tumor-induced systemic inflammatory responses[23,24]. Hemoglobin and albumin are the two most common indicators of nutritional status. At the same time, serum albumin can also reflect the inflammation of patients. Various scores and indicators based on inflammation and nutritional status have been produced to predict the prognosis of cancer, such as the controlling nutritional status score, C-reactive protein to albumin ratio, NLR, PLR, prognostic nutrition index and systemic immune inflammation index[25-27].




**DOI:** 10.4240/wjgs.v14.i6.580 

**Figure 3 Relationships between hemoglobin to albumin ratio and prognostic factors, including stage, T classification, and tumor size, CA125, fibrinogen to lymphocyte ratio, platelet to albumin ratio, platelet to lymphocyte ratio and hemoglobin to fibrinogen ratio.** HAR: Hemoglobin to albumin ratio; FLR: Fibrinogen to lymphocyte ratio; HFR: Hemoglobin to fibrinogen ratio; PAR: Platelet to albumin ratio; PLR: Platelet to lymphocyte ratio.

Deng *et al*[28] showed that the preoperative PLR was significantly associated with poor prognosis in GC patients with surgical resection. Gu *et al*[29] also found that GC patients with elevated PLR had poor overall survival. Sun *et al*[30] indicated that the combination of NLR and PLR was an independent risk factor for the overall survival of stage III GC patients undergoing radical resection. In addition, Suzuki *et al*[31] found that high plasma fibrinogen was related to tumor progression and poor overall survival in GC patients. Huang *et al*[32] showed that elevated FLR was a high risk factor for peritoneal metastasis in patients with GC. This study also showed that PLR and FLR were significantly related to the prognosis of GC patients.

Hemoglobin is used to determine anemia. Hypoxia caused by anemia, on the one hand, may accelerate tumor angiogenesis to promote tumor progression; on the other hand, it may make tumor cells resistant to radiotherapy and chemotherapy through proteomics and genomic changes[13,33,34]. Moreover, it is well known that hypoxia-inducible factor 1 can regulate gene products that promote tumor progression, and hypoxia increases its expression[35]. However, the molecular mechanisms of hypoxia need to be further elucidated. Previous studies have found that anemia was an independent risk factor for poor prognosis in patients with malignant tumors[36,37].

Huang *et al*[38] found that GC patients with low hemoglobin levels before surgery had poor survival. Liu *et al*[39] demonstrated that preoperative low hemoglobin concentrations were significantly related to not only large tumor sizes but also poor 5-year overall survival and high postoperative complication rates in advanced GC patients. Shen *et al*[40] suggested that preoperative anemia was markedly related to large tumor sizes, deep invasion depths and high stages and showed that stage I and II GC patients with anemia before surgery had a low long-term survival rate compared with patients without anemia before surgery.

Malnutrition and inflammation can inhibit albumin synthesis. Serum albumin was an independent prognostic indicator of malignant tumors[14,41]. Lien *et al*[42] showed that serum albumin was effectively associated with the 5-year survival of GC patients. Moreover, relevant studies have indicated that low albumin levels are related to poor prognosis in GC[14,43]. However, Crumley *et al*[14] demonstrated that GC patients with low albumin levels had a poor prognosis compared with those with high albumin levels, but this factor was not an independent predictor of prognosis. Moreover, Toyokawa *et al*[44] believed that C-reactive protein to albumin ratio was an independent prognostic

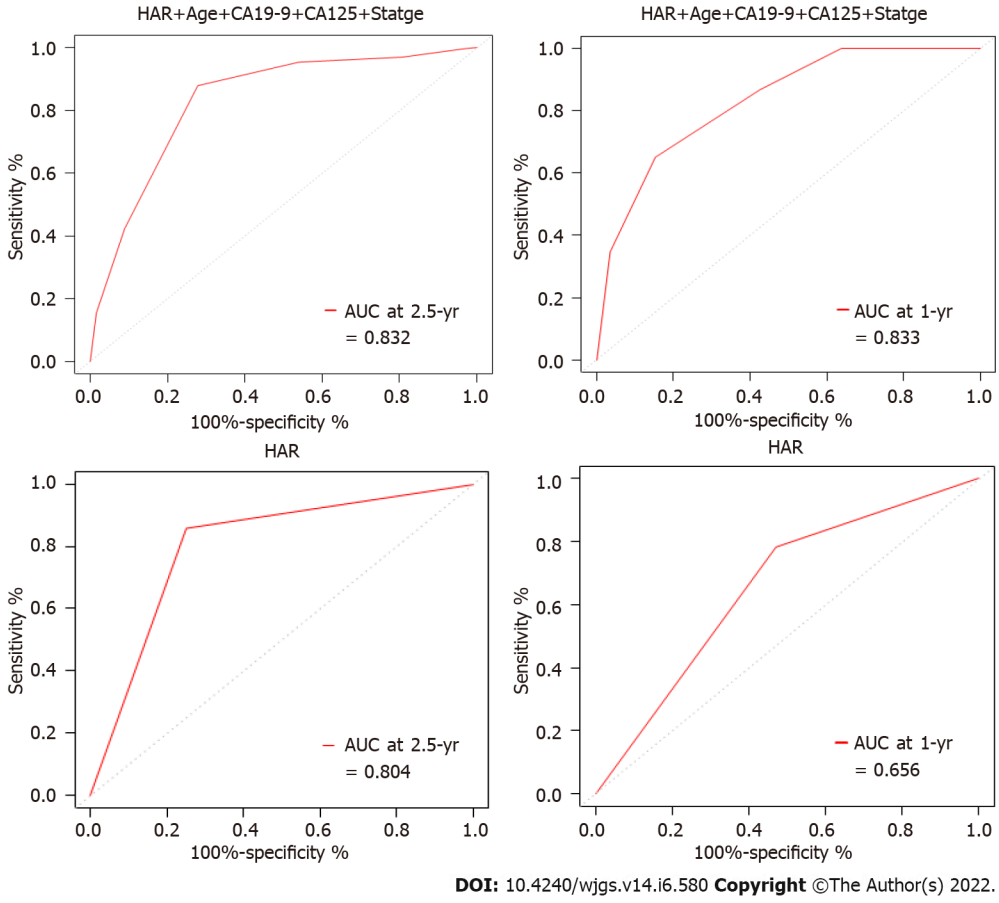



**Figure 4 Receiver operating characteristic curve of hemoglobin to albumin ratio or combined factors to predict the short-term survival of gastric cancer patients.** HAR: Hemoglobin to albumin ratio; AUC: Area under the curve.

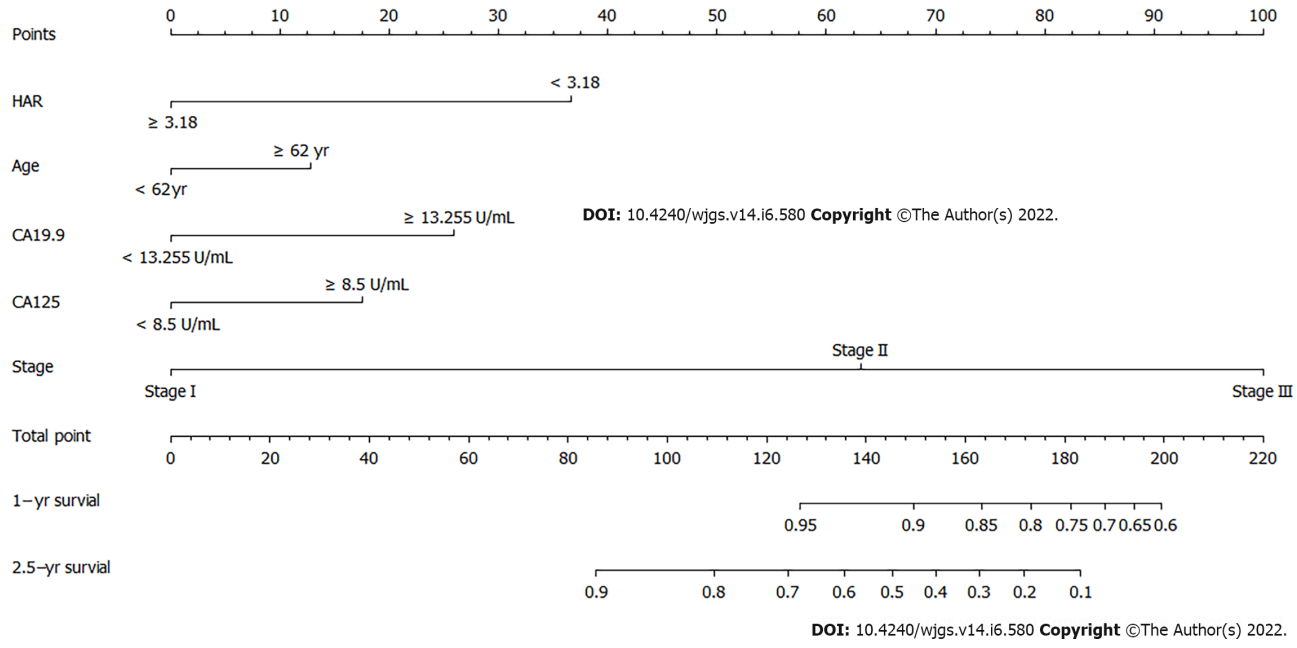



**Figure 5 Nomogram of the logistic regression model.** HAR: Hemoglobin to albumin ratio.

factor for overall survival in patients who underwent R0 resection for stage III gastric cancer.

This study indicated that HAR, stage and age were independent risk factors for the short-term survival of GC patients. Logistic regression analysis showed that a low HAR was markedly correlated with high stage, T classification and large tumor size in GC patients. To further analyze the relationships

between HAR and prognostic factors, we divided GC patients into a low HAR group and a high HAR group according to the median HAR value, and the results showed that patients with low HAR had high stage, T classification, CA125 and large tumor size. In addition, Kaplan-Meier analysis indicated that low HAR was related to short survival in GC patients.

Serum tumor markers can be used to predict the prognosis of cancer. Previous studies have found that elevated CEA, CA19-9 and CA125 levels were related to the prognosis of GC[45-47]. Related studies have also indicated that preoperative CEA and CA19-9 levels are related to tumor invasion depth and stage and can be used to predict prognosis[48,49]. Kochi *et al*[50] indicated that serum CA125 and CA19-9 were independent predictors of GC prognosis. This study also showed that CEA, CA19-9 and CA125 were associated with the prognosis of GC patients. The prognosis of patients with GC was evaluated mainly according to the American Joint Committee on Cancer TNM classification system[3,4]. However, this system has some limitations in clinical application.

Currently, nomograms combining prognostic factors have been developed, and it has been found that nomograms including inflammation and tumor markers can predict the prognosis of cancer more accurately than the traditional TNM classification system[51-53]. In this study, HAR, stage, age, CA19-9 and CA125 were used to construct a nomogram model for the short-term survival of GC patients, and the C-index for model evaluation was 0.820. The accuracy, sensitivity and specificity of this model for predicting the 1-year survival of GC patients were 83.30%, 86.83% and 84.77%, respectively, and the accuracy, sensitivity and specificity of the model for predicting the 2.5-year survival of GC patients were 83.20%, 87.87% and 72.18%, respectively, indicating that the model had a certain validity in predicting the short-term survival of patients with GC.

This study has some limitations. First, this was a single-center, small-sample retrospective study. Second, several other inflammatory markers correlated with prognosis were not included. Therefore, multicenter large-scale prospective randomized controlled trials are necessary.

In conclusion, this is the first study to apply HAR to predict the prognosis of GC patients with D2 radical resection and to construct a short-term survival prognostic nomogram for GC patients. Preoperative low HAR was associated with short survival in GC patients. The prognostic nomogram model based on HAR, stage, age, CA19-9 and CA125 can correctly predict the short-term survival of GC patients with D2 radical resection, thus providing a reference for the development of personalized postoperative treatment and follow-up plans.

## CONCLUSION

Preoperative low HAR was associated with short survival in GC patients. The prognostic nomogram model can accurately predict the short-term survival of GC patients with D2 radical resection.

## ARTICLE HIGHLIGHTS

### *Research background*

Hemoglobin and albumin are associated with the prognosis of gastric cancer (GC) patients. However, the prognostic value of the hemoglobin to albumin ratio (HAR) for the short-term survival of GC patients with D2 radical resection has not been studied.

### *Research motivation*

The clinical value of the HAR in the prognosis of GC patients with D2 radical resection has not been reported. Nomogram can provide the overall probability of specific outcomes for individual patients and provide more accurate predictions than the traditional TNM staging system, thereby improving personalized treatment decisions.

### *Research objectives*

The aim of this study was to investigate the significance of the HAR in evaluating the short-term survival of GC patients after D2 radical resection and to construct a nomogram to predict the prognosis in GC patients after surgery.

### *Research methods*

Cox regression and Kaplan-Meier analysis was used for prognostic analysis. Logistic regression was used to analyze the relationships between HAR and the clinicopathological characteristics of the GC patients. A prognostic nomogram model for the short-term survival of GC patients was constructed by R software.

### Research results

HAR was an independent risk factor for the short-term survival of GC patients. GC patients with a low HAR had a poor prognosis ($P < 0.001$). Low HAR was markedly related to high stage [odds ratio (OR) = 0.45 for II *vs* I; OR = 0.48 for III *vs* I], T classification (OR = 0.52 for T4 *vs* T1) and large tumor size (OR = 0.51 for ≥ 4 cm *vs* < 4 cm) (all $P < 0.05$). The nomogram model was based on HAR, age, CA19-9, CA125 and stage, and the C-index was 0.820.

### Research conclusions

Preoperative low HAR was associated with short survival in GC patients. The prognostic nomogram model can accurately predict the short-term survival of GC patients with D2 radical resection.

### Research perspectives

The significance of the HAR in evaluating the short-term survival of GC patients after D2 radical resection and to construct a nomogram to predict the prognosis in GC patients after surgery may provide a reference for the development of postoperative individualized treatment and follow-up plans.

## FOOTNOTES

**Author contributions:** Hu BE and Hu CG designed the study and contributed equally to this work; Hu BE, Hu CG and Zhu JF collected the clinical data; Hu BE analyzed the data and wrote the manuscript with contributions from all authors; Zhu ZM and Huang C provided critical comments for this paper; All authors read and approved the final version of the paper.

**Supported by** National Natural Science Foundation of China, No. 81560389; and Key Research and Development Program of Jiangxi Province, No. 20181BBG70015.

**Institutional review board statement:** The study was reviewed and approved by the Medical Research Ethics Committee of the Second Affiliated Hospital of Nanchang University Institutional Review Board (Approval No. 20191130).

**Conflict-of-interest statement:** The authors declare that they have no conflicts of interest.

**Data sharing statement:** No additional data are available.



**Country/Territory of origin:** China

**ORCID number:** Ce-Gui Hu 0000-0002-3854-7234; Bai-E Hu 0000-0002-3854-7889; Jin-Feng Zhu 0000-0002-7238-3876; Zheng-Ming Zhu 0000-0002-4414-2970; Chao Huang 0000-0003-1818-9449.

**S-Editor:** Ma YJ
**L-Editor:** Filipodia
**P-Editor:** Ma YJ

## REFERENCES

1 **Van Cutsem E**, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. *Lancet* 2016; **388**: 2654-2664 [PMID: 27156933 DOI: 10.1016/S0140-6736(16)30354-3]
2 **Songun I**, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 2010; **11**: 439-449 [PMID: 20409751 DOI: 10.1016/S1470-2045(10)70070-X]
3 **Japanese Gastric Cancer Association**. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer* 2017; **20**: 1-19 [PMID: 27342689 DOI: 10.1007/s10120-016-0622-4]
4 **Ajani JA**, D'Amico TA, Almhanna K, Bentrem DJ, Chao J, Das P, Denlinger CS, Fanta P, Farjah F, Fuchs CS, Gerdes H, Gibson M, Glasgow RE, Hayman JA, Hochwald S, Hofstetter WL, Ilson DH, Jaroszewski D, Johung KL, Keswani RN, Kleinberg LR, Korn WM, Leong S, Linn C, Lockhart AC, Ly QP, Mulcahy MF, Orringer MB, Perry KA, Poultsides GA, Scott WJ, Strong VE, Washington MK, Weksler B, Willett CG, Wright CD, Zelman D, McMillian N, Sundar H. Gastric Cancer, Version 3.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2016; **14**: 1286-1312

[PMID: 27697982 DOI: 10.6004/jnccn.2016.0137]
5 **Shah MA**, Ajani JA. Gastric cancer--an enigmatic and heterogeneous disease. *JAMA* 2010; **303**: 1753-1754 [PMID: 20442394 DOI: 10.1001/jama.2010.553]
6 **Fujitani K**, Yang HK, Mizusawa J, Kim YW, Terashima M, Han SU, Iwasaki Y, Hyung WJ, Takagane A, Park DJ, Yoshikawa T, Hahn S, Nakamura K, Park CH, Kurokawa Y, Bang YJ, Park BJ, Sasako M, Tsujinaka T; REGATTA study investigators. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. *Lancet Oncol* 2016; **17**: 309-318 [PMID: 26822397 DOI: 10.1016/S1470-2045(15)00553-7]
7 **Elinav E**, Nowarski R, Thaiss CA, Hu B, Jin C, Flavell RA. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. *Nat Rev Cancer* 2013; **13**: 759-771 [PMID: 24154716 DOI: 10.1038/nrc3611]
8 **Ogino S**, Galon J, Fuchs CS, Dranoff G. Cancer immunology--analysis of host and tumor factors for personalized medicine. *Nat Rev Clin Oncol* 2011; **8**: 711-719 [PMID: 21826083 DOI: 10.1038/nrclinonc.2011.122]
9 **Balkwill F**, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet* 2001; **357**: 539-545 [PMID: 11229684 DOI: 10.1016/S0140-6736(00)04046-0]
10 **Obermair A**, Simunovic M, Isenring L, Janda M. Nutrition interventions in patients with gynecological cancers requiring surgery. *Gynecol Oncol* 2017; **145**: 192-199 [PMID: 28173966 DOI: 10.1016/j.ygyno.2017.01.028]
11 **Kuroda D**, Sawayama H, Kurashige J, Iwatsuki M, Eto T, Tokunaga R, Kitano Y, Yamamura K, Ouchi M, Nakamura K, Baba Y, Sakamoto Y, Yamashita Y, Yoshida N, Chikamoto A, Baba H. Controlling Nutritional Status (CONUT) score is a prognostic marker for gastric cancer patients after curative resection. *Gastric Cancer* 2018; **21**: 204-212 [PMID: 28656485 DOI: 10.1007/s10120-017-0744-3]
12 **Oh SE**, Choi MG, Seo JM, An JY, Lee JH, Sohn TS, Bae JM, Kim S. Prognostic significance of perioperative nutritional parameters in patients with gastric cancer. *Clin Nutr* 2019; **38**: 870-876 [PMID: 29503057 DOI: 10.1016/j.clnu.2018.02.015]
13 **Vaupel P**. The role of hypoxia-induced factors in tumor progression. *Oncologist* 2004; **9** Suppl 5: 10-17 [PMID: 15591418 DOI: 10.1634/theoncologist.9-90005-10]
14 **Crumley AB**, Stuart RC, McKernan M, McMillan DC. Is hypoalbuminemia an independent prognostic factor in patients with gastric cancer? *World J Surg* 2010; **34**: 2393-2398 [PMID: 20602101 DOI: 10.1007/s00268-010-0641-y]
15 **Oñate-Ocaña LF**, Aiello-Crocifoglio V, Gallardo-Rincón D, Herrera-Goepfert R, Brom-Valladares R, Carrillo JF, Cervera E, Mohar-Betancourt A. Serum albumin as a significant prognostic factor for patients with gastric carcinoma. *Ann Surg Oncol* 2007; **14**: 381-389 [PMID: 17160496 DOI: 10.1245/s10434-006-9093-x]
16 **Artigas A**, Wernerman J, Arroyo V, Vincent JL, Levy M. Role of albumin in diseases associated with severe systemic inflammation: Pathophysiologic and clinical evidence in sepsis and in decompensated cirrhosis. *J Crit Care* 2016; **33**: 62-70 [PMID: 26831575 DOI: 10.1016/j.jcrc.2015.12.019]
17 **Caro JJ**, Salas M, Ward A, Goss G. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. *Cancer* 2001; **91**: 2214-2221 [PMID: 11413508]
18 **Saito H**, Kono Y, Murakami Y, Shishido Y, Kuroda H, Matsunaga T, Fukumoto Y, Osaki T, Ashida K, Fujiwara Y. Prognostic Significance of the Preoperative Ratio of C-Reactive Protein to Albumin and Neutrophil-Lymphocyte Ratio in Gastric Cancer Patients. *World J Surg* 2018; **42**: 1819-1825 [PMID: 29270656 DOI: 10.1007/s00268-017-4400-1]
19 **Yu Q**, Li KZ, Fu YJ, Tang Y, Liang XQ, Liang ZQ, Bai JH. Clinical significance and prognostic value of C-reactive protein/albumin ratio in gastric cancer. *Ann Surg Treat Res* 2021; **100**: 338-346 [PMID: 34136430 DOI: 10.4174/astr.2021.100.6.338]
20 **Han DS**, Suh YS, Kong SH, Lee HJ, Choi Y, Aikou S, Sano T, Park BJ, Kim WH, Yang HK. Nomogram predicting long-term survival after d2 gastrectomy for gastric cancer. *J Clin Oncol* 2012; **30**: 3834-3840 [PMID: 23008291 DOI: 10.1200/JCO.2012.41.8343]
21 **Li Y**, Jia H, Yu W, Xu Y, Li X, Li Q, Cai S. Nomograms for predicting prognostic value of inflammatory biomarkers in colorectal cancer patients after radical resection. *Int J Cancer* 2016; **139**: 220-231 [PMID: 26933932 DOI: 10.1002/ijc.30071]
22 **Harrell Jr FE**. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis: Springer; 2015 [DOI: 10.1111/biom.12569]
23 **Schreiber RD**, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science* 2011; **331**: 1565-1570 [PMID: 21436444 DOI: 10.1126/science.1203486]
24 **Lee SE**, Lee JH, Ryu KW, Nam BH, Cho SJ, Lee JY, Kim CG, Choi IJ, Kook MC, Park SR, Kim YW. Preoperative plasma fibrinogen level is a useful predictor of adjacent organ involvement in patients with advanced gastric cancer. *J Gastric Cancer* 2012; **12**: 81-87 [PMID: 22792520 DOI: 10.5230/jgc.2012.12.2.81]
25 **Liu X**, Sun X, Liu J, Kong P, Chen S, Zhan Y, Xu D. Preoperative C-Reactive Protein/Albumin Ratio Predicts Prognosis of Patients after Curative Resection for Gastric Cancer. *Transl Oncol* 2015; **8**: 339-345 [PMID: 26310380 DOI: 10.1016/j.tranon.2015.06.006]
26 **McQuade JL**, Daniel CR, Hess KR, Mak C, Wang DY, Rai RR, Park JJ, Haydu LE, Spencer C, Wongchenko M, Lane S, Lee DY, Kaper M, McKean M, Beckermann KE, Rubinstein SM, Rooney I, Musib L, Budha N, Hsu J, Nowicki TS, Avila A, Haas T, Puligandla M, Lee S, Fang S, Wargo JA, Gershenwald JE, Lee JE, Hwu P, Chapman PB, Sosman JA, Schadendorf D, Grob JJ, Flaherty KT, Walker D, Yan Y, McKenna E, Legos JJ, Carlino MS, Ribas A, Kirkwood JM, Long GV, Johnson DB, Menzies AM, Davies MA. Association of body-mass index and outcomes in patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy: a retrospective, multicohort analysis. *Lancet Oncol* 2018; **19**: 310-322 [PMID: 29449192 DOI: 10.1016/S1470-2045(18)30078-0]
27 **Yang Y**, Gao P, Song Y, Sun J, Chen X, Zhao J, Ma B, Wang Z. The prognostic nutritional index is a predictive indicator of prognosis and postoperative complications in gastric cancer: A meta-analysis. *Eur J Surg Oncol* 2016; **42**: 1176-1182 [PMID: 27293109 DOI: 10.1016/j.ejso.2016.05.029]
28 **Deng Q**, He B, Liu X, Yue J, Ying H, Pan Y, Sun H, Chen J, Wang F, Gao T, Zhang L, Wang S. Prognostic value of pre-operative inflammatory response biomarkers in gastric cancer patients and the construction of a predictive model. *J Transl*

