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

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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

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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

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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

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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].

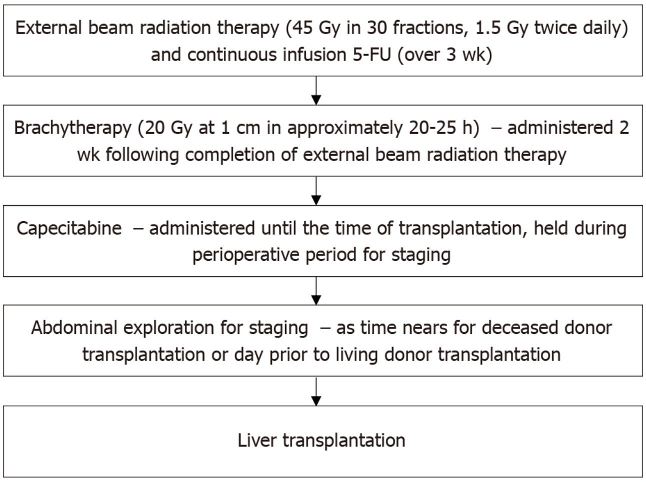

Figure 1 Mayo clinic protocol for neoadjuvant chemoradiation and staging laparoscopy prior to liver transplantation. Gy: Gray units of ionizing radiation; 5-FU: 5-Fluorouracil.

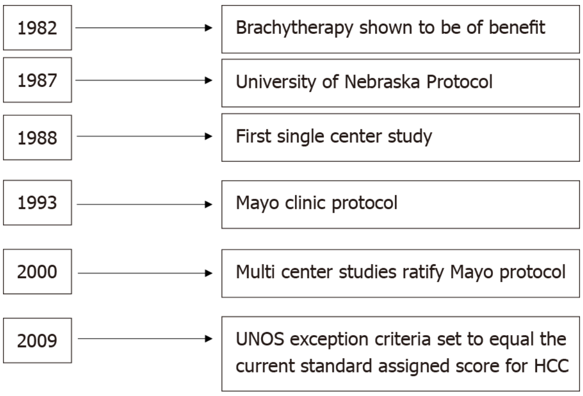

Figure 2 History of liver transplantation in perihilar cholangiocarcinoma, including the development of the original transplantation protocols, United Network for Organ Sharing approval, and standard exception point for liver transplantation. UNOS: United Network for Organ Sharing; HCC: Hepatocellular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

