ISSN 1948-9366 (online)

World Journal of

Gastrointestinal Surgery

World J Gastrointest Surg 2021 December 27; 13(12): 1523-1769

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

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INDEXING/ABSTRACTING

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

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

NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

ISSN
ISSN 1948-9366 (online)

LAUNCH DATE
November 30, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Shu-You Peng, Varut Lohsiriwat

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

PUBLICATION DATE
December 27, 2021

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

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https://www.wjgnet.com/bpg/GerInfo/287

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World J Gastrointest Surg 2021 December 27; 13(12): 1523-1535

DOI: 10.4240/wjgs.v13.i12.1523

ISSN 1948-9366 (online)

FRONTIER

Photodynamic therapy: A next alternative treatment strategy for hepatocellular carcinoma?

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Author contributions: Zhu F, Wang B and Zhu Z contributed equally to this work and drafted the manuscript; Li M and Zhu F revised the manuscript; Zhu F, Wang S and Chai C collected the references; Li M and Shang D designed the work; all authors made the final approval of this version.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Supported by the Wuhan Municipal Health Commission, No. WX14B22; and the National Natural Science Foundation of China, No. 81874208 and No. 81700425.

Country/Territory of origin: China

Specialty type: Gastroenterology and hepatology

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

Peer-review report's scientific

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Abstract

Liver cancer is one of the most common cancers in the world. Of all types of liver cancer, hepatocellular carcinoma (HCC) is known to be the most frequent primary liver malignancy and has seriously compromised the health status of the general population. Locoregional thermal ablation techniques such as radiofrequency and microwave ablation, have attracted attention in clinical practice as an alternative strategy for HCC treatment. However, their aggressive thermal effect may cause undesirable complications such as hepatic decompensation, hemorrhage, bile duct injury, extrahepatic organ injuries, and skin burn. In recent years, photodynamic therapy (PDT), a gentle locoregional treatment, has attracted attention in ablation therapy for patients with superficial or luminal tumors as an alternative treatment strategy. However, some inherent defects and extrinsic factors of PDT have limited its use in clinical practice for deep-seated HCC. In this contribution, the aim is to summarize the current status and challenges of PDT in HCC treatment and provide potential strategies to overcome these deficiencies in further clinical translational practice.

Key Words: Hepatocellular carcinoma; Photodynamic therapy; Photosensitizers;

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

Received: April 25, 2021
Peer-review started: April 25, 2021
First decision: June 13, 2021
Revised: June 20, 2021
Accepted: September 8, 2021
Article in press: September 8, 2021
Published online: December 27, 2021

P-Reviewer: Kumar SKY, Tajiri K
S-Editor: Wang LL
L-Editor: Kerr C
P-Editor: Wu RR

Aggregation-induced emission; Targeted therapy; Nanoparticles

Core tip: The application of photodynamic therapy (PDT) in hepatocellular carcinoma (HCC) therapy is limited due to its low penetration depth of light irradiation, the reduced generation of reactive oxygen species by conventional photosensitizers in the aggregated state, and the nontargeted accumulation in cancer cells. Once these problems are resolved, PDT will be a promising alternative treatment strategy for HCC.

Citation: Zhu F, Wang BR, Zhu ZF, Wang SQ, Chai CX, Shang D, Li M. Photodynamic therapy: A next alternative treatment strategy for hepatocellular carcinoma? *World J Gastrointest Surg* 2021; 13(12): 1523-1535
URL: https://www.wjgnet.com/1948-9366/full/v13/i12/1523.htm
DOI: https://dx.doi.org/10.4240/wjgs.v13.i12.1523

INTRODUCTION

Liver cancer is one of the most common causes of cancer-related death worldwide[1]. Of all types of liver cancer, hepatocellular carcinoma (HCC) is known to be the most frequent liver malignancy[2,3]. The main risk factors for HCC are chronic hepatitis B virus or hepatitis C virus infection, alcohol consumption and the resulting cirrhosis, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, dietary intake of aflatoxin B1, *etc*[4,5]. The incidence and mortality of HCC are rapidly rising in the USA and several European regions and slightly declining in traditionally high-risk regions such as East Asia and Africa[4]. Population-based studies have revealed that the incidence rate continues to approximate the death rate, indicating that most patients who develop HCC die of it[6]. HCC has seriously compromised the health status of the general population. In general, there are several treatment options for the management of HCC, but each treatment has its limitations and side effects[7]. In recent years, photodynamic therapy (PDT) has been a palliative treatment option that could improve quality of life and median survival with minimal invasion for cancer patients [8] and some studies have investigated its applications in ablation therapy for HCC. The aim of this frontier article was to summarize the current status and challenges of PDT for HCC as an alternative locoregional ablation and to propose potential strategies to overcome the deficiencies in clinical translational practice.

THERAPY

In general, several treatment options have emerged for the management of HCC. These options include surgical treatment with curative intents such as hepatic resection[9] or liver transplantation[10], systemic therapy (*e.g.*, sorafenib, lenvatinib, regorafenib and apatinib)[11,12], immunotherapy (*e.g.*, atezolizumab plus bevacizumab, nivolumab, pembrolizumab, ramucirumab, and camrelizumab)[13-16], external beam radiotherapy and catheter based embolic therapies (*e.g.*, chemoembolization and radioembolization)[17-20]. In addition, locoregional therapies include ablative techniques inducing tumor necrosis by injection of chemicals (*e.g.*, ethanol and acetic acid), and temperature modification (ablation by radiofrequency, microwave, laser or cryoablation)[21-25]. Recently, locoregional thermal ablation techniques, radiofrequency and microwave ablation, have attracted interest in clinical practice as alternative strategies for HCC treatment[26-28]. According to the guidelines of the China Liver Cancer Staging, locoregional ablation is recommended for HCC patients in stages Ia, Ib and IIa as an alternative treatment[29]. The obvious benefits of radiofrequency ablation are its minimally invasive nature, lower rate of complications, and decreased cost of treatment. The efficiency of microwave ablation allows for an increased volume of necrosis, better vessel coagulation, and decreased ablation times [7]. However, the aggressive thermal effect of locoregional ablations may cause

undesirable complications, such as hepatic decompensation, hemorrhage, bile duct injury, extrahepatic organ injuries, and skin burn[30]. Therefore, the development of a novel locoregional ablation technique is an imperative task for alternative treatment strategies for HCC therapy.

PDT

PDT is a palliative treatment option that can improve quality of life and median survival with minimal invasion for patients, and has caused extensive concern for tumor therapy in recent years since *Paramecium* spp. killing was described through the interaction between acridine and infrared radiation by Oscar Raab in 1900[31]. Due to its low economic cost, few side effects, less invasiveness than surgery, short treatment time, precise targeting, and repeated treatment at the same site, PDT has been extended to the treatment of a variety of tumors, such as brain tumors[32], head and neck tumors[33,34], skin tumors[35], breast cancer[36], esophageal cancer[37], gastrointestinal tumors[38], lung cancer[39], extrahepatic cholangiocarcinoma[40-43], and bladder cancer[44].

PDT kills cancer cells by reactive oxygen species (ROS) generated from light-activated photosensitizers (PSs), resulting in the destruction of tumor cells and blood vessels and the stimulation of the host immune system[45-47]. Specifically, after activation by light irradiation, PSs accumulating in malignant tissues are electronically excited and transfer an electron to molecular oxygen or other electron acceptors to yield superoxide anions and radicals (*i.e.*, type I reaction, in a hypoxic microenvironment) or transfer their electronic energy to ground-state molecular oxygen to yield singlet oxygen (*i.e.*, type II reaction in a hyperoxic microenvironment)[48], which leads to antitumor effects and stimulates immune effects[49]. Moreover, activating the innate immune system increases the priming of tumor-specific T lymphocytes that can recognize and destroy distant tumor cells and lead to the development of immune memory that can combat the recurrence of cancer at a later point in time[50].

Among the three essential elements, PSs play a crucial role in ensuring the successful implementation of PDT. However, several inherent limitations of conventional PSs, such as high demand for oxygen in the microenvironment, inefficient generation of ROS and no organelle targeting, limit therapeutic outcomes in PDT[51]. In other words, several extrinsic factors impact the effectiveness of PDT. For instance, conventional PSs hardly have active accumulation in tumor lesions and tumor cell uptake[52], resulting in inefficient anticancer effects and phototoxicity of other normal tissues.

PDT FOR HCC

Although the clinical practice of PDT for deep-seated solid tumors has been limited by the penetration of laser irradiation and the defects of PSs, many studies have shown that PDT has better potential to improve HCC treatment than other traditional therapies owing to its noninvasiveness and localized therapeutic effect in the presence of specialized laser irradiation[8]. For example, experimental studies have shown that PDT can effectively kill hepatoma cells and shrink tumor tissues[53-55], and clinical investigations have also revealed that PDT can prolong the survival rate in patients with inoperable cancers to significantly improve their quality of life[56,57]. Specifically, this work summarizes the previous literature on PDT for HCC in Tables 1 and 2, to provide some insight for future research on PDT for HCC.

As described in Table 1, indocyanine green (ICG) is a clinical infrared imaging agent approved by the US Food and Drug Administration[70,71] and has been applied in optical imaging in liver surgery[72-74], fluorescence angiography[75], cancer theranostics[72], surgical navigation[76], vascular grafts[77] and so on. In addition, a large number of studies have shown that ICG is widely used as a PS in PDT, and is able to rapidly generate singlet oxygen upon exposure to a near-infrared (NIR) laser and thus destroy cancerous cells[78,79]. Hence, ICG has been considered a promising theranostic agent. In addition, HCC cells notably take up ICG molecules with high efficiency but it cannot be easily excreted to bile ducts owing to the abnormal structures of bile capillaries[80]; thus, the retained ICG in HCC can kill cancer cells *via* PDT. For example, Kim *et al*[58] tested the cytotoxicity of ICG after NIR light irradiation in cancerous cell lines (Huh-7 and Hep3B) *in vitro* and investigated the tumoricidal ability after treatment with intravenous injection of ICG (5–20 mg/kg^2)

Table 1 Summary of photosensitizers molecules in photodynamic therapy for hepatocellular carcinoma in recent years

PSs	Animal model	Ref.
ICG	Patient-derived orthotopic xenograft mice	Hong *et al*[58]
ICG	Huh-7 tumor-bearing nude mice	Shirata *et al*[49]
m-THPC (Foscan®)	Rat model with Walker-256 hepatoma cells	Wang *et al*[59]
Endogenous PpIX from 5-ALA	Diethylnitrosamine-induced HCC in Fisher-344 rats	Otake *et al*[60]
HpD	2-Acetylaminofluorene-induced HCC in Fisher-344 rats	Kita *et al*[61]

PSs: Photosensitizers; ICG: Indocyanine green; *m*-THPC: Meta-tetra (hydroxyphenyl) chlorin/temoporfin; PpIX: Protoporphyrin IX; 5-ALA: 5-aminolaevulinic acid; HpD: Hematoporphyrin derivatives; HCC: Hepatocellular carcinoma.

Table 2 Summary of photosensitizers-loaded nanoparticles-mediated drug delivery systems in photodynamic therapy for hepatocellular carcinoma evaluated in recent years

PSs	Delivery vehicle	Ligand	Matching receptor	Drug agent	Animal model	Ref.
Pu-18-*N*-butylimide-NMGA	Gold NPs	/	/	/	Huh-7 tumor-bearing nude mice	Kwon *et al*[62]
ZnPc	BSA-assembled NPs	/	/	Sorafenib	SMMC-7721 tumor-bearing nude mice	Yu *et al*[51]
ICG	Nanoliposomes	/	/	Sorafenib	Hep3B tumor-bearing nude mice	He *et al*[63]
Porphyrin	MOF	Folic acid	Folate receptor	/	Doxycycline-induced HCC in $kras^{G12V}$ zebrafish	Chen *et al*[64]
Ce6	SPIONs	Cancer cell membrane	/	/	SMMC-7721 tumor-bearing nude mice	Li *et al*[65]
Porphyrin	PEGylated Zr-MOF	Galactose	ASGPR	DOX	Huh-7 tumor-bearing nude mice	Hu *et al*[66]
Mitoxantrone	PEGylated UCNP micelles	Anti-EpCAM antibody	EpCAM	/	BEL-7404 tumor-bearing nude mice	Han *et al*[46]
Ce6	DNA hybrids	TLS11a aptamer	/	DOX	HepG2 tumor-bearing nude mice	Zhang *et al*[67]
Ce6	Gold NPs	TLS11a aptamer	/	AQ4N	HepG2 tumor-bearing nude mice	Zhang *et al*[68]
IR780	Phospholipid/Pluronic F68 NPs	Pullulan	ASGPR	Paclitaxel	MHCC-97H tumor-bearing nude mice	Wang *et al*[69]

PSs: Photosensitizers; Pu-18-*N*-butylimide-NMGA: Purpurin-18-*N*-butylimide-*N*-methyl-*D*-glucamine; NPs: Nanoparticles; ZnPc: Zinc phthalocyanine; BSA: Bovine serum albumin; ICG: Indocyanine green; MOF: Metal-organic frameworks; Ce6: Chlorin e6; SPIONs: Superparamagnetic iron oxide nanoparticles; ASGPR: Asialoglycoprotein receptor; DOX: Doxorubicin; AQ4N: Banoxantrone.

and daily NIR exposure (0.5–1.75 W/cm^2) in a patient-derived orthotopic xenograft (PDoX) mouse model *in vivo*. The results demonstrated that complete remission of deep-seated PDoX hepatoma could be achieved through NIR-irradiated ICG, indicating that ICG-based PDT is promising for the noninvasive destruction of deep-seated HCC. Meanwhile, a series of fluorogens, such as chlorin e6[81], porphyrin[64], and 5-aminolaevulinic acid[82] were investigated as new PSs for anti-HCC therapy.