*Med* 2015; **13**: 66 [PMID: 25885254 DOI: 10.1186/s12967-015-0409-0]
29 **Gu X**, Gao XS, Cui M, Xie M, Peng C, Bai Y, Guo W, Han L, Gu X, Xiong W. Clinicopathological and prognostic significance of platelet to lymphocyte ratio in patients with gastric cancer. *Oncotarget* 2016; **7**: 49878-49887 [PMID: 27409665 DOI: 10.18632/oncotarget.10490]
30 **Sun X**, Liu X, Liu J, Chen S, Xu D, Li W, Zhan Y, Li Y, Chen Y, Zhou Z. Preoperative neutrophil-to-lymphocyte ratio plus platelet-to-lymphocyte ratio in predicting survival for patients with stage I-II gastric cancer. *Chin J Cancer* 2016; **35**: 57 [PMID: 27342313 DOI: 10.1186/s40880-016-0122-2]
31 **Suzuki T**, Shimada H, Nanami T, Oshima Y, Yajima S, Ito M, Washizawa N, Kaneko H. Hyperfibrinogenemia is associated with inflammatory mediators and poor prognosis in patients with gastric cancer. *Surg Today* 2016; **46**: 1394-1401 [PMID: 27160890 DOI: 10.1007/s00595-016-1339-z]
32 **Huang C**, Liu Z, Xiao L, Xia Y, Huang J, Luo H, Zong Z, Zhu Z. Clinical Significance of Serum CA125, CA19-9, CA72-4, and Fibrinogen-to-Lymphocyte Ratio in Gastric Cancer With Peritoneal Dissemination. *Front Oncol* 2019; **9**: 1159 [PMID: 31750248 DOI: 10.3389/fonc.2019.01159]
33 **Vaupel P**, Mayer A, Höckel M. Impact of hemoglobin levels on tumor oxygenation: the higher, the better? *Strahlenther Onkol* 2006; **182**: 63-71 [PMID: 16447012 DOI: 10.1007/s00066-006-1543-7]
34 **Franco P**, Montagnani F, Arcadipane F, Casadei C, Andrikou K, Martini S, Iorio GC, Scartozzi M, Mistrangelo M, Fornaro L, Cassoni P, Cascinu S, Ricardi U, Casadei Gardini A. The prognostic role of hemoglobin levels in patients undergoing concurrent chemo-radiation for anal cancer. *Radiat Oncol* 2018; **13**: 83 [PMID: 29720197 DOI: 10.1186/s13014-018-1035-9]
35 **Semenza GL**. Hypoxia, clonal selection, and the role of HIF-1 in tumor progression. *Crit Rev Biochem Mol Biol* 2000; **35**: 71-103 [PMID: 10821478 DOI: 10.1080/10409230091169186]
36 **Fyles A**, Milosevic M, Hedley D, Pintilie M, Levin W, Manchul L, Hill RP. Tumor hypoxia has independent predictor impact only in patients with node-negative cervix cancer. *J Clin Oncol* 2002; **20**: 680-687 [PMID: 11821448 DOI: 10.1200/JCO.2002.20.3.680]
37 **Obermair A**, Handisurya A, Kaider A, Sevelda P, Kölbl H, Gitsch G. The relationship of pretreatment serum hemoglobin level to the survival of epithelial ovarian carcinoma patients: a prospective review. *Cancer* 1998; **83**: 726-731 [PMID: 9708937]
38 **Huang XZ**, Yang YC, Chen Y, Wu CC, Lin RF, Wang ZN, Zhang X. Preoperative Anemia or Low Hemoglobin Predicts Poor Prognosis in Gastric Cancer Patients: A Meta-Analysis. *Dis Markers* 2019; **2019**: 7606128 [PMID: 30719182 DOI: 10.1155/2019/7606128]
39 **Liu X**, Qiu H, Huang Y, Xu D, Li W, Li Y, Chen Y, Zhou Z, Sun X. Impact of preoperative anemia on outcomes in patients undergoing curative resection for gastric cancer: a single-institution retrospective analysis of 2163 Chinese patients. *Cancer Med* 2018; **7**: 360-369 [PMID: 29341506 DOI: 10.1002/cam4.1309]
40 **Shen JG**, Cheong JH, Hyung WJ, Kim J, Choi SH, Noh SH. Pretreatment anemia is associated with poorer survival in patients with stage I and II gastric cancer. *J Surg Oncol* 2005; **91**: 126-130 [PMID: 16028285 DOI: 10.1002/jso.20272]
41 **Tateishi R**, Yoshida H, Shiina S, Imamura H, Hasegawa K, Teratani T, Obi S, Sato S, Koike Y, Fujishima T, Makuuchi M, Omata M. Proposal of a new prognostic model for hepatocellular carcinoma: an analysis of 403 patients. *Gut* 2005; **54**: 419-425 [PMID: 15710994 DOI: 10.1136/gut.2003.035055]
42 **Lien YC**, Hsieh CC, Wu YC, Hsu HS, Hsu WH, Wang LS, Huang MH, Huang BS. Preoperative serum albumin level is a prognostic indicator for adenocarcinoma of the gastric cardia. *J Gastrointest Surg* 2004; **8**: 1041-1048 [PMID: 15585392 DOI: 10.1016/j.gassur.2004.09.033]
43 **Liu X**, Qiu H, Liu J, Chen S, Xu D, Li W, Zhan Y, Li Y, Chen Y, Zhou Z, Sun X. A Novel Prognostic Score, Based on Preoperative Nutritional Status, Predicts Outcomes of Patients after Curative Resection for Gastric Cancer. *J Cancer* 2016; **7**: 2148-2156 [PMID: 27877232 DOI: 10.7150/jca.16455]
44 **Toyokawa T**, Muguruma K, Yoshii M, Tamura T, Sakurai K, Kubo N, Tanaka H, Lee S, Yashiro M, Ohira M. Clinical significance of prognostic inflammation-based and/or nutritional markers in patients with stage III gastric cancer. *BMC Cancer* 2020; **20**: 517 [PMID: 32493247 DOI: 10.1186/s12885-020-07010-0]
45 **Wang W**, Seeruttun SR, Fang C, Chen J, Li Y, Liu Z, Zhan Y, Li W, Chen Y, Sun X, Xu D, Guan Y, Zhou Z. Prognostic Significance of Carcinoembryonic Antigen Staining in Cancer Tissues of Gastric Cancer Patients. *Ann Surg Oncol* 2016; **23**: 1244-1251 [PMID: 26620645 DOI: 10.1245/s10434-015-4981-6]
46 **Xiao J**, He X, Wang Z, Hu J, Sun F, Qi F, Yang S, Xiao Z. Serum carbohydrate antigen 19-9 and prognosis of patients with gastric cancer. *Tumour Biol* 2014; **35**: 1331-1334 [PMID: 24234331 DOI: 10.1007/s13277-013-1177-1]
47 **Emoto S**, Ishigami H, Yamashita H, Yamaguchi H, Kaisaki S, Kitayama J. Clinical significance of CA125 and CA72-4 in gastric cancer with peritoneal dissemination. *Gastric Cancer* 2012; **15**: 154-161 [PMID: 21892754 DOI: 10.1007/s10120-011-0091-8]
48 **Marchegiani G**, Andrianello S, Malleo G, De Gregorio L, Scarpa A, Mino-Kenudson M, Maggino L, Ferrone CR, Lillemoe KD, Bassi C, Castillo CF, Salvia R. Does Size Matter in Pancreatic Cancer? *Ann Surg* 2017; **266**: 142-148 [PMID: 27322188 DOI: 10.1097/SLA.0000000000001837]
49 **Imaoka H**, Shimizu Y, Senda Y, Natsume S, Mizuno N, Hara K, Hijioka S, Hieda N, Tajika M, Tanaka T, Ishihara M, Niwa Y, Yamao K. Post-adjuvant chemotherapy CA19-9 levels predict prognosis in patients with pancreatic ductal adenocarcinoma: A retrospective cohort study. *Pancreatology* 2016; **16**: 658-664 [PMID: 27178104 DOI: 10.1016/j.pan.2016.04.007]
50 **Kochi M**, Fujii M, Kanamori N, Kaiga T, Kawakami T, Aizaki K, Kasahara M, Mochizuki F, Kasakura Y, Yamagata M. Evaluation of serum CEA and CA19-9 levels as prognostic factors in patients with gastric cancer. *Gastric Cancer* 2000; **3**: 177-186 [PMID: 11984734 DOI: 10.1007/pl00011715]
51 **Kattan MW**, Karpeh MS, Mazumdar M, Brennan MF. Postoperative nomogram for disease-specific survival after an R0 resection for gastric carcinoma. *J Clin Oncol* 2003; **21**: 3647-3650 [PMID: 14512396 DOI: 10.1200/JCO.2003.01.240]
52 **Sternberg CN**. Are nomograms better than currently available stage groupings for bladder cancer? *J Clin Oncol* 2006; **24**: 3819-3820 [PMID: 16864852 DOI: 10.1200/JCO.2006.07.1290]

53 **Touijer K**, Scardino PT. Nomograms for staging, prognosis, and predicting treatment outcomes. *Cancer* 2009; **115**: 3107-3111 [PMID: 19544538 DOI: 10.1002/cncr.24352]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 June 27; 14(6): 594-610

DOI: 10.4240/wjgs.v14.i6.594

ISSN 1948-9366 (online)

META-ANALYSIS

# Comparison between laparoscopic uncut Roux-en-Y and Billroth II with Braun anastomosis after distal gastrectomy: A meta-analysis

Ya-Jun Jiao, Ting-Ting Lu, De-Ming Liu, Xue Xiang, Liu-Li Wang, Shi-Xun Ma, Yong-Feng Wang, Ya-Qiong Chen, Ke-Hu Yang, Hui Cai

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Chue KM, Singapore; Masaki S, Japan

**Received:** November 22, 2021
**Peer-review started:** November 22, 2021
**First decision:** December 27, 2021
**Revised:** January 9, 2022
**Accepted:** May 13, 2022
**Article in press:** May 13, 2022
**Published online:** June 27, 2022

**Ya-Jun Jiao, De-Ming Liu, Xue Xiang,** School of Clinical Medicine, Ningxia Medical University, Yinchuan 750000, Ningxia Province, China

**Ya-Jun Jiao, De-Ming Liu, Xue Xiang, Liu-Li Wang, Shi-Xun Ma, Yong-Feng Wang, Ya-Qiong Chen, Hui Cai,** General Surgery Clinical Medical Center, Gansu Provincial Hospital, Lanzhou 730000, Gansu Province, China

**Ting-Ting Lu,** Institution of Clinical Research and Evidence Based Medicine, Gansu Provincial Hospital, Lanzhou 730000, Gansu Province, China

**Ke-Hu Yang,** Evidence Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Lanzhou 730000, Gansu Province, China

**Corresponding author:** Hui Cai, MD, PhD, Chief Doctor, Director, Professor, Surgical Oncologist, General Surgery Clinical Medical Center, Gansu Provincial Hospital, No. 204 Donggang West Road, Chengguan District, Lanzhou 730000, Gansu Province, China. caialonteam@163.com

## Abstract

### *BACKGROUND*

Conventional Billroth II (BII) anastomosis after laparoscopic distal gastrectomy (LDG) for gastric cancer (GC) is associated with bile reflux gastritis, and Roux-en-Y anastomosis is associated with Roux-Y stasis syndrome (RSS). The uncut Roux-en-Y (URY) gastrojejunostomy reduces these complications by blocking the entry of bile and pancreatic juice into the residual stomach and preserving the impulse originating from the duodenum, while BII with Braun (BB) anastomosis reduces the postoperative biliary reflux without RSS. Therefore, the purpose of this study was to compare the efficacy and safety of laparoscopic URY with BB anastomosis in patients with GC who underwent radical distal gastrectomy.

### *AIM*

To evaluate the value of URY in patients with GC.

### *METHODS*

PubMed, Embase, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure, Wanfang, Chinese Biomedical Database, and VIP Database for Chinese Technical Periodicals (VIP) were used to search relevant studies published from January 1994 to August 18, 2021. The following databases were

also used in our search: Clinicaltrials.gov, Data Archiving and Networked Services, the World Health Organization International Clinical Trials Registry Platform Search Portal (https://www.who.int/clinical-trials-registry-platform/the-ictrp-search-portal), the reference lists of articles and relevant conference proceedings in August 2021. In addition, we conducted a relevant search by Reference Citation Analysis (RCA) (https://www.referencecitationanalysis.com). We cited high-quality references using its results analysis functionality. The methodological quality of the eligible randomized clinical trials (RCTs) was evaluated using the Cochrane Risk of Bias Tool, and the non-RCTs were evaluated using the Newcastle-Ottawa scale. Statistical analyses were performed using Review Manager (Version 5.4).

***RESULTS***

Eight studies involving 704 patients were included in this meta-analysis. The incidence of reflux gastritis [odds ratio = 0.07, 95% confidence interval (CI): 0.03-0.19, $P < 0.00001$] was significantly lower in the URY group than in the BB group. The pH of the postoperative gastric fluid was lower in the URY group than in the BB group at 1 d [mean difference (MD) = -2.03, 95%CI: (-2.73)-(-1.32), $P < 0.00001$] and 3 d [MD = -2.03, 95%CI: (-2.57)-(-2.03), $P < 0.00001$] after the operation. However, no significant difference in all the intraoperative outcomes was found between the two groups.

***CONCLUSION***

This work suggests that URY is superior to BB in gastrointestinal reconstruction after LDG when considering postoperative outcomes.

**Key Words:** Gastric cancer; Laparoscopy; Uncut Roux-en-Y; Anastomosis; Meta-analysis; Conventional Billroth II



**Core Tip:** No consensus is available in the literature regarding the more beneficial technique between laparoscopic Uncut Roux-en-Y (URY) and Billroth II combined Braun (BB) anastomosis for radical distal gastrectomy. This is the first systematic review and meta-analysis comparing URY and BB anastomosis. These two techniques were investigated in terms of surgical outcomes, postoperative recovery, and postoperative complications.

**Citation:** Jiao YJ, Lu TT, Liu DM, Xiang X, Wang LL, Ma SX, Wang YF, Chen YQ, Yang KH, Cai H. Comparison between laparoscopic uncut Roux-en-Y and Billroth II with Braun anastomosis after distal gastrectomy: A meta-analysis. *World J Gastrointest Surg* 2022; 14(6): 594-610
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i6/594.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i6.594

## INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer worldwide and the third most common cause of death from cancer[1]. The latest update from 2018 showed that GC accounted for 5.7% of all cancer cases, 8.2% of all deaths related to cancer, and approximately 782685 total deaths, representing a serious threat to human life and health[2]. The development of the treatments used to cure cancer revealed that radiotherapy as well as neoadjuvant and adjuvant chemotherapy may improve the outcomes, but surgery (*e.g.*, traditional open surgery and laparoscopic surgery) is the primary option for an effective cure[3].

Laparoscopic distal gastrectomy (LDG) was reported for the first time in Japan in 1994[4], when it was performed in combination with Billroth I (BI) gastroduodenostomy in a patient with GC at an early stage. It has been subsequently applied in Asia, due to its low trauma and rapid recovery of the patient. To date, a growing number of studies demonstrated that LDG is an oncologic safe alternative to open distal gastrectomy (ODG) in the treatment of early and advanced GC[5-7]. However, the choice of the most appropriate type of gastrointestinal reconstruction after LDG is still under debate.

Gastrointestinal reconstruction is an important part of GC surgery as well as tumor resection and lymph node dissection, since it is necessary to maintain a satisfactory nutritional status and quality of life, with a postoperative morbidity as low as possible[8]. BI reconstruction has the physiological advantage of allowing food passage through the duodenum[9] and reducing the postoperative weight loss[10]. However, the incidence of short-term complications, such as gastrointestinal fistulas classified

as Clavien-Dindo grade IIIa or higher, is high in the BI group due to excessive anastomotic tension[11-13]. BII anastomosis resolves the anastomotic tension, but is prone to postoperative complications potentially associated to residual GC such as postoperative biliary reflux, alkaline reflux gastritis, and esophagitis[14]. Roux-en-Y (RY) anastomosis does not cause anastomotic tension, and the gastric content enters directly into the jejunum, reducing the duodenal lumen pressure and the development of delayed gastric emptying and reflux gastritis. However, Roux-Y stasis syndrome (RSS) has an incidence of 10%-30% due to the abnormal activity in the distal jejunum of the anastomosed stomach[15]. On the other hand, postoperative biliary reflux without RSS can be reduced by performing BII with Braun (BB) anastomosis[16,17]. In addition, a new method of reconstructing the digestive tract, "uncut Roux-en-Y (URY) anastomosis", was introduced in 1988, which is an improvement of the RY anastomosis, since it can effectively prevent the development of RSS, reflux gastritis, and reflux esophagitis[18,19].

Therefore, this systematic review and meta-analysis were performed by including the most recent and comprehensive studies, to systematically evaluate the safety and efficacy of the two approaches (URY and BB) for the reconstruction surgery of distal gastrectomy.

## MATERIALS AND METHODS

This systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis statement[20].

### *Literature search strategy*

A systematic literature search was performed from January 1994 to August 18, 2021 using PubMed, Embase, Web of science, Cochrane Library, China National Knowledge Infrastructure, Wanfang, Chinese Biomedical Database, and Chinese Science and Technology Journal Database (VIP). The following databases were also used in our search: Clinicaltrials.gov (https://clinicaltrials.gov), Data Archiving and Networked Services, the World Health Organization International Clinical Trials Registry Platform Search Portal (https://www.who.int/clinical-trials-registry-platform/the-ictrp-search-portal), and the reference lists of articles and relevant conference proceedings in August 2021. In addition, we conducted a relevant search by Reference Citation Analysis (RCA) (https://www.referencecitationanalysis.com). We cited high-quality references using its results analysis functionality. The search strategy used a combination of the Mesh terms and free terms, such as: "Stomach neoplasms" and "laparoscopy or laparoscopes" and "gastroenterostomy" and "gastric bypass"[21]. All the identified studies were imported into Endnote X9 to identify duplicates and screen eligible studies.

### *Eligibility criteria*

Randomized clinical trials (RCTs) and non-RCTs comparing the outcomes of URY with those of BB anastomosis in the treatment of patients with GC were included in this study. In case of two or more studies from the same author or institution and the overlap of the study intervals or patients involved, the most recent study or the study with the largest sample size was selected. No language restriction was considered in including the studies. The exclusion criteria were the following: (1) Studies that did not include outcomes of interest; (2) Studies that did not show the statistical analysis necessary to perform the meta-analysis; (3) Studies with mixed LDG and ODG groups, unless the LDG-related data were presented separately; (4) Studies that did not specify the type of reconstruction; and (5) Posters, review articles, commentaries, and abstract-only articles. Two reviewers independently evaluated the titles and abstracts and read the full text to identify the eligible studies according to the inclusion and exclusion criteria[22]. A third reviewer could be involved in case of disagreement between the two reviewers.

### *Definitions*

Bile reflux means the reflux of bile into the stomach. Bile can easily enter the stomach after gastrectomy, causing a series of discomforts such as acid regurgitation, which can lead to reflux gastritis over time. Inflammation and bleeding may occur in the gastric mucosa, as observed using gastroscopy. The definition of reflux gastritis varies from study to study; whenever a postoperative complication in a study reports alkaline reflux gastritis or bile reflux gastritis, it is directly categorized as reflux gastritis. Postoperative gastroparesis is a disorder characterized by delayed gastric emptying of solid food in the absence of a mechanical obstruction of the stomach, resulting in the cardinal symptoms of early satiety, postprandial fullness, nausea, vomiting, belching, and bloating[23]. Postoperative ileus is a transient interruption of coordinated bowel motility after surgical intervention, which prevents the effective transit of the intestinal contents or tolerance of oral intake[24].

### *Data extraction and quality assessment*

Two reviewers independently extracted the data from the eligible studies using a standardized form including the first author, year of publication, number of patients, study design, participant characteristics, operative details, and outcomes. The surgical outcomes included the operative time, time to

perform the anastomosis, number of removed lymph nodes, and intraoperative blood loss. Postoperative recovery indicators included the postoperative hospital stay, time to first passage of flatus or defecation, postoperative gastric fluid pH, and time to first solid diet at days 1 and 3 post operation. Postoperative complications included reflux gastritis, gastroparesis, anastomotic leakage, and ileus. If an outcome was observed at different times in the study, the data at the time of the last observation were extracted.

### Risk of bias assessment

The risk of bias for all the included RCTs was assessed using the Cochrane Risk of Bias Tool[25]. The domain included the random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias. As regards the non-RCTs, the quality of the studies was evaluated using the modified Newcastle-Ottawa scale (NOS)[26] according to three main factors: (1) Selection of the studied groups; (2) Comparability among groups; and (3) Determination of the outcomes. Each study was scored on an NOS of 0-9, with eligible studies with a score of 6 and high quality studies with a score of 8 and above[27].

### Statistical analysis

The meta-analysis was performed using Review manager (Version 5.4). The results of the dichotomous data are expressed as an odds ratio (OR) with 95% confidence interval (CI), while the effect size of the continuous outcomes was measured as the weighted mean difference (MD) with 95%CI. Heterogeneity was assessed by the $\chi^2$ test and $I^2$ statistics and was classified as low ($I^2$ < 25%), moderate (25%< $I^2$ < 50%), and high heterogeneity ($I^2$ > 50%)[28]. When the $I^2$ value was less than 50%, a fixed effects model was used; otherwise, a random effects model was used. Evaluation of publication bias was not conducted because less than ten studies were included. Subgroup analysis was conducted to explore the sources of heterogeneity according to the type of study (RCTs and non-RCTs). The considered information was extracted from the published articles; thus, the authors were not contacted for asking the data. A $P$ value < 0.05 was considered statistically significant.

## RESULTS

### Study selection

A total of 908 potentially relevant articles were identified, and among these, 36 were selected to read the full text. A total of eight studies were finally included and among them[29-36], three were RCTs[30,31,34] and five were non-RCTs[29,32,33,35,36]. Two reviewers indicated that the techniques of the two anastomosis methods were sufficiently similar so that the results could be pooled. No disagreement occurred between the two reviewers during the study selection process, and all the included articles were chosen after discussion and mutual agreement. The flow diagram of the study selection demonstrating the details of the selection process is shown in Figure 1[37].

### Characteristics of the studies and quality assessment

The included articles described investigations performed in China and published between 2017 and 2021, and the type of procedure was laparoscopy in all of them. A total of 704 patients were included, and among them, 354 underwent URY and 350 underwent BB. In addition, among them, 272 (38.6% of all the included cases) were from the three included RCTs, and 136 (38.4% of all the URY cases) were in the URY group. The information regarding the characteristics of the included studies is summarized in Table 1. The quality assessment of the RCTs is shown in Table 2. The included RCTs of surgical interventions had certain problems with blinding[38]. The quality of non-RCTs studies had scores between 6 and 8, with a mean of 7.4 (Table 1).

### Meta-analysis: Surgical outcomes

**Operative time:** Seven studies reported the operative time of the two procedures[29-34,36]. A fixed-effect model was used ($\chi^2$ = 1.05, $P$ = 0.98, $I^2$ = 0%) for meta-analysis, revealing that there was no significant difference between the two groups [MD = 1.22, 95%CI: (-4.16)-6.60, $P$ = 0.66] (Figure 2A). The subgroup analysis also revealed no significant difference between the RCTs [MD = 0.93, 95%CI: (-5.87)-7.73, $P$ = 0.79] and non-RCTs subgroups [MD = 1.71, 95%CI: (-7.09)-10.05, $P$ = 0.70] (Table 3).