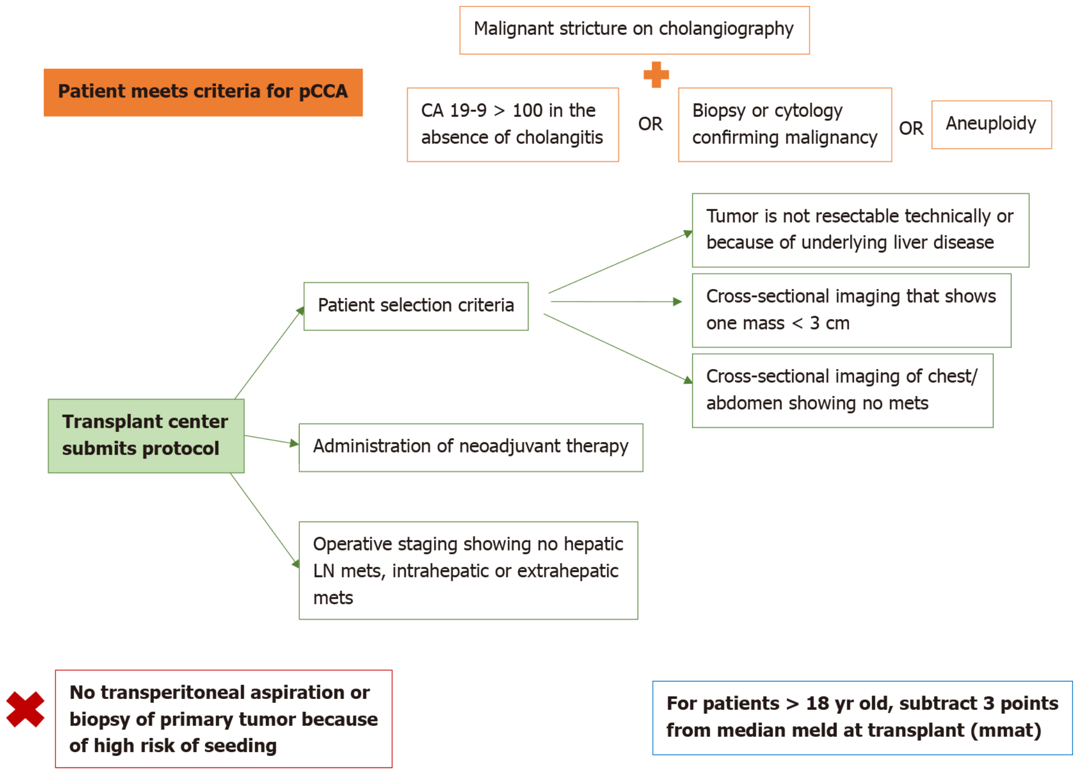

Figure 3 Model for end-stage liver disease exception point for perihilar cholangiocarcinoma, as developed by the United Network for Organ Sharing. pCCA: Perihilar cholangiocarcinoma; CA 19-9: Cancer-antigen 19-9; LN: Lymph node.

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.

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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

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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

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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

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.

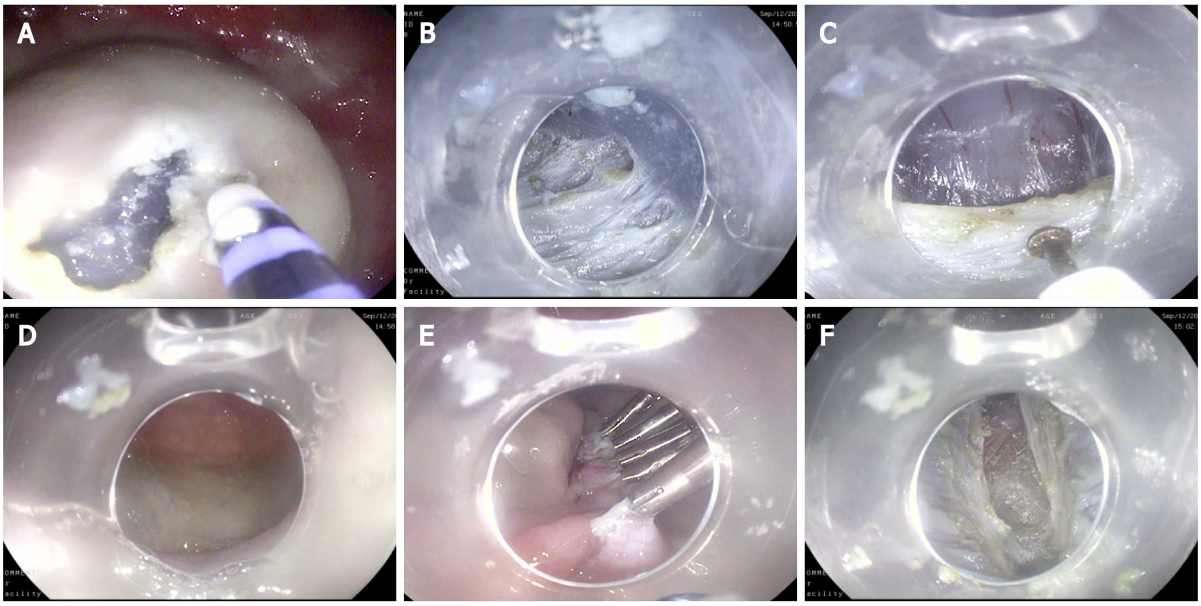

Figure 1 Technical aspects of gastric per-oral endoscopic myotomy. A: Making of mucosal incision after lifting; B: Creating of submucosal tunnel with dissection technique; C: Exposure of pyloric ring; D: Study of mucosa of duodenal bulb; E: Execution of myotomy of pyloric ring; F: Endoscopic suture using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

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World Journal of Gastrointestinal Surgery

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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

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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 8th 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.