However, traditional PSs have low selectivity for accumulation in neoplastic tissues with an affinity for healthy tissues, which results in phototoxicity during treatment[83, 84]. Therefore, a long period of light protection is required for patients after PDT. Additionally, PSs are easily degraded and excreted in blood circulation and have a tendency to aggregate in aqueous milieu, resulting in low bioavailability and the loss of photodynamic activity[85]. Recently, nanocarrier systems have shown potential to overcome the defects mentioned above[86-88]. In tumorous tissues, the absence of vasculature supportive tissues intimates the formation of leaky vessels and pores (100

nm to 2 μm in diameter). Meanwhile, the poor lymphatic system offers a great opportunity to treat cancer, and this phenomenon is known as the enhanced permeability and retention (EPR) effect[89,90]. Nanoparticles (NPs) can essentially deliver PSs to tumor lesions, which contribute to their passive tumor-targeting abilities (*via* the EPR effect)[91-93]. For example, He's group[94] reported a new type of NP, copper–cysteamine (Cu–Cy), as a novel PS for anti-HCC treatment. Cu–Cy NPs not only significantly reduced the activity of HepG2 cells at a low dose after a short time of ultraviolet radiation *in vitro,* but also inhibited tumor growth *in vivo*. To further enhance the anti-HCC effects, Xu and his colleagues[63] designed NIR fluorescence imaging-guided nanoliposomes co-encapsulated with ICG and sorafenib. As expected, this nanocarrier could overcome the drawbacks of free ICG solution, such as instability in aqueous solution, rapid clearance in blood circulation, and lack of targeting, which leads it to achieve the PDT effect with negative targeting. Moreover, sorafenib also decreased the expression of vascular endothelial growth factor (VEGF) that was upregulated by PDT, which is a critical signaling factor for tumor recurrence. As such, this nanocarrier could inhibit HCC with synergistic therapeutic effects in a Hep3B tumor-bearing xenograft nude mouse model *in vivo*.

The free NPs used by PDT are subjected to inactive uptake and lack cancer cell-targeting abilities; hence, they cannot be internalized into cancer cells *via* active targeting with high efficiency[95,96]. Due to this limitation of free NPs, the paradigm of HCC treatment by PDT is now markedly shifting from NPs conjugating PSs to the tumor-specific targeting approach, which could lead to significantly improved PDT efficacy due to enhanced cellular uptake and minimize the toxic effects of associated therapeutic molecules[97,98]. Active targeting strategies using, for instance, specific ligands such as vitamins, antibodies or peptides, aptamers, could be a solution to overcome this limitation and achieve tumor-specific targeting properties[93]. The ligands can specifically bind with matching receptors on the hepatoma cell membrane and trigger receptor-mediated endocytosis[99]. For example, Li *et al*[64] designed and synthesized nanoscale gadolinium–porphyrin metal-organic frameworks as a skeleton for folic acid (FA) conjugation (FA–NPMOFs) to enhance the delivery of porphyrin into HCC cells. FA–NPMOFs exhibited a strong affinity for HCC cells with positive folate receptors and were delivered to tumor tissues in a targeted manner. Then, the porphyrin that accumulated in the tumor tissues could possess dual-function of fluorescence imaging and PDT in HCC tumor-bearing zebrafish model. After exposure to light at a specific wavelength, the singlet oxygen generated from porphyrin exerts a prominent anti-HCC effect rather than damaging the normal tissues contributing to the active targeting between FA of FA–NPMOFs and FR on HCC cells.

Another common problem of traditional PSs, such as the most widely used porphyrin derivatives and ICG, lies in their high hydrophobia and rigid planar structures as shown in Figure 1. Such a problem can collectively cause them to form aggregates in aqueous media through π–π stacking, resulting in an aggregation-caused quenching effect. This performance induces quenched fluorescence and a significant decrease in ROS generation that diminishes the imaging quality and PDT efficacy[100,101]. Conversely, aggregation-induced emission (AIE) molecules with a twisted configuration that suppresses strong intermolecular interactions represent a new class of PSs for image-guided PDT[102-104]. These PSs with AIE characteristics (denoted as AIE PSs) present weak emission in the molecular state but exhibit strong fluorescence emission and efficient photosensitization ability in the aggregated state[105-107]. Thus, formulating targeted AIE PS dots for image-guided PDT is expected to be a new treatment for tumors[40,105,106,108,109]. In previous work[40], our group designed and fabricated integrin $\alpha_v\beta_3$-targeted organic nanodots for image-guided PDT based on a red emissive AIE PS. The tetraphenylene derivative with typical AIE characteristic (TPETS)-encapsulated nanodots was prepared by nanoprecipitation method and further conjugated with thiolated cRGD through a click reaction to yield the targeted TPETS nanodots (T-TPETS nanodots), which could facilitate cellular uptake through active targeting by specific binding between cRGD and integrin $\alpha_v\beta_3$ and enhance ROS generation based on AIE PSs as the core of nanodots in the aggregate state. The data showed that the obtained nanodots showed bright red fluorescence and highly effective $^1O_2$ generation in the aggregated state. The T-TPETS nanodots could accumulate in tumor tissue through the EPR effect and further expedite internalization by HCC cells *via* receptor-mediated endocytosis. Based on these multiple features, both *in vitro* and *in vivo* experiments demonstrated that the nanodots exhibited excellent HCC-targeted imaging performance, which promoted image-guided PDT for tumor ablation in a HepG2-bearing nude mouse model. After light irradiation, the nanodots inhibited the growth of tumor foci and significantly extended survival. Moreover, further analysis revealed that nanodot-mediated PDT could induce time-

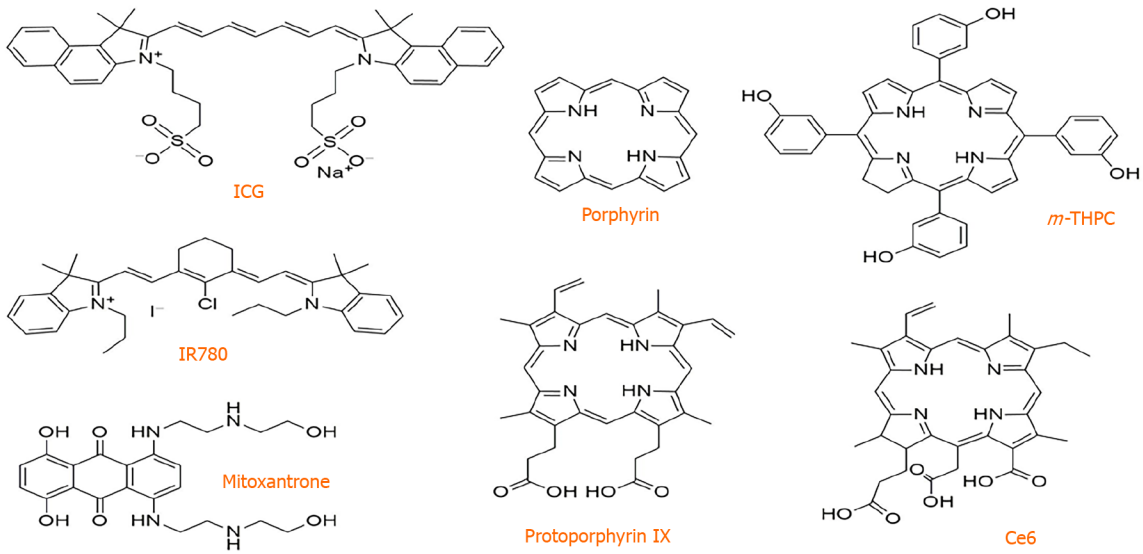

Figure 1 Chemical structures of common traditional photosensitizers for hepatocellular carcinoma in previous literatures.

and concentration-dependent cell death. Specifically, the high PDT intensity resulted in direct cell necrosis, while the mitochondria-apoptosis pathway was triggered under low PDT intensity. These results suggest that the targeted NPs loaded with AIE PSs are promising image-guided PDT agents in HCC treatment.

LIMITATIONS AND PERSPECTIVE

In recent years, numerous clinical trials have been registered of PDT for many types of tumors, but there are scarcely any trials on HCC. Therefore, some critical problems need to be conquered before further clinical practice of PDT for HCC can be realized (Figure 2). First, one major drawback of the currently available PDT is its low tissue penetration depth of light irradiation caused by the short-wavelength absorption of most PSs, which limits their clinical application[46]. The use of a self-illuminating system as a light source provides an intriguing solution to the light penetration issues of conventional PDT[110]. Some self-illuminating systems, including chemiluminescence[111] and bioluminescence[112], are promising candidates as internal light sources for PDT. These self-illuminators are small in size (ranging from the atomic/molecular to the nanometer scale) and thus can be delivered to any pathological tissue[113]. In addition, X-PDT exploits a nanoscale scintillator to down-convert external X-ray photons to visible light photons, and then the latter in turn activates nearby PSs to trigger PDT. Therefore, X-rays afford superior tissue penetration and can overcome this limitation of PDT[114,115]. Recently, Liu and her colleagues[116] developed a novel X-PDT system, taking advantage of an AIE PS with bright fluorescence and highly efficient $^1O_2$ generation in the aggregated state. Based on the high penetration of X-ray irradiation, this system could use ionizing irradiation to trigger localized PDT, indicating that effective ·OH and SO generation was induced *via* radiosensitization-mediated energy transfer from X-rays to the AIE PS and then realized marked killing of cancer cells. This pioneering exploration revealed the great potential of AIE PSs in novel X-PDT systems to overcome the drawback of light irradiation penetration.

Second, another critical limiting factor of conventional cancer PDT is the lack of specificity of PSs. Moreover, most PSs accumulate in normal and cancer tissues indiscriminately. This performance leads to both significantly important side effects and decreased therapeutic efficacy[117,118]. Due to these obstacles, many studies have focused on the development of strategies to deliver effective therapeutic concentrations of PSs and anti-cancer agents specifically to the tumor, thereby increasing their therapeutic efficacy while reducing toxicity[99,118]. Therefore, targeted delivery of phototherapeutics, such as NP-mediated targeted drug delivery systems, is promising to minimize drug toxicity to healthy tissues through both target-specific drug delivery and by precisely controlling phototherapy-initiating external light sources[99,119,120].

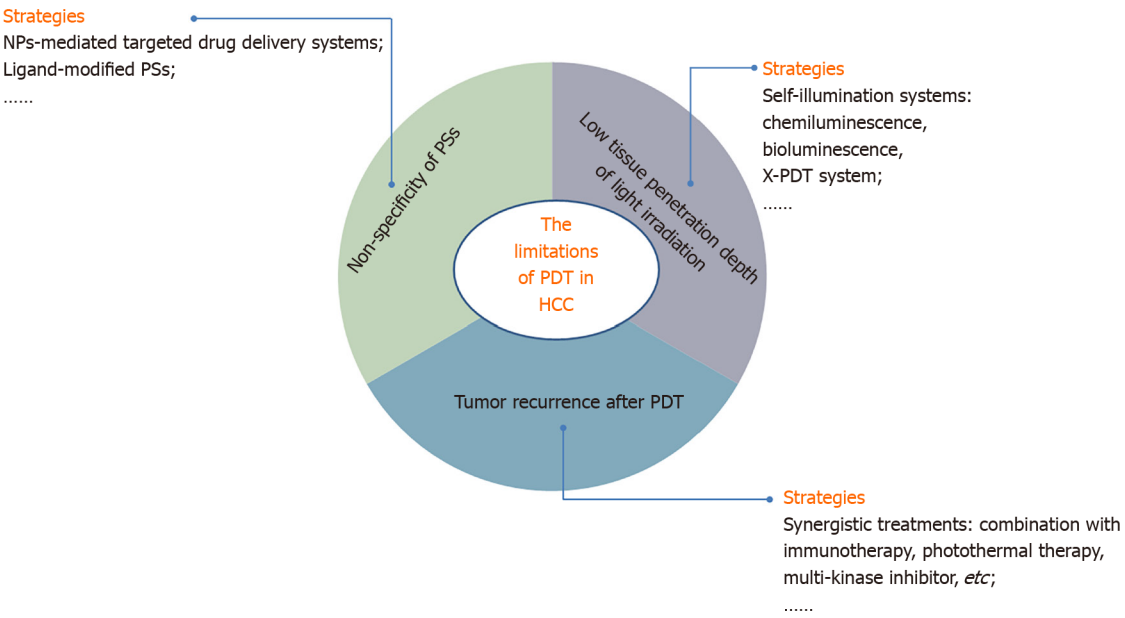

Figure 2 The limitations of photodynamic therapy in clinical practice for hepatocellular carcinoma and potential strategies to overcome the obstacles in further research.

Finally, the hypoxic microenvironment induced by PDT could secondarily accelerate the upregulation of angiogenic factors, such as hypoxia-inducible factor 1 and VEGF, and if the tumor cells are not killed completely under low light intensity, revascularization in tumor foci can be promoted, triggering the activation of signaling pathways for tumor recurrence[121,122]. Therefore, multiple combination regimens in the treatment of HCC, including immunotherapy, PDT/photothermal therapy, multikinase inhibitors and anti-VEGF agents, have attracted focus in recent years [123]. Combination therapies will hopefully increase objective responses and overall survival, contributing to the synergistic treatment of PDT and other anti-HCC therapies[124]. The multitude of available complementary and additive treatment modalities should encourage clinicians to implement a multidisciplinary treatment approach to improve the outcome in HCC patients[125].

CONCLUSION

The application of PDT in HCC has been limited due to its low tissue penetration depth of light irradiation, reduced generation of ROS, nontargeted accumulation in cancer cells, and tumor recurrence after PDT. There are several potential strategies to overcome these limitations, such as creating self-illuminating systems, NP-mediated targeted drug delivery systems, and synergistic treatments. Once these problems are resolved, PDT will be a promising alternative treatment strategy for HCC.

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2021 December 27; 13(12): 1536-1549

DOI: 10.4240/wjgs.v13.i12.1536

ISSN 1948-9366 (online)

REVIEW

Role of mesenteric component in Crohn's disease: A friend or foe?

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Author contributions: Yin Y and Zhu ZX contributed equally to this work; Yin Y and Zhu ZX designed and wrote the final version of the manuscript; Li Z and Chen YS were critical for the acquisition of data and drafting the manuscript; Zhu WM made critical revisions to the design and gave final approval for the article to be submitted.

Conflict-of-interest statement: All authors declare no conflicts of interest for this article.

Country/Territory of origin: China

Specialty type: Pathology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

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Abstract

Crohn's disease (CD) is a complex and relapsing gastrointestinal disease with mesenteric alterations. The mesenteric neural, vascular, and endocrine systems actively take part in the gut dysbiosis-adaptive immunity-mesentery-body axis, and this axis has been proven to be bidirectional. The abnormalities of morphology and function of the mesenteric component are associated with intestinal inflammation and disease progress of CD *via* responses to afferent signals, neuropeptides, lymphatic drainage, adipokines, and functional cytokines. The hypertrophy of mesenteric adipose tissue plays important roles in the pathogenesis of CD by secreting large amounts of adipokines and representing a rich source of proinflammatory or profibrotic cytokines. The vascular alteration, including angiogenesis and lymphangiogenesis, is concomitant in the disease course of CD. Of note, the enlarged and obstructed lymphatic vessels, which have been described in CD patients, are likely related to the early onset submucosa edema and being a cause of CD. The function of mesenteric lymphatics is influenced by endocrine of mesenteric nerves and adipocytes. Meanwhile, the structure of the mesenteric lymphatic vessels in hypertrophic mesenteric adipose tissue is mispatterned and ruptured, which can lead to lymph leakage. Leaky lymph factors can in turn stimulate adipose tissue to proliferate and effectively elicit an immune response. The identification of the role of mesentery and the crosstalk between mesenteric tissues in intestinal inflammation may shed light on understanding the underlying mechanism of CD and help explore new therapeutic targets.