**Reconstruction time:** Six studies compared the reconstruction time necessary to perform URY and BB [29,30,32-35]. A high heterogeneity ($I^2$ = 81%) was observed among inter-studies; thus, a random effects model was used. The results demonstrated that the reconstruction time was similar between the URY group and BB group [MD = 0.90, 95%CI: (-2.05)-3.85, $P$ = 0.55] (Figure 2B). Moreover, the subgroup analysis did not find any statistically significant difference between the two subgroups [RCTs: MD = 3.32, 95%CI: (-3.85)-10.49, $P$ = 0.36; non-RCTs: MD = -0.41, 95%CI: (-3.85)-3.03, $P$ = 0.81] (Table 3).

**Table 1 Characteristics of the included studies**

| Ref. | Study type | Country | Period | Number (URY/BB) | Gender (M/F) | Age (URY/BB) | BMI | ASA (I/II/III) | Tumor stage (I/II/III/IV) | Differentiation (H/M/L) | Matched factors[1] | NOS score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Chen[30], 2018 | RCT | China | 2016.5-2017.9 | URY 30, BB 30 | 17/13, 16/14 | 55.00 ± 5.40, 53.50 ± 7.56 | 22.89 ± 4.23, 21.38 ± 2.02 | NR | 3/10/17/0, 4/12/14/0 | 5/15/10, 4/14/12 | 1, 2, 3, 4, 7, 8, 12 | NA |
| Gao and Xiang [29], 2018 | Retro | China | 2014.1-2017.1 | URY 26, BB 34 | 17/9, 21/13 | 60.61 ± 11.14, 59.72 ± 10.79 | 21.58 ± 1.86, 21.35 ± 1.93 | NR | 0/5/14/7, 0/7/18/9 | 8/7/11, 10/11/13 | 1, 2, 3, 5, 6, 9, 10, 11, 12, 13 | 8 |
| Li *et al*[32], 2017 | Retro | China | 2010.1-2016.1 | URY 30, BB 33 | 21/9, 21/12 | 52.81 ± 5.39, 52.09 ± 6.47 | 21.66 ± 2.54, 21.81 ± 2.62 | NR | NG | 8/11/11, 9/12/12 | 1, 2, 3, 5, 6, 9, 12 | 7 |
| Ren *et al*[31], 2020 | RCT | China | 2015.6-2016.12 | URY 44, BB 44 | 30/14, 28/16 | 59.61 ± 11.14, 59.72 ± 10.79 | 21.51 ± 1.86, 21.38 ± 1.93 | NR | 0/8/25/11, 0/9/23/12 | 14/13/17, 13/14/17 | 1, 3, 5, 6, 9, 10, 11, 13 | NA |
| Wang *et al*[36], 2018 | Retro | China | 2015.3-2017.6 | URY 81, BB 58 | 52/29, 46/12 | 56 (30-79), 56.5 (24-77) | NR | NR | 41/20/17/0, 28/13/16/0 | NR | 1, 3, 4, 5, 6, 9 | 8 |
| Wang *et al*[34], 2021 | RCT | China | 2017.1-2018.5 | URY 62, BB 62 | 44/18, 44/18 | 54.84 ± 8.31; 54.69 ± 10.07 | 22.43 ± 3.07, 22.46 ± 3.17 | 27/28/7, 16/41/5 | NG | NR | 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12 | NA |
| Wu *et al*[33], 2021 | Retro | China | 2016.1-2019.4 | URY 45, BB 50 | 27/18, 31/19 | 59.1 ± 6.2, 59.1 ± 6.3 | 23.3 ± 3.0, 23.2 ± 2.9 | NR | 45/0/0/0, 50/0/0/0 | 7/15/23, 8/19/23 | 1, 2, 3, 4, 5, 9, 10, 11, 12, 13 | 6 |
| Zhou *et al*[35], 2018 | Retro | China | 2010.6-2015.4 | URY 36, BB 39 | 22/14, 24/15 | 61 ± 5, 61 ± 8 | 23 ± 3, 22 ± 4 | 21/15/0, 23/16/0 | 36/0/0/0, 39/0/0/0 | 11/16/9, 10/19/10 | 2, 3, 4, 5, 6, 9, 10, 13 | 8 |

[1]Outcomes: (1) Operative time; (2) Reconstruction times; (3) Intraoperative bleeding; (4) Total number of harvested lymph nodes; (5) Time to first passage of flatus or defecation; (6) Time to first solid diet; (7) Mean gastric pH at day 1; (8) Mean gastric pH at day 3; (9) Post-operative hospitalization time; (10) Anastomotic leakage; (11) Ileus; (12) Reflux gastritis; and (13) Gastroparesis.

ASA: American Society of Anesthesiologists score; BMI: Body mass index; NOS: Newcastle-Ottawa Scale; NR: Not reported; Retro: Retrospective observational study; NA: Not applicated; RCT: Randomised controlled trial; URY: Uncut Roux-en-Y; BB: BII combined Braun; NG: Not given.

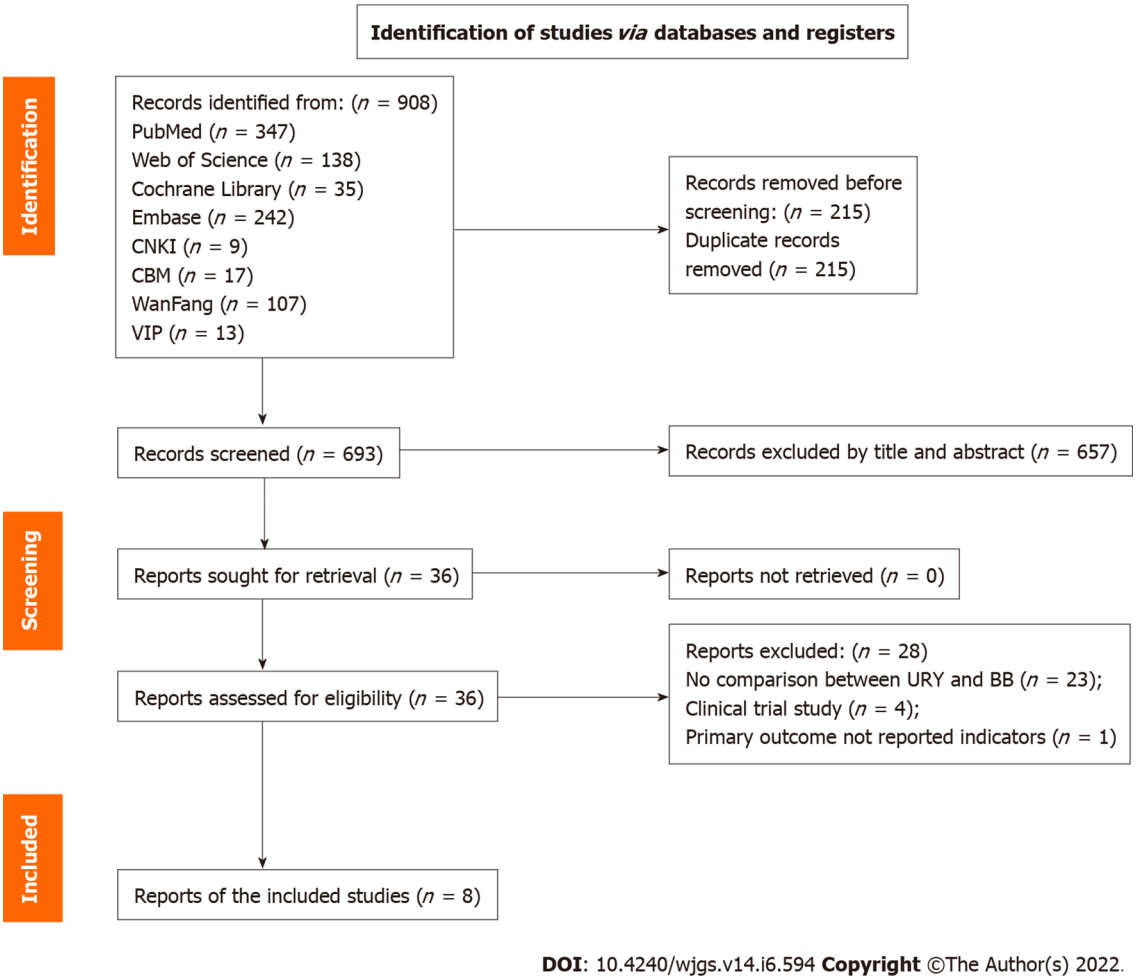
**Intraoperative blood loss:** The intraoperative blood loss was reported in all studies. The evidence suggested a small difference in the intraoperative blood loss between the URY and BB groups [MD = 0.84, 95%CI: (-2.21)-3.90, $P$ = 0.59] (Figure 2C). The meta-analysis among the RCTs indicated no significant difference in the intraoperative blood loss between the two groups [MD = 3.87, 95%CI: (-7.02)-14.75, $P$ = 0.49] with low statistical heterogeneity ($P$ = 0.49, $I^2$ = 45%). The pooled data in the non-RCTs revealed a similar result [MD = 0.58, 95%CI: (-2.60)-3.77, $P$ = 0.72] with the absence of statistical heterogeneity ($P$ = 0.91, $I^2$ = 0%) (Table 3).

**Total number of harvested lymph nodes:** Five articles reported the total number of harvested lymph nodes[30,33-36]. A fixed effect model was used, which showed a low statistical heterogeneity ($I^2$ = 0%). The pooled result revealed no significant difference between the two groups [MD = 1.01, 95%CI: (-0.20)-2.22, $P$ = 0.10] (Figure 2D). The subgroup analysis showed no evident statistical difference in the total number of harvested lymph nodes between the URY and BB groups in both the RCT and non-RCT

**Table 2 Results of risk of bias assessment (randomised controlled trials)**

| Ref. | Sequence generation | Allocation concealment | Blind of participant and personnel | Blind of assessment | Outcome of incomplete data | Selective report | Other bias |
|---|---|---|---|---|---|---|---|
| Chen[30], 2018 | Low | Unclear | High | Unclear | Low | Unclear | Unclear |
| Ren *et al* [31], 2020 | Low | Unclear | Unclear | Unclear | Low | Unclear | Unclear |
| Wang *et al* [34], 2021 | Low | Low | Low | Unclear | Low | Low | Unclear |

The level of bias was determined as follows: "High" indicating a risk of bias; "Unclear" indicating an uncertain risk of bias; and "Low" indicating no risk of bias.




**DOI**: 10.4240/wjgs.v14.i6.594 **Copyright** ©The Author(s) 2022.

**Figure 1 Study flow diagram.** URY: Uncut Roux-en-Y; BB: BII combined Braun; CNKI: Chinese National Knowledge Infrastructure; CBD: Chinese Biomedical Database.

subgroups [RCTs: MD = 0.15, 95%CI: (-1.86)-2.16, $P$ = 0.88; non-RCTs: MD = 1.90, 95%CI: (-0.14)-3.95, $P$ = 0.05] (Table 3).

### *Postoperative recovery*

**Time to first passage of flatus or defecation:** Seven studies involving 644 patients reported the time to first passage of flatus or defecation[29,31-36]. The meta-analysis revealed that URY was associated with a shorter time to first passage of flatus or defecation than BB [MD = -0.26, 95%CI: (-0.51)-(-0.02), $P$ = 0.03] (Figure 3A). A significant heterogeneity was observed among studies ($\chi^2$ = 17.34, $P$ = 0.008, $I^2$ = 65%); thus, a random effects model was used. However, no significant difference was found after performing the subgroup analysis between the non-RCT and RCT subgroups [RCTs: MD = -0.26, 95%CI: (-0.87)-0.34,

**Table 3 Subgroup analysis of all the outcomes according to study type**

| Subgroup | Type | No. of studies | No. of patients | | Meta-analysis results | | Assessment of heterogeneity | |
|---|---|---|---|---|---|---|---|---|
| | | | URY | BB | OR/MD (95%CI) | *P* value | $I^2$ | *P* value |
| Operative time | RCTs | 3 | 136 | 136 | 0.93 [(-5.87)-7.73] | 0.79 | 0 | 0.95 |
| | Non-RCTs | 4 | 182 | 175 | 1.71 [(-7.09)-10.51] | 0.70 | 0 | 0.82 |
| Reconstruction time | RCTs | 2 | 92 | 92 | 3.32 [(-3.85)-10.49] | 0.36 | 0.92 | 0.0005 |
| | Non-RCTs | 4 | 137 | 156 | -0.41 [(-3.85)-3.03] | 0.81 | 0.74 | 0.0009 |
| Intraoperative blood loss | RCTs | 3 | 136 | 136 | 3.87 [(-7.02)-14.75] | 0.49 | 0.45 | 0.16 |
| | Non-RCTs | 4 | 218 | 214 | 0.58 [(-2.60)-3.77] | 0.72 | 0 | 0.91 |
| Total number of harvested lymph nodes | RCTs | 2 | 92 | 92 | 0.15 [(-1.86)-2.16] | 0.88 | 0 | 0.98 |
| | Non-RCTs | 3 | 163 | 147 | 1.90 [(-0.14)-3.94] | 0.07 | 0 | 0.39 |
| Time to first passage of flatus or defecation | RCTs | 2 | 106 | 106 | -0.26 [(-0.87)-0.34] | 0.40 | 0.77 | 0.04 |
| | Non-RCTs | 5 | 218 | 214 | -0.29 [(-0.59)-0.01] | 0.05 | 0.56 | 0.06 |
| Time to first solid diet | RCTs | 1 | 44 | 44 | -0.05 [(-1.14)-1.04] | 0.93 | Not applicable | |
| | Non-RCTs | 4 | 173 | 164 | -0.29 [(-0.53)-(-0.05)] | 0.02 | 0 | 0.67 |
| Postoperative hospitalization time | RCTs | 2 | 106 | 106 | -0.01 [(-0.16)-0.14)] | 0.87 | 0 | 0.84 |
| | Non-RCTs | 5 | 218 | 214 | -0.26 [(-0.78)-0.26] | 0.32 | 0 | 0.63 |
| Reflux gastritis | RCTs | 2 | 92 | 92 | 0.03 (0.01-0.11) | < 0.00001 | 0 | 0.70 |
| | Non-RCTs | 3 | 193 | 209 | 0.15 (0.03-0.66) | 0.01 | 0 | 0.77 |
| Anastomotic leakage | RCTs | 2 | 106 | 106 | 0.73 (0.15-3.48) | 0.69 | Not applicable | |
| | Non-RCTs | 3 | 107 | 123 | 1.16 (0.23-5.87) | 0.85 | 0 | 0.85 |

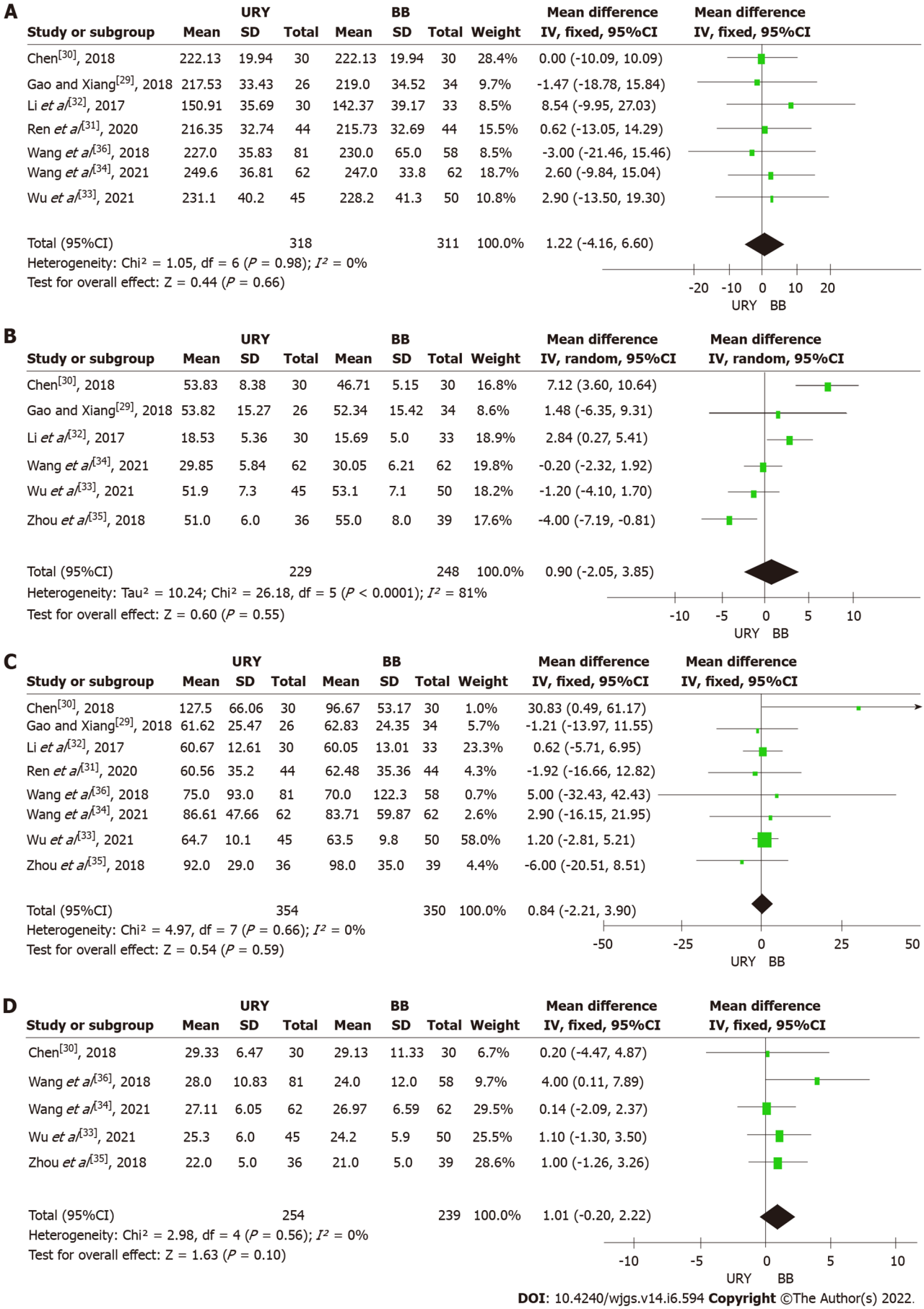
URY: Uncut Roux-en-Y; BB: BII combined Braun; RCTs: Randomised controlled trials; OR: Odds ratio; MD: Mean difference; CI: Confidence interval.

*P* = 0.40; non-RCTs: MD = -0.29, 95%CI: (-0.59)-0.01, *P* = 0.05] (Table 3).

**Time to first solid diet:** Five studies contributed to the meta-analysis regarding this parameter[29,31,32,35,36]. A fixed effects model was used due to a low heterogeneity ($I^2$ = 0%). The meta-analysis results showed a significant difference in the time to first solid diet between the URY and BB groups [MD = -0.28, 95%CI: (-0.51)-(-0.05), *P* = 0.02] (Figure 3B). The subgroup analysis revealed that the URY group had a shorter time to first solid diet than the BB [MD = -0.29, 95%CI: (-0.53)-(-0.05), *P* = 0.02] in the non-RCTs subgroup, while no statistically significant difference between the two groups was found in the RCT subgroup [MD = -0.05, 95%CI: (-1.14)-1.04, *P* = 0.93] (Table 3).

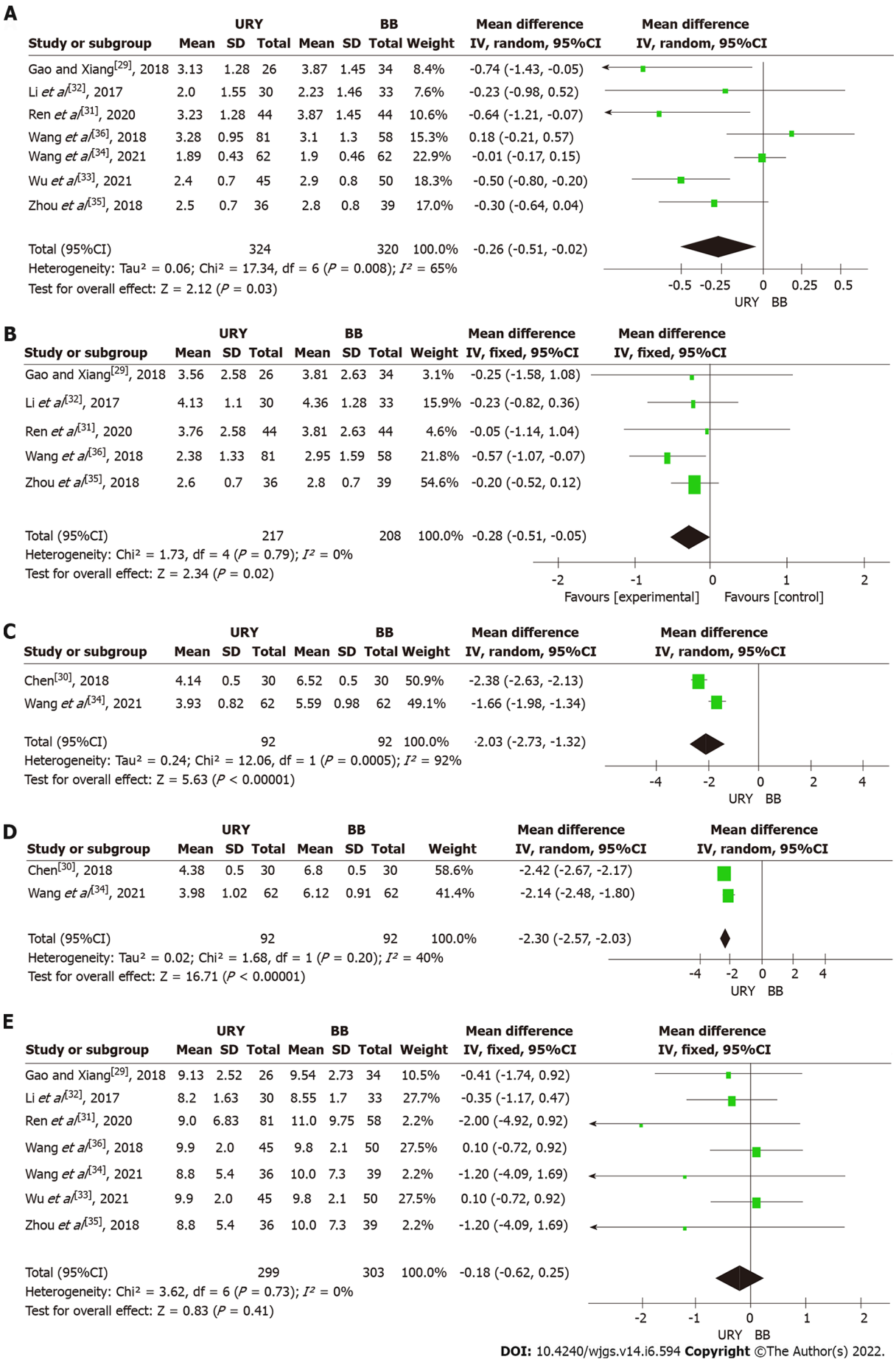
**Postoperative gastric fluid pH:** Two RCTs reported the postoperative pH of the gastric fluid[30,34]. The pooled result on days 1 and 3 revealed that this parameter was superior in the URY than in BB [day 1: MD = -2.03, 95%CI: (-2.73)-(-1.32), *P* < 0.00001 (Figure 3C); day 3: MD = -2.30, 95%CI: (-2.57)-(-2.03), *P* < 0.00001 (Figure 3D)]. However, a high heterogeneity was observed in the postoperative gastric fluid pH between days 1 and 3 ($I^2$ = 92% and $I^2$ = 40%, respectively).

**Postoperative length of hospital stay:** Seven articles reported the postoperative length of hospital stay [29,31-36]. A fixed effects model was used because no significant heterogeneity was present among studies ($I^2$ = 0%). The meta-analysis revealed no significant difference between the two groups [MD = -0.18, 95%CI: (-0.62)-0.25, *P* = 0.41] (Figure 3E). The subgroup analysis also showed no statistically significant difference between the URY and BB groups in both the non-RCT subgroup [MD = -0.26,




**DOI**: 10.4240/wjgs.v14.i6.594 

**Figure 2 Results of meta-analysis.** A: Operative time; B: Reconstruction time; C: Intraoperative blood loss; D: Total number of harvested lymph nodes. URY: Uncut Roux-en-Y; BB: Billroth II combined Braun; CI: Confidence interval.