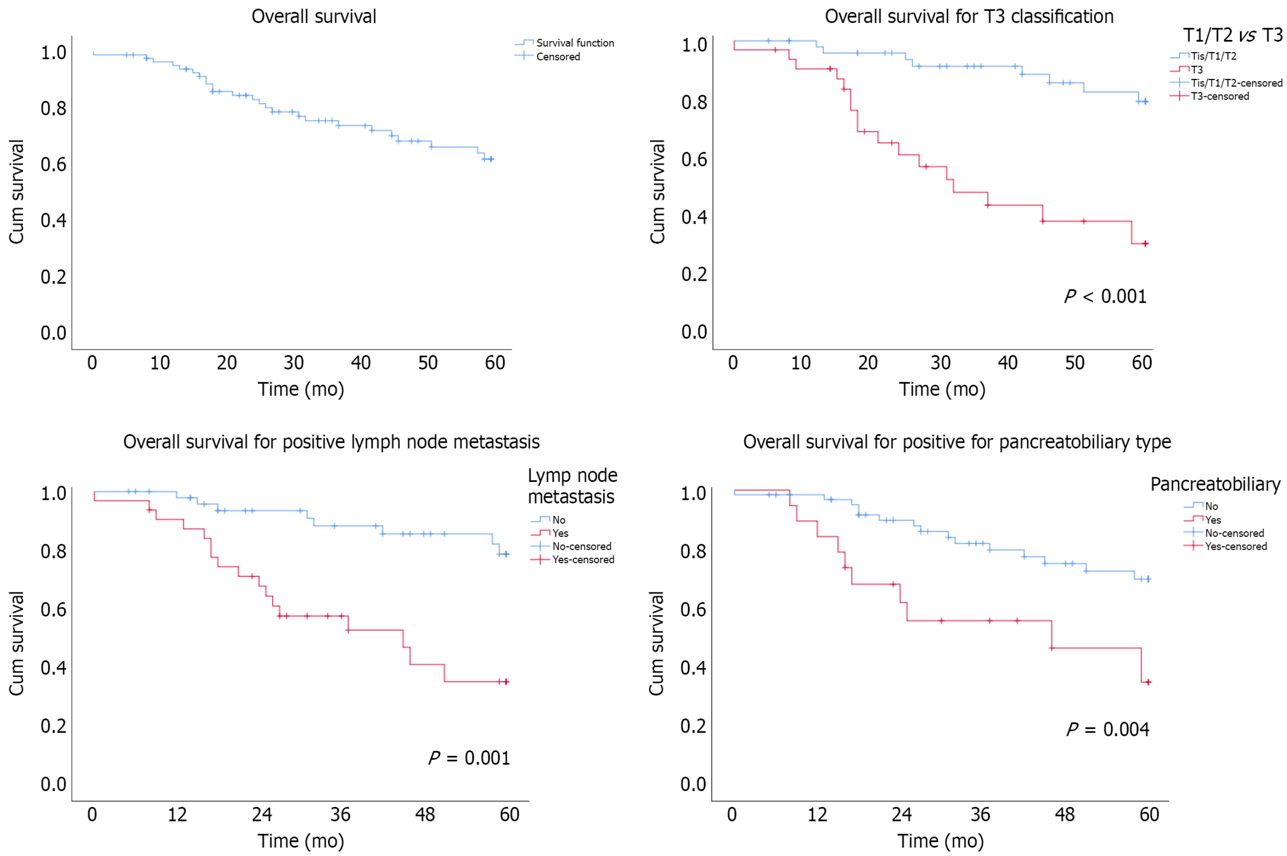

Figure 1 Survival probability of patients with adenocarcinoma of the ampulla of Vater undergoing pancreaticoduodenectomy.

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.