Key Words: Crohn's disease; Mesenteric nerves; Angiogenesis; Lymphatic drainage; Mesenteric adipose tissue

Received: January 29, 2021
Peer-review started: January 29, 2021
First decision: July 29, 2021
Revised: August 1, 2021
Accepted: November 25, 2021
Article in press: November 25, 2021
Published online: December 27, 2021

P-Reviewer: Fonseca-Alves CE
S-Editor: Ma YJ
L-Editor: Filipodia
P-Editor: Ma YJ

Core Tip: Crohn's disease (CD) is a complex autoimmune disease with increasing incidence worldwide, especially in Asian countries in recent years. There has been excellent progress in understanding the role of the mesentery in the pathogenesis and disease progress of CD. The crosstalk between components and intestinal inflammation has aroused many researchers' interests. Herein, we will discuss the basic function and the alteration under inflammatory state of mesenteric nerves, blood vessels, lymphatics, and fat mass. Existing therapeutic strategies associated with mesentery components will also be summarized.

Citation: Yin Y, Zhu ZX, Li Z, Chen YS, Zhu WM. Role of mesenteric component in Crohn's disease: A friend or foe? *World J Gastrointest Surg* 2021; 13(12): 1536-1549
URL: https://www.wjgnet.com/1948-9366/full/v13/i12/1536.htm
DOI: https://dx.doi.org/10.4240/wjgs.v13.i12.1536

INTRODUCTION

Crohn's disease (CD) is a chronic relapsing autoimmune disease that can affect the entire gastrointestinal tract and is mainly characterized by segmental intestinal inflammation[1]. The mesentery is now well recognized as the collection of tissues that maintains all abdominal digestive organs in position and in continuity with other systems. The mesentery is made up of adipose tissue, a connective tissue matrix, nerve tissue, lymphatics, blood vessels, and immune cells[2-4]. The macroscopic lesions of mesentery including thickening, stiff, and hypertrophy are hallmarks of CD[5,6]. The histopathological findings of the mesentery from patients with CD demonstrates fibrosis, dilated lymphatic vessels (LV), perivascular inflammation, perineuronal chronic inflammation, and small-sized adipocytes[7,8]. However, the role and the involvement of the mesentery in the pathogenesis and clinical course of CD is still unclear and controversial. Some research points to the mesentery as a protective organ, able to mount a controlled inflammatory response following abnormal intestinal bacterial translocation[9,10]. On the opposing side, there is evidence suggesting that the participation and involvement of the mesentery in the setting of CD is negative, fueling the pathogenesis of the disease[11]. This review aims to describe the role of mesenteric nerves, lymphatics, blood vessels, and adipose tissue in the systemic and local inflammation in CD. Recent studies and progress on this topic will be reviewed to investigate the relationship between the mesentery and disease course of CD and the potential therapeutic target for CD treatment.

NERVES

There have been several studies indicating the involvement of the neuroendocrine and enteric nervous system in CD[12]. However, the role of mesenteric nerves in the pathogenesis and prognosis of CD is still unclear. In fact, as a vital part of the brain-gut axis, the mesenteric nerves provide a physiological link between the central nerve system and gastrointestinal tract[13]. Based on anatomical considerations, the mesenteric nerves include the vagal and sympathetic nerves. The vagus nerve (VN) is the main component of the parasympathetic nerve system, which is composed of afferent and efferent fibers[14]. Peripheral sensations can be integrated into the central autonomic network *via* vagal afferents, and then the efferent response of the VN is able to modulate gastrointestinal nociception and inflammation[15]. The sympathetic nerve enters the intestinal tract along with the artery and terminates in the enteric nervous system, innervating the intestinal layers and intestinal associated lymphoid tissue[16,17].

Previous studies have confirmed that vagal and sympathetic nerves play an important role in regulating inflammation[18]. In trinitrobenzene sulfonic acid–induced colitis and acetic acid-induced colitis mice models, hyperexcitable visceromotor neurons were observed in the inferior mesenteric ganglia[19]. A recent animal experiment also confirmed that vagotomy increased the susceptibility to colitis in mice, mainly by inhibiting the alpha7 nicotinic acetylcholine receptors-mediated cholinergic anti-inflammatory pathway[20], whereas treatment with nicotine (alpha7

nicotinic acetylcholine receptors agonist) and galantamine (cholinesterase inhibitors) was shown to reverse the severity of colitis induced by dextran sulfate sodium[21,22]. In addition, another study found that vagal innervation was involved in the formation of tertiary lymphoid tissue in colitis, which is lymphoid tissue that forms as a result of chronic inflammation in a tissue or organ[23]. Unfortunately, the role of this lymphoid tissue in inflammatory bowel disease (IBD) remains unclear. Similarly, sympathectomy aggravated colitis (induced by dextran sulfate sodium or *via* T cell transfer) in mice. It was also observed in this experiment that intestine-specific vagal nerve denervation had no effect in dextran sulfate sodium-induced colitis[24]. Meanwhile, some researchers proved that the sympathetic nerve played a pivotal role in inhibiting innate immune cells against microorganism, likely *via* the adrenergic β2 receptor[25], which not only inhibited the secretion of tumor necrosis factor alpha (TNFα) but also drove rapid interleukin (IL)-10 secretion from innate cells[26]. In addition, several studies have shown that anxiety and depression can interact with intestinal inflammation through the bidirectionality of the brain-gut axis in patients with IBD[27]. The positive implementation of psychological intervention in patients with CD can alleviate the changes of their condition[28]. Therefore, we have reasons to believe that the pathogenesis of CD is closely related to the changes of mesenteric nerves.

Indeed, the tone of the vagus system is altered in patients with CD[29]. A matched cohort study for nearly 60 years found a positive correlation between vagotomy and IBD, especially in CD patients, which indirectly highlighted the beneficial role of vagal tone in intestinal inflammation[30]. A study has also confirmed that the sympathetic innervation of intestinal mucosa and the catecholamine neurotransmitters released by sympathetic nerve in CD patients decreased[31]. Interestingly, as a form of IBD, ulcerative colitis (UC) was not associated with the loss of sympathetic nerve fibers. By contrast, increased density of the sympathetic nerve network was found in UC patients[32]. Thus, the underlying mechanism of CD and UC seems different in intestinal immunity regulated by sympathetic nerves. Based on these studies, a research group conducting a clinical trial of VN stimulation in patients with active CD reported clinical, biological, and endoscopic remission in 5 of 7 patients treated with VN stimulation and restored vagal tone[33].

In summary, the mesenteric nerves have been proven to be involved in the bidirectional regulation of inflammation and emotion of the brain-gut axis and in the pathogenesis of CD. The clinical trials with VN stimulation intervention provide a neotarget for CD treatment. Meanwhile, drugs targeting neurotransmitter receptors also seem promising and worth exploring. Anti-depression treatment helps decrease the mesenteric afferent nerve activity and further ameliorates intestinal inflammation, which can be a potential therapeutic target for CD treatment.

BLOOD VESSELS

The abnormality of mesenteric blood supply in CD has been confirmed, although the underlying mechanism is not well clarified. Histopathological features of injured blood vessels, including vascular injury, focal arteritis, fibrin deposition, arterial occlusion, and even granulomatous vasculitis, are observed in diseased segment in CD [34,35]. Meanwhile, the microvascular dysfunction was found to be correlated with disease activity and relapse of CD[36,37]. Radiological evidence of mesenteric hypervascularity (also known as the "comb sign") coupled with radiological evidence of nodal enlargement is associated with endoscopic evidence of mucosal ulceration [38]. The association between splanchnic hemodynamics and disease activity of CD has also been investigated by Doppler sonography[39]. Of note, the superior mesenteric artery flow has been accessed for Crohn's ileitis diagnosis and for disease activity monitoring[40,41]. The velocity of blood flow in the superior mesenteric artery was markedly higher in CD patients compared to controls. By contrast, the resistance index of the superior mesenteric artery was lower in active CD than controls[42,43]. The cumulative clinical evidence suggests that the function of vasculature is altered in CD.

Angiogenesis is an important component of CD pathogenesis. Molecular studies have confirmed that angiogenesis is crucial to inflammation and is associated with activation and proliferation of endothelial cells and capillary and venule remodeling, resulting in an expansion of the tissue microvascular bed[44-46]. A potential consequence of this expansion is notable promotion of inflammation through various cytokines, chemokines, and matrix metalloproteinases[47,48]. The involvement of hypoxia inducible factor (HIF) has been extensively studied. Increased expression of

HIF-1 and HIF-2 has been detected in inflamed tissue of IBD patients[49]. Importantly, HIF stimulates angiogenesis *via* vascular endothelial growth factor (VEGF) induction [50]. Of note, VEGF-A is markedly increased in the tissue and serum of patients with CD[51-53] and is implicated in angiogenesis in experimental colitis[54]. The importance of the VEGF family proteins in the pathogenesis and disease course of IBD has also been demonstrated in studies assessing the efficacy of different therapeutic regimens for IBD. Recently, Algaba *et al*[55] found that circulating levels of VEGF-A significantly decreased after anti-TNF-α therapy and that elevated VEGF-A levels at baseline might predict a poor response to TNF-α inhibitors.

Endothelial cell adhesion molecules also play an important role in vascular proliferation through recruitment of inflammatory cells to the site of inflamed intestine. The activated vascular endothelial cells express several cell adhesion molecules, which are essential for the regulation of leukocyte trafficking and migration[56]. Three main families of cell adhesion molecules and their ligands (selectins, integrins, and immunoglobulin superfamily) are engaged in the process. The binding of the integrins α4β7 and α4β1 on leukocytes to their ligands on the endothelial cells, mucosal addressin cell adhesion molecule-1 (MadCAM-1) and vascular CAM-1, seem to be one of the most important interaction[57]. Previous studies have proved that mucosal addressin CAM-1 is overexpressed on intestinal high endothelial venules during active IBD, which promotes homing and tethering of inflammatory cells[57,58]. Anti-integrin therapeutics, including gut-selective antibodies against the β7 integrin subunit (etrolizumab) and the α4β7 integrin heterodimer (vedolizumab and abrilumab), the non-gut selective anti-α4 integrin (natalizumab), as well as small molecules (AJM300) were developed for IBD treatment. Among which, vedolizumab and etrolizumab demonstrate similar inhibition of dynamic adhesion of lymphocytes from IBD patients to mucosal addressin CAM-1.

The abnormal upregulation of endothelial cell adhesion molecules and increased adhesion of leukocytes likely result in coagulation abnormalities. In fact, CD patients are at high risk of developing mesenteric thrombosis[59,60]. Among patients with CD, mesenteric venous thrombosis is associated with bowel stenosis and CD-related intestinal surgery[60]. Purposed risk factors also include the use of conjugated estrogens, surgery-associated trauma, intestinal stricture, pregnancy, and history of blood clot[61]. As aforementioned, anti-adhesion molecule therapy, which deters leukocyte recruitment, has been shown to be effective in the treatment of CD. The clinical evidence has confirmed angiogenesis as a component of CD[62] and angiogenesis blockade as a new therapeutic approach to experimental colitis[63].

LYMPHATICS

Although the pathophysiology of CD remains unknown, the involvement of the lymphatic system in CD has long been suggested. Abnormal lymphatics, such as lymphangiogenesis and enlarged and obstructed LVs, has been described in CD patients and is likely related to early onset submucosa edema (Figure 1)[64]. It is reported that intestinal granulomas[65], granulomas in the mesenteric lymph nodes, decreased intestinal, and mesenteric LV density[66] are associated with the postoperative recurrence of CD.

Lymph flow plays an important role in transporting antigens, dendritic cells, and macrophages[67,68]. Many studies have reported that lymphatic dysfunction can lead to immunosuppression[69,70]. It is believed that lymph flow is enhanced during an inflammatory state. However, inflammation may in turn impair lymphatic pumping with lymphatic obstruction and impaired lymphatic contraction, leading to a poor drainage of interstitial fluid[71,72]. It is well-known that inflammatory mediators, such as prostaglandins and cytokines, can increase vascular permeability, causing submucosal edema. These inflammatory mediators play a potential role in altering LV contractions and lymph flow during their transport from inflammatory tissues to draining lymph nodes, impairing immune response[72]. Rahier *et al*[73] reported that the LV density increased in inflammatory bowel disease. One possible reason for the lymphangiogenesis may be contributing to improved lymphatic drainage in response to mesenteric lymphatic obstruction, marked lacteal dilatation, and extensive submucosal edema[72].

The molecular underlying mechanism of lymphangiogenesis in CD patients remains largely unknown. Many factors are involved in lymphangiogenesis, such as members of the VEGF family, hepatocyte growth factor, insulin-like growth factor-2, platelet-derived growth factor-BB, and fibroblast growth factor-2[74-77]. VEGF-C and VEGF-D

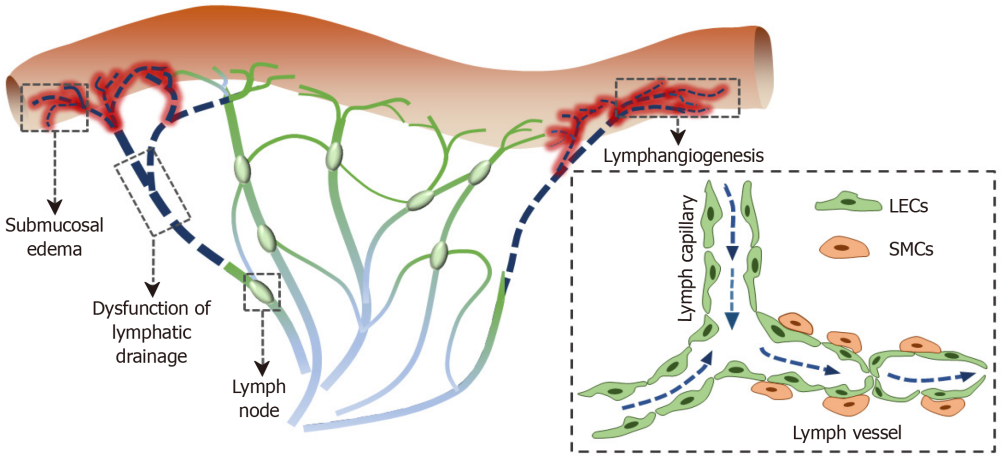

Figure 1 Alteration of both structures and functions of mesenteric lymphatic vessels aggravates intestinal inflammation in Crohn's disease. LECs: Lymphatic epithelial cells; SMCs: Smooth muscle cells.

are members of the VEGF family, which mediate lymphangiogenesis *via* their receptor VEGFR3[78]. The blockade of the VEGFR3 signaling pathway can suppress lymphangiogenesis and further aggravate intestinal inflammation. Of note, lymphangiogenic factor VEGF-C has shown promising therapeutic effects in experimental colitis, both clinically and histologically[79]. These studies suggest that mesenteric lymphatics may be a promising potential target for CD treatment. Recently, we found that intestinal inflammation was significantly improved by the application of lymphatics-targeting drug release in the IL-10$^{-/-}$ spontaneous experimental colitis, suggesting that mesenteric LVs are potential targets for CD treatment[80].