**DOI:** 10.4240/wjgs.v14.i6.594 

**Figure 3 Results of meta-analysis of postoperative recovery.** A: Time to first passage of flatus or defecation; B: Time to first solid diet; C: Mean gastric pH

at day 1; D: Mean gastric pH at day 3; E: Postoperative hospitalization time. URY: Uncut Roux-en-Y; BB: BII combined Braun; CI: Confidence interval.

95%CI: (-0.78)-0.26, $P$ = 0.32] and RCT subgroup [MD = -0.01, 95%CI: (-0.16)-0.14, $P$ = 0.87] (Table 3).

### Postoperative complications

**Anastomotic leakage:** Five studies reported the presence of anastomotic leakage[29,31,32-35]. A fixed effects model was used ($I^2$ = 0%) due to a low heterogeneity. The incidence of postoperative anastomotic leakage was similar between the URY and BB groups (OR = 0.91, 95%CI: 0.30-2.80; $P$ = 0.88) (Figure 4A). The subgroup analysis between RCTs and non-RCTs indicated no significant difference in postoperative anastomotic leakage between the two groups (RCTs: OR = 0.73, 95%CI: 0.15-3.48, $P$ = 0.69; non-RCTs: OR = 1.16, 95%CI: 0.23-5.87, $P$ = 0.85) (Table 3).

**Ileus:** Four articles reported the incidence of postoperative ileus[29,31,33,34]. The meta-analysis showed no statistically significant difference between the two groups (OR = 0.26, 95%CI: 0.04-1.62, $P$ = 0.15). However, a low heterogeneity ($I^2$ = 22%) was observed among studies, and a fixed effects model was used (Figure 4B).

**Reflux gastritis:** Five studies compared the reflux gastritis between the two groups[29,30,32-34]. A fixed effects model was used due to a low heterogeneity ($I^2$ = 0%). The incidence of reflux gastritis was significantly lower in the URY group than in the BB group (OR = 0.07; 95%CI: 0.03-0.19; $P$ < 0.00001) (Figure 4C). The subgroup analysis showed that the incidence of reflux gastritis was lower in the URY group than in the BB group, regardless of the subgroup RCT or non-RCT (RCTs: OR = 0.03, 95%CI: 0.01-0.11, $P$ < 0.00001; non-RCTs: OR = 0.15, 95%CI: 0.03-0.66, $P$ = 0.01) (Table 3).

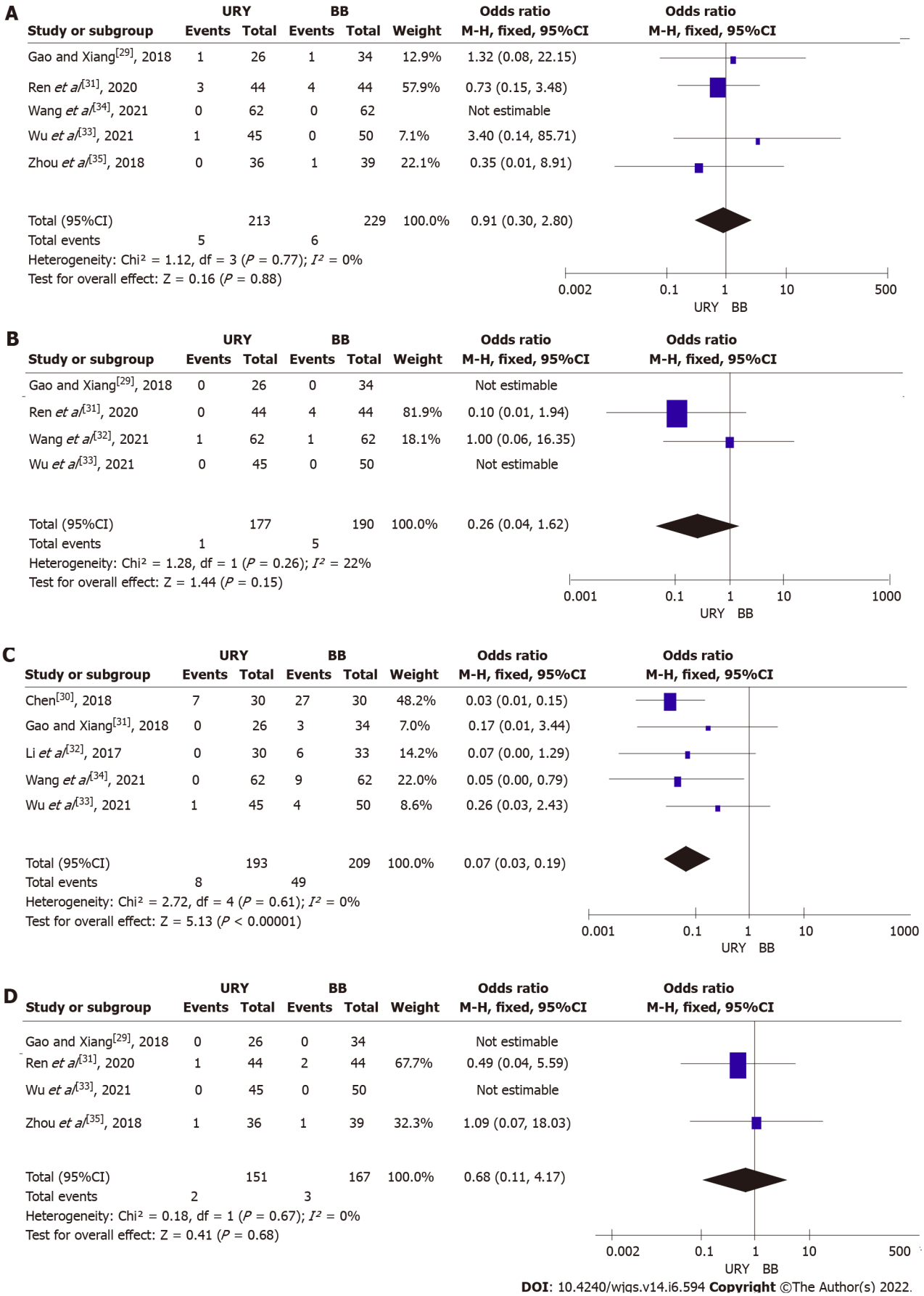
**Gastroparesis:** A total of four studies reported the incidence of postoperative gastroparesis[29,31,33,35], and among them, two had an incidence of 0[29,33]. The meta-analysis revealed that the incidence of postoperative gastroparesis was not significantly different between the two groups (OR = 0.68, 95%CI: 0.11-4.17, $P$ = 0.68), and it was without significant heterogeneity ($I^2$ = 0%) (Figure 4D).

### Sensitivity analysis

In the present study, a sensitivity analysis was performed on the operative time, intraoperative bleeding, reconstruction time, total number of harvested lymph nodes, time to first passage of flatus or defecation, time to first solid diet, postoperative hospitalization time, anastomotic leakage, and reflux gastritis to explore the stability of the included studies by the removal of each study from the meta-analysis and then examining the impact of the removed study on the overall composite estimate. After the exclusion of the relevant studies, when the CIs were within 95%, no significant effect was observed on the overall combined results.

## DISCUSSION

No consensus exists on the most appropriate method to reconstruct the digestive tract for reducing complications and improving the quality of life after LDG. BII reconstruction has been a commonly used anastomosis method nowadays. However, bile reflux occurs frequently after BII due to the structural defects of this type of reconstruction. Therefore, BB's anastomosis was designed specifically to reduce the flow of bile into the stomach[17], actually also reducing ileus and postoperative gastrointestinal symptoms[16]. URY reconstruction was first reported by Van Stiegman *et al*[39] in 1988. URY gastrojejunostomy is an improved technique composed of the BII procedure and the BB anastomosis, which includes the additional step of closing the jejunal lumen proximal to the gastrojejunostomy[40]. At the end of distal gastrectomy, a gastrojejunostomy is performed between the residual stomach and the jejunum, approximately 30 cm away from the ligament of Treitz. The side-to-side or end-to-side gastrojejunostomy is performed more often selecting the greater curvature of the residual stomach. Then, a side-to-side jejunojejunostomy is established between the afferent and efferent jejunal limbs, approximately 20 cm distal from the ligament of Treitz and 40 cm distal from the gastrojejunostomy site. Finally, the jejunal lumen is occluded at a site 5 cm proximal to the gastrojejunostomy using different methods[40]. The common methods of jejunal occlusion without transection are the following: Stapling with non-bladed six-row linear staplers or four-row staplers (knifeless GIA, Covidien), placement of four or five tightly tied 3-0 polypropylene seromuscular stitches circularly around the jejunal wall, and jejunal ligature with No. 7 silk and reinforcement by suturing the serosal layers of the upper and lower jejunum at the occlusion site. This anastomosis is considered as a controversial but promising method for gastrointestinal reconstruction after distal gastrectomy. Therefore, this systematic review and meta-analysis were performed to evaluate and compare the safety and efficacy of URY reconstruction (Figure 5A) and BB reconstruction (Figure 5B) after distal gastrectomy.




**DOI**: 10.4240/wjgs.v14.i6.594 

**Figure 4 Results of meta-analysis.** A: Anastomotic leakage; B: Ileus; C: Reflux gastritis; D: Gastroparesis. URY: Uncut Roux-en-Y; BB: BII combined Braun; CI: Confidence interval.

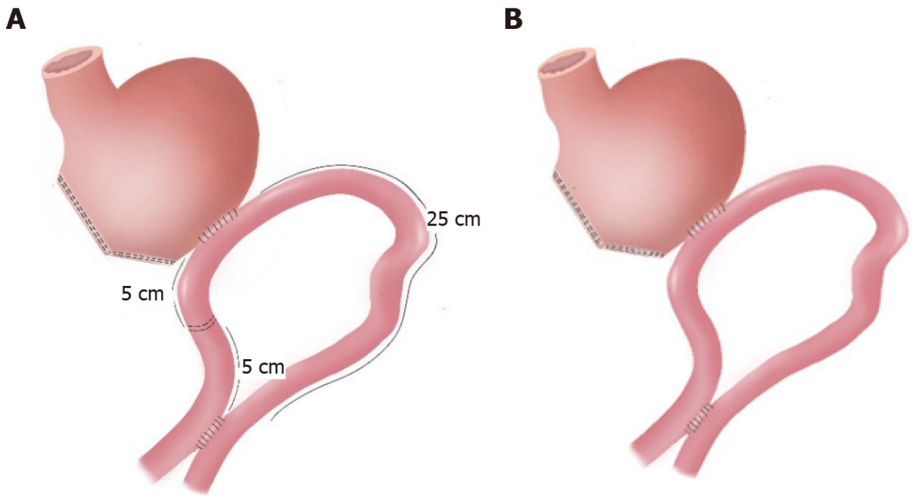





**Figure 5 Anastomosis method.** A: Uncut Roux-en-Y; B: Billroth II with Braun.

Eight studies involving 704 patients were included in this meta-analysis, divided into 354 who received URY and 350 who received BB[29-36]. No statistical difference in surgical outcomes between the two groups was observed in terms of operative time, intraoperative bleeding, reconstruction time, and lymph node dissection. Our analysis revealed that the reconstruction time had a high degree of heterogeneity both in the total and subgroup analyses, which might be due to factors such as study design, proficiency of the surgeon in performing anastomosis, and cooperation within the surgical team. Our results were like those of a previous study[41], except for the fact that URY in our study had a shorter operative time as well as reconstruction time. This might be due to differences in surgical experience among different reconstructive procedures that might lead to biased results and inconsistent reconstructive approaches (*in vivo* or *ex vivo*).

During the postoperative recovery, the mean gastric pH at days 1 and 3 post operation and time to first solid diet were significantly shorter in the URY group than in the BB group. However, the heterogeneity of these observations in our study was high. This might be related to Chen[30]'s study because the author did not use a new negative pressure drainage tube in a timely manner at the beginning of the study to measure the postoperative gastric fluid, leading to a large error in measuring the pH of the gastric fluid in the experimental group in the early stage. The sensitivity analysis of the time to first passage of flatus or defecation, time to first solid diet, and post-operative hospitalization time showed consistency. In addition, URY did not increase the postoperative length of stay compared to BB, which was consistent with the results of Park and Kim[41] and Chen *et al*[42]. The time to first passage of flatus or defecation in the URY group was shorter than that in the BB group. However, the subgroup analysis showed significance only in the non-RCTs with high heterogeneity, and it was also highly subjective; thus, our results should be interpreted with caution.

In terms of postoperative complications, the URY group had a lower incidence of postoperative reflux gastritis. This result is probably due to the fact that duodenal secretions are diverted to the distal jejunum though the jejunojejunostomy after URY anastomosis compared to BB anastomosis[16]. The uncut limb during the URY procedure preserved the original normal electrical conduction and direction of conduction[40]. This dual action promotes the normal recovery of the postoperative intestinal motility. Reflux gastritis is commonly observed in patients who underwent DG. Endoscopy remains the cornerstone of the diagnosis; the characteristic endoscopic features are adherent mucus, edema, mucosal friability, and erosions. The medical treatment includes antacids and cholestyramine alone or together. Severe cases require surgical treatment. Our study shows that URY is a good way to avoid postoperative reflux gastritis in patients subjected to LDG. Noh *et al*[43] reported that uncircumcised gastrojejunal RY anastomosis prevents RSS and reduces the alkaline reflux gastritis compared with conventional surgery. A recent clinical study by Park and Kim[41] also indicated that sufficient evidence is available to demonstrate that URY anastomosis reduces postoperative gastritis, duodenal secretion reflux, and gastric residuals. No significant difference in the probability of anastomotic leakage, gastroparesis, or ileus was found in the postoperative period between the two groups. Ma *et al*[44] demonstrated that URY does not increase the occurrence of postoperative anastomotic leakage and gastrointestinal motility dysfunction for conventional anastomoses.

Although gastrojejunostomy RY anastomosis is an effective method to prevent bile reflux gastritis after DG surgery, the incidence of postoperative RSS is high, seriously affecting the quality of life of patients. URY is a reliable anastomosis after distal radical GC surgery, resulting in few postoperative complications[45], with a lower incidence of RSS compared to RY[18,46,47]. URY gastrojejunostomy

reduces RSS by maintaining jejunal continuity (through normal conduction of myoelectric pulses), thereby maintaining the conduction of duodenal pacemaker activity[47]. BI reconstruction is one of the most popular reconstructive procedures after DG, and the incidence of postoperative complications is low; thus, it is considered a good option for surgeons[48]. However, it is not suitable for severe GC cases that require extensive dissection of the stomach, since this approach can lead to excessive anastomotic tension[11]. Our study also demonstrated that the postoperative complication rates after URY were significantly lower than those after BB. Thus, URY might be considered the primary option for reducing the incidence of reflux gastritis and RSS.

Our meta-analysis has several advantages. First, it is the first study comparing URY with BB anastomosis. Second, unlike the comparison of the procedures in previous works, our work considered BB because the URY gastrojejunostomy is a modification of the BII procedure with the BB anastomosis. Third, all the extracted data were cross-checked, and subgroup analysis was performed according to the type of the included studies to improve the credibility of our results. However, several limitations were also present in this study. First, most of the included studies were conducted in tertiary centers, and the recruited patients were carefully selected and had relatively low morbidity and low body mass index, which might result in a limited generalization of these findings. Second, the included studies are mostly observational ones, thus, with a potential selection bias. Third, the included RCTs have a certain bias in the implementation of blinding. This is inevitable because the surgeon cannot perform the procedure without knowing the assigned procedure. Therefore, a large sample size and a rigorously designed RCT are needed to confirm our results. Finally, all the LDG procedures were performed in China, probably because the incidence of GC is higher in East Asia than in most Western countries and distal tumors are more common in Eastern countries[2,49]. Nonetheless, our study provides clinical evidence for surgeons in deciding the optimal reconstruction technique for their patients. Moreover, our hope is that this topic can attract the attention of surgeons in more countries.

## CONCLUSION

URY anastomosis is a safe and effective technique after LDG, and it is better than BB in terms of early postoperative recovery, postoperative gastric juice pH close to normal, and low incidence of reflux gastritis; thus, it can be recommended for gastrointestinal reconstruction after LDG. However, a rigorous RCT design and larger sample size cohorts (including long-term follow-up data) are still necessary to confirm our conclusions.

## ARTICLE HIGHLIGHTS

### *Research background*

Gastric cancer (GC) patients have a poor prognosis and high mortality. The efficacy and safety of uncut Roux-en-Y (URY) anastomosis after laparoscopic distal gastrectomy (LDG) are still controversial.

### *Research motivation*

The URY gastrojejunostomy reduces these complications by blocking the entry of bile and pancreatic juice into the residual stomach and preserves the impulse originating from the duodenum, while BII combined Braun (BB) anastomosis reduces the postoperative biliary reflux without Roux-Y stasis syndrome. Therefore, the purpose of this study was to compare the efficacy and safety of laparoscopic URY with BB anastomosis in patients with GC who underwent radical distal gastrectomy.

### *Research objectives*

The purpose of this study was to perform a systematic review and meta-analysis to evaluate the application value of URY anastomosis in LDG.

### *Research methods*

PubMed, Embase, Web of science, Cochrane Library, Chinese National Knowledge Infrastructure, Wanfang, Chinese Biomedical Database, and VIP Database for Chinese Technical Periodicals (VIP) were used to search relevant studies published from January 1994 to August 18, 2021. The following databases were also used in our search: Clinicaltrials.gov (https://clinicaltrials.gov), Data Archiving and Networked Services, the World Health Organization International Clinical Trials Registry Platform Search Portal (https://www.who.int/clinical-trials-registry-platform/the-ictrp-search-portal), and the reference lists of articles and relevant conference proceedings in August 2021. In addition, we conducted a relevant search by Reference Citation Analysis (RCA) (https://www.referencecitationanalysis.com). We cited high-quality references using its results analysis functionality. The methodological quality of the eligible randomized clinical trials (RCTs) was evaluated using the Cochrane Risk of Bias Tool, and

the non-RCTs were evaluated using the Newcastle-Ottawa scale. Statistical analyses were performed using Review Manager (Version 5.4).

### *Research results*

Eight studies involving 704 patients were included in this meta-analysis. The incidence of reflux gastritis [odds ratio = 0.07, 95% confidence interval (CI): 0.03-0.19, $P < 0.00001$) was significantly lower in the URY group than in the BB group. The pH of the postoperative gastric fluid was lower in the URY group than in the BB group at 1 d [mean difference (MD) = -2.03, 95%CI: (-2.73)-(-1.32), $P < 0.00001$] and 3 d [MD = -2.03, 95%CI: (-2.57)-(-2.03), $P < 0.00001$] after the operation. However, no significant difference in all the intraoperative outcomes was found between the two groups.

### *Research conclusions*

This work demonstrated that URY is superior to BB in patients with GC when the postoperative outcome is considered. Therefore, this evidence supports the recommendation of URY gastrojejunostomy for gastrointestinal reconstruction after LDG.

### *Research perspectives*

Several limitations were present in this study. First, most of the included studies were conducted in tertiary centers, and the recruited patients were carefully selected and had relatively low morbidity and low body mass index, which might result in a limited generalization of these findings. Second, the included studies are mostly observational ones, thus, with a potential selection bias. Third, the included RCTs has a certain bias in the implementation of blinding. This is inevitable because the surgeon cannot perform the procedure without knowing the assigned procedure. Therefore, a large sample size and a rigorously designed RCTs are needed for confirming our results. Finally, all the LDG procedures were performed in China, probably because the incidence of GC is higher in East Asia than in most Western countries and distal tumors are more common in Eastern countries. Moreover, our hope is that this topic can attract the attention of surgeons in more countries.

## ACKNOWLEDGEMENTS

The authors thank the Key Laboratory of Molecular Diagnostics and Precision Medicine for Surgical Oncology in Gansu Province and the DaVinci Surgery System Database (DSSD, http://www.davincisurgerydatabase.com) for their help and support in the methodology and meta-analysis process. Thanks to Rui Yang of Ningxia Medical University for her help with the article graphics.

## FOOTNOTES

**Author contributions:** Jiao YJ, Lu TT, Yang KH, and Cai H designed the research; Jiao YJ, Liu DM, Wang LL, Ma SX, and Chen YQ conducted the literature search; Jiao YJ and Xiang X collected and retrieved the data; Jiao YJ, Liu DM, and Wang YF analyzed the data; Jiao YJ wrote and revised the manuscript; and all authors approved the final version.

**Supported by** Natural Science Foundation of Gansu Province, China, No. 18JR3RA052; National Scientific Research Project Cultivation Plan of Gansu Provincial People's Hospital, No. 19SYPYA-1; National Key Research and Development Program, No. 2018YFC1311506; Gansu Province Da Vinci Robot High End Diagnosis and Treatment Personnel Training Project, No. 2020RCXM076.

**Conflict-of-interest statement:** The authors declare no conflicts of interest for this article.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.



**Country/Territory of origin:** China

**ORCID number:** Ya-Jun Jiao 0000-0003-3980-2492; Ting-Ting Lu 0000-0002-6964-3237; De-Ming Liu 0000-0002-4634-359X; Xue Xiang 0000-0003-4239-125X; Liu-Li Wang 0000-0003-1596-1093; Shi-Xun Ma 0000-0002-4208-9248; Yong-Feng Wang 0000-0003-3832-0926; Ya-Qiong Chen 0000-0001-8040-2832; Ke-Hu Yang 0000-0001-7864-3012; Hui Cai 0000-0001-

5857-1744.