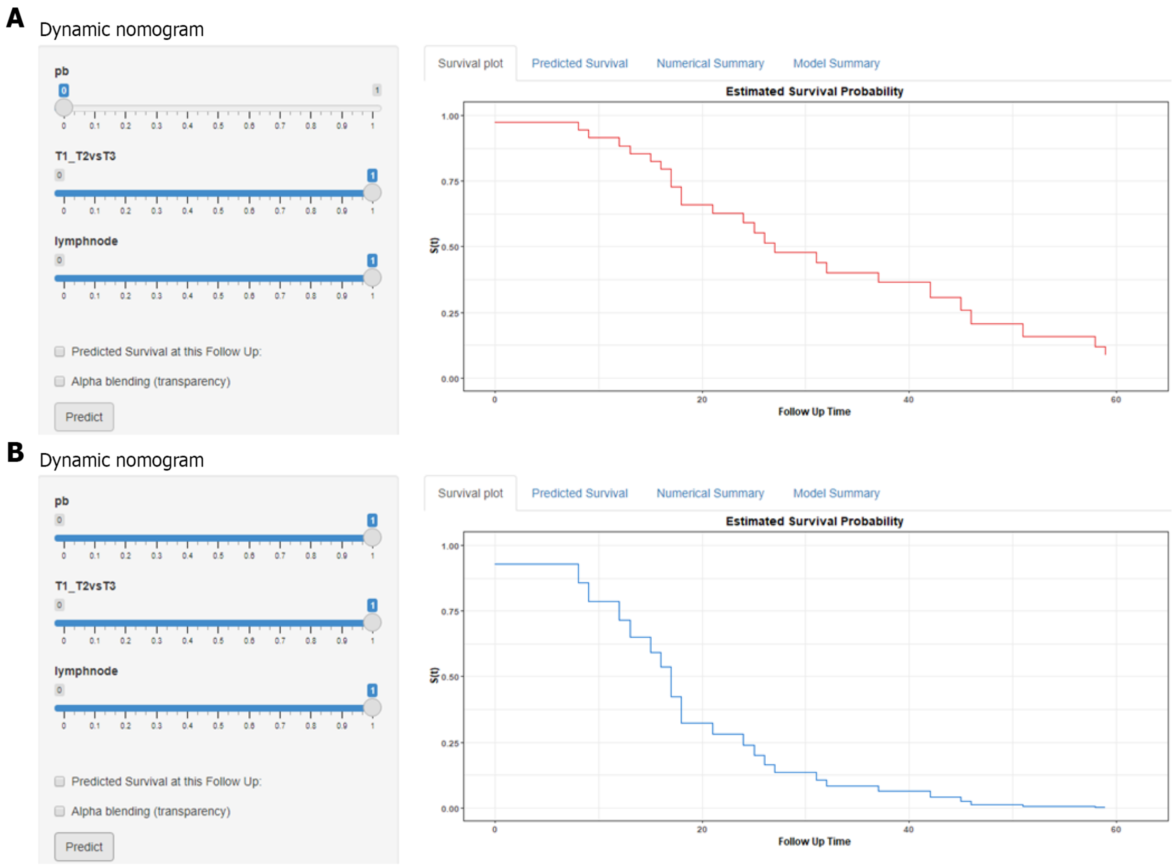

Figure 2 Comparison of survival probability between the intestinal/other (A) and pancreaticobiliary (B) types in patients with pT3 and pN^{+} adenocarcinoma of the ampulla of Vater.

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.

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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

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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

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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

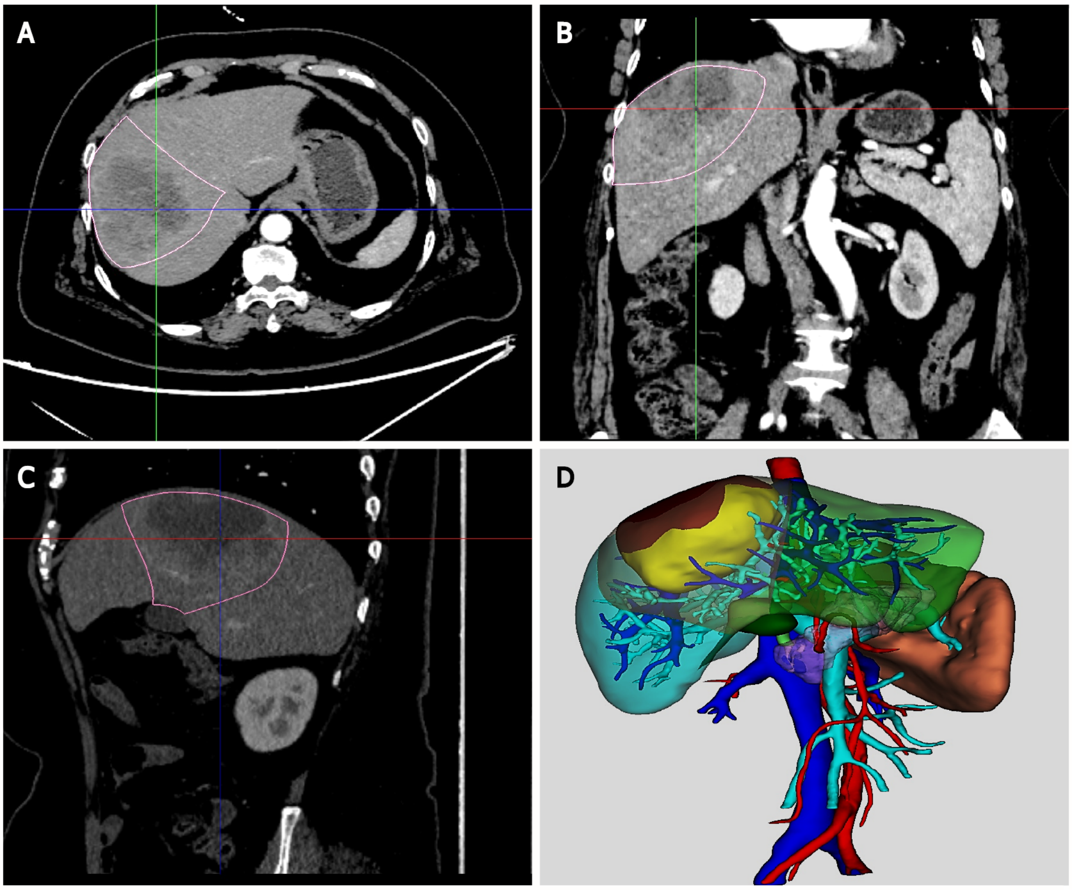

Figure 1 Two-dimensional imaging and three-dimensional reconstruction. A-C: Two-dimensional imaging (2D) abdominal enhanced computed tomography images of a patient with hepatocellular carcinoma; D: Three-dimensional (3D) hologram reconstructed by mixed reality software.