The lymphoid aggregates resembling tertiary lymphoid organs, composed of CD3^{+} T cells surrounding CD20^{+} B cell clusters, have been observed in the mesentery of CD patients[81-83]. Guedj *et al*[81] recently proposed a notion that mesenteric adipose cells can participate in the process of tertiary lymphoid organ formation in the creeping fat of CD-affected mesentery. In addition, lymphoid cells invade the LV wall in CD-affected mesentery, suggesting the involvement of tertiary lymphoid organs in the lymphatic remodeling[82]. The lymphatic remodeling includes lymphangiogenesis, LV dilation, and lymph leakage. Interestingly, the lymph leakage in surrounding mesenteric adipose tissue can stimulate the growth of adipose tissue. The leaky antigens, lipids, and cytokines released from adipose cells can effectively promote immune response[84].

As described above, increased LV density in the intestinal wall has been found in CD patients. Recently, a study has found that decreased LV density in intestinal mucosa is associated with higher risk of endoscopic recurrence after surgical intervention[85], suggesting that increased LV density may contribute to reduced recurrence of CD, which was consistent with the notion that increased lymphangiogenesis could be a compensatory response to lymphatic dysfunction. By contrast, the results reported by Li *et al*[66] showed that increased mesenteric LV density in the proximal margin was associated with higher risk of early clinical recurrence after surgery in CD patients. One possible reason for the difference is that the locations of the LV densities were different.

Granulomas are observed only in some patients with CD (less than 13%), and they are associated with a more aggressive disease phenotype of CD[86]. In this case, patients with granulomas, who have undergone surgery for CD, have a higher risk for reoperation[86]. Of note, Li *et al*[87] reported that the presence of granulomas in mesenteric lymph nodes instead of the granulomas in the intestine is an independent risk factor for postoperative recurrence in CD patients. In conclusion, accumulating studies have demonstrated the involvement of the lymphatic system in CD. Although the underlying mechanism of the alterations of mesenteric lymphatics is not well clarified, promoting lymphatic function in CD patients could improve prognosis.

ADIPOSE TISSUE

Mesenteric adipose tissue hypertrophy is regarded as a feature of CD and was firstly

reported by Dr. Burrill B. Crohn himself to be a consistent symptom of the disease[8]. The pathologically altered mesenteric fat tissue is called "creeping fat," defined as expansion of mesenteric adipose tissue around the inflamed and fibrotic intestine (Figure 2)[5]. The creeping fat takes place at the mesenteric transition zone, where the intestinal wall and mucosa change synchronizing with the mesentery[88]. Additionally, creeping fat has been used as an anatomical marker for surgeons to determine the margin of resection during surgery[89]. Meanwhile, a number of studies revealed that creeping fat might play an important role in the pathogenesis of CD, by secreting large amounts of adipokines and representing a rich source of TNF, IL-6, IL-10, and other proinflammatory or profibrotic cytokines[90].

It has been demonstrated that adipokines are strongly associated with severity of intestinal inflammation. However, their exact role in the pathogenesis and disease course of IBD has not been concluded. Herein, we are discussing three important adipokines (adiponectin, leptin, and apelin) and their roles in the crosstalk with intestinal inflammation.

Adiponectin is a well-explored adipokine and plays a key role in regulating insulin sensitivity[91]. According to previous studies, adiponectin is markedly upregulated in the creeping fat of CD compared to the non-creeping fat of CD, UC, and healthy controls[92]. Its molecular architecture is strikingly similar to that of TNF-α in the terminal structure of the globular domain, despite lacking homology in the primary sequence[93]. Therefore, adiponectin presents an anti-inflammatory effect based on the antagonistic effect of TNF-α[94]. On the other hand, it is demonstrated that adiponectin inhibits the expression of adhesion molecules, metalloproteinases, and proinflammatory mediators[95].

Leptin is mainly secreted by white adipose tissue and regulates the differentiation, function, and metabolism of a variety of immune cell subpopulations and intestinal epithelial cells[96-98]. Previous studies described that leptin expression was upregulated in the mesenteric tissue of CD patients[99]. It has been shown that leptin modulates intestinal inflammation in experimental colitis[100]. Moreover, several studies have demonstrated that leptin deficiency and the pharmacologic blockade of the leptin receptor notably ameliorate colitis[101]. Leptin promotes T cell proliferation, resulting in an increased production of type 1 T helper cell-related cytokines[98]. A recent study revealed that leptin was crucial to human immune homeostasis and contributed to autoimmunity in a TNFα-dependent manner[102].

Apelin induces proliferation of intestinal epithelial cells[103]. Meanwhile, it was revealed that apelin plays a significant role in the development and stabilization of LVs[104,105]. Ge *et al*[106] reported that apelin was highly expressed in the mesenteric fat and in colon tissues of CD patients, which strongly suggested that apelin may ameliorate intestinal inflammation by enhancing lymphatic drainage. Han *et al*[103] indicated that the intraperitoneal injection of apelin-13 decreased mucosal inflammation, inhibited the infiltration of inflammatory cells, and decreased expression of proinflammatory cytokine mRNA levels in the murine colonic tissue. Exogenous apelin can also enhance tissue repair by increasing the colonic epithelial cell proliferation[103].

As aforementioned, leptin promotes the M2 macrophage subtype and subsequently enhances fibrosis by secreting large amounts of profibrotic factors such as tumor growth factor-β[107,108]. Meanwhile, Rieder *et al*[109] observed that creeping fat derived mediators such as free fatty acids (FFAs), induced a differential and selective proliferative response by human intestinal fibroblast and human intestinal muscle cells. FFA can promote the proliferation of human intestinal muscle cells and human intestinal fibroblasts rather than increase the proliferation of epithelial cells, endothelial cells, or adipocytes. This suggests that the proliferation induced by FFAs is intestinal mesenchymal cell specific. The proliferation induced by long-chain FFAs is dependent on the kinases p38 mitogen-activated protein kinase, protein kinase C, and phosphoinositide 3-kinase[109]. These studies suggest that creeping fat correlates with the stricture formation.

Bacteria translocate from the intestine to the mesentery through transmural inflammation in CD, largely resulting from impaired epithelial integrity[110]. Adipocytes and pre-adipocytes in the mesenteric fat express functional pattern recognition receptors, such as toll-like receptors and nucleotide oligomerization domain receptor-1 [111-114]. These receptors respond to the translocated bacteria by sensing microbe-derived molecules[10]. The downstream signaling cascade leads to activation of transcription factors (such as nuclear factor-κB) and induction of proinflammatory cytokines and chemokines[115]. Moreover, pre-adipocytes can differentiate into macrophages and then modulate the inflammatory reaction, including phagocytic activity and proinflammatory cytokine release[116].

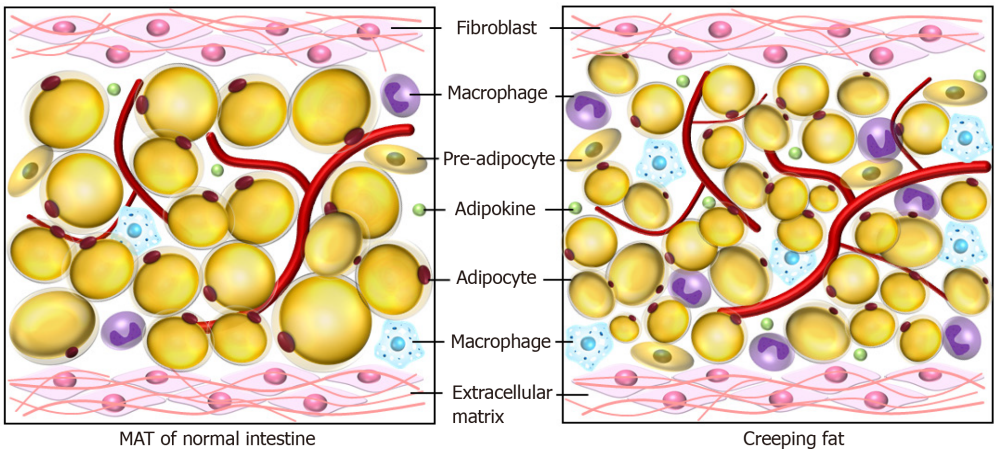

Figure 2 The creeping fat with small-size adipocytes within is a main source of proinflammatory mediators and adipokines. MAT: Mesenteric adipose tissue.

It is revealed the visceral adipose tissue presents a microbiome signature enriched in Proteobacteria of patients with CD[117]. Meanwhile, the abundance of bacteria in visceral adipose tissue can be altered with the clinical status of CD patients. Patients with active CD showed a higher abundance of common mucosal bacteria (*i.e.* Bacteroidetes). Additionally, the formation of creeping fat is associated with translocation of gut bacteria[118]. The creeping fat seems to be a protective response to prevent systemic dissemination of potentially harmful bacterial antigens. The crosstalk between mesentery adipose tissue and microbiota needs further investigation, and the results may provide a new perspective for the management of CD patients.

CROSSTALK BETWEEN MESENTERIC TISSUES

Mesenteric nerves, blood vessels, lymphatics, and adipose tissue are not only associated with intestinal inflammation but also influence other parts of the mesentery [70,119]. The function of mesenteric lymphatics is influenced by endocrine of mesenteric nerves and adipocytes. Nerve fibers around submucosal arteries and mesenteric LVs markedly increase in CD patients, suggesting that neurogenic inflammation is likely associated with early onset lymphatic vascular dilation and submucosa edema. Meanwhile, the structure of the mesenteric LV in hypertrophic mesenteric adipose tissue is mispatterned and ruptured, which can lead to lymph leakage. Leaky lymph factors stimulate adipose tissue to proliferate and effectively elicit an immune response. LVs mediate lipid absorption and transport, share an intimate spatial association with adipose tissue, and regulate the traffic of immune cells[120,121]. Adipokines such as apelin can in turn ameliorate chronic colitis in IL-10$^{-/-}$ mice by promoting intestinal lymphatic function[106]. The neuropeptides, such as vasoactive intestinal peptide, alter lymphatic pumping by decreasing the frequency of lymphatic contractions and hyperpolarizing the lymphatic muscle membrane potential in a concentration-dependent manner[122]. The complex crosstalk between mesenteric nerves, blood vessels, lymphatics, and adipose tissue suggests dysregulation of mesenteric homeostasis in patients with CD. The interaction is likely to play a role in the pathogenesis and disease course of inflammation and remodeling in mesenteric adipose tissue in CD.

CONCLUSION

Accumulating evidence has shown that mesenteric organs including mesenteric nerves, blood vessels, lymphatics, and adipose tissue play a crucial role in the pathogenesis and progress of CD. Existing and emerging clinical evidence strongly suggests that the gut-mesentery axis is bidirectional. The intestinal inflammation and the dysregulation of the crosstalk among mesenteric components interact with each other and contribute to disease aggravation. The mesenteric inflammation may be an independent clinical risk factor associated with surgical outcomes. Recently, Coffey *et*

al[88] reported that inclusion of the mesentery in ileocolic resection for CD is associated with reduced recurrence requiring reoperation, which suggests a more radical resection of mesenteric tissue along with the diseased bowel leads to better surgical outcomes, especially postoperative disease recurrence.

The evaluation of changes in morphology and function of mesenteric nerves, vasculature, lymphatics, and fat mass provide more potential targets for CD treatment. Our group has shown that apelin can ameliorate chronic colitis in Il-10$^{-/-}$ mice by promoting intestinal lymphatic functions[106]. Moreover, a chylomicrons-simulating strategy has been developed, fulfilling sustained drug release in mesenteric lymphatics and enhancing the therapeutic effect on intestinal inflammation by increasing lymphatic drainage[80]. We do believe that more and more agents and strategies targeting mesenteric content will be developed and bring more alternative therapies for CD patients. Mucosal healing has been emphasized as the current dominant standard for disease remission, whereas the changes in morphology and function of mesenteric nerves, vasculature, lymphatics, and adipose tissue can also be monitored during treatment. The improvement or resolution of inflammation of the submucosa, regulation of angiogenesis, enhancement of lymphatic drainage, and amelioration of adipose tissue-associated inflammation could be the next therapeutic goals for CD patients.

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2021 December 27; 13(12): 1550-1566

DOI: 10.4240/wjgs.v13.i12.1550

ISSN 1948-9366 (online)

REVIEW

Neoadjuvant treatment strategies for hepatocellular carcinoma

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Author contributions: Xu L wrote the paper; Chen L revised the manuscript; Zhang W proposed the topic and finalized this review.

Conflict-of-interest statement: The authors declare no conflicts of interest for this article.

Supported by National Natural Science Foundation of China, No. 81860117.

Country/Territory of origin: China

Specialty type: Oncology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

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Abstract

The incidence of hepatocellular carcinoma (HCC) remains high globally. Surgical treatment is the best treatment for improving the prognosis of patients with HCC. Neoadjuvant therapy plays a key role in preventing tumor progression and even downstaging HCC. The liver transplantation rate and resectability rate have increased for neoadjuvant therapy. Neoadjuvant therapy is effective in different stages of HCC. In this review, we summarized the definition, methods, effects, indications and contraindications of neoadjuvant therapy in HCC, which have significance for guiding treatment.

Key Words: Hepatocellular carcinoma; Neoadjuvant therapy; Prognosis; Indications; Contraindications

Core Tip: Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in the world. A considerable number of patients cannot receive radical therapy due to advanced HCC at the first diagnosis, leading to a poor prognosis. Neoadjuvant treatment enables more patients with HCC inside or outside the Milan criteria to receive surgical treatment, such as partial liver resection and liver transplantation. In this study, we reviewed the current status of neoadjuvant therapy in HCC.