**S-Editor:** Wang JJ
**L-Editor:** Wang TQ
**P-Editor:** Wang JJ

## REFERENCES

1 **Suh YS**, Lee J, Woo H, Shin D, Kong SH, Lee HJ, Shin A, Yang HK. National cancer screening program for gastric cancer in Korea: Nationwide treatment benefit and cost. *Cancer* 2020; **126**: 1929-1939 [PMID: 32031687 DOI: 10.1002/cncr.32753]
2 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]
3 **Mocan L**. Surgical Management of Gastric Cancer: A Systematic Review. *J Clin Med* 2021; **10** [PMID: 34207898 DOI: 10.3390/jcm10122557]
4 **Kitano S**, Iso Y, Moriyama M, Sugimachi K. Laparoscopy-assisted Billroth I gastrectomy. *Surg Laparosc Endosc* 1994; **4**: 146-148 [PMID: 8180768]
5 **Yakoub D**, Athanasiou T, Tekkis P, Hanna GB. Laparoscopic assisted distal gastrectomy for early gastric cancer: is it an alternative to the open approach? *Surg Oncol* 2009; **18**: 322-333 [PMID: 18922689 DOI: 10.1016/j.suronc.2008.08.006]
6 **Best LM**, Mughal M, Gurusamy KS. Laparoscopic versus open gastrectomy for gastric cancer. *Cochrane Database Syst Rev* 2016; **3**: CD011389 [PMID: 27030300 DOI: 10.1002/14651858.CD011389.pub2]
7 **Chen X**, Feng X, Wang M, Yao X. Laparoscopic versus open distal gastrectomy for advanced gastric cancer: A meta-analysis of randomized controlled trials and high-quality nonrandomized comparative studies. *Eur J Surg Oncol* 2020; **46**: 1998-2010 [PMID: 32758382 DOI: 10.1016/j.ejso.2020.06.046]
8 **Piessen G**, Triboulet JP, Mariette C. Reconstruction after gastrectomy: which technique is best? *J Visc Surg* 2010; **147**: e273-e283 [PMID: 20934934 DOI: 10.1016/j.jviscsurg.2010.09.004]
9 **Kalmár K**, Németh J, Kelemen D, Agoston E, Horváth OP. Postprandial gastrointestinal hormone production is different, depending on the type of reconstruction following total gastrectomy. *Ann Surg* 2006; **243**: 465-471 [PMID: 16552196 DOI: 10.1097/01.sla.0000205740.12893.bc]
10 **Terashima M**, Tanabe K, Yoshida M, Kawahira H, Inada T, Okabe H, Urushihara T, Kawashima Y, Fukushima N, Nakada K. Postgastrectomy Syndrome Assessment Scale (PGSAS)-45 and changes in body weight are useful tools for evaluation of reconstruction methods following distal gastrectomy. *Ann Surg Oncol* 2014; **21** Suppl 3: S370-S378 [PMID: 24590434 DOI: 10.1245/s10434-014-3583-z]
11 **Xiong JJ**, Altaf K, Javed MA, Nunes QM, Huang W, Mai G, Tan CL, Mukherjee R, Sutton R, Hu WM, Liu XB. Roux-en-Y versus Billroth I reconstruction after distal gastrectomy for gastric cancer: a meta-analysis. *World J Gastroenterol* 2013; **19**: 1124-1134 [PMID: 23467403 DOI: 10.3748/wjg.v19.i7.1124]
12 **Van Cutsem E**, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. *Lancet* 2016; **388**: 2654-2664 [PMID: 27156933 DOI: 10.1016/S0140-6736(16)30354-3]
13 **Shoji Y**, Kumagai K, Ida S, Ohashi M, Hiki N, Sano T, Nunobe S. Features of the complications for intracorporeal Billroth-I and Roux-en-Y reconstruction after laparoscopic distal gastrectomy for gastric cancer. *Langenbecks Arch Surg* 2021; **406**: 1425-1432 [PMID: 33604820 DOI: 10.1007/s00423-021-02136-6]
14 **Kumagai K**, Shimizu K, Yokoyama N, Aida S, Arima S, Aikou T; Japanese Society for the Study of Postoperative Morbidity after Gastrectomy. Questionnaire survey regarding the current status and controversial issues concerning reconstruction after gastrectomy in Japan. *Surg Today* 2012; **42**: 411-418 [PMID: 22391980 DOI: 10.1007/s00595-012-0159-z]
15 **Masui T**, Kubora T, Nakanishi Y, Aoki K, Sugimoto S, Takamura M, Takeda H, Hashimoto K, Tokuka A. The flow angle beneath the gastrojejunostomy predicts delayed gastric emptying in Roux-en-Y reconstruction after distal gastrectomy. *Gastric Cancer* 2012; **15**: 281-286 [PMID: 22041869 DOI: 10.1007/s10120-011-0107-4]
16 **Cui LH**, Son SY, Shin HJ, Byun C, Hur H, Han SU, Cho YK. Billroth II with Braun Enteroenterostomy Is a Good Alternative Reconstruction to Roux-en-Y Gastrojejunostomy in Laparoscopic Distal Gastrectomy. *Gastroenterol Res Pract* 2017; **2017**: 1803851 [PMID: 28163716 DOI: 10.1155/2017/1803851]
17 **Vogel SB**, Drane WE, Woodward ER. Clinical and radionuclide evaluation of bile diversion by Braun enteroenterostomy: prevention and treatment of alkaline reflux gastritis. An alternative to Roux-en-Y diversion. *Ann Surg* 1994; **219**: 458-65; discussion 465 [PMID: 8185396 DOI: 10.1097/00000658-199405000-00003]
18 **Sun MM**, Fan YY, Dang SC. Comparison between uncut Roux-en-Y and Roux-en-Y reconstruction after distal gastrectomy for gastric cancer: A meta-analysis. *World J Gastroenterol* 2018; **24**: 2628-2639 [PMID: 29962819 DOI: 10.3748/wjg.v24.i24.2628]
19 **Yang D**, He L, Tong WH, Jia ZF, Su TR, Wang Q. Randomized controlled trial of uncut Roux-en-Y *vs* Billroth II reconstruction after distal gastrectomy for gastric cancer: Which technique is better for avoiding biliary reflux and gastritis? *World J Gastroenterol* 2017; **23**: 6350-6356 [PMID: 28974902 DOI: 10.3748/wjg.v23.i34.6350]
20 **Pieper D**, Buechter RB, Li L, Prediger B, Eikermann M. Systematic review found AMSTAR, but not R(evised)-AMSTAR, to have good measurement properties. *J Clin Epidemiol* 2015; **68**: 574-583 [PMID: 25638457 DOI: 10.1016/j.jclinepi.2014.12.009]
21 **Sampson M**, McGowan J, Cogo E, Grimshaw J, Moher D, Lefebvre C. An evidence-based practice guideline for the peer review of electronic search strategies. J Clin Epidemiol 2009;62:944-52. [PMID: 19230612 DOI:

10.1016/j.jclinepi.2008.10.012]
22 **Li J**, Gao W, Punja S, Ma B, Vohra S, Duan N, Gabler N, Yang K, Kravitz RL. Reporting quality of N-of-1 trials published between 1985 and 2013: a systematic review. *J Clin Epidemiol* 2016; **76**: 57-64 [PMID: 26769257 DOI: 10.1016/j.jclinepi.2015.11.016]
23 **Kim D**, Gedney R, Allen S, Zlomke H, Winter E, Craver J, Pinnola AD, Lancaster W, Adams D. Does etiology of gastroparesis determine clinical outcomes in gastric electrical stimulation treatment of gastroparesis? *Surg Endosc* 2021; **35**: 4550-4554 [PMID: 32909214 DOI: 10.1007/s00464-020-07928-3]
24 **Bragg D**, El-Sharkawy AM, Psaltis E, Maxwell-Armstrong CA, Lobo DN. Postoperative ileus: Recent developments in pathophysiology and management. *Clin Nutr* 2015; **34**: 367-376 [PMID: 25819420 DOI: 10.1016/j.clnu.2015.01.016]
25 **Higgins JP**, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343**: d5928 [PMID: 22008217 DOI: 10.1136/bmj.d5928]
26 **Luchini C**, Stubbs B, Solmi M, Veronese N. Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale. *World J Meta-Anal* 2017; **5**: 80-84 [DOI: 10.13105/wjma.v5.i4.80]
27 **Stang A**. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; **25**: 603-605 [PMID: 20652370 DOI: 10.1007/s10654-010-9491-z]
28 **Higgins JP**, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539-1558 [PMID: 12111919 DOI: 10.1002/sim.1186]
29 **Gao DS**, Xiang BH. Study of different anastomoses of B-II+Braun and Uncut Roux-en-Y in radical surgery for distal gastric cancer. *Zhejiang Clinical Medical Journal* 2018; **20**: 3
30 **Chen LF**. The contrast on effect of nondetached Roux-en-Y and BillrothII plus Braun on prevention of bile reflux postoperative gastric cancer. Lanzhou University, 2018
31 **Ren N**, Liu XL, Wei LM, Cui JF. Comparison of Billroth II combining Braun anastomosis and Roux-en-Y anastomosis in laparoscopic distal gastric cancer surgery. *Chin J Curr Adv Gen Surg* 2020; **23**: 197-199, 206 [DOI: 10.3969/j.issn.1009-9905.2020.03.008]
32 **Li ST**, Ji G, Fen J, Zhang B, Wang LR, Liu ZH, Yang YJ. Comparison of the results of different methods of gastrointestinal tract reconstruction in laparoscopic distal gastric cancer surgery. *Med J National Defending Forces Southwest China* 2017; **27**: 717-719 [DOI: 10.3969/j.issn.1004-0188.2017.07.025]
33 **Wu SH**, Liu SH, Zhou F. Clinical comparative study of different anastomosis methods of B-II+Braun and Uncut Roux-en-Y during radical laparoscopic radical gastrectomy. *J Clin Surg* 2021; **29**: 154-157 [DOI: 10.3969/j.issn.1005-6483.2021.02.017]
34 **Wang J**, Wang Q, Dong J, Yang K, Ji S, Fan Y, Wang C, Ma Q, Wei Q, Ji G. Total Laparoscopic Uncut Roux-en-Y for Radical Distal Gastrectomy: An Interim Analysis of a Randomized, Controlled, Clinical Trial. *Ann Surg Oncol* 2021; **28**: 90-96 [PMID: 32556870 DOI: 10.1245/s10434-020-08710-4]
35 **Zhou JF**, He QL, Wang JX, Qian HY. Application value of different digestive tract reconstruction methods in labparoscopic distal gastrectomy. *Chin J Dig Surg* 2018; **17**: 592-598 [DOI: 10.3760/cma.j.issn.1673-9752.2018.06.011]
36 **Wang Y**, Li Z, Shan F, Zhang L, Li S, Jia Y, Chen Y, Xue K, Miao R, Gao X, Yan C, Wu Z, Ji J. [Comparison of the safety and the costs between laparoscopic assisted or totally laparoscopic uncut Roux-en-Y and BillrothII(+Braun reconstruction--a single center prospective cohort study]. *Zhonghua Wei Chang Wai Ke Za Zhi* 2018; **21**: 312-317 [PMID: 29577220]
37 **Page MJ**, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; **372**: n71 [PMID: 33782057 DOI: 10.1136/bmj.n71]
38 **McCulloch P**, Taylor I, Sasako M, Lovett B, Griffin D. Randomised trials in surgery: problems and possible solutions. *BMJ* 2002; **324**: 1448-1451 [PMID: 12065273 DOI: 10.1136/bmj.324.7351.1448]
39 **Van Stiegmann G**, Goff JS. An alternative to Roux-en-Y for treatment of bile reflux gastritis. *Surg Gynecol Obstet* 1988; **166**: 69-70 [PMID: 3336817]
40 **Huang Y**, Wang S, Shi Y, Tang D, Wang W, Chong Y, Zhou H, Xiong Q, Wang J, Wang D. Uncut Roux-en-Y reconstruction after distal gastrectomy for gastric cancer. *Expert Rev Gastroenterol Hepatol* 2016; **10**: 1341-1347 [PMID: 27748146 DOI: 10.1080/17474124.2016.1248404]
41 **Park JY**, Kim YJ. Uncut Roux-en-Y Reconstruction after Laparoscopic Distal Gastrectomy Can Be a Favorable Method in Terms of Gastritis, Bile Reflux, and Gastric Residue. *J Gastric Cancer* 2014; **14**: 229-237 [PMID: 25580354 DOI: 10.5230/jgc.2014.14.4.229]
42 **Chen XJ**, Chen YZ, Chen DW, Chen YL, Xiang J, Lin YJ, Chen S, Peng JS. The Development and Future of Digestive Tract Reconstruction after Distal Gastrectomy: A Systemic Review and Meta-Analysis. *J Cancer* 2019; **10**: 789-798 [PMID: 30854084 DOI: 10.7150/jca.28843]
43 **Noh SM**. Improvement of the Roux limb function using a new type of "uncut Roux" limb. *Am J Surg* 2000; **180**: 37-40 [PMID: 11036137 DOI: 10.1016/s0002-9610(00)00421-9]
44 **Ma Y**, Li F, Zhou X, Wang B, Lu S, Wang W, Yu S, Fu W. Four reconstruction methods after laparoscopic distal gastrectomy: A systematic review and network meta-analysis. *Medicine (Baltimore)* 2019; **98**: e18381 [PMID: 31860999 DOI: 10.1097/MD.0000000000018381]
45 **Park YS**, Shin DJ, Son SY, Kim KH, Park DJ, Ahn SH, Kim HH. Roux Stasis Syndrome and Gastric Food Stasis After Laparoscopic Distal Gastrectomy with Uncut Roux-en-Y Reconstruction in Gastric Cancer Patients: A Propensity Score Matching Analysis. *World J Surg* 2018; **42**: 4022-4032 [PMID: 29915987 DOI: 10.1007/s00268-018-4715-6]
46 **Jangjoo A**, Mehrabi Bahar M, Aliakbarian M. Uncut Roux-en-y esophagojejunostomy: A new reconstruction technique after total gastrectomy. *Indian J Surg* 2010; **72**: 236-239 [PMID: 23133254 DOI: 10.1007/s12262-010-0059-7]
47 **Tu BN**, Kelly KA. Elimination of the Roux stasis syndrome using a new type of "uncut Roux" limb. *Am J Surg* 1995; **170**: 381-386 [PMID: 7573733 DOI: 10.1016/s0002-9610(99)80308-0]

48 **Kim MS**, Kwon Y, Park EP, An L, Park H, Park S. Revisiting Laparoscopic Reconstruction for Billroth 1 Versus Billroth 2 Versus Roux-en-Y After Distal Gastrectomy: A Systematic Review and Meta-Analysis in the Modern Era. *World J Surg* 2019; **43**: 1581-1593 [PMID: 30756163 DOI: 10.1007/s00268-019-04943-x]

49 **Strong VE**, Song KY, Park CH, Jacks LM, Gonen M, Shah M, Coit DG, Brennan MF. Comparison of gastric cancer survival following R0 resection in the United States and Korea using an internationally validated nomogram. *Ann Surg* 2010; **251**: 640-646 [PMID: 20224369 DOI: 10.1097/SLA.0b013e3181d3d29b]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 June 27; 14(6): 611-620

DOI: 10.4240/wjgs.v14.i6.611

ISSN 1948-9366 (online)

CASE REPORT

# Intestinal perforation with abdominal abscess caused by extramedullary plasmacytoma of small intestine: A case report and literature review

Ke-Wei Wang, Nan Xiao

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B, B, B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

**P-Reviewer:** Majerović M, Croatia; Perse M, Slovenia; Vij M, India
**A-Editor:** Yao QG, China

**Received:** September 27, 2021
**Peer-review started:** September 27, 2021
**First decision:** January 12, 2022
**Revised:** January 26, 2022
**Accepted:** May 22, 2022
**Article in press:** May 22, 2022
**Published online:** June 27, 2022

**Ke-Wei Wang, Nan Xiao,** Department of Gastrointestinal Surgery, The First Affiliated Hospital of China Medical University, Shenyang 110001, Liaoning Province, China

**Corresponding author:** Ke-Wei Wang, MD, PhD, Associate Professor, Surgeon, Department of Gastrointestinal Surgery, The First Affiliated Hospital of China Medical University, No. 155 Nanjing North Street, Heping District, Shenyang 110001, Liaoning Province, China.
kwwang@cmu.edu.cn

## Abstract

*BACKGROUND*

Extramedullary plasmacytoma (EMP) of the gastrointestinal tract is an extremely rare disease. Clinical manifestations of EMPs are varied and depend on the location and progression of the tumor.

*CASE SUMMARY*

Here, we firstly report a case of intestinal perforation with abdominal abscess caused by EMP of the small intestine in a 55-year-old female patient. The patient received emergency surgery immediately after the necessary preoperative procedures. During the operation, EMP was found to have caused the perforation of the small intestine and the formation of multiple abscesses in the abdominal cavity. Partial resection of the small intestine with peritoneal irrigation and drainage was performed. EMP was finally confirmed by postoperative histopathology and laboratory tests. Additionally, we performed a literature review of gastrointestinal EMP to obtain a deeper understanding of this disease.

*CONCLUSION*

EMP of the small intestine may have spontaneous perforation, which requires emergency surgery. Surgical resection can obtain good therapeutic effects.

**Key Words:** Extramedullary plasmacytoma; Perforation; Small intestine; Gastrointestinal tract; Treatment; Case report

**Core Tip:** Extramedullary plasmacytoma (EMP) of the gastrointestinal tract is an extremely rare disease, accounting for only 7% of all EMPs. Clinical manifestations of EMPs are varied and depend on the location and progression of the tumor. Here, we firstly report a case of intestinal perforation with abdominal abscess caused by EMP of the small intestine in a 55-year-old female patient. Additionally, we discussed the diagnosis and treatment of gastrointestinal EMP after a review of the literature worldwide to provide an overview of this disease.

**Citation:** Wang KW, Xiao N. Intestinal perforation with abdominal abscess caused by extramedullary plasmacytoma of small intestine: A case report and literature review. *World J Gastrointest Surg* 2022; 14(6): 611-620
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i6/611.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i6.611

## INTRODUCTION

Plasmacytoma is a malignant tumor that originates from bone marrow hematopoietic tissue. It is characterized by an imbalance in the monoclonal proliferation of plasma cells. Extramedullary plasmacytoma (EMP) refers to a localized monoclonal plasma cell proliferation that occurs in soft tissues without bone marrow involvement. It is a rare type of malignant monoclonal plasma cell lesion, accounting for approximately 2%-3% of all plasmacytomas[1,2]. Plasmacytoma primarily occurs in the upper respiratory tract but is rarely found in the gastrointestinal tract. Gastrointestinal EMP only accounts for approximately 7% of all EMPs[3]. EMP is found in all parts of the gastrointestinal tract, including the small intestine[4-7]. Clinical manifestations of gastrointestinal EMPs vary with the location and progression of the tumor and lack specificity. Common clinical manifestations include abdominal pain, abdominal discomfort, changes in bowel habits, gastrointestinal bleeding and intestinal obstruction[8-12]. However, there are no reports of spontaneous perforation and abdominal abscess caused by EMP of the small intestine. Reports on EMP of the small intestine are mostly single case reports, and most of the patients underwent routine surgery[7,13]. It is rare to find this disease during an emergency surgery. In this paper, we firstly present a case of intestinal perforation with abdominal abscess caused by EMP of the small intestine and review the relevant literature from PubMed.

## CASE PRESENTATION

### *Chief complaints*

A 55-year-old female was admitted to the Department of Emergency of our hospital with sudden abdominal pain and abdominal distension.

### *History of present illness*

The patient's symptoms started 3 d prior and were accompanied by nausea and vomiting without gas or defecation. Since onset, the patient had a loss of appetite, limited diet, poor sleep and decreased urination. No significant change in body weight was noted.

### *History of past illness*

The patient's previous medical history was not remarkable. She and her family had no history of multiple myeloma (MM) or other gastrointestinal diseases.

### *Personal and family history*

The patient has no personal and family history.

### *Physical examination*

During physical examination, the patient had a normal heart rate and mild hypotension. The patient's abdomen was slightly distended, and the abdominal tenderness was more severe in the left upper abdomen accompanied by rebound pain and muscle tension.

### *Laboratory examinations*

Laboratory tests showed the following: White blood cells 10.5 × $10^{-9}$/L, neutrocyte (NE) 9.63 × $10^{-9}$/L, NE% 91.7%, hemoglobin 108 g/L, and platelet 330 × $10^{-9}$/L. Liver and kidney function were normal.

### *Imaging examinations*

Enhanced computed tomography (CT) showed that the small intestinal lumen in the upper left abdomen was dilated with gas and fluid accumulation, and showed multiple fluid-gas level changes were noted. The intestinal wall was edematous and thickened, and the density of the surrounding fat interspace had increased. Small air bubbles were scattered under the left diaphragm, and multiple encapsulated effusions were observed between the small intestines. These imaging findings suggested local perforation and multiple abscesses in the abdominal cavity (Figure 1).

## FINAL DIAGNOSIS

Microscopic analysis showed that the pathological specimen displayed a large number of neoplastic plasma cells with inflammatory cell infiltration (Figure 2A). These plasma cells were positive for CD38 (+), CD138 (+), kappa (+), lambda (week+), CD79a (week+), and MUM1 (+) and negative for creatine kinase (-), CD117 (-), Dog-1 (-), S-100 (-), B cell lymphoma-2 (-), beta-catenin (-), CD56 (-), immunoglobulin G4 (-) and Pax-5 (-) with a Ki-67 proliferative index of 10% (Figures 2B-F). The final pathological specimens were highly suspicious of plasmacytoma. Postoperative laboratory tests showed that the bone marrow cytology was normal and no abnormal monoclonal plasma cells were detected in the flow cytometric analysis. Urine free light chain and serum immunofixation electrophoresis were also normal. Lytic lesions were not found on X-rays. Therefore, the final diagnosis of this patient was primary EMP of the small intestine.

## TREATMENT

Considering that the patient may have a perforation of the digestive tract, we performed emergency surgery. During the operation, we found that the small intestinal serosa 100 cm away from the Treitz ligament had a dark-red polyp-like protrusion with a perforation approximately 0.5 cm in diameter at the top. The local intestinal wall was hyperemic, edematous and thickened, and the surface of the surrounding small intestine and lateral peritoneum was covered with many purulent masses (Figure 3). Several abscesses were observed between the left paracolic groove and small intestine and filled with a yellow, turbid fluid. After the abscesses were removed, the abdominal cavity was flushed with a large amount of warm normal saline. Then, a segment of the jejunum 33 cm in length was resected, and a primary side-to-end anastomosis of the small intestine was performed. The lumen of the intestinal tube 6 cm from the nearest end resection margin was narrow with a diameter of approximately 1.5 cm. The serosal surface was similar to a polypoid with a size of approximately 2 cm × 1 cm × 1 cm.

## OUTCOME AND FOLLOW-UP

The patient had a good postoperative recovery with no complications, and she was discharged smoothly from the hospital one week after her surgery. As of August 1, 2021, she has been regularly followed up for 2 years at an outpatient clinic, and there have been no signs of recurrence or metastasis.