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

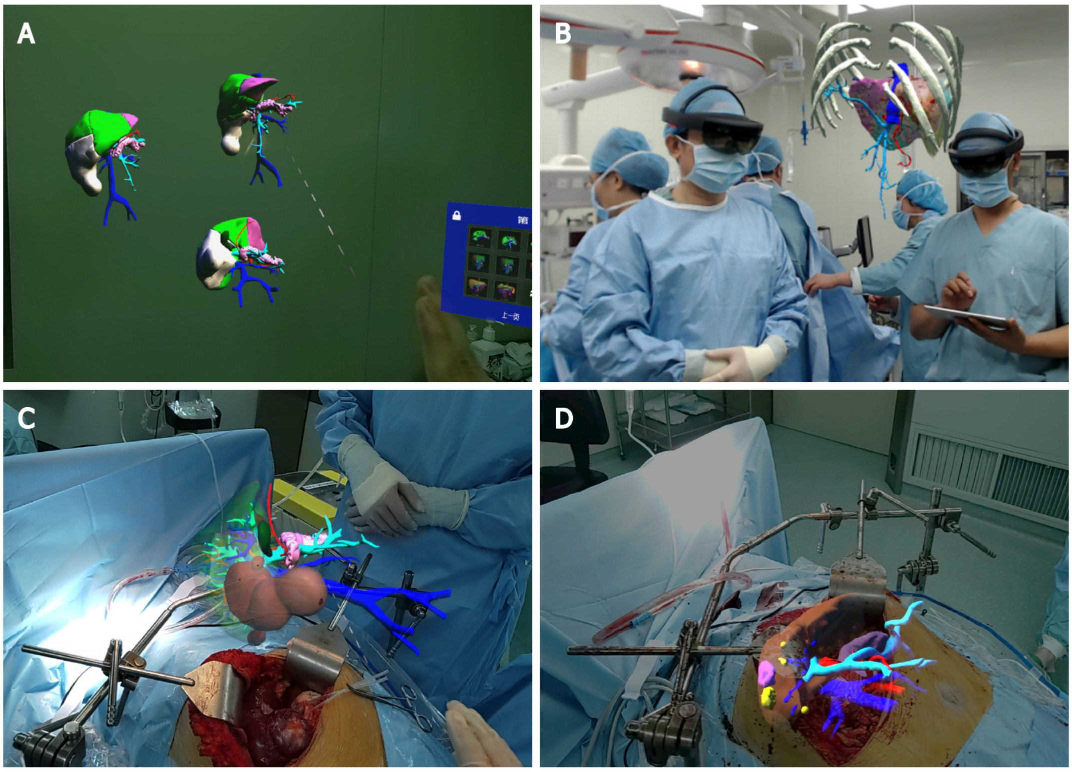

Figure 2 Mixed reality-assisted hepatectomy guided by three-dimensional holograms. A: Three-dimensional (3D) holograms were observed with the mixed reality head-mounted display in the operating room; B: The surgeon observed the tumor location and vascular anatomy with a 3D hologram and determined the 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.

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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

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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 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

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:

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,

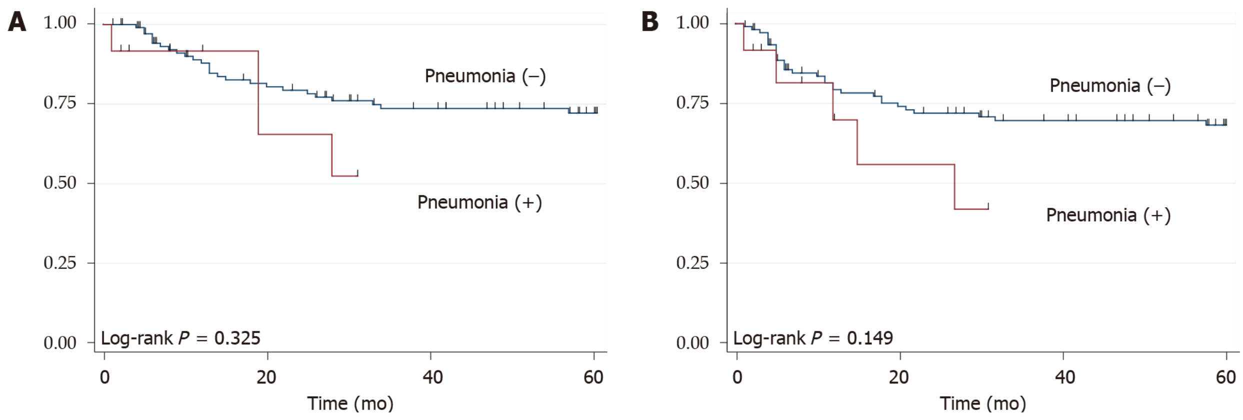

Figure 1 Kaplan-Meier survival curves, according to the presence of pneumonia. A: Overall survival; B: Recurrence-free survival. Red and blue lines indicate the groups with and without pneumonia, respectively.