Citation: Xu L, Chen L, Zhang W. Neoadjuvant treatment strategies for hepatocellular carcinoma. *World J Gastrointest Surg* 2021; 13(12): 1550-1566
URL: https://www.wjgnet.com/1948-9366/full/v13/i12/1550.htm
DOI: https://dx.doi.org/10.4240/wjgs.v13.i12.1550

Received: April 19, 2021
Peer-review started: April 19, 2021
First decision: June 13, 2021
Revised: June 27, 2021
Accepted: November 30, 2021
Article in press: November 30, 2021
Published online: December 27, 2021

P-Reviewer: Boninsegna E, Gupta P
S-Editor: Wang JL
L-Editor: Filipodia
P-Editor: Wang JL

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide [1]. The incidence and mortality of HCC are still increasing in most parts of the world, including China[2]. Viral hepatitis B is the main risk factor for HCC in East Asia and Africa, while nonalcoholic fatty liver disease is becoming an important risk factor in developed countries[1,3,4]. For patients with HCC with surgical indications, surgery [liver resection (LR) and liver transplantation (LT)] is the best treatment for improving their prognosis, with a 5-year survival rate of 60%-80%[5]. However, many patients are beyond the indications for surgery due to advanced tumor stage or severe liver disease at the time of diagnosis, leading to a median overall survival between 3 and 26 mo[6, 7].

Neoadjuvant therapy is a new concept of multidisciplinary treatment for malignancies to prevent tumor progression and even downstage solid tumors in recent years[8]. Neoadjuvant therapies for HCC include transcatheter embolization (TACE), radiotherapy, ablation therapy, chemotherapy, targeted therapy and immunotherapy [9]. LT is the optimal treatment for HCC and liver cirrhosis, but many patients with HCC outside the Milan criteria are not suitable candidates for LT[10]. With neoadjuvant therapy, the success rate in downstaging HCC within the Milan criteria can be more than 60% in selected patients[11]. Some clinical studies have confirmed that patients who underwent LT after successful downstaging treatment can achieve prognosis similar to that of patients who received LT without downstaging treatment [12-14]. In the same way, patients with initial unresectable HCC could also receive LR once the lesions were well controlled by neoadjuvant therapy[15]. However, the indications, side effects and effect on the long-term prognosis of neoadjuvant therapy in HCC are still controversial. In this article, we reviewed the clinical application of neoadjuvant therapy in HCC, including clinical indications, evaluation of efficacy, adverse events and effects on prognosis.

WHAT IS NEOADJUVANT THERAPY FOR HCC?

Over the past decade, the overall survival rate of patients who underwent LT has continued to rise. Due to the shortage of livers for transplantation (even patients with HCC within the Milan criteria need to wait for liver donors), the dropout rate during the waiting period remains high[16]. Increasing tumor burden during the waiting period is also detrimental to survival after transplantation. In addition, one of the major factors for the poor prognosis of patients with HCC is the low resectability rate, which is only approximately 20%[17]. How to slow the progression of tumors before surgical treatment and lower the tumor stage to surgical indications is the focus of oncologists and surgeons, and this is the significance of neoadjuvant therapy for HCC.

When defining neoadjuvant therapy, we have to distinguish between bridging, downstaging and conversion therapy and clarify the difference between neoadjuvant therapy and adjuvant therapy. Neoadjuvant therapy refers to local or systemic treatment applied before surgical treatment for malignant tumors, and there are four purposes of neoadjuvant therapy for HCC.

The first point is to prevent patients from dropping out due to tumor progression during the waiting period, ensuring that the patients meet the indications for LT. This is the so-called bridging therapy[18]. In an observational study, up to 8.2% of patients with T1 stage and 13.5% of patients with T2 stage who initially had operable HCC were not candidates for LT due to tumor progression while waiting for the 6th mo without intervention[19]. Alpha fetoprotein ≥ 500 ng/mL on the first diagnosis of T1 stage HCC and rapid tumor progression were risk factors for dropping out during the waiting period for LT[20], which suggests that the bridging effect of neoadjuvant therapy is critical. Bridging therapy can reduce the dropout rate to 0%-10% in candidates for LT with HCC meeting the Milan criteria[21]. One of the focuses of oncology surgery is whether patients with HCC within the Milan criteria should undergo direct radical resection if a long waiting period for a donor liver is required, but no clinical studies have yet confirmed this.

The second point is to shrink or reduce tumors outside the Milan criteria to meet the indications for LT[22]. This is the definition of downstage treatment. The expected 5-year survival rate of patients with HCC within the Milan criteria receiving LT was approximately 65%-80%, which was far higher than those outside the Milan criteria [23]. In all, 25%-70% of patients with HCC outside the Milan criteria achieve tumor downstaging after receiving neoadjuvant therapy; they received LT and achieved

comparable prognosis to those who underwent initial LT[24] (Table 1). A meta-analysis also confirmed this conclusion[25]. Patients with T3 stage HCC who received neoadjuvant therapy before LT had significantly improved prognosis compared with patients who did not. However, patients with T1 and T2 stage HCC showed no difference[26]. Even patients who have failed downstaging can achieve better prognosis than those without neoadjuvant therapy (median overall survival: 10.3 mo *vs* 4.0 mo)[27]. Patients with ruptured advanced HCC may also be candidates for LT after successful downstaging, with a significantly improved prognosis compared with nonsurgical treatment[28]. This confirmed the efficacy and broad applicability of neoadjuvant therapy. Several clinical studies have shown similar outcomes for patients who received neoadjuvant therapy and those who did not[29-31], which was related to the patients enrolled in the studies. Although some studies have suggested that neoadjuvant therapy may increase the risk of recurrence after LT, the prognosis of patients with advanced HCC is encouraging enough[32].

The third point is to increase the LR rate of HCC through neoadjuvant therapy and convert unresectable HCCs into resectable tumors[33]. Conversion therapy can be performed to increase future liver volume and reduce tumor stage[34]. In this case, more patients would have the opportunity to receive salvage LR. A meta-analysis suggested that the prognosis of patients with extensive HCC after hepatectomy was poorer than that of patients with non-extensive HCC, and tumor volume was related to the efficacy of LR[35]. Recent studies have shown that the prognosis of patients receiving hepatectomy after successful conversion is comparable to that of patients receiving initial resection (5-year overall survival: 24.9%-57.0% *vs* 42.0%-64.0%)[15,36,37]. Conversion therapy is necessary and beneficial in resectable or unresectable HCC.

Finally, approximately 40% of patients are eligible for radical treatment with an overall survival rate of 70%[38]. Metastasis and new lesions are common types of recurrence. Neoadjuvant therapy plays a certain role in preventing recurrence after radical treatment. Patients with operable HCC receiving neoadjuvant therapy (5-year disease-free survival: about 50%) tend to achieve superior prognosis compared with those receiving hepatectomy only (5-year disease-free survival: 0%-31%)[39]. The effect of reducing tumor recurrence is related to the tumor response of neoadjuvant therapy [40] (Figure 1). Prognostic comparison of patients with neoadjuvant therapy and those with initial resectable or transplantable hepatocellular carcinoma was summarized in Table 1[14,27,29,30,41-45].

PATIENT SELECTION

Bridging treatment is necessary for patients with HCC within the Milan criteria during a long waiting period. Patients with HCC for tumor downstaging require a high degree of selection. A clinical study showed that neoadjuvant therapy was not beneficial for the prognosis of patients with Barcelona Clinic Liver Cancer (BCLC) stage 0/A HCC[46], increasing the recurrence risk after LT instead[38]. Moreover, a meta-analysis demonstrated that neoadjuvant therapy had no efficacy for the overall survival and disease-free survival of patients with HCC within the Milan criteria[27].

The indications for downstaging treatment involve physical condition, liver function and tumor stage as well as tumor biomarkers such as alpha fetoprotein and abnormal prothrombin are often considered one of the protocols[47]. There is no uniform and definite limit on the number and size of HCC in downstaging treatment. One retrospective study limited no other restrictions on the tumor conditions of patients with HCC, except no distant metastasis, and their results showed a success rate of 30% in downstaging treatment and comparable prognosis with patients within the Milan criteria after LT[48].

There are some guidelines for downstaging treatment in HCC. One of the most widely used recommendations is the University of California, San Francisco (UCSF) protocol. The indications for downstaging treatment according to the UCSF criteria were as follows: (1) Single HCC > 5 and ≤ 8 cm; (2) 2-3 lesions, each no more than 5 cm in diameter, with the sum of diameters ≤ 8 cm; and (3) 4-5 lesions, each ≤ 3 cm, with the sum of diameters ≤ 8 cm[29]. The success rate of downstaging treatment was approximately 24%-58% according to UCSF criteria[14,29,48,49]. The criteria adopted by the Bologna Liver Transplant Committee are: (1) Single HCC ≤ 8 cm; (2) Two lesions, each ≤ 5 cm; and (3) Multiple lesions within 5 nodules, with the sum of diameters ≤ 12 cm. The success rate was 68.3% on the basis of the Bologna criteria[32]. The Brazilian selection protocol is a relatively relaxed standard and is as follows: (1) No extrahepatic metastasis or major vascular invasion; and (2) Only TACE was

Table 1 Prognostic comparison of patients with neoadjuvant therapy and those with initial resectable or transplantable hepatocellular carcinoma

Year	Study design	Neoadjuvant group						Resectable or transplantable group			Ref.
		Neoadjuvant therapy	Times of neoadjuvant therapy	Tumor condition	Success rate	Subsequent therapy	Prognosis	Tumor condition	Tumor treatment	Prognosis	
2017	Retrospective study	DEB-TACE	1.38	Within Milan criteria 88%	89.0%	OLT	3-yr OS: 79%; 3-yr DFS: 79%	Within Milan criteria 77%	OLT	3-yr OS: 73.0%; 3-yr DFS: 70.0%	[29]
2015	Retrospective study	TACE	NA	Over 10 cm	28.4%	LR/OLT	1-yr OS: 76.5%	HCC over 10 cm	BSC	1-yr OS: 3.7%	[27]
2019	Retrospective study	TACE, RFA; TACE + RFA	NA	Within Milan criteria 56.7%	25.2%	LT	Downstage: 5-yer DFS: 86%; No downstage: 5-yr DFS: 71.5%	Within Milan criteria 68.4%	LT	5-yr DFS: 83.0%	[30]
2013	Retrospective study	TACE, RFA; HIFU, *etc.*	1.6 ± 0.4	Outside Milan criteria	NA	LT	5-yr OS: 70.7%	Within Milan criteria	LT	5-yr OS: 74.1%	[14]
2015	Retrospective study	TACE, RFA	NA	Outside UNOS T2 criteria	65.3%	LT	5-yr OS: 77.8%; 5-yr DFS: 90.8%	Within UNOS T2 criteria	LT	5-yr OS: 81.0%; 5-yr DFS: 88.0%	[41]
2019	Retrospective study	TACE, RFA; SIRT, *etc.*	NA	Outside Milan criteria	45.2%	LT	5-yr OS: 76.0%; 5-yr DFS: 89.0%	Within Milan criteria	LT	5-yr OS: 81.0%; 5-yr DFS: 98.3%	[42]
2017	Retrospective study	TACE, RFA; Sorafenib	NA	Outside Milan criteria	26.7%	OLT	NA, comparable with those within Milan criteria	Within Milan criteria	OLT	NA	[43]
2015	Retrospective study	TACE, RFA	NA	Outside Milan criteria	36.4%	LT	5-yr RFS: 81.8%	Within Milan criteria	LT	5-yr RFS: 94.6%	[44]
2019	Retrospective study	NA	NA	Outside Milan criteria	68.4%	LT	5-yr OS: 63.0%	Within Milan criteria	LT	5-yr OS: 77.0%	[45]

DEB-TACE: Drug-eluting beads transarterial chemoembolization; TACE: Transarterial chemoembolization; RFA: Radiofrequency ablation; HIFU: High intensity focused ultrasound; OLT: Orthotopic liver transplantation; LT: Liver transplantation; OS: Overall survival; DFS: Disease-free survival; RFS: Recurrence-free survival: UNOS: United Network for Organ Sharing; NA: Not available; LR: Liver resection; SIRT: Selective interval radiation therapy; HCC: Hepatocellular carcinoma; BSC: Best supportive care.

applied as downstaging treatment[50]. Some studies have also used total tumor volume as a criterion for downstaging treatment in HCC[37]. Even if tumors develop definite progression during downstaging therapy, treatment should be continued as long as tumors are within the indication[51].

There are also contraindications of downstaging treatment for LT. First, the contraindications of the treatment itself cannot be ignored[52]. Second, extrahepatic metastasis and major vascular invasion are also contraindications to downstaging treatment[53]. Finally, downstaging treatment is not recommended for tumors exceeding the criteria. Clinical research has suggested that overall survival is significantly shortened in patients with HCC exceeding the UCSF criteria receiving LT after downstaging treatment[54].