## DISCUSSION

Primary plasmacytoma of the small intestine is rare in clinical practice. Here, we firstly report a case of intestinal perforation with abdominal abscess caused by EMP of the small intestine in a 55-year-old female. The diagnosis is based on a pathologically confirmed small intestinal mass with clonal growth of plasma cells, normal bone marrow histological examination, and normal serum monoclonal immunoglobulin levels[14]. EMP can be divided into two types: Primary and secondary. EMP can also present as a secondary tumor of another plasma cell neoplasm, such as MM[15]. MM must be excluded before the diagnosis of primary EMP[16]. The case we reported had no positive laboratory or imaging findings of MM, which met the diagnostic criteria of primary EMP. In this paper, we performed a review of the well-documented primary gastrointestinal EMP cases in the last 20 years and presented these results in table form[4-7,11,17-45] (Table 1). These results show that gastrointestinal EMP is common in patients over the age of 50 years, and the incidence rate is higher in men compared with women (2:1). The clinical manifestations of gastrointestinal EMPs vary with the location of the tumor and lack specificity. In the early stage, this disease is often asymptomatic, and patients often seek medical treatment because of pain or discomfort caused by local tumor compression. Other clinical manifestations include gastrointestinal bleeding or obstruction, changes in bowel habits, *etc*. In our case, the patient presented with sudden abdominal pain and abdominal distension, which may have been caused by intestinal

**Table 1 Well documented case reports of primary gastrointestinal extramedullary plasmacytoma**

| Ref. | Age | Gender | Location | Presentation | Operative | Non-operative | Outcome |
|---|---|---|---|---|---|---|---|
| Katodritou *et al* [17], 2008 | 68 | Male | Stomach | Upper-gastrointestinal bleeding | None | Bortezomib, dexamethasone | No recurrence 13 mo after diagnosis |
| Park *et al*[18], 2009 | 50 | Female | Stomach | None | Endoscopic submucosal dissection | None | No recurrence during 12 mo follow-up |
| Krishnamoorthy *et al*[19], 2010 | 57 | Male | Stomach | Upper-gastrointestinal bleeding | Gastrectomy | None | N/A |
| Park *et al*[20], 2014 | 70 | Male | Stomach | Indigestion | Endoscopic submucosal resection | Oral thalidomide therapy | No recurrence during 24 mo follow-up |
| Zhao *et al*[21], 2014 | 79 | Male | Stomach | Epigastric pain | Surgical resection | None | No recurrence during 8 mo follow-up |
| Fukuhara *et al* [22], 2016 | 36 | Male | Stomach | Dyspnoea, fatigue | Total gastrectomy, lymphadenectomy | Chemotherapy and autologous peripheral blood stem-cell transplantation | No recurrence during 18 mo follow-up |
| Kang *et al*[23], 2016 | 78 | Female | Stomach | Epigastric pain | Refused | High-dose dexamethasone | Completely regressed and remission was maintained for over 1 yr |
| Takahashi *et al* [24], 2016 | 64 | Female | Stomach | Loss of appetite and reduced body weight | Surgical resection | None | No recurrence during 36 mo follow-up |
| Oliveira *et al*[25], 2017 | 61 | Male | Stomach | Upper gastrointestinal bleeding | Endoscopic polypectomy | None | No recurrence during 6 yr follow-up |
| Ding *et al*[6], 2019 | 65 | Male | Stomach | Epigastric discomfort and mass | Distal gastrectomy | None | No recurrence during 3 mo follow-up |
| Weidenbaum *et al* [26], 2022 | 83 | Female | Stomach | None | None | Radiation therapy, chemotherapy | N/A |
| Carneiro *et al*[27], 2009 | 72 | Male | Duodenum | Epigastric pain, vomiting and weight loss | Resection of the fourth part of the duodenum and proximal segment of jejunum | None | No recurrence after 12 mo follow-up |
| Ammar *et al*[28], 2010 | 69 | Female | Duodenum | Fatigue, melaena | Percutaneous transhepatic biliary drainage | Extra-corporeal radiotherapy | N/A |
| Yoshida *et al*[29], 2004 | 70 | Female | Ileum | High fever, bowel obstruction | Combined resection of the terminal ileum and ascending colon | Chemotherapy | Died of cachexia 4 mo after surgery |
| Moriyama *et al* [30], 2006 | 73 | Female | Ileum | Abdominal pain | Local resection of the tumor | None | No recurrence after 28 mo follow-up |
| Gabriel *et al*[31], 2014 | 62 | Male | Ileocecum | Melena | Right hemicolectomy | None | N/A |
| Zhang *et al*[32], 2017 | 63 | Female | Ileocecum | Episodic pain around the umbilicus | Right hemicolectomy surgery | None | N/A |
| Hanawa *et al*[7], 2019 | 63 | Male | Ileocecum | Abdominal distention and weight loss | Surgically removed stenotic lesion of small intestine | Anti-Crohn's disease | No recurrence during 36 mo follow-up |
| Evans *et al*[5], 2020 | 35 | Male | Appendix | Upper abdominal pain | Appendectomy | None | Alive without evidence of disease |
| Doki *et al*[33], 2008 | 64 | Male | Ascending colon | Aggravated pain in the right lower abdomen | Surgical resection | Chemotherapy (recurrence) | Recurrence 4 mo after surgery. Dead after 12 mo |
| Zhu *et al*[11], 2017 | 67 | Female | Ascending colon | Abdominal pain, and reduced gas and stool passage | Refused | Chemotherapy | Died of agranulo-cytosis and sepsis |
| Han *et al*[34], 2014 | 49 | Male | Transverse | Periumbilical | Extended laparoscopic left | None | No recurrence during |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | colon | abdominal pain | hemicolectomy | | 36 mo follow-up |
| Lee *et al*[35], 2013 | 45 | Male | Descending colon | Lower abdominal pain, diarrhoea, weight loss | Laparoscopic extended left hemicolectomy with lymph node dissection | None | No recurrence during 36 mo follow-up |
| Zihni *et al*[36], 2014 | 54 | Male | Descending colon | Abdominal pain | Left hemicolectomy, small bowel resection | None | Died on the thirty-fifth post-operative day due to sepsis |
| Lattuneddu *et al* [37], 2004 | 86 | Male | Sigmoid colon | Abdominal pain, rectal bleeding and asthenia | Segmental resection of the left colon, with a complementary colecystectomy | None | No recurrence during 6 mo follow-up |
| Jones *et al*[38], 2008 | 65 | Male | Sigmoid colon | Dysuria, constant left lower quadrant abdominal pain | Sigmoid colon resection | None | N/A |
| | 57 | Male | Sigmoid colon | Fatigue, hematochezia | Hartmann resection of the sigmoid colon | None | Died on day 19 after surgery |
| Mjoli *et al*[39], 2016 | 42 | Male | Sigmoid colon | Rectal bleeding | Sigmoid colectomy | None | No recurrence during 3 mo follow-up |
| Kitamura *et al* [40], 2018 | 77 | Female | Sigmoid colon | Lower abdominal pain, nausea | Resection of the sigmoid colon, artificial anus | None | No recurrence during 14 mo follow-up |
| Gupta *et al*[41], 2007 | 42 | Male | Colon (multiple sites) | Diarrhea, progressive weight loss and malaise | Subtotal colectomy | Adjuvant chemotherapy (melphalan, prednisolone) | No recurrence during 17 mo follow-up |
| Nakagawa *et al* [42], 2011 | 84 | Female | Cecum, rectum | None | Endoscopic mucosal resection | None | N/A |
| Gohil *et al*[43], 2015 | 55 | Male | Rectum | Perianal pain, altered bowel habits | Surgical resection | Adjuvant radiotherapy | No recurrence during 17 mo follow-up |
| Bhangoo *et al*[44], 2021 | 82 | Male | Rectosigmoid colon | Rectal bleeding and obstruction | Open sigmoid low anterior resection | Radiotherapy | N/A |
| Lin *et al*[4], 2021 | 80 | Male | Rectum | Change of his bowel habit and inhibited defecation | Radical resection of the mass by laparoscope | None | N/A |
| Antunes *et al*[45], 2010 | 61 | Male | Anal canal | Abdominal discomfort, tenesmus, perineal pain | None | Radiotherapy | No recurrence during 24 mo follow-up |

perforation. CT images usually show an infiltrating mass with clear boundaries. When the mass is large, a liquefied necrotic area may appear in the center. However, until now, there has been no description of the specific imaging characteristics of EMP[46]. Therefore, the role of imaging examinations in differentiating gastrointestinal EMP from other neoplastic diseases is limited. EMP may be occasionally misdiagnosed as cancer[47], stromal tumors or inflammatory bowel disease[41]. Hence, the accurate diagnosis of gastrointestinal EMP still depends on histopathological results. For gastrointestinal EMP, endoscopic biopsy is a convenient and practical diagnostic method.

Given the rarity of gastrointestinal EMP, unified treatment guidelines for this disease are not available. At present, complete surgical resection is a good choice for the treatment of gastrointestinal EMP. Several studies have reported that patients with gastrointestinal EMP can be completely cured after surgical resection of tumors[21,24,34,40]. Most of the patients underwent routine surgery. However, the EMP patient we reported with perforation of the small intestine required emergency surgery. In addition to perforation of small intestinal EMPs, perforation of colon EMPs can also occur. Kitamura *et al*[40] reported one case of EMP in the sigmoid colon with perforation. The patient underwent emergency surgery without postoperative adjuvant chemotherapy with no recurrence after 14 mo of regular follow-up. In recent years, endoscopic treatments, such as endoscopic mucosal resection or endoscopic submucosal dissection, have become increasingly popular in gastrointestinal EMP surgery and have obtained a good therapeutic effect[18,20,25]. Due to the high sensitivity of primary EMP to radiotherapy, local radiotherapy is also an effective treatment method[45,48]. At present, many hospitals use radiotherapy as an adjuvant treatment for patients with gastrointestinal EMP after surgery to prevent local recurrence or metastasis. Moreover, radiotherapy can also represent an additional therapeutic option for cases with incomplete resection, lymph node involvement or recurrence. There are also some results suggesting that EMP is well controlled with a dose of 40 Gy or more[49]. In cases that are small, well-defined, or postexcision with positive margins, 40 Gy is acceptable[50]. Currently, most studies in this area are retrospective, and more prospective randomized controlled studies are needed to verify these results.

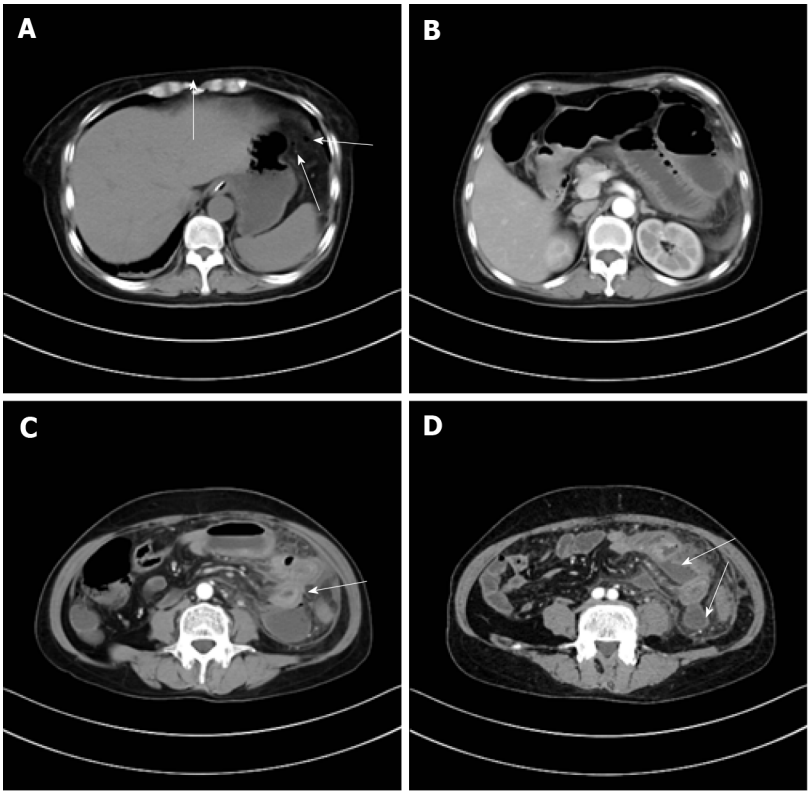





**Figure 1 Preoperative computed tomography scan findings.** A: There are small air bubbles scattered under the left diaphragm (indicated by white arrow); B: The small intestinal lumen in the upper left abdomen is dilated with gas and fluid accumulation, showing multiple fluid-gas level changes; C: The intestinal wall presents edematous thickening (indicated by white arrow), and the density of local mesentery increases; D: Multiple abscesses can be seen between the intestinal lumen (indicated by white arrow).

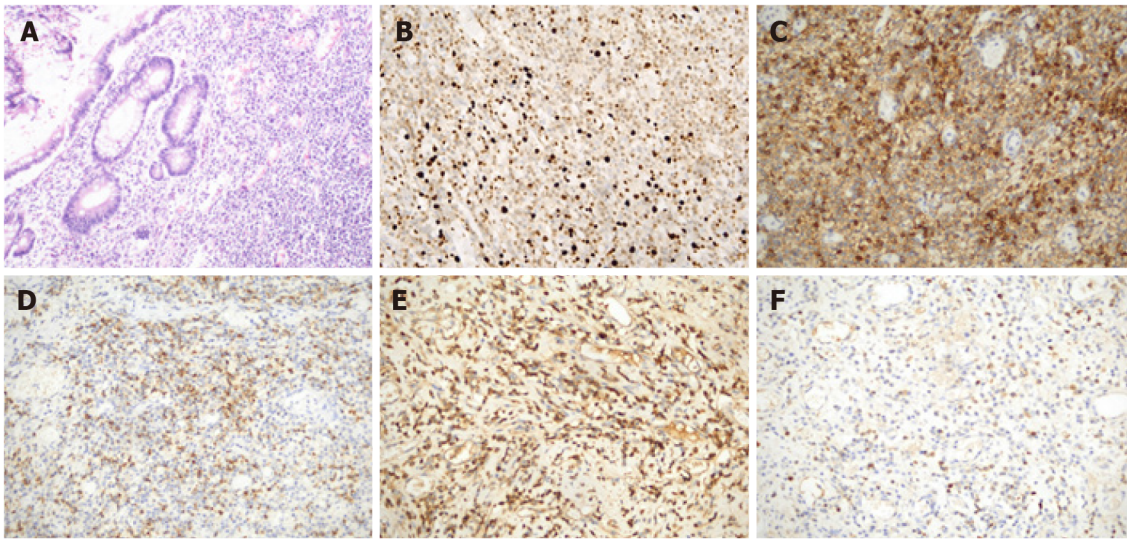
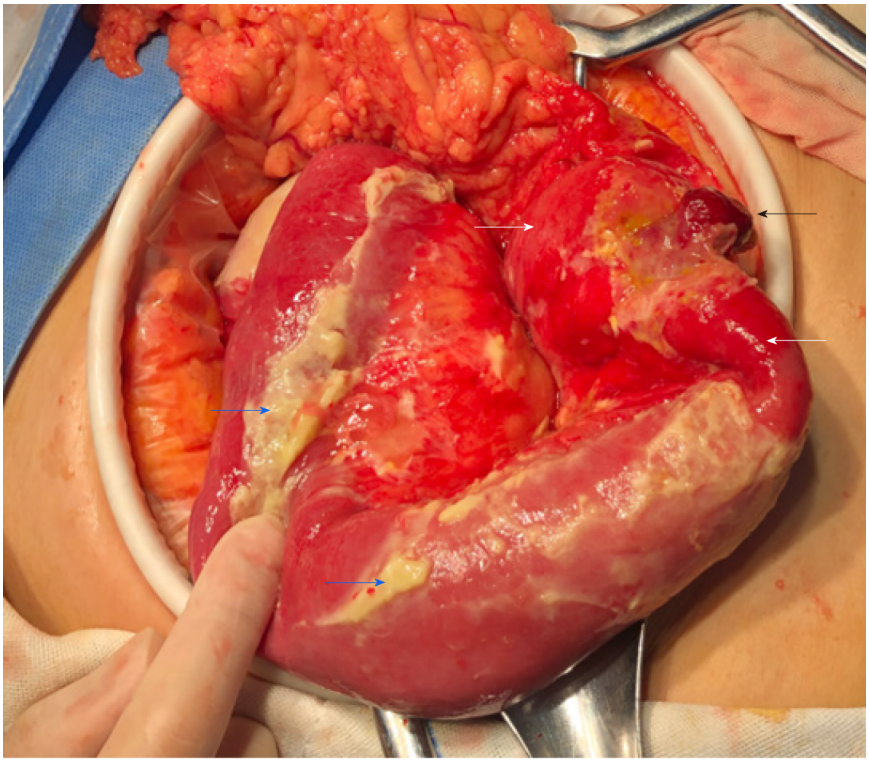





**Figure 2 Histopathological examination of extramedullary plasmacytoma of small intestine.** Microscopic view of the resected extramedullary plasmacytoma originating from small intestine. A: Hematoxylin and eosin staining, magnification × 100; B: Ki67, magnification × 200; C: CD38, magnification × 200; D: CD138, magnification × 200; E: Kappa, magnification × 200; F: Lambda, magnification × 200.

EMP is a low malignancy tumor with a good prognosis. Local recurrence or recurrence at other sites occurred in 7.5% and 10% of patients, respectively, and the 15-year survival rate was 78%[51]. Given that EMP may recur or progress to MM in some patients, regular long-term follow-up is recommended and necessary. Detailed medical records, physical examination, laboratory tests, including complete blood cell count, beta-2 microglobulin and immunoglobulin levels, renal function, and imaging



**DOI:** 10.4240/wjgs.v14.i6.611 

**Figure 3 Intra-operative findings.** The small intestinal serosa has a dark red polyp-like protrusion (black arrow) with a perforation about 0.5 cm in diameter at the top. The local intestinal wall presents hyperemia, edema and thickening (white arrow). The surface of the surrounding small intestine is covered with a large amount of purulent material (blue arrow).

examination of the abdomen are required for patients during follow-up[52].

## CONCLUSION

In conclusion, EMP of the small intestine is extremely rare and lacks specific clinical and imaging manifestations. EMP may be associated with spontaneous perforation, which requires emergency surgery. We firstly report a case of intestinal perforation caused by EMP of the small intestine. The diagnosis of EMP still depends on the histopathological results. Surgical resection and radiotherapy can obtain good therapeutic effects. The cooperation of a multidisciplinary team, including pathologists, hematologists, radiologists and surgeons, is needed to develop the best diagnostic and therapeutic plan for gastrointestinal EMP.

## FOOTNOTES

**Author contributions:** Wang KW reviewed the literature and contributed to manuscript drafting; Xiao N was responsible for the collection and analysis of case data; and all authors issued final approval for the version to be submitted.

**Supported by** the Natural Science Foundation of Education Department of Liaoning Province, No. QNZR2020008.

**Informed consent statement:** Informed written consent was obtained from the patient for publication of this report and any accompanying images.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

**Country/Territory of origin:** China

**ORCID number:** Ke-Wei Wang 0000-0002-3816-1024; Nan Xiao 0000-0003-2948-3184.

**S-Editor:** Wang JJ
**L-Editor:** A
**P-Editor:** Wang JJ

## REFERENCES

1 **Knowling MA**, Harwood AR, Bergsagel DE. Comparison of extramedullary plasmacytomas with solitary and multiple plasma cell tumors of bone. *J Clin Oncol* 1983; **1**: 255-262 [PMID: 6668499 DOI: 10.1200/JCO.1983.1.4.255]
2 **Liebross RH**, Ha CS, Cox JD, Weber D, Delasalle K, Alexanian R. Clinical course of solitary extramedullary plasmacytoma. *Radiother Oncol* 1999; **52**: 245-249 [PMID: 10580871 DOI: 10.1016/s0167-8140(99)00114-0]
3 **Dores GM**, Landgren O, McGlynn KA, Curtis RE, Linet MS, Devesa SS. Plasmacytoma of bone, extramedullary plasmacytoma, and multiple myeloma: incidence and survival in the United States, 1992-2004. *Br J Haematol* 2009; **144**: 86-94 [PMID: 19016727 DOI: 10.1111/j.1365-2141.2008.07421.x]
4 **Lin QT**, Cai XR. Extramedullary plasmacytoma involving rectum: A case report and literature review. *Radiol Case Rep* 2021; **16**: 785-788 [PMID: 33537109 DOI: 10.1016/j.radcr.2021.01.023]
5 **Evans MG**, Zhao X, Lin F, Wang BY. First Reported Case of Extramedullary Plasmacytoma of the Appendix. *Gastroenterology Res* 2020; **13**: 85-87 [PMID: 32362968 DOI: 10.14740/gr1277]
6 **Ding W**, Tan Y, Qian Y, Xue W, Wang Y, Xi C, Gu K, Xu Y, Xu X. Primary plasmablastic plasmacytoma in the stomach of an immunocompetent adult: A case report. *Medicine (Baltimore)* 2019; **98**: e14235 [PMID: 30681607 DOI: 10.1097/MD.0000000000014235]
7 **Hanawa Y**, Higashiyama M, Horiuchi K, Ayaki K, Ito S, Mizoguchi A, Nishii S, Wada A, Inaba K, Sugihara N, Furuhashi H, Takajo T, Shirakabe K, Watanabe C, Tomita K, Komoto S, Nagao S, Miura S, Shimazaki H, Takeuchi K, Ueno H, Hokari R. Crohn's Disease Accompanied with Small Intestinal Extramedullary Plasmacytoma. *Intern Med* 2019; **58**: 2019-2023 [PMID: 30918171 DOI: 10.2169/internalmedicine.1687-18]
8 **Glasbey JC**, Arshad F, Almond LM, Vydianath B, Desai A, Gourevitch D, Ford SJ. Gastrointestinal manifestations of extramedullary plasmacytoma: a narrative review and illustrative case reports. *Ann R Coll Surg Engl* 2018; **100**: 371-376 [PMID: 29692194 DOI: 10.1308/rcsann.2018.0015]
9 **Comba IY**, Torres Luna NE, Cooper C, W Crespo M, Carilli A. A Rare Case of Extramedullary Plasmacytoma Presenting as Massive Upper Gastrointestinal Bleeding. *Cureus* 2019; **11**: e3993 [PMID: 30972272 DOI: 10.7759/cureus.3993]
10 **Iosif E**, Rees C, Beeslaar S, Shamali A, Lauro R, Kyriakides C. Gastrointestinal bleeding as initial presentation of extramedullary plasma cell neoplasms: A case report and review of the literature. *World J Gastrointest Endosc* 2019; **11**: 308-321 [PMID: 31040892 DOI: 10.4253/wjge.v11.i4.308]
11 **Zhu Z**, Cao H, Chen L. Incomplete Colonic Obstruction Caused by Extramedullary Plasmacytoma. *Clin Gastroenterol Hepatol* 2017; **15**: e69-e70 [PMID: 27613261 DOI: 10.1016/j.cgh.2016.08.043]
12 **Alnimer L**, Zakaria A, Alshare B, Samhouri Y, Raphael M. A Rare Case of Small Bowel Extramedullary Plasmacytomas Presenting With Intestinal Obstruction. *Cureus* 2021; **13**: e15704 [PMID: 34277289 DOI: 10.7759/cureus.15704]
13 **Ignjatović M**, Bezmarević M, Cerović S. Solitary extramedullary plasmacytoma of the duodenum and pancreas: A case report and review of the literature. *Vojnosanit Pregl* 2016; **73**: 402-407 [PMID: 29309111 DOI: 10.2298/VSP1410311142I]
14 **Soutar R**, Lucraft H, Jackson G, Reece A, Bird J, Low E, Samson D; Working Group of the UK Myeloma Forum; British Committee for Standards in Haematology; British Society for Haematology. Guidelines on the diagnosis and management of solitary plasmacytoma of bone and solitary extramedullary plasmacytoma. *Clin Oncol (R Coll Radiol)* 2004; **16**: 405-413 [PMID: 15487132 DOI: 10.1016/j.clon.2004.02.007]
15 **Fagkrezos D**, Manes K, Paraskeva K, Lenos M, Triantopoulou C, Apessou D, Maniatis P. Secondary extramedullary plasmacytoma of sigmoid colon in a patient with multiple myeloma: a case report. *J Med Case Rep* 2018; **12**: 379 [PMID: 30583721 DOI: 10.1186/s13256-018-1888-4]
16 **Wallace E**, Stewart Z, Theriot D, Shaffer W, Guillory S, Hanemann M, Danrad R, Spieler B. Atypical Presentation of Extramedullary Plasmacytoma. *Ochsner J* 2018; **18**: 101-103 [PMID: 29559881]
17 **Katodritou E**, Kartsios C, Gastari V, Verrou E, Mihou D, Banti A, Lazaraki G, Lazaridou A, Kaloutsi V, Zervas K. Successful treatment of extramedullary gastric plasmacytoma with the combination of bortezomib and dexamethasone: first reported case. *Leuk Res* 2008; **32**: 339-341 [PMID: 17560647 DOI: 10.1016/j.leukres.2007.04.016]
18 **Park CH**, Lee SM, Kim TO, Kim DU, Jung WJ, Kim GH, Song GA. Treatment of solitary extramedullary plasmacytoma of the stomach with endoscopic submucosal dissection. *Gut Liver* 2009; **3**: 334-337 [PMID: 20431772 DOI: 10.5009/gnl.2009.3.4.334]
19 **Krishnamoorthy N**, Bal MM, Ramadwar M, Deodhar K, Mohandas KM. A rare case of primary gastric plasmacytoma: an unforeseen surprise. *J Cancer Res Ther* 2010; **6**: 549-551 [PMID: 21358099 DOI: 10.4103/0973-1482.77067]
20 **Park SY**, Moon HS, Seong JK, Jeong HY, Yoon BY, Hwang SW, Song KS. Successful treatment of a gastric plasmacytoma using a combination of endoscopic submucosal dissection and oral thalidomide. *Clin Endosc* 2014; **47**: 564-567 [PMID: 25505724 DOI: 10.5946/ce.2014.47.6.564]
21 **Zhao ZH**, Yang JF, Wang JD, Wei JG, Liu F, Wang BY. Imaging findings of primary gastric plasmacytoma: a case report.