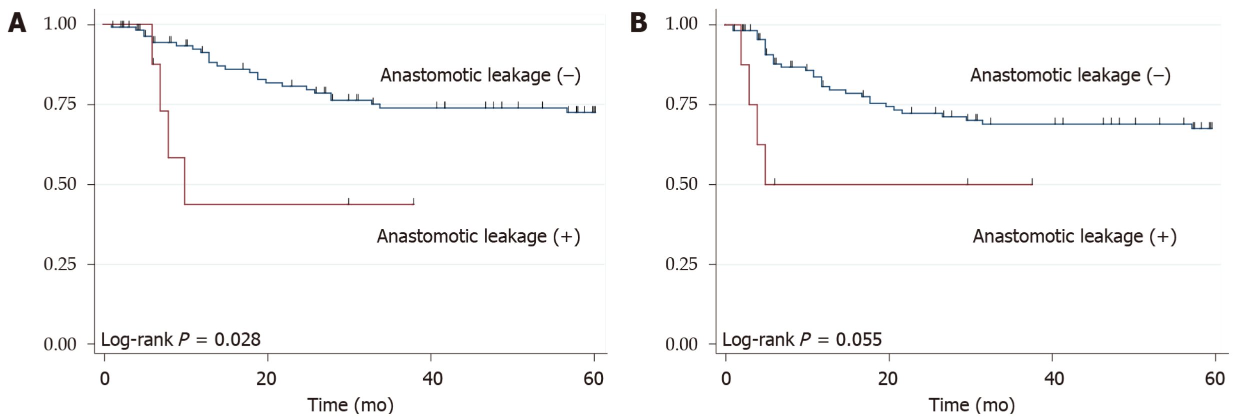

Figure 2 Kaplan–Meier survival curves, according to the presence of anastomotic leakage. A: Overall survival; B: Recurrence-free survival. Red and blue lines indicate the groups with and without anastomotic leakage, respectively.