Most patients receiving conversion therapy suffered from HCC that was more advanced than those receiving downstaging therapy. There were more restrictions for patients receiving conversion therapy. The neoplastic features of unresectable HCC include: (1) Insufficient future remnant liver (FLR) volume after hepatectomy; (2) Extensive multiple intrahepatic tumors; (3) Extrahepatic metastasis; and (4) Tumor thrombus in the main portal vein, hepatic vein and inferior vena cava[15]. First,

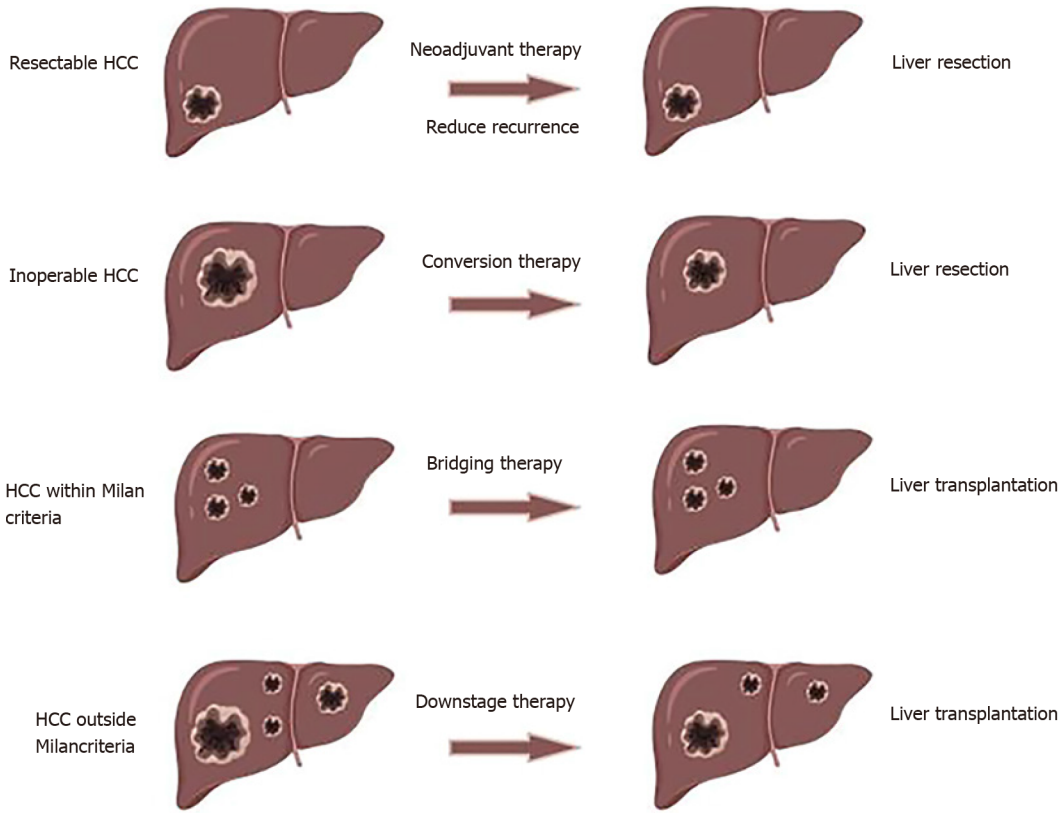

Figure 1 Summary of the goals of neoadjuvant therapy in hepatocellular carcinoma. HCC: Hepatocellular carcinoma.

insufficient residual liver volume after hepatectomy is a contraindication to hepatectomy but not an absolute contraindication. Portal vein embolization (PVE) can be performed to increase the volume of unembolized liver and improve liver function [55]. PVE should be an alternative when the standardized liver volume ratio is no more than 20% in normal liver, 30% in injured liver and 40% in cirrhosis or fibrosis [56]. Second, multiple tumors, major vascular invasion and distant metastasis are not contraindicated in neoadjuvant therapy for patients with normal liver function. A small proportion of patients with advanced HCC after conversion therapy can receive radical therapy, while others also benefit from neoadjuvant therapy[15,57]. Finally, only patients with Child-Pugh grade A and selected patients with Child-Pugh grade B can be candidates for hepatectomy after conversion therapy[58]. A Model of End-Stage Liver Disease score greater than 10 after conversion therapy should be considered a contraindication for hepatectomy[28]. Patients who cannot undergo hepatectomy due to decompensation of liver function are not eligible for conversion therapy.

EFFICACY EVALUATION

Radiological assessment is the main method to evaluate the efficacy of HCC. World Health Organization (WHO) criteria were first performed to evaluate the efficacy of solid tumors based on tumor size[59]. However, WHO criteria lack specific requirements for tumor size measurement and imaging modality was also not clearly specified, leading to incorrect assessment of tumor burden[60]. Response Evaluation Criteria in Solid Tumors (RECIST) criteria made up for many deficiencies in WHO criteria, defining target lesions and non-target lesions, clarifying the method of tumor size measurement and specifying the tumor imaging modality[61]. RECIST 1.1 criteria supplemented the clear definition of lymph nodes and other state lesions on the basis of RECIST criteria, as well as a discussion for fluorodeoxyglucose-positron emission tomography to assess new lesions[62]. The effects of treatment other than tumor reduction were not included in WHO and RECIST/RECIST 1.1 criteria. Given the need to assess efficacy accurately, experts established European Association for the Study of the Liver (EASL) criteria in 2001. The highlight is the measurement of arterially enhanced tumors, taking into account tumor necrosis. EASL criteria also led to a

stricter requirement of tumor response. The modified RECIST criteria simplified the complex steps of EASL criteria, integrates the main advantages of RECIST criteria and puts forward a new suggestion of target lesions, non-target lesions and new lesions [63]. The overall tumor response in modified RECIST criteria is comparable with that in EASL criteria[64]. Due to the delayed treatment of immune checkpoint inhibitors, immune RECIST criteria was also applied in HCC patients receiving immunotherapy [65].

The modified RECIST criteria were performed to evaluate the efficacy of patients receiving neoadjuvant treatment by computed tomography or magnetic resonance imaging in most HCC cases[63]. Efficacy evaluation only considers viable tumors. It takes a period of at least 3 mo of observation for successful downstaging to LT[66]. If the tumor progresses beyond the Milan criteria during this period, LT cannot be performed. If the tumor progresses within downstaging protocols, patients should continue to take downstaging treatment[67], but the Brazilian selection protocol requires no observation period[51]. Most protocols require patients undergoing downstaging treatment to undergo abdominal computed tomography or magnetic resonance imaging every 3 mo.

HOW TO IMPLEMENT NEOADJUVANT THERAPY IN HCC

TACE

TACE combines local embolic ischemia and the cytotoxic effects of chemotherapy, and it has become the recommended first-line treatment for intermediate-stage HCC with preserved liver function[5,68]. Recent research has demonstrated that TACE is the most common first treatment for HCC in China, Korea, North America and Europe. The most common method of TACE is hepatic arterial emulsion with lipiodol plus chemotherapy drugs and embolization with gelatin. TACE can reduce the dropout rate to 3%-13% in patients with early-stage HCC being considered for LT, especially those patients whose waiting time is expected to exceed 6 mo[69,70]. The successful downstaging rate ranged from 23.7% to 63.0% in patients with advanced HCC[71,72]. Patients receiving TACE as downstaging treatment could achieve improved survival (5-year overall survival rate: 77.6%), but TACE cannot improve the long-term prognosis of patients with HCC receiving bridging treatment[73,74]. Clinical studies have shown that the tumor response of pre-transplantation TACE was related to the recurrence rate after transplantation[75].

Drug-eluting beads are non-absorbable embolic microspheres releasing drugs continuously. Compared with conventional TACE, some previous studies indicated that drug-eluting bead TACE (DEB-TACE) not only seemed to be more capable of inducing tumor necrosis but also reduced the systemic blood concentration[76-78]. Other studies have suggested that DEB-TACE led to no advantage in tumor response and survival time compared with conventional TACE[79-82]. There is not enough evidence to support that DEB-TACE is superior to conventional TACE in terms of treatment effect and complications in HCC patients[83]. Approximately 73%-78% of patients within the UCSF criteria achieved successful downstaging, and 40% of them received LT after DEB-TACE[82,84]. The disease control rate was 75%-94%[85-87].

Several studies have demonstrated that appropriate pre-transplant TACE does not increase the risk of LT[88], but others have suggested that the incidence of hepatic artery thrombosis and re-transplantation was significantly higher in patients who received pre-transplant TACE than in those who did not[89]. Tsochatzis *et al*[90] found that the high recurrence rate after LT is associated with the absence of pre-transplant TACE as neoadjuvant therapy (odds ratio 5.395, 95%CI: 1.289-22.577).

Trans-arterial radioembolization

Trans-arterial radioembolization refers to the injection of radioactive substances through the hepatic artery, such as microspheres containing yttrium-90 (Y-90), iodine-131 and iodized oil[91]. HCC is sensitive to radiotherapy[92]. Radioembolization (RE) can achieve different degrees of regression in 25%-50% of HCC patients[93-96]; the success rate of bridging treatment with Y-90 RE can be up to 100%[97,98]. Approximately 20% of patients with an initially unresectable HCC received radical surgery after Y-90 RE[99]. Clinicians have found that Y-90 RE can even be a neoadjuvant treatment for BCLC C stage patients with portal vein tumor thrombosis[100]. However, others also indicated that Y-90 RE can prevent the progression of target lesions but not the generation of new lesions[101]. Complications of radiotherapy embolization mainly stem from the inability to predict precise dosimetry during RE.

Table 2 summarized the outcomes of pre-transplant TACE and trans-arterial radioembolization in downstage treatment for hepatocellular carcinoma[86,89,90,95,96,102-105].

Hepatic arterial infusion chemotherapy

Hepatic arterial infusion chemotherapy (HAIC) can deliver chemotherapeutics to the arterial branches of the HCC at higher concentrations[106]. Compared with traditional systemic chemotherapy, HAIC provides a higher local drug concentration and fewer side effects. The tumor response rate of HAIC is 7%-81%[107,108]. Hepatic artery infusion of FOLFOX (folinic acid, fluorouracil and oxaliplatin), cisplatin plus 5-fluorouracil and cisplatin are common chemotherapy regimens[109-111]. Patients can tolerate HAIC well, and no adverse events above grade 3 have been observed[112]. Recent studies have shown that HAIC is more effective and safer than sorafenib in the treatment of HCC[113]. Preoperative HAIC prolongs the long-term survival of patients [114]. For initially unresectable HCCs, approximately 12% of patients can receive hepatectomy after successful conversion with HAIC[115]. HAIC can prevent the progression of inferior vena cava tumor thrombi, and clinicians have suggested that LR should be performed in patients who initially have no inferior vena cava tumor thrombus and inferior vena cava tumor thrombus controlled by HAIC[116]. Moreover, preoperative HAIC cannot prolong the overall survival of patients with early-stage HCC, but it may be able to prevent intrahepatic distant recurrence[117].

PVE

PVE was originally used to prevent the spread of portal vein thrombi[118] and was found to increase the volume of the unembolized liver. Postoperative liver insufficiency or even liver failure after hepatectomy is closely related to FLR volume. PVE can lead to a significant increase in FLR volume in normal livers or those with chronic disease[119]. There would be functional and volumetric increases in unembolized liver after PVE[120]. The increase in liver volume after PVE is a predictor of postoperative safety. Palavecino *et al*[121] suggested that preoperative PVE was helpful to reduce complications after hepatectomy, and patients with PVE achieved comparable prognosis with those without PVE. However, there were also researchers suggesting that PVE accelerates the growth of tumors in the embolized liver lobe[122].

Repeatedly reversible PVE has achieved satisfactory results in animal experiments, and this new method of PVE requires more evidence[123]. Portal vein ligation can achieve effects similar to PVE, but it is performed less due to its high invasiveness and the risk of treatment-related complications[124]. FLR volume could be insufficient in some patients receiving PVE, and a meta-analysis showed that hepatic and PVE could be an ideal alternative for patients who failed to increase FLR volume with PVE[125].

Radiation therapy

Radiotherapy can be used for more advanced HCC as compared to TACE[126]. Hasan *et al*[127] suggested that radiotherapy is effective in downstaging and bridging therapy for pre-transplant HCC, especially in advanced HCC, which is outside the indications for TACE. Various methods of radiotherapy have been applied in HCC. Clinical studies have demonstrated that stereotactic ablative radiation therapy, selective internal radiation therapy and stereotactic radiotherapy can be effective in the pre-transplant period, with a successful downstaging rate of approximately 60%[128]. For patients with HCC with portal vein tumor thrombosis, radiotherapy before major hepatectomy can achieve a significantly better prognosis. Radiotherapy combined with TACE seemed to be a more effective treatment option, providing a better prognosis [129].

Radiofrequency ablation

Radiofrequency ablation is a radical alternative to surgical resection for BCLC stage 0/A HCC and a palliative treatment for advanced HCC at the same time[5,130]. de Haas *et al*[131] suggested that preoperative radiotherapy had no adverse effects on patient prognosis while providing downstaging and bridging effects. Radiofrequency ablation before LT may indeed cause inflammation and adhesions, increasing the difficulty of operation, but clinical studies have shown that the perioperative mortality and morbidity of the local ablation group are comparable with that of the non-local ablation group[131]. The disease control rate of radiofrequency ablation combined with TACE was significantly higher than that of monotherapy, and the sequence of radiofrequency ablation and TACE appeared to lead no effect on prognosis[132].

Table 2 Summary of pre-transplant transarterial chemoembolization and trans-arterial radioembolization in downstage treatment for hepatocellular carcinoma

Year	Neoadjuvant treatment	Entry criteria	Success downstage rate	Subsequent therapy	Adverse events	Incidence rate	Ref.
2015	Conventional TACE; I^{131} Metuximab TACE	Patients within USCF criteria	NA	OLT	Hepatic artery thrombosis hepatic aneurysm	1.5%	[89]
2015	DEB-TACE	BCLC 0/A/B stage	26.7%	OLT	Grade 3/4	3.2%	[102]
2017	TACE		NA	OLT	Hepatic artery thrombosisRetransplant	27%22.7%	[90]
2020	DEB-TACE	AJCC stage ≤ T3a	73.3%	OLT	Grade 3Grade 4	3.1%0.0%	[86]
2006	Y-90 RE	UNOS stage T3	66.0%	OLT	NA	NA	[103]
2017	Y-90 RE	BCLC A/B/C stage	78.9%	OLT	NA	NA	[104]
2011	Y-90 RE	UNOS stage T2, T3, T4a	50.0%	OLT	Hyperbilirubinemia (Grade3)	13.0%	[105]
2013	Y-90 RE	UNOS stage T3, T4a	33.0%	OLT	NA	NA	[95]
2021	Y-90 RE	UNOS stage T1, T2, T3, T4	43.0%	OLT	NA	NA	[96]

DEB-TACE: Drug-eluting beads transarterial chemoembolization; TACE: Transarterial chemoembolization; Y-90 RE: Yttrium-90 radioembolization; UCSF: University of California, San Francisco; BCLC: Barcelona Clinic Liver Cancer; AJCC: American Joint Committee on Cancer; UNOS: United Network for Organ Sharing; NA: Not available; I^{131}: Iodine-131; OLT: Orthotopic liver transplantation.

Systemic therapy

Chemotherapy is effective for the treatment of HCC, but the incidence of adverse events is very high. Up to 44% of patients develop grade 3-4 adverse events[133]. Neoadjuvant therapy rarely uses chemotherapy alone. Localized concurrent chemoradiotherapy could lead to a downstaging rate of 26.5% in advanced HCC so that surgery can be performed[134]. Even in patients with portal vein tumor thrombosis, the operation rate can reach 26.5% after concurrent chemoradiotherapy[134]. The feasibility of chemotherapy combined with targeted drugs requires more clinical research in downstaging and bridging in pre-transplant HCC[135,136].

Sorafenib is a milestone in the systematic treatment of HCC. It was clinically observed that one patient who received sorafenib for downstaging achieved a good prognosis after LT[137]. Sorafenib is also effective in conversion therapy of advanced HCC and even ruptured HCC[138,139]. A decline of more than 20% from baseline in early alpha fetoprotein levels is a predictor of tumor response to sorafenib[140]. However, due to the relatively low response rate of sorafenib in HCC, the application of neoadjuvant therapy is limited[141]. To date, there have been few reports of successful conversion after receiving sorafenib[142-144]. More evidence is required to support the role of sorafenib in neoadjuvant therapy because of the small sample size of clinical studies on sorafenib in neoadjuvant therapy[145]. Compared with other targeted drugs, lenvatinib leads to a higher response rate of approximately 40.6% [146]. Targeted therapy should be an alternative in patients who cannot benefit from TACE. It can be more effective when lenvatinib is administered before TACE in patients with BCLC B stage HCC[147]. Regorafenib and other targeted drugs can also be potential neoadjuvant treatments[148]. Surgery-related complications of molecular targeted drugs must be noted, such as increased bleeding and hindered liver regeneration[149], but clinical research has suggested that the surgical blood loss and complications in the sorafenib group were comparable to those in the control group [150].