*World J Gastroenterol* 2014; **20**: 10202-10207 [PMID: 25110449 DOI: 10.3748/wjg.v20.i29.10202]

22 **Fukuhara S**, Tazawa H, Okanobu H, Kida M, Kido M, Takafuta T, Nishida T, Ohdan H, Sakimoto H. Successful treatment of primary advanced gastric plasmacytoma using a combination of surgical resection and chemotherapy with bortezomib: A case report. *Int J Surg Case Rep* 2016; **27**: 133-136 [PMID: 27611798 DOI: 10.1016/j.ijscr.2016.08.041]

23 **Kang DY**, Kim GB, Choi BS, Seo JW, Lim HJ, Hong R, Park SG. Successful treatment of a primary gastric plasmacytoma mimicking intractable gastric ulcer by using high-dose dexamethasone therapy: a case report. *J Med Case Rep* 2016; **10**: 79 [PMID: 27036197 DOI: 10.1186/s13256-016-0863-1]

24 **Takahashi T**, Morita T, Matsuno Y. Primary Extramedullary Plasmacytoma in the Gastroduodenal Canal Associated With Epstein-Barr Virus-Associated Adenocarcinoma of the Stomach: A Case Report. *Int J Surg Pathol* 2016; **24**: 757-762 [PMID: 27466321 DOI: 10.1177/1066896916659359]

25 **Oliveira RC**, Amaro P, Julião MJ, Cipriano MA. Primary gastric plasmacytoma: a rare entity. *BMJ Case Rep* 2017; **2017** [PMID: 28167693 DOI: 10.1136/bcr-2016-218967]

26 **Weidenbaum C**. Case report: gastric plasmacytoma resistant to radiation therapy. *Postgrad Med* 2022; **134**: 122-123 [PMID: 34813388 DOI: 10.1080/00325481.2021.2008726]

27 **Carneiro FP**, Sobreira MN, Maia LB, Sartorelli AC, Franceschi LE, Brandão MB, Calaça BW, Lustosa FS, Lopes JV. Extramedullary plasmocytoma associated with a massive deposit of amyloid in the duodenum. *World J Gastroenterol* 2009; **15**: 3565-3568 [PMID: 19630116 DOI: 10.3748/wjg.15.3565]

28 **Ammar T**, Kreisel F, Ciorba MA. Primary antral duodenal extramedullary plasmacytoma presenting with melena. *Clin Gastroenterol Hepatol* 2010; **8**: A32 [PMID: 19286477 DOI: 10.1016/j.cgh.2009.03.005]

29 **Yoshida T**, Soda K, Yamada S, Nakahara M, Nishida J, Kametaka M, Konishi F. Biclonal extramedullary plasmacytoma arising in the peritoneal cavity: report of a case. *Surg Today* 2004; **34**: 379-382 [PMID: 15052459 DOI: 10.1007/s00595-003-2705-1]

30 **Moriyama H**, Kawahara K, Noguchi T, Kikuchi R, Wada S, Takeno S, Kashima K. Primary extramedullary plasmacytoma of the small intestine. A case report and review of the literature. *J Exp Clin Cancer Res* 2006; **25**: 129-134 [PMID: 16761629]

31 **Gabriel EM**, Savu M. Discovery of a rare ileocecal plasmacytoma. *J Surg Case Rep* 2014; **2014** [PMID: 24876398 DOI: 10.1093/jscr/rju016]

32 **Zhang D**, Cao D, Shen D, Mulmi Shrestha S, Yin Y. Extramedullary plasmacytoma occuring in ileocecum: A case report and literature review. *Medicine (Baltimore)* 2017; **96**: e9313 [PMID: 29390503 DOI: 10.1097/MD.0000000000009313]

33 **Doki T**, Takeuchi O, Kaiho T, Tsuchiya S, Matsuzaki O, Miyazaki M. Primary isolated extramedullary plasmacytoma of the colon. *Int J Colorectal Dis* 2008; **23**: 719-720 [PMID: 18239923 DOI: 10.1007/s00384-008-0439-7]

34 **Han YJ**, Park SJ, Park MI, Moon W, Kim SE, Ku KH, Ock SY. Solitary extramedullary plasmacytoma in the gastrointestinal tract: report of two cases and review of literature. *Korean J Gastroenterol* 2014; **63**: 316-320 [PMID: 24870305 DOI: 10.4166/kjg.2014.63.5.316]

35 **Lee SH**, Ahn BK, Baek SU, Chang HK. Primary Isolated Extramedullary Plasmacytoma in the Colon. *Gastroenterology Res* 2013; **6**: 152-155 [PMID: 27785246 DOI: 10.4021/gr552w]

36 **Zihni İ**, Dinç R, Canpolat S, Cengiz F, Uslu A. Extramedullary plasmacytoma of the colon: a case report. *Ulus Cerrahi Derg* 2014; **30**: 231-233 [PMID: 25931923 DOI: 10.5152/UCD.2013.45]

37 **Lattuneddu A**, Farneti F, Lucci E, Garcea D, Ronconi S, Saragoni L. A case of primary extramedullary plasmacytoma of the colon. *Int J Colorectal Dis* 2004; **19**: 289-291 [PMID: 14689207 DOI: 10.1007/s00384-003-0560-6]

38 **Jones JE**, Brand MI, Saclarides TJ, Jakate S. Primary extramedullary plasmacytomas of the colon. *Am Surg* 2008; **74**: 873-874 [PMID: 18807681]

39 **Mjoli M**, Vorajee N, Naidoo Y, Madiba T. Solitary extramedullary plasmacytoma of the colon, rectum and anus. *S Afr J Surg* 2016; **54**: 45-47 [PMID: 28240504]

40 **Kitamura F**, Doi K, Ishiodori H, Ohchi T, Baba H. Primary extramedullary plasmacytoma of the sigmoid colon with perforation: a case report. *Surg Case Rep* 2018; **4**: 28 [PMID: 29619633 DOI: 10.1186/s40792-018-0437-0]

41 **Gupta V**, Nahak B, Sakhuja P, Agarwal AK, Kumar N, Mishra PK. Primary isolated extramedullary plasmacytoma of colon. *World J Surg Oncol* 2007; **5**: 47 [PMID: 17470287 DOI: 10.1186/1477-7819-5-47]

42 **Nakagawa Y**, Nagai T, Okawara H, Nakashima H, Hisamatsu A, Syutou M, Yamauchi M, Kai S, Nakayama T, Yokoyama S, Murakami K, Fujioka T. Minute primary extramedullary plasmacytomas of the large intestine. *Endoscopy* 2011; **43** Suppl 2 UCTN: E105-E106 [PMID: 21424997 DOI: 10.1055/s-0030-1256138]

43 **Gohil MH**, Bhavsar DC, Suryanarayana U, Jetly DH. Plasmacytoma rectum extending to para-rectal region. *J Cancer Res Ther* 2015; **11**: 662 [PMID: 26458684 DOI: 10.4103/0973-1482.140799]

44 **Bhangoo RS**, McCullough AE, Yang M. Obstructive rectosigmoid colon solitary extramedullary plasmacytoma. *Dig Liver Dis* 2021; **53**: 496-497 [PMID: 33376074 DOI: 10.1016/j.dld.2020.12.008]

45 **Antunes MI**, Bujor L, Grillo IM. Anal canal plasmacytoma-An uncommon presentation site. *Rep Pract Oncol Radiother* 2010; **16**: 36-39 [PMID: 24376953 DOI: 10.1016/j.rpor.2010.12.002]

46 **Ryu SW**, Cohen-Hallaleh V. Imaging features of extramedullary plasmacytoma. *J Med Imaging Radiat Oncol* 2020; **64**: 44-51 [PMID: 31785037 DOI: 10.1111/1754-9485.12975]

47 **Parnell K**, Ahmed M, Smalligan RD, Nadesan S. Extramedullary plasmacytoma mimicking colon carcinoma: an unusual presentation and review of the literature. *BMJ Case Rep* 2015; **2015** [PMID: 26498668 DOI: 10.1136/bcr-2015-210973]

48 **Barzenje DA**, Kolstad A, Ghanima W, Holte H. Long-term outcome of patients with solitary plasmacytoma treated with radiotherapy: A population-based, single-center study with median follow-up of 13.7 years. *Hematol Oncol* 2018; **36**: 217-223 [PMID: 28393375 DOI: 10.1002/hon.2415]

49 **Alghisi A**, Borghetti P, Maddalo M, Roccaro AM, Tucci A, Mazzola R, Magrini SM, Lo Casto A, Bonù ML, Tomasini D, Pasinetti N, Peretto G, Bertagna F, Tomasi C, Buglione M, Triggiani L. Radiotherapy for the treatment of solitary plasmacytoma: 7-year outcomes by a mono-institutional experience. *J Cancer Res Clin Oncol* 2021; **147**: 1773-1779 [PMID: 33201300 DOI: 10.1007/s00432-020-03452-y]

50 **Tsang RW**, Campbell BA, Goda JS, Kelsey CR, Kirova YM, Parikh RR, Ng AK, Ricardi U, Suh CO, Mauch PM, Specht L, Yahalom J. Radiation Therapy for Solitary Plasmacytoma and Multiple Myeloma: Guidelines From the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys* 2018; **101**: 794-808 [PMID: 29976492 DOI: 10.1016/j.ijrobp.2018.05.009]

51 **Galieni P**, Cavo M, Pulsoni A, Avvisati G, Bigazzi C, Neri S, Caliceti U, Benni M, Ronconi S, Lauria F. Clinical outcome of extramedullary plasmacytoma. *Haematologica* 2000; **85**: 47-51 [PMID: 10629591]

52 **Lopes da Silva R**. Extramedullary plasmacytoma of the small intestine: clinical features, diagnosis and treatment. *J Dig Dis* 2012; **13**: 10-18 [PMID: 22188911 DOI: 10.1111/j.1751-2980.2011.00544.x]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 June 27; 14(6): 621-625

DOI: 10.4240/wjgs.v14.i6.621

ISSN 1948-9366 (online)

*CASE REPORT*

# Bowel intussusception caused by a percutaneously placed endoscopic gastrojejunostomy catheter: A case report

Maarten WJ Winters, Sjoerd Kramer, Albert HA Mazairac, Ewoud H Jutte, Paul G van Putten

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Unsolicited article; Externally peer reviewed

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Sato Y, Japan; Zharikov YO, Russia
**A-Editor:** Yang YZ

**Received:** November 25, 2021
**Peer-review started:** November 25, 2021
**First decision:** January 8, 2022
**Revised:** January 23, 2022
**Accepted:** May 16, 2022
**Article in press:** May 16, 2022
**Published online:** June 27, 2022

**Maarten WJ Winters, Sjoerd Kramer, Paul G van Putten,** Department of Gastroenterology and Hepatology, Medical Center Leeuwarden, Leeuwarden 8934 AD, Netherlands

**Albert HA Mazairac,** Department of Radiology, Medical Center Leeuwarden, Leeuwarden 8934 AD, Netherlands

**Ewoud H Jutte,** Department of Surgery, Medical Center Leeuwarden, Leeuwarden 8934 AD, Netherlands

**Corresponding author:** Maarten WJ Winters, MD, Doctor, Department of Gastroenterology and Hepatology, Medical Center Leeuwarden, Henri Dunantweg 2, Leeuwarden 8934 AD, Netherlands. m.w.j.winters@gmail.com

## Abstract

*BACKGROUND*

In adults, bowel intussusception is a rare diagnosis and is mostly due to an organic bowel disorder. In rare cases, this is a complication of a percutaneously placed endoscopic gastro (jejunostomy) catheter.

*CASE SUMMARY*

We describe a case of a 73-year-old patient with a history of myocardial infarction, chronic idiopathic constipation and Parkinson's disease. For the admission of his Parkinson's medication, a percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) was placed. The patient presented three times at the emergency department of the hospital with intermittent abdominal pain with nausea and vomiting. There were no distinctive abnormalities from the physical and laboratory examinations. An abdominal computed tomography scan showed a small bowel intussusception. By push endoscopy, a jejunal bezoar at the tip of the PEG-J catheter was found to be the cause of small bowel intussusception. The intussusception was resolved after removing the bezoar during push enteroscopy.

*CONCLUSION*

Endoscopic treatment of bowel intussusception caused by PEG-J catheter bezoar.

**Key Words:** Bowel intussusception; Percutaneous endoscopic gastrojejunostomy; Bezoar; Percutaneous endoscopic gastrostomy; Case report

**Core Tip:** In patients with a proximal feeding catheter and complaints of acute or intermittent abdominal pain, intussusception must be considered. An abdominal computed tomography scan is recommended for additional investigation. If small bowel intussusception is present/suspected, we recommend first investigating the cause *via* gastroscopy/push enteroscopy and, if possible, treating it endoscopically immediately so that surgery can be prevented.

**Citation:** Winters MW, Kramer S, Mazairac AH, Jutte EH, van Putten PG. Bowel intussusception caused by a percutaneously placed endoscopic gastrojejunostomy catheter: A case report. *World J Gastrointest Surg* 2022; 14(6): 621-625
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i6/621.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i6.621

## INTRODUCTION

If normal oral intake of food or medication is insufficient or poorly tolerated for a longer period of time, an endoscopically placed percutaneous gastric tube (PEG) can be considered. PEG can be extended to the jejunum (PEG-J) or placed directly in the jejunum (PEJ). These procedures are considered to be safe [1-3]. Common complications of a PEG are a clogged or dislocated PEG catheter, pain at the insertion site, infection and peristomal leakage. Severe complications are rare, including bleeding, perforation, buried bumper syndrome, necrotizing fasciitis and metastatic spread[1,2]. In this case, we describe proximal intussusception of the small intestine as a rare complication of a PEG-J catheter.

## CASE PRESENTATION

### *Chief complaints*

The patient was a 73-year-old man who visited the emergency care centre on three occasions in three weeks with intermittent epigastric and lower thoracic pain accompanied by nausea and vomiting.

### *History of present illness*

At the first two presentations, no clear leads were found in anamnesis, physical examination or exploratory additional examinations. No abnormalities were found on point-of-care ultrasound of the abdominal wall or abdomen. Additionally, no anomaly of the PEG-J catheter was found. There were no signs of myocardial ischaemia, as indicated by a normal electrocardiogram (ECG) and troponins. Gastroscopy showed candida oesophagitis, for which fluconazole was prescribed. Due to chronic constipation, laxatives were also started. During the last presentation, the stool pattern had improved, and defecation was daily and of normal consistency.

### *History of past illness*

The patient had a history of myocardial infarction, chronic idiopathic constipation and Parkinson's disease. PEG-J (AbbVie PEG 15 Fr; J extension 9 Fr) was placed 1.5 years ago for the administration of Parkinson medication (levodopa/carbidopa).

### *Personal and family history*

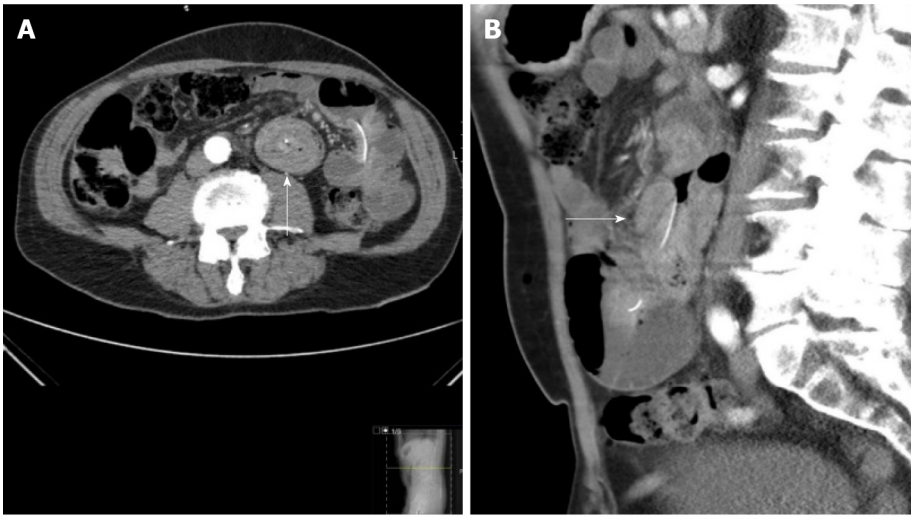
The patient has no personal and family history.

### *Physical examination*

On physical examination, the patient was damp and sweaty, with normal vitals: Heart rate (67/min), blood pressure (141/80 mmHg) and temperature (36.6 °C). Auscultation of the heart and lungs showed a regular heart rhythm without murmur and clear lung sounds. During abdominal examination, sparse, normal-sounding peristalsis was heard. Palpation gave severe pressure pain in the upper left abdomen and in the epigastrio, without rebound pain. No rigidity or guarding was observed. The insertion of the PEG catheter appeared normal without redness, bleeding or hard subcutaneous swelling. PEG-J was open and well situated against the abdominal wall and easy to submerge and reapply.

### *Laboratory examinations*

The laboratory examinations showed (normal values in parentheses) mildly elevated C-reactive protein of 39 mg/L (< 5), normal lipase of 14 U/L (< 60) and a stable troponin-T of 16 ng/L compared to three days prior (< 14). Renal and liver function were normal. Remarkably, an elevated creatine kinase of 366




DOI: 10.4240/wjgs.v14.i6.621 Copyright ©The Author(s) 2022.

**Figure 1 Abdominal computed tomography scan with intravenous contrast in the arterial and portal venous phases of a 73-year-old man with intussusception at the duodenojejunal junction.** A: The transverse section shows a 'target sign'; B: The sagittal section shows a 'sausage sign'.

U/L (< 200) and a mildly elevated lactate of 2.2 mmol/L (0.5-1.6) were detected. The ECG showed a sinus rhythm of 68/min, with no ST-T abnormalities.

### *Imaging examinations*

In the differential diagnosis of peptic/duodenal ulcer disease, cholecystitis, perforation, constipation due to bowel mobility problems in Parkinson's disease, intestinal ischaemia and a complication of PEG-J were considered. Due to these considerations, abdominal computed tomography (CT) scans were performed with intravenous contrast in the arterial and portal venous phases (Figure 1), which showed intussusception at the duodenojejunal junction. There was no evident leadpoint for intussusception, and the intestinal loops proximal to intussusception were not dilated.

## FINAL DIAGNOSIS

Small bowel intussusception.

## TREATMENT

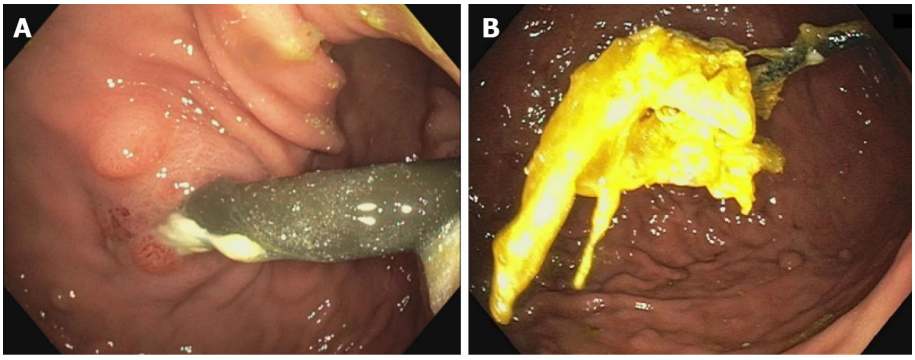
Proximal push enteroscopy was performed on suspicion of an intussusception possibly caused by PEG-J, a malignant or benign tumor. The button of the PEG was not situated against the stomach wall, and there was traction at the jejunum extension (Figure 2A). A lumen-filling bezoar, *i.e.*, a stony mass, was found in the small intestine at the distal part of the jejunum extension. The bezoar was reduced endoscopically, after which the jejunal extension luxated and returned to the stomach with the remnant of the bezoar (Figure 2B). The jejunum extension was replaced, and the patient was discharged in good condition.

## OUTCOME AND FOLLOW-UP

On the first outpatient revision, the patient had no complaints.

## DISCUSSION

Bowel intussusception, in which a part of the intestine slides into the next part of the intestine ("telescoping"), is rare in adults. In adults, 1%-5% of intestinal obstructions are caused by intussusception. Most cases (90%) are due to an organic condition, such as inflammatory bowel disease, postoperative adhesions, (Meckel's) diverticula, polyps or carcinoma. An iatrogenic factor is sometimes




**DOI:** 10.4240/wjgs.v14.i6.621 

**Figure 2 Push enteroscopy: In a 73-year-old man with intussusception.** A: Showing a view of the stomach. Due to traction at the jejunal extension, the button of the percutaneous endoscopic gastrostomy catheter was not situated against the stomach wall; B: Showing the luxated jejunum extension with remnant bezoar after endoscopic reduction.

the cause of intussusception, such as after bariatric surgery or in the presence of intestinal feeding probes[4].

The use of PEG catheters is increasing in popularity because it is considered to be a safe method for the administration of nutrition and medication[1]. Severe complications of a PEG-J catheter are rare, and few case reports have described intussusception after the placement of PEG catheters (PEG/PEG-J/PEJ)[5-8]. Only one similar case has been described in the literature, in which a bezoar was attached to the distal end of a jejunum extension of a PEG[5]. The most likely mechanism causing intussusception in our case was the formation of a bezoar at the jejunum extension and the migration of this bezoar distally through the small intestine by intestinal peristalsis. This served as a lead point, causing intussusception.

Symptoms of intussusception in adults are often nonspecific and can be both acute or chronic. The most common symptom is abdominal pain. Other complaints include nausea, vomiting, gastrointestinal bleeding, abdominal distension and constipation[4,9]. Other PEG complications that can cause similar nonspecific symptoms include, *i.e.*, malpositioning of the PEG, gastric/bowel perforation, or migration of the PEG catheter balloon into the pylorus or duodenum[1,10,11].

If a complication of PEG is suspected, a CT scan should be considered to differentiate between the complications of PEG. In adults, a CT abdomen is preferred in the diagnosis of intussusception because of its 90%-100% accuracy. A "target sign", "sausage sign" or oedematous wall thickening will be observed. Comparatively, ultrasounds have an accuracy of 50%-60%, while X-rays are not sensitive[9,12]. As intussusception in adults is often caused by organic abnormalities, surgery is the most common intervention[12].

Our case illustrates that PEG can be complicated by proximal intussusception of the small intestine. Our advice is to perform imaging for intussusception when a patient with a PEG catheter has acute or intermittent abdominal pain. In addition, when intussusception is diagnosed, a patient should first undergo endoscopic exploration while being treated, if possible, to avoid more invasive surgical treatment.

## CONCLUSION

Intussusception is a rare complication of a PEG catheter, with nonspecific clinical presentation. In patients with a PEG catheter complaining of acute or chronic abdominal pain with nausea, vomiting or obstipation, intussusception should be considered. The most accurate diagnostic tool is a CT scan. In cases of intussusception of the small intestine, we recommend immediately exploring and if possible, treating the intussusception endoscopically, to prevent surgical intervention.

## FOOTNOTES

**Author contributions:** All authors were involved in the care of the patient; Winters MW and Kramer S reviewed the literature and contributed to the manuscript drafting; van Putten PG, Mazairac AH and Jutte EH revised the manuscript for important intellectual content; and all authors issued final approval for the version to be submitted.

**Informed consent statement:** Informed written consent was obtained from the patient for publication of this report and any accompanying images.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).



**Country/Territory of origin:** Netherlands

**ORCID number:** Maarten WJ Winters 0000-0001-7334-0784; Sjoerd Kramer 0000-0003-2025-3067; Albert HA Mazairac 0000-0003-3735-1915; Ewoud H Jutte 0000-0002-2562-7390; Paul G van Putten 0000-0001-5994-037X.