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

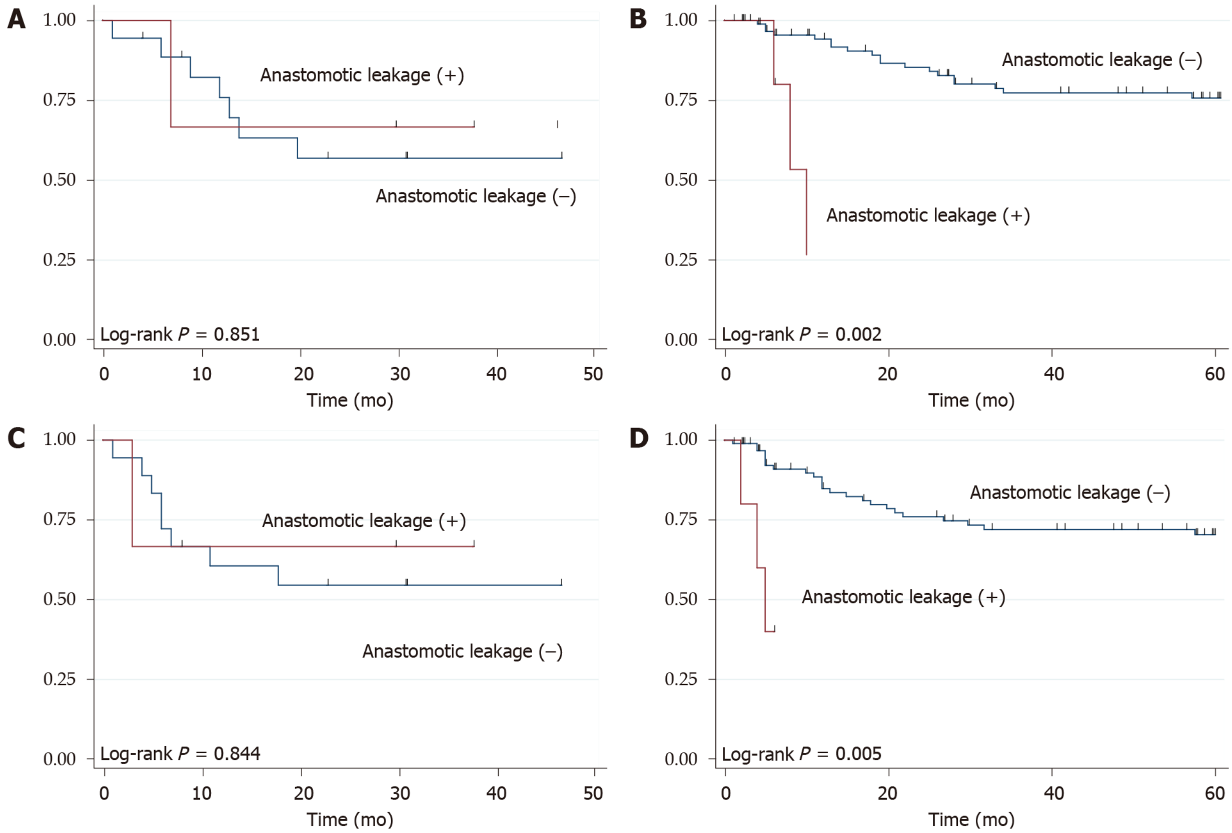

Figure 3 Kaplan–Meier survival curves, according to the presence of anastomotic leakage and type of anastomosis. A and B: The overall survival (A) in patients with cervical anastomosis and (B) in patients with intrathoracic anastomosis; C and D: The recurrence-free survival (C) in patients with cervical 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.

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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

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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.

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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,

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

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

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.

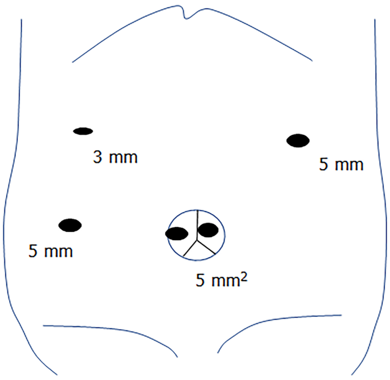


Figure 1 Ports placed in laparoscopic surgery.

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).

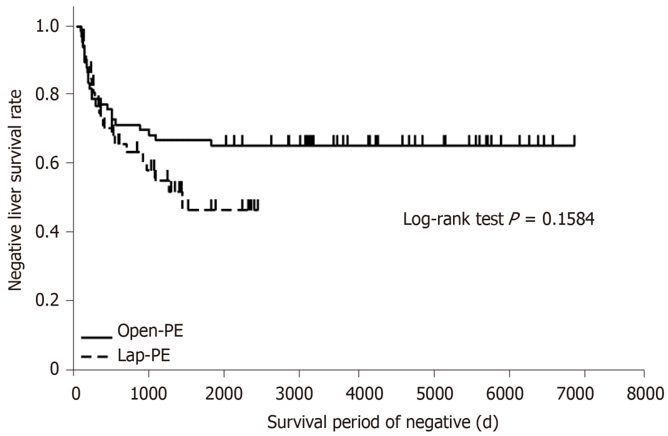
DISCUSSION

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.

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W J G S
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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

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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.

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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]$P \le 0.05$ 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, $P \le 0.05$). 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