Immunotherapy is an emerging systemic treatment for solid tumors[151]. The combination of atezolizumab and bevacizumab showed a strong antitumor effect, with a relatively low rate of grade 3-4 adverse events (15.2%)[152]. Targeted drugs plus immune checkpoint inhibitors can achieve a tumor response rate of 30%, leading to a new emerging treatment[153-155]. Lenvatinib plus pembrolizumab can also be an important treatment option for neoadjuvant therapy. The combination of immuno-

therapy and other treatments, such as chemotherapy and radiotherapy, still requires more evidence to demonstrate efficacy[155,156].

CONCLUSION

To reduce the drop-out rate during the waiting period and downstaging more HCCs outside the Milan criteria, effective neoadjuvant therapy is critical in prolonging patient prognosis. Adverse events of neoadjuvant therapy are manageable under strict indications. The establishment of unified protocols of neoadjuvant therapy requires more clinical studies.

ACKNOWLEDGEMENTS

We thank the hepatic surgery of Tongji Hospital for the platform support.

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2021 December 27; 13(12): 1567-1583

DOI: 10.4240/wjgs.v13.i12.1567

ISSN 1948-9366 (online)

REVIEW

Mucinous adenocarcinoma: A unique clinicopathological subtype in colorectal cancer

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Author contributions: Gu J contributed to conceptualization; Huang A, Li YK and Xu JX contributed to literature search and data analysis; Huang A wrote original draft preparation; Yang Y, Shi JY, Cheng Y reviewed and edited manuscript; Gu J supervised manuscript.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Supported by the Beijing Municipal Science & Technology Commission, Clinical Application and Development of Capital Characteristic, No. Z171100001017087.

Country/Territory of origin: China

Specialty type: Gastroenterology and hepatology

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

Peer-review report's scientific quality classification

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Abstract

Mucinous adenocarcinoma (MAC) is a unique clinicopathological subtype of colorectal cancer, which is characterized by extracellular mucinous components that comprise at least 50% of the tumor tissue. The clinical characteristics, molecular features, response to chemo-/radiotherapy, and prognosis of MAC are different from that of non-MAC (NMAC). MAC is more common in the proximal colon, with larger volume, higher T-stage, a higher proportion of positive lymph nodes, poorer tumor differentiation, and a higher proportion of peritoneal implants compared to NMAC. Although biopsy is the main diagnostic method for MAC, magnetic resonance imaging is superior in accuracy, especially for rectal carcinoma. The aberrant expression of mucins, including MUC1, MUC2 and MUC5AC, is a notable feature of MAC, which may be related to tumor invasion, metastasis, inhibition of apoptosis, and chemo-/radiotherapy resistance. The genetic origin of MAC is mainly related to *BRAF* mutation, microsatellite instability, and the CpG island methylator phenotype pathway. In addition, the poor prognosis of rectal MAC has been confirmed by various studies, and that of colonic MAC is still controversial. In this review, we summarize the epidemiology, clinicopathological characteristics, molecular features, methods of diagnosis, and treatments of MAC in order to provide references for further fundamental and clinical research.

Key Words: Mucinous adenocarcinoma; Colorectal cancer; Mucin; Microsatellite

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

Received: May 29, 2021
Peer-review started: May 29, 2021
First decision: June 23, 2021
Revised: July 2, 2021
Accepted: August 30, 2021
Article in press: August 30, 2021
Published online: December 27, 2021

P-Reviewer: Ros J
S-Editor: Liu M
L-Editor: Kerr C
P-Editor: Zhang YL

instability; Magnetic resonance imaging; Treatment

Core tip: Colorectal mucinous adenocarcinoma (MAC) is a unique clinicopathological subtype in colorectal cancer. MAC exhibits a higher frequency of microsatellite instability, higher CpG island methylator phenotype of high degree, higher frequency of *BRAF* and *KRAS* gene mutations, and lower frequency of *TP53* mutations. One of the most important features of MAC is the aberrant expression of a large number of mucins, including MUC1, MUC2 and MUC5AC. We discuss the epidemiology, clinicopathological characteristics, molecular features, methods of diagnosis, and treatments of MAC in order to provide references for further fundamental and clinical research.

Citation: Huang A, Yang Y, Shi JY, Li YK, Xu JX, Cheng Y, Gu J. Mucinous adenocarcinoma: A unique clinicopathological subtype in colorectal cancer. *World J Gastrointest Surg* 2021; 13(12): 1567-1583
URL: https://www.wjgnet.com/1948-9366/full/v13/i12/1567.htm
DOI: https://dx.doi.org/10.4240/wjgs.v13.i12.1567

INTRODUCTION

Colorectal cancer (CRC) has caused a great burden on global health. The World Health Organization (WHO) estimated > 1.9 million new CRC cases and 935 000 CRC-related deaths occurred in 2020, with 10% (third) and 9.4% (second) incidence and mortality rates, respectively, among all cancer types[1]. According to the WHO classification of tumors of the digestive system, the histological subtypes of CRC include adenocarcinoma, adenosquamous carcinoma, spindle cell carcinoma, squamous cell carcinoma, and undifferentiated carcinoma (Figure 1). Adenocarcinoma originating from epithelial cells of the colorectal mucosa accounts for more than 90% of CRC cases. Mucinous adenocarcinoma (MAC) is a unique subtype of adenocarcinoma characterized by more than 50% of the tumor tissue being extracellular mucinous components. Malignant epithelial cells float in the mucus, forming alveolar, row-like, or single-scattered cells. Tumors with a significant mucinous component (10-50%) are usually referred to as adenocarcinoma with mucinous features or mucinous differentiation[2,3]. Although the highly malignant biological behavior of MAC is well known, its related mechanisms have not been extensively studied.

Compared to non-MAC (NMAC), the clinicopathological characteristics, molecular features, response to chemo-/radiotherapy, and prognosis of MAC are evidently different. MAC are divided into two types based on the degree of histological structural differences: One type is the low-grade MAC, which originates from well-differentiated to moderately differentiated adenocarcinoma and papillary carcinoma, whereas the other type is the high-grade MAC, originated from poorly differentiated adenocarcinoma and signet ring cell carcinoma (SRCC)[4]. Currently, the prognosis of MAC remains controversial. Previous studies have suggested that colorectal MAC is associated with poor prognosis[5-8], while other studies reported no significant difference in prognosis between MAC and NMAC[9,10]. However, the poor prognosis of rectal MAC has been confirmed in most studies[11-13]. The clinicopathological characteristics of MAC suggest that it is a unique subtype of CRC.

EPIDEMIOLOGICAL AND CLINICOPATHOLOGICAL CHARACTERISTICS OF COLORECTAL MAC

Various studies have demonstrated regional differences in the occurrence of MAC in CRC. The occurrence of MAC in CRC was 6.9%[14], 8.9%[15], 8.17%[16] in China, 3.82%[17], 2.8%[18] in Japan, 11.6%[19], 10%[5] and 11%[20] in the USA, which ranged from 3.9% in Asia to 10%-13.6% in Europe and North America[21]. A large national

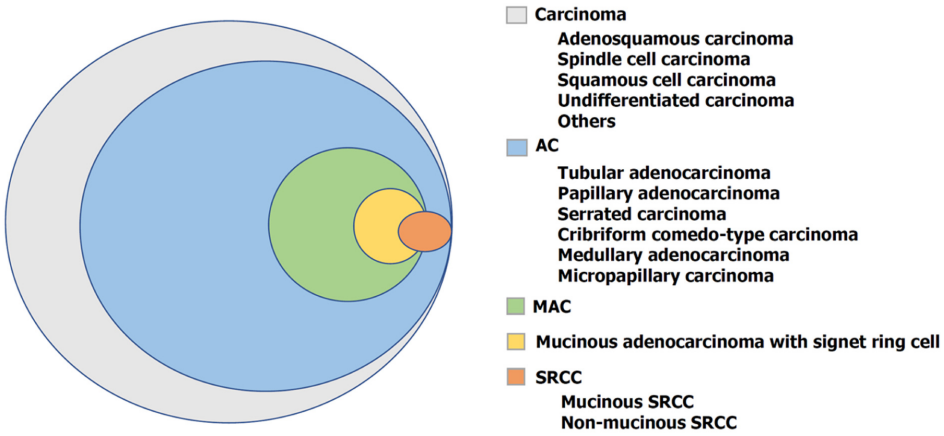

Figure 1 World Health Organization histological classification of colorectal carcinoma. AC: Adenocarcinoma; MAC: Mucinous adenocarcinoma; SRCC: Signet ring cell carcinoma.

cancer database study in the USA demonstrated that the distribution of histological subtypes of CRC among Caucasians, African Americans, and other races were similar [22]. However, another study reported that the occurrence of MAC in Chinese Americans with CRC (7.5%) was lower than that in Caucasians (9.3%) and African Americans (9.4%)[23]. This might be due to genetic differences between races as well as other factors (such as lifestyle and dietary habits). Studies on American[6] and German patients[24] found that MAC occurred in a higher proportion of women (MAC *vs* NMAC, 52.1% *vs* 48.6%, 47% *vs* 41%, respectively). In addition, a German study observed no difference in the age of patients with MAC and NMAC, whereas an American study observed that the proportion of MAC in patients aged > 65 years was higher. However, studies on Chinese patients reported no statistical difference in gender between patients with MAC and NMAC, and that MAC was more common in patients aged < 50 years[25].

Compared with that in NMAC, in MAC, the proportion of tumors occurring in the right hemicolon was higher (MAC *vs* NMAC, 35.0% *vs* 18.9% in China[25], 65.3% *vs* 46.2% in the USA[6], 51.0% *vs* 28.0% in Germany[24]), while the proportion of tumors in the rectum was lower (MAC *vs* NMAC, 41.0% *vs* 50.7% in China, 9.9% *vs* 17.7% in the USA, 27.0% *vs* 40.0% in Germany) in MAC. MAC was diagnosed with larger tumors, higher T stage, higher proportion of lymph node infiltration and peritoneal implantation, and poorer tumor differentiation compared to NMAC (Table 1)[6,24-27].

MOLECULAR CHARACTERISTICS OF COLORECTAL MAC

MAC exhibited a higher frequency of microsatellite instability (MSI) and *BRAF* and *KRAS* gene mutations, higher CpG island methylator phenotype of high degree (CIMP-H), and lower frequency of *TP53* mutations[28]. Gene expression analysis illustrated that compared to NMAC, 317 genes were differentially regulated in MAC, of which 182 were upregulated and 135 were downregulated. These altered genes were primarily involved in O-glycan biosynthesis, keratin sulfate metabolism, lacto-series glycosphingolipid metabolism, histidine-glutamate-glutamine and proline metabolism, p38-MAPK pathway, coenzyme A biosynthesis, and 14-3-3 protein in cell cycle regulation[26]. Among them, O-glycan biosynthesis is associated with mucins synthesis. One of the most important features of MAC, the aberrant expression of several mucins, is associated with O-polysaccharide biosynthesis, including MUC1, MUC2, and MUC5AC[29].

Expression of mucins in MAC

Mucins are a class of high-molecular-weight epithelial glycoproteins with a high content of clustered oligosaccharides O-glycosidically linked to tandem repeat peptides rich in threonine, serine and proline[29]. They are differentially expressed by specialized epithelial cells on the mucosal surface in a specific way for organs and cells [30]. Mucins are classified as membrane-associated and secreted mucins. Secreted mucins are either gel-forming or non-gel-forming subtypes[31]. Under normal circumstances, mucins form a mucus barrier that protects the epithelial cells. In the process of

Table 1 Clinicopathological characteristics of patients with mucinous adenocarcinoma or non-mucinous adenocarcinoma in China, USA and Germany[6,24,25]

	China			USA			Germany		
	MAC (%)	NMAC (%)	*P*	MAC (%)	NMAC (%)	*P*	MAC (%)	NMAC (%)	*P*
Age(yr)	21.4% (< 50)	11.3% (< 50)	0.005	62.6% (> 65)	56.3% (> 65)	< 0.001	67 (25-88)	65 (15-96)	0.037
Gender			0.603			< 0.001			0.034
Male	58.1	55.4		47.9	51.4		52.8	58.5	
Female	41.9	44.6		52.1	48.6		47.2	41.5	
Tumor location			< 0.001			< 0.001			< 0.001
Right hemicolon	35.0	18.9		65.3	46.2		51.5	27.5	
Left hemicolon	23.9	30.4		24.8	36.2		18.9	29.8	
Rectum	41.0	50.7		9.9	17.6		27.5	40.1	
Tumor size (cm)			< 0.001			< 0.001			-
≤ 5	34.2	54.2		48.93	68.34		-	-	
> 5	65.8	45.8		51.07	31.66		-	-	
Primary tumor (T)			0.001			< 0.001			< 0.001
T1, T2	28.2	44.5		13.8	26.5		13.3	30.5	
T3, T4	71.8	55.4		86.2	73.5		86.7	69.5	
Regional lymph nodes (N)			< 0.001			< 0.001			0.018
N0	35.9	55.0		52.5	57.0		49.1	55.6	
N1, N2	64.0	45.0		47.5	43.0		50.9	44.4	
Distant metastasis (M)			0.001			0.004			< 0.001
M0	56.4	72.4		84.7	85.8		75.5	78.5	
M1	43.6	27.6		15.3	14.2		24.5	21.5	
Stage			0.001			< 0.001			< 0.001
I, II	28.2	44.5		21.5	31.2		44.8	52.0	
III, IV	71.8	55.5		78.5	68.8		55.2	48.0	
Histological grading			< 0.001			< 0.001			< 0.001
G1, G2	82.9	89.8		76.4	80.1		55.2	69.6	
G3, G4	17.1	10.1		23.6	19.9		44.8	30.4	

P value of the χ^2 test was used to compare the NMAC and MAC groups. MAC: mucinous adenocarcinoma; NMAC: nonmucinous adenocarcinoma.

tumorigenesis, aberrant expression of specific mucins may be related to tumor invasion, metastasis, apoptosis inhibition, and chemoradiotherapy resistance[32]. MUC1, MUC2 and MUC5AC are aberrantly expressed in colorectal MAC. MUC1 is a membrane-associated mucin, while MUC2 and MUC5AC are secreted gel-forming mucins[31].

MUC1 is expressed in almost all glandular epithelial cell membranes, making MUC1 overexpression one of the most common changes in cancers. During pathogen infection, upregulation of MUC1 expression in the mucosal barrier suppresses pathogen-mediated inflammation[33]. However, MUC1 expression is induced by inflammatory cytokines [tumor necrosis factor-α, interferon-γ, and interleukin (IL)-6], and abnormal activation of MUC1 may lead to chronic inflammation and cancers in the absence of IL-10 and corresponding anti-inflammatory responses[34]. MUC1 C-terminal transmembrane subunit (MUC1-C) can activate both the inhibitor of nuclear factor-κB (NF-κB) kinase-β (IKKβ) and the NF-κB family member RELA, while the activation of the IKKβ-NF-κB pathway is a likely mediator of inflammation-induced cancer progression[35,36]. Meanwhile, MUC1 can inhibit tumor cell apoptosis *via* the

abnormal activation of NF-κB and Wnt/β-catenin signaling pathways, inhibition of the JNK1 signaling pathway, and formation of a physical barrier to prevent chemotherapeutic drugs from reaching tumor cells[32]. The resistance of MAC to chemoradiotherapy may be reversed by reducing the production of mucins or inhibiting their functions. Studies have been targeting MUC1 as a cancer vaccine for CRC, which reduces tumor burden and induces tumor regression in mouse models[37,38]. However, their application to patients with MAC requires further research.

MUC2 primarily exists in goblet cells of the colorectum, especially in the proximal colon, and is an important component of normal intestinal mucus, which acts as a physical barrier thereby limiting the damage to the epithelium by pathogens and weaken the activation of natural and acquired immune responses[39]. Feagins *et al* observed that the degree of ulcerative colitis was associated with reduction in MUC2 levels, while chronic inflammation associated with inflammatory bowel disease increased the risk of colon cancer[40]. MUC2 is strongly expressed in normal colon tissues (mean composite score ± standard error, 12 ± 0), and decreases sequentially in inflammation, hyperplastic polyps, and adenomas (11.4 ± 0.4, 9.7 ± 1.1, 7.4 ± 0.6, respectively), while in adenocarcinoma, the expression of MUC2 is significantly decreased (3.8 ± 0.9)[41]. Low levels of MUC2 are associated with poor overall survival (OS) [hazard ratio (HR) = 1.67, 95% confidence interval (CI): 1.43-1.94, $P < 0.00001$] [42], which suggests that MUC2 can act as a tumor suppressor. However, compared to NMAC, MAC with no better prognosis overexpresses MUC2, which is inconsistent with the observation that MUC2 acts as a tumor suppressor. Gratchev *et al*[43] found that the strong expression of MUC2 in normal human goblet cells and human colorectal MAC tissues was related to ~50% of the average degree of methylation at the CpG site of each MUC2 promoter. MUC2 promoters in normal columnar cells and NMAC tissues that do not express MUC2 are methylated to nearly 100%. In this regard, MUC2 expression in carcinomas might reflect the origin of these tumors from cells that normally express MUC2, rather than a role for this mucin in the malignant process itself[34].

Another component of the mucus secreted by colorectal MAC is MUC5AC, which is usually secreted by tracheobronchial goblet cells, gastric epithelial cells, conjunctiva, and lacrimal gland cells, but is not expressed in the normal colonic mucosa[31,44]. Studies have shown that during adenoma-adenocarcinoma progression, the expression of MUC5AC is upregulated[41], which may be associated with transcription factors such as Smad-4, SP-1[45], GATA-6 and HNF-4α[46], sex determining region Y-box 2[47], and trefoil factor 3[48]. Although MUC5AC expression is upregulated in MAC, the expression of MUC5AC in low-grade MAC is significantly higher than that of high-grade MAC[4]. At the same time, the lack of MUC5AC expression is an indication of more aggressive colorectal tumors, as patients with negative MUC5AC expression have a poorer prognosis than those with positive expression[49]. However, it has been shown that MUC5AC promotes tumorigenicity through the transmembrane protein CD44, enhances the proliferation, invasion, and migration of CRC, and plays a positive role in maintaining specific subsets of cancer stem cell populations[50]. Therefore, the expression of MUC5AC and its mechanism in colorectal MAC need to be further studied.

Genetic origins

There are two main pathways for the occurrence of CRC (Figure 2)[51,52]: The conventional adenoma-carcinoma pathway, which accounts for 70%-80% of CRC cases. Usually mutations in *APC*, *KRAS* and *TP53*, account for 60%, 45% and 54% of cases, respectively. The other is the serrated pathway, which accounts for 20%-30% of CRC cases and usually has a high frequency of *BRAF* mutations (70%-100%), CIMP-H, and high MSI (MSI-H)[53-55]. A meta-analysis of 46 studies involving 17 746 patients demonstrated that MAC had higher *KRAS* [odds ratio (OR) = 1.46, 95%CI: 1.08-2.0, $P = 0.014$], *BRAF* (OR = 3.49, 95%CI: 2.50-4.87, $P < 0.001$), higher MSI (OR = 3.98, 95%CI: 3.30-4.79, $P < 0.001$), and CIMP-H (OR = 3.56, 95%CI: 2.85-4.43, $P < 0.001$), and lower p53 expression (OR = 0.46, 95%CI: 0.31-0.67; $P < 0.001$) compared to NMAC, which suggests that the genetic origin of MAC is primarily associated with the serrated pathway[56]. Some researchers have proposed that MAC can be divided into two subtypes. The first type, characterized by MSI, is mostly confined to the proximal colon, usually presents with loss of expression of hMLH1 and p27, and has a good prognosis. The second subtype, characterized by microsatellite stability, is more common in the distal colon and rectum, with normal expression of hMLH1 and p27, and a poor prognosis[57].

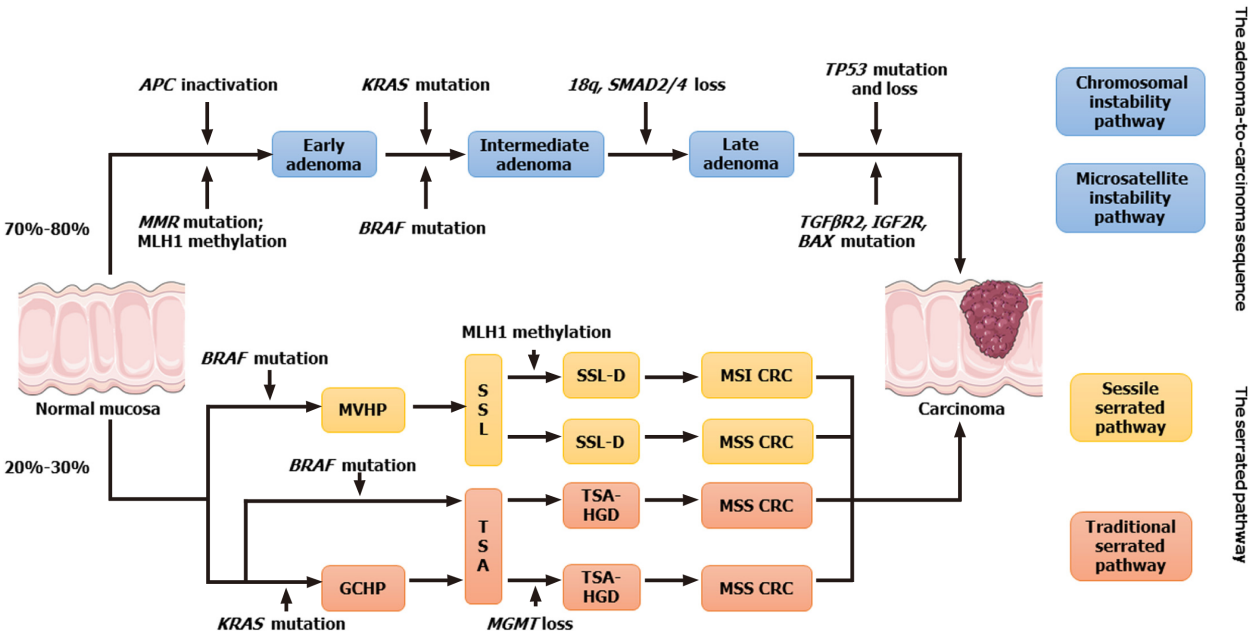

Figure 2 Main pathways for the occurrence of colorectal cancer and the genetic and epigenetic features involved in the development of colorectal cancer. CRC: Colorectal cancer; MMR: Mismatch repair; MVHP: Microvesicular hyperplastic polyp; SSL: Sessile serrated lesion; SSL-D: Sessile serrated lesion with dysplasia; MSI: Microsatellite instability; MSS: Microsatellite stability; GCHP: Goblet cell-rich hyperplastic polyp; TSA: Traditional serrated adenoma; TSA-HGD: Traditional serrated adenoma with high-grade dysplasia.

MSI is present in 15% of CRC cases[58], of which 3%[59] are present in Lynch syndrome, and 12% are sporadic cancers[60]. Currently, four pathogenic genes associated with Lynch syndrome have been characterized namely *MSH2* plus *EpCAM*, *MLH1*, *MSH6* and *PMS2*. Germline mutations in *MLH1* and *MSH2* account for most cases (60%-80%), with a limited number of Lynch syndrome cases with germline mutations in *MSH6* and *PMS2*, and particularly rare germline *EPCAM* mutations that epigenetically inactivate *MSH2*[61]. Sporadic MSI CRC is primarily caused by acquired methylation in the promoter region of the *MLH1* gene[60]. The association of *BRAF* mutations (usually *V600E* mutations) with MSI and CIMP-H has been well established [62]. *BRAF* mutations are extremely rare in Lynch syndrome[63], suggesting that MSI in MAC is primarily sporadic.

DIAGNOSIS

Currently, the diagnosis of MAC is primarily based on computed tomography (CT), magnetic resonance imaging (MRI), colorectal endoscopy, or postoperative pathological biopsy. Compared to NMAC and SRCC, CT of MAC shows more heterogeneous enhancement (MAC *vs* NMAC *vs* SRCC, 95.8% *vs* 54.1% *vs* 32.8%), larger attenuation area (greater than two thirds of the tumor tissue, 54.2% *vs* 5.9% *vs* 3.0%), and more calcification (17.9% *vs* 6.8% *vs* 3.0%)[64].

MRI can distinguish MAC from NMAC, which facilitates early diagnosis of MAC rather than relying on postoperative histopathological diagnosis. Since NMAC shows moderate signal intensity on T2-weighted imaging (T2WI), mucus displays low signal intensity on T1-weighted imaging, whereas T2WI shows high signal intensity (similar to or higher than that of the rectum fat signals) (Figure 3)[65]. MRI has an accuracy of 96%-97%, a sensitivity of 94%-100%, and a specificity of 95%-98% in diagnosing histological types of mucus[66]. Stanley *et al* believed that MRI was superior to preoperative biopsy for MAC diagnosis[67]. Before treatment, MRI diagnosed 60/330 (18%) mucinous rectal cancer cases, and initial biopsy diagnosed 15 (5%) (diagnostic OR = 4.67, $P < 0.05$) cases. The 60 patients who underwent surgery were ultimately confirmed to have mucinous tumors using histopathological analysis. MRI has great advantages not only in the diagnosis of MAC, but also in predicting the response of MAC to neoadjuvant therapy. Cao *et al*[68] used preoperative T2WI to clarify the mucus pool (high signal) and tumor solid components (medium signal), and classified MAC into two types: mixed type, where the mucus was rich in solid tumor components, and separated type, where the secretory mucus component was located

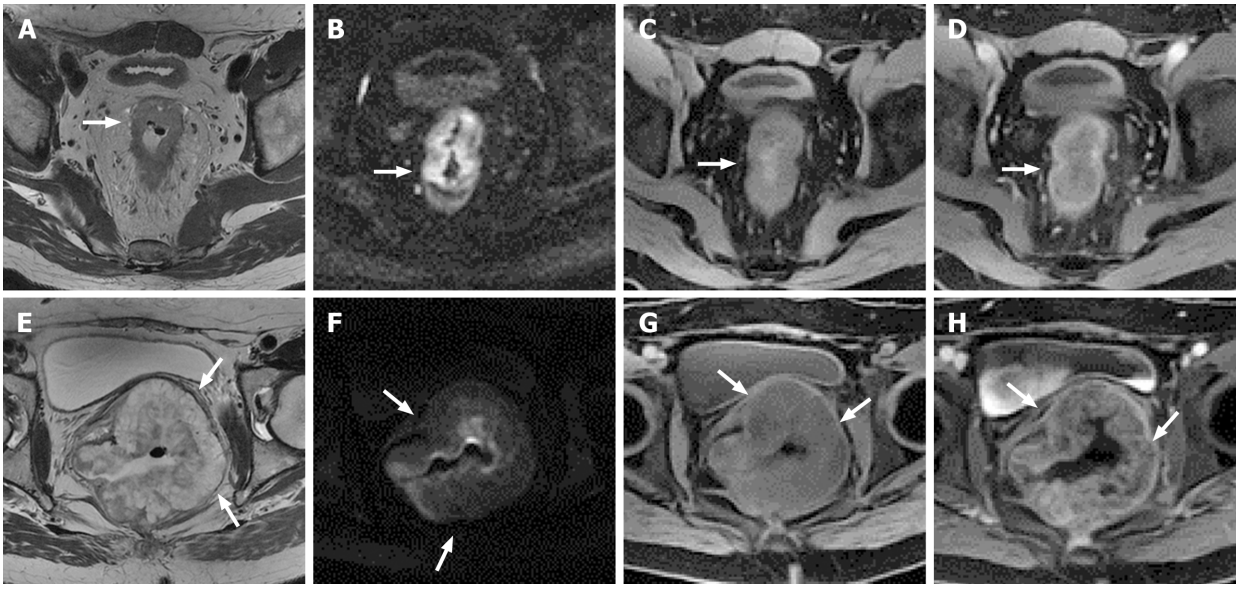

Figure 3 Magnetic resonance imaging of rectal adenocarcinoma and mucinous adenocarcinoma. A-D: Rectal adenocarcinoma; E-H: Rectal mucinous adenocarcinoma. A: Axial non-lipid-suppressing T2-weighted imaging (T2WI) showing irregular circumferential thickening of the rectal wall, with slightly higher T2WI signal, lower than that of fat; B: Diffusion-weighted imaging (DWI) showing that the lesion was high signal; C: Low signal on plain T1-weighted imaging (T1WI); D: Axial enhanced T1WI showing moderate to high enhancement of the tumor; E: Axial non-lipid-suppressive T2WI showing that the rectal wall was thickened approximately three quarters of the circumference, and the left side wall was mainly with high signal on T2WI, which was close to the fat T2 high signal, with a low signal interlaced distribution; F: DWI showing that the lesion was mainly high signal; G: Low signal on plain T