**S-Editor:** Wang JJ
**L-Editor:** A
**P-Editor:** Wang JJ

## REFERENCES

1 **Rahnemai-Azar AA**, Rahnemaiazar AA, Naghshizadian R, Kurtz A, Farkas DT. Percutaneous endoscopic gastrostomy: indications, technique, complications and management. *World J Gastroenterol* 2014; **20**: 7739-7751 [PMID: 24976711 DOI: 10.3748/wjg.v20.i24.7739]
2 **Blumenstein I**, Shastri YM, Stein J. Gastroenteric tube feeding: techniques, problems and solutions. *World J Gastroenterol* 2014; **20**: 8505-8524 [PMID: 25024606 DOI: 10.3748/wjg.v20.i26.8505]
3 **Chang FC**, Kwan V, van der Poorten D, Mahant N, Wolfe N, Ha AD, Griffith JM, Tsui D, Kim SD, Fung VS. Intraduodenal levodopa-carbidopa intestinal gel infusion improves both motor performance and quality of life in advanced Parkinson's disease. *J Clin Neurosci* 2016; **25**: 41-45 [PMID: 26777085 DOI: 10.1016/j.jocn.2015.05.059]
4 **Marinis A**, Yiallourou A, Samanides L, Dafnios N, Anastasopoulos G, Vassiliou I, Theodosopoulos T. Intussusception of the bowel in adults: a review. *World J Gastroenterol* 2009; **15**: 407-411 [PMID: 19152443 DOI: 10.3748/wjg.15.407]
5 **Dixon R**, Burton S, Taylor LJ, Richeson BL, Fang JC. Bezoar formation on percutaneous endoscopic gastrojejunostomy tube causing gastric outlet obstruction and small-intestinal intussusception. *VideoGIE* 2019; **4**: 416-417 [PMID: 31517166 DOI: 10.1016/j.vgie.2019.05.006]
6 **Kakiuchi T**, Nakayama A, Nojiri J, Yamanouchi T, Matsuo M. Jejuno-jejunal intussusception caused by a percutaneous endoscopic gastrojejunostomy tube in a pediatric patient: A case report. *Medicine (Baltimore)* 2020; **99**: e19888 [PMID: 32312016 DOI: 10.1097/MD.0000000000019888]
7 **Ibegbu E**, Relan M, Vega KJ. Retrograde jejunoduodenogastric intussusception due to a replacement percutaneous gastrostomy tube presenting as upper gastrointestinal bleeding. *World J Gastroenterol* 2007; **13**: 5282-5284 [PMID: 17876902 DOI: 10.3748/wjg.v13.i39.5282]
8 **Satoh T**, Sawada K, Satoh M, Yohko K, Yamada M, Zaitsu M, Osada T, Sawaya R, Nata T, Ueno N, Moriichi K, Ikuta K, Mizukami Y, Watari J, Fujiya M, Kohgo Y. Small intestinal intussusceptions due to the placement of a percutaneous endoscopic jejunostomy tube. *BMJ Case Rep* 2011; **2011** [PMID: 22715249 DOI: 10.1136/bcr.07.2010.3169]
9 **Honjo H**, Mike M, Kusanagi H, Kano N. Adult intussusception: a retrospective review. *World J Surg* 2015; **39**: 134-138 [PMID: 25192846 DOI: 10.1007/s00268-014-2759-9]
10 **Shah J**, Sunkara T, Yarlagadda KS, Rawla P, Gaduputi V. Gastric Outlet and Duodenal Obstruction as a Complication of Migrated Gastrostomy Tube: Report of Two Cases and Literature Review. *Gastroenterology Res* 2018; **11**: 71-74 [PMID: 29511412 DOI: 10.14740/gr954w]
11 **Becker BA**, Walker TC. Gastric Outlet Obstruction Due to Malposition of Replacement Gastrostomy Tube. *Clin Pract Cases Emerg Med* 2019; **3**: 442-443 [PMID: 31763613 DOI: 10.5811/cpcem.2019.7.43626]
12 **Wang N**, Cui XY, Liu Y, Long J, Xu YH, Guo RX, Guo KJ. Adult intussusception: a retrospective review of 41 cases. *World J Gastroenterol* 2009; **15**: 3303-3308 [PMID: 19598308 DOI: 10.3748/wjg.15.3303]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 June 27; 14(6): 626-628

DOI: 10.4240/wjgs.v14.i6.626

ISSN 1948-9366 (online)

LETTER TO THE EDITOR

# Important role of acute care surgery during pandemic time

Ming Yang, Chun-Ye Zhang

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Ding WW, China; Liu CH, Taiwan; Nisi F, Italy
**A-Editor:** Garg P, India

**Received:** August 29, 2021
**Peer-review started:** August 29, 2021
**First decision:** November 17, 2021
**Revised:** November 21, 2021
**Accepted:** May 27, 2022
**Article in press:** May 27, 2022
**Published online:** June 27, 2022

**Ming Yang,** Department of Surgery, University of Missouri, Columbia, MO 65211, United States

**Chun-Ye Zhang,** Department of Veterinary Pathobiology, University of Missouri, Columbia, MO 65201, United States

**Corresponding author:** Ming Yang, DVM, PhD, Postdoctoral Fellow, Department of Surgery, University of Missouri, 1030 Hitt Street, NextGen Precision Health Building, Room 2203, Columbia, MO 65211, United States. yangmin@health.missouri.edu

## Abstract

Pandemic impacts acute care surgery for diseases, such as gallbladder disease and acute appendicitis. At the early stage of coronavirus disease 2019 (COVID-19) pandemic, the case number of patients needing surgery decreased in hospitals from different countries. This decline was associated with the stay-home order and fear of getting COVID-19 infection. However, recent reports show that the case number for acute surgery returns to the normal level, which is comparable to that before the beginning of the pandemic. In addition, a variety of diseases show more severe than the cases before the pandemic, which might be caused by factors such as lack of regular follow-up and screening diagnosis and infection of viruses.

**Key Words:** Pandemic impact; Acute care surgery; Outcome; Disease pattern and severity



**Core Tip:** The coronavirus disease 2019 (COVID-19) pandemic impacts the number of cases and disease patterns that required acute care surgery. At the early stage of pandemic COVID-19, the case number of patients for surgery care decreased in hospitals from different countries. The decline was associated with the stay-home order and fear of COVID-19 infection. However, recent reports show that the case number for acute surgery returns to the normal level, which is comparable to that before the beginning of the pandemic. COVID-19 pandemic increases the severity of diseases, such as gallbladder disease and acute appendicitis. This change may be caused by factors including lack of regular follow-up and screening diagnosis and infection of viruses.

**Citation:** Yang M, Zhang CY. Important role of acute care surgery during pandemic time. *World J Gastrointest Surg* 2022; 14(6): 626-628
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i6/626.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i6.626

## TO THE EDITOR

We read with great interest an observational study recently published by Farber *et al*[1], which investigated the impact of the coronavirus disease 2019 (COVID-19) pandemic on acute care surgery for gallbladder disease and acute appendicitis. This study showed that comparing clinical cases in COVID-19 pandemic time from March to June in 2020 with that in the same period in 2019 at a single tertiary academic medical center in Northern California, more patients with gallbladder disease showed acute and severe cholecystitis, and patients with appendicitis showed more severe situation with a perforated appendix[1].

The COVID-19 pandemic is caused by the infection of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[2], which poses a big challenge to all healthcare systems. During the early COVID-19 pandemic outbreak, the number of cases in patients who needed surgical care is significantly decreased in many hospitals. For example, the total surgical activity performed at Innsbruck Medical University Hospital in Austria was dramatically decreased, including elective, acute, and oncological surgeries[3]. Another study also showed during March 29 to April 25 in 2020, the number of emergency department (ED) visits in the Northeast part of the United States was lower compared to that in 2019[4]. However, a study located in the northern part of Kentucky showed that the number of trauma incidences was comparable, whereas the pattern of trauma to the ED changed, with more cases such as burns and fewer cases of falls[5]. Furthermore, the pandemic also decreased the academic training research activities in Nigeria[6]. The decline of cases is associated with the stay-at-home policy, social distance requirement, and the fear of getting SARS-CoV-2 infection. However, the reduced number caused by the early lockdown turns back to a normal level at the third lockdown time in 2021 at some institutions[7].

Farber *et al*[1] also found that the 30-d re-presentation rate in patients with appendicitis was dramatically increased in 2020 than before[1]. Another study showed that the length of hospital stay increased for trauma patients with COVID-19 infection[8]. In addition, the case pattern and severity of cases are changed during pandemic time. Ajayi *et al*[9] showed that during the second wave of COVID-19 infection, three times more patients with trauma that was caused mainly by fall and traffic accidents were diagnosed with COVID-19 infection, and two times more patients who required surgical operation, but the mortality was decreased compared to the first wave of the pandemic[9]. In contrast, a study in Brazil showed that elective neurosurgical surgery decreased more than emergency surgery, but the mortality rate was increased even though the overall hospitalization was decreased[10].

Although the overall case number for acute care surgery may not be significantly impacted during the pandemic, the severity and pattern of diseases required emergency care may change. Lack of earlier diagnosis and screening for disease and routine follow-up may be the major reason that causes the severity of disease during the pandemic period[11]. Moreover, one study reported that an acute care surgery division is able to manage the intensive care for COVID-19 patients independent of surgical procedures[12].

In conclusion, infection of COVID-19 for patients with trauma or other surgical procedure can increase the risk of morbidity and mortality. A good management procedure and pre-operative COVID-19 testing for patients waiting for surgery care could provide favorable outcomes. With their expertise and experience, surgeons can aid the hospital to provide proper procedures to prevent the potential co-infection of COVID-19 for patients with non-surgical and surgical treatments.

## FOOTNOTES

**Author contributions:** Yang M and Zhang CY collected data, wrote, finalized the letter, and contributed equally.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.



**Country/Territory of origin:** United States

**ORCID number:** Ming Yang 0000-0002-4895-5864; Chun-Ye Zhang 0000-0003-2567-029X.

**S-Editor:** Wang JJ
**L-Editor:** A
**P-Editor:** Wang JJ

## REFERENCES

1 **Farber ON**, Gomez GI, Titan AL, Fisher AT, Puntasecca CJ, Arana VT, Kempinsky A, Wise CE, Bessoff KE, Hawn MT, Korndorffer JR Jr, Forrester JD, Esquivel MM. Impact of COVID-19 on presentation, management, and outcomes of acute care surgery for gallbladder disease and acute appendicitis. *World J Gastrointest Surg* 2021; **13**: 859-870 [PMID: 34512909 DOI: 10.4240/wjgs.v13.i8.859]
2 **Castagnoli R**, Votto M, Licari A, Brambilla I, Bruno R, Perlini S, Rovida F, Baldanti F, Marseglia GL. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review. *JAMA Pediatr* 2020; **174**: 882-889 [PMID: 32320004 DOI: 10.1001/jamapediatrics.2020.1467]
3 **Abram J**, Gasteiger L, Putzer G, Spraider P, Mathis S, Hell T, Martini J. Impact of COVID-19 Related Lockdown on the Frequency of Acute and Oncological Surgeries-Lessons Learned From an Austrian University Hospital. *Front Public Health* 2021; **9**: 625582 [PMID: 34409000 DOI: 10.3389/fpubh.2021.625582]
4 **Hartnett KP**, Kite-Powell A, DeVies J, Coletta MA, Boehmer TK, Adjemian J, Gundlapalli AV; National Syndromic Surveillance Program Community of Practice. Impact of the COVID-19 Pandemic on Emergency Department Visits - United States, January 1, 2019-May 30, 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 699-704 [PMID: 32525856 DOI: 10.15585/mmwr.mm6923e1]
5 **Aljuboori Z**, Sieg E. The early effects of social distancing resultant from COVID-19 on admissions to a Level I trauma center. *Injury* 2020; **51**: 2332 [PMID: 32605787 DOI: 10.1016/j.injury.2020.06.036]
6 **Tolani MA**, Fidelis L, Oyelowo N, Mustapha A, Adebayo WO, Okeke CJ, Alioke II, Abdulsalam KI, Aruna AA, Okonji NO, Okeke UA. Impact of the COVID-19 pandemic on surgical practice, training, and research in Nigeria. *Pan Afr Med J* 2021; **39**: 59 [PMID: 34422182 DOI: 10.11604/pamj.2021.39.59.23678]
7 **Hickland MM**, Massouh P, Sutthakorn RE, Greenslade C, Jennings C, Cantle F, Bew D. The impact of the COVID-19 pandemic on the number of presentations of penetrating injuries to a UK major trauma centre. *J Public Health (Oxf)* 2022; **44**: e126-e132 [PMID: 34428291 DOI: 10.1093/pubmed/fdab333]
8 **Kaufman EJ**, Ong AW, Cipolle MD, Whitehorn G, Ratnasekera A, Stawicki SP, Martin ND. The impact of COVID-19 infection on outcomes after injury in a state trauma system. *J Trauma Acute Care Surg* 2021; **91**: 559-565 [PMID: 34074996 DOI: 10.1097/TA.0000000000003310]
9 **Ajayi B**, Trompeter AJ, Umarji S, Saha P, Arnander M, Lui DF. Catching the second wave: clinical characteristics and nosocomial infection rates in major trauma and orthopaedic patients during the COVID-19 pandemic. *Bone Jt Open* 2021; **2**: 661-670 [PMID: 34405683 DOI: 10.1302/2633-1462.28.BJO-2021-0078.R1]
10 **de Macêdo Filho LJM**, Aragão ACA, Dos Santos VTD, Galvão LBA, Shlobin NA, De Biase G, Suarez-Meade P, Almeida JPC, Quinones-Hinojosa A, de Albuquerque LAF. Impact of COVID-19 on Neurosurgery in Brazil's Health System: The Reality of a Developing Country Affected by the Pandemic. *World Neurosurg* 2021; **155**: e142-e149 [PMID: 34400327 DOI: 10.1016/j.wneu.2021.08.030]
11 **Hossain N**, Naidu V, Hosny S, Khalifa M, Mathur P, Al Whouhayb M. Hospital Presentations of Acute Diverticulitis During COVID-19 Pandemic may be More Likely to Require Surgery due to Increased Severity: A Single-Centre Experience. *Am Surg* 2022; **88**: 133-139 [PMID: 33356444 DOI: 10.1177/0003134820982560]
12 **Choron RL**, Butts CA, Bargoud C, Krumrei N, Teichman AL, Schroeder M, Bover Manderski MT, To J, Moffa SM, Rodricks MB, Lissauer M, Gupta R. Surgeons in surge - the versatility of the acute care surgeon: outcomes of COVID-19 ICU patients in a community hospital where all ICU patients are managed by surgical intensivists. *Trauma Surg Acute Care Open* 2020; **5**: e000557 [PMID: 34192160 DOI: 10.1136/tsaco-2020-000557]

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

*World J Gastrointest Surg* 2022 June 27; 14(6): 629-631

DOI: 10.4240/wjgs.v14.i6.629

ISSN 1948-9366 (online)

LETTER TO THE EDITOR

# Advances and effectiveness of the immunotherapy after liver transplantation

Sai Swarupa R Vulasala, Nirmal K Onteddu, Sindhu P Kumar, Chandana Lall, Priya Bhosale, Mayur K Virarkar

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

**P-Reviewer:** Chen YH, China; Koc ÖM, Belgium
**A-Editor:** Garg P, India

**Received:** November 23, 2021
**Peer-review started:** November 23, 2021
**First decision:** January 12, 2022
**Revised:** January 15, 2022
**Accepted:** June 13, 2022
**Article in press:** June 13, 2022
**Published online:** June 27, 2022

**Sai Swarupa R Vulasala, Sindhu P Kumar, Chandana Lall, Mayur K Virarkar,** Department of Radiology, University of Florida College of Medicine, Jacksonville, FL 32209, United States

**Nirmal K Onteddu,** Department of Internal Medicine, Flowers Hospital, Dothan, AL 36305, United States

**Priya Bhosale,** Division of Diagnostic Imaging, Department of Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, United States

**Corresponding author:** Sai Swarupa R Vulasala, MBBS, Research Assistant, Department of Radiology, University of Florida College of Medicine, 655 West 8th Street, C90, 2nd Floor, Clinical Center, Jacksonville, FL 32209, United States. vulasalaswarupa@gmail.com

## Abstract

Transplant recipients usually have increased chances of graft rejection and graft *vs* host disease, requiring chronic immunosuppressive therapy. Nonetheless, long-term immunosuppression risks malignancies such as skin cancer, lymphoma, and Kaposi sarcoma. However, there are very few studies that included solid organ transplant recipients while studying the efficacy of immunotherapy. "Immuno-therapy after liver transplantation: Where are we now?" is a study, where the authors described the mechanism of action and outcomes of immune checkpoint inhibitors specific to liver transplant recipients. The authors reported the graft rejection rates and the factors contributing to the rejection in the liver transplant recipients.

**Key Words:** Immunotherapy; Hepatocellular carcinoma; Immune checkpoint inhibitors; Liver transplantation; Solid organ transplant; Graft rejection

**Core Tip:** There is an increased risk of cancer among transplant recipients receiving chronic immunosuppression. Immunotherapy has a beneficiary effect over immunosuppressors in reducing the overall cancer risk. However, there are very few studies that included solid organ transplant recipients while studying the efficacy of immunotherapy. "Immunotherapy after liver transplantation: Where are we now?" is a study, where the authors described the mechanism of action and outcomes of immune checkpoint inhibitors specific to liver transplant recipients.

**Citation:** Vulasala SSR, Onteddu NK, Kumar SP, Lall C, Bhosale P, Virarkar MK. Advances and effectiveness of the immunotherapy after liver transplantation. *World J Gastrointest Surg* 2022; 14(6): 629-631
**URL:** https://www.wjgnet.com/1948-9366/full/v14/i6/629.htm
**DOI:** https://dx.doi.org/10.4240/wjgs.v14.i6.629

## TO THE EDITOR

Au *et al*[1] studied the consequences of immunotherapy in patients who underwent liver transplantation (LT) for hepatocellular carcinoma (HCC). We are writing to thank the authors after reading their article conscientiously. Many trials were conducted in the literature studying the efficacy of immunotherapy. However, they excluded organ transplant recipients due to the higher risk of fatal graft rejection.

Transplant recipients usually have increased chances of graft rejection and graft *vs* host disease (GVHD), requiring chronic immunosuppressive therapy. Nonetheless, long-term immunosuppression risks malignancies such as skin cancer, lymphoma, and Kaposi sarcoma. These malignancies constitute the second most common cause of death in organ transplant recipients[2]. Immunotherapy is a breakthrough in managing transplant recipients and acts through interruption of the cancer-immunity cycle. Immune checkpoints, cytotoxic T-lymphocyte antigen 4 (CTLA-4), and programmed cell death 1 (PD-1) are physiologically responsible for preventing effector T cell overactivation.

Immunotherapy includes antibodies against CTLA-4 and PD-1, thereby upregulating the T-cell immune response to the cancer antigen[3]. Although the host immunity against tumor antigens is restored, on the other hand, T-cell stimulation is one of the significant components of graft rejection. The overall rejection rates following immunotherapy are 29%-54% and 25%, respectively, in patients who underwent solid organ transplantation and LT[4-6]. Kidney (40%) is associated with higher rates of graft rejection than liver (35%) and heart (20%)[3]. Au *et al*[1] studied that the graft rejection rates were seen in 32% of patients who specifically underwent an LT. The rejection rates among individuals who received immunotherapy within 2.9 years of transplant were increased compared to 5.3 years of transplant. They also noticed a higher mortality rate of 56% among graft rejected patients.

Compared with CTLA-4 inhibitors, PD-1 inhibitors are associated with higher rates of graft rejection and graft loss in LT recipients[7,8]. Kittai *et al*[9] reported graft rejection in 4 of 8 patients treated with anti-PD-1, whereas no rejections were detected in patients receiving anti-CTLA-4 therapy. Programmed death-ligand 1 (PD-L1) expression on the graft lymphocytes aids as a marker of rejection after immunotherapy[2]. Tacrolimus-based or combination agents (corticosteroids, antimetabolites, calcineurin inhibitors, and mechanistic target of rapamycin inhibitors) immunosuppression is shown to reduce graft rejection and improve the response to immunotherapy[2]. A 10%-20% of post-transplant patients encounter recurrence of HCC[10]. In such cases, immunotherapy is effective only in 11% of patients.

A higher dose of immunotherapy medication, a shorter interval between LT and immunotherapy initiation, expression of PD-L1 on the graft lymphocytes, and a previous GVHD history are positively related with the risk of and response to graft rejection[4]. Studies on patient characteristics such as gender, age, pathological type of primary tumor, donor type, type, and duration of ischemia during LT and post-operative hepatitis virus status of the patient are necessary to learn the factors associated with favorable outcomes after immunotherapy. Proper patient selection is quintessential to preventing lethal graft rejection. Hence, a close collaboration among oncologists and transplant specialists is encouraged when handling patients who require immunotherapy. However, prospective studies focusing on: (1) Although the PD-1 pathway is dominant in establishing immune tolerance, whether anti-PD-1 and anti-CTLA-4 antibodies are associated with graft rejection[9]; (2) The treatment of immunotherapy related graft rejection; and (3) Its efficacy is there any difference in treatment modality between immunotherapy related graft rejection and isolated graft rejection, are required beforehand to recommend immune checkpoint inhibitors in transplant recipients.

## FOOTNOTES

**Author contributions:** Vulasala SSR, Onteddu NK, Kumar SP, Lall C, Bhosale P, and Virarkar MK have equal contributions to this article.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.



**Country/Territory of origin:** United States

**ORCID number:** Sai Swarupa R Vulasala 0000-0002-9387-3673; Nirmal K Onteddu 0000-0002-6267-0240; Sindhu P Kumar 0000-0002-3862-7453; Chandana Lall 0000-0002-5318-4160; Priya Bhosale 0000-0003-4014-4941; Mayur K Virarkar 0000-0002-5825-3102.

**S-Editor:** Wang JJ
**L-Editor:** A
**P-Editor:** Wang JJ

## REFERENCES

1 **Au KP**, Chok KSH. Immunotherapy after liver transplantation: Where are we now? *World J Gastrointest Surg* 2021; **13**: 1267-1278 [PMID: 34754394 DOI: 10.4240/wjgs.v13.i10.1267]
2 **Kumar V**, Shinagare AB, Rennke HG, Ghai S, Lorch JH, Ott PA, Rahma OE. The Safety and Efficacy of Checkpoint Inhibitors in Transplant Recipients: A Case Series and Systematic Review of Literature. *Oncologist* 2020; **25**: 505-514 [PMID: 32043699 DOI: 10.1634/theoncologist.2019-0659]
3 **Fisher J**, Zeitouni N, Fan W, Samie FH. Immune checkpoint inhibitor therapy in solid organ transplant recipients: A patient-centered systematic review. *J Am Acad Dermatol* 2020; **82**: 1490-1500 [PMID: 31302190 DOI: 10.1016/j.jaad.2019.07.005]
4 **Hu B**, Yang XB, Sang XT. Liver graft rejection following immune checkpoint inhibitors treatment: a review. *Med Oncol* 2019; **36**: 94 [PMID: 31605245 DOI: 10.1007/s12032-019-1316-7]
5 **Ijaz A**, Khan AY, Malik SU, Faridi W, Fraz MA, Usman M, Tariq MJ, Durer S, Durer C, Russ A, Parr NNC, Baig Z, Sagar F, Ali Z, McBride A, Anwer F. Significant Risk of Graft-versus-Host Disease with Exposure to Checkpoint Inhibitors before and after Allogeneic Transplantation. *Biol Blood Marrow Transplant* 2019; **25**: 94-99 [PMID: 30195074 DOI: 10.1016/j.bbmt.2018.08.028]
6 **Gassmann D**, Weiler S, Mertens JC, Reiner CS, Vrugt B, Nägeli M, Mangana J, Müllhaupt B, Jenni F, Misselwitz B. Liver Allograft Failure After Nivolumab Treatment-A Case Report With Systematic Literature Research. *Transplant Direct* 2018; **4**: e376 [PMID: 30255136 DOI: 10.1097/TXD.0000000000000814]
7 **Tio M**, Rai R, Ezeoke OM, McQuade JL, Zimmer L, Khoo C, Park JJ, Spain L, Turajlic S, Ardolino L, Yip D, Goldinger SM, Cohen JV, Millward M, Atkinson V, Kane AY, Ascierto PA, Garbe C, Gutzmer R, Johnson DB, Rizvi HA, Joshua AM, Hellmann MD, Long GV, Menzies AM. Anti-PD-1/PD-L1 immunotherapy in patients with solid organ transplant, HIV or hepatitis B/C infection. *Eur J Cancer* 2018; **104**: 137-144 [PMID: 30347289 DOI: 10.1016/j.ejca.2018.09.017]
8 **Wanchoo R**, Riella LV, Uppal NN, Lopez CA, Nair V, Devoe C, Jhaveri KD. Immune checkpoint inhibitors in the cancer patient with an organ transplant. *J Onco-Nephrol* 2017; **1**: 42-48 [DOI: 10.5301/jo-n.5000006]
9 **Kittai AS**, Oldham H, Cetnar J, Taylor M. Immune Checkpoint Inhibitors in Organ Transplant Patients. *J Immunother* 2017; **40**: 277-281 [PMID: 28719552 DOI: 10.1097/CJI.0000000000000180]
10 **Johnston MP**, Khakoo SI. Immunotherapy for hepatocellular carcinoma: Current and future. *World J Gastroenterol* 2019; **25**: 2977-2989 [PMID: 31293335 DOI: 10.3748/wjg.v25.i24.2977]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
**Telephone:** +1-925-3991568
**E-mail:** bpgoffice@wjgnet.com
**Help Desk:** https://www.f6publishing.com/helpdesk
https://www.wjgnet.com