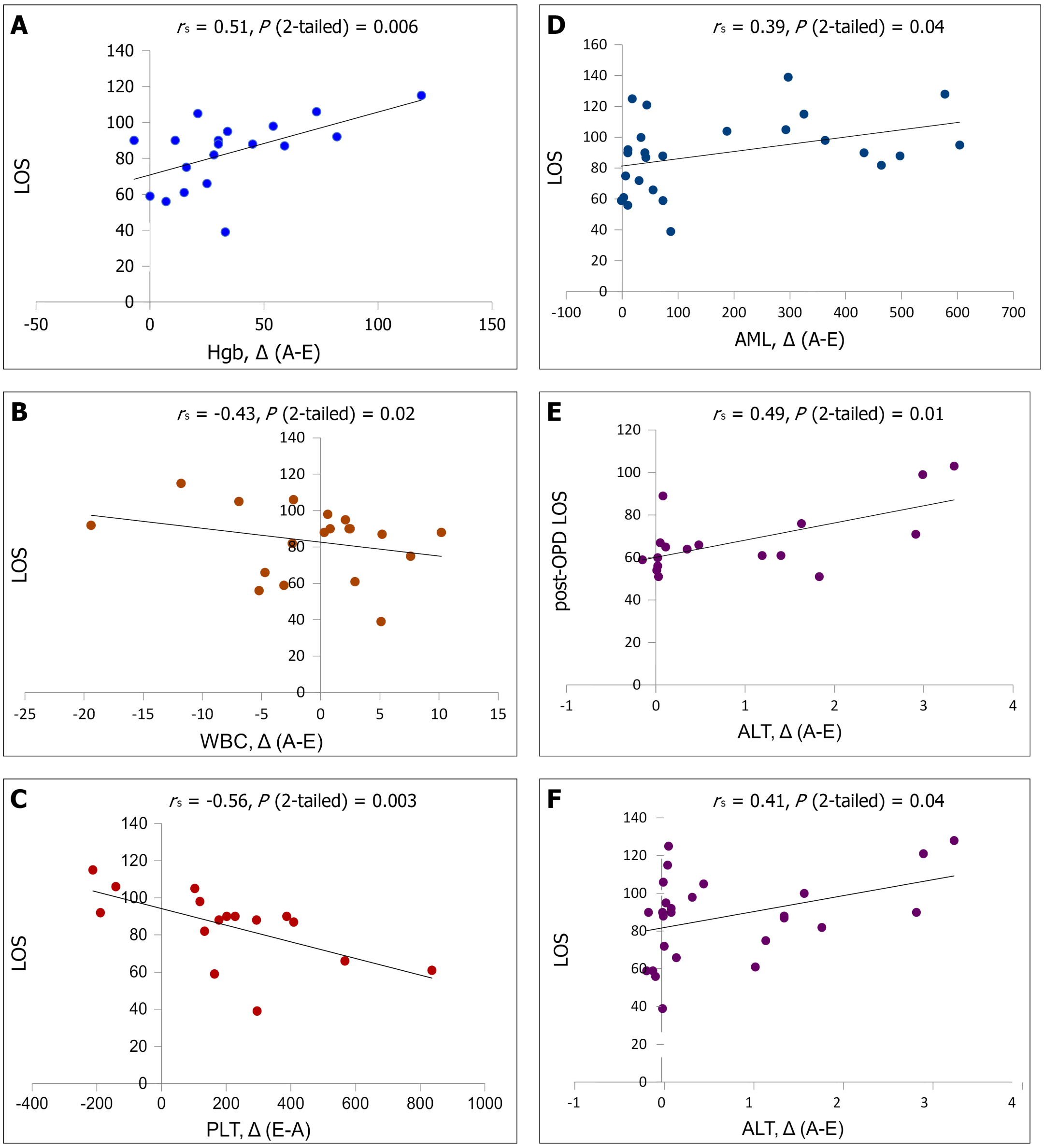

Figure 1 Correlations between dynamic changes of laboratory variables. A: Hemoglobin; B: Total white blood cell count; C: Total platelets count; D: α-amylase; E: Alanine aminotransferase; F: total and post-surgical length of stay. Δ(A-E) = value on admission – value the day before the surgery; Δ(E-A) = 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.

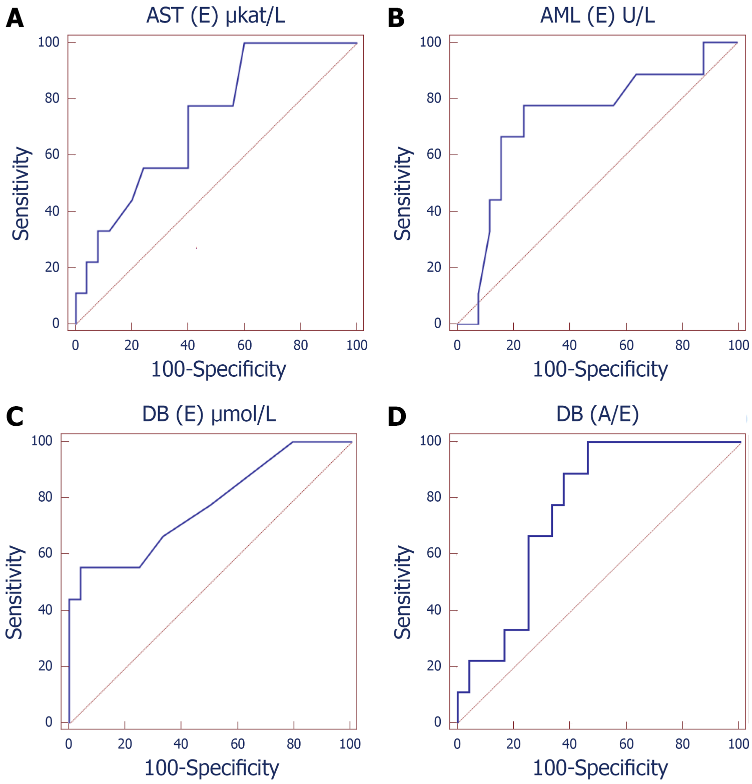

Figure 2 Receiver operating characteristic curves of aspartate aminotransferase, α-amylase, and direct bilirubin for hospital mortality prediction in acute necrotizing pancreatitis patients. A: Receiver operating characteristic (ROC) curves of aspartate aminotransferase the day before the surgery; B: 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.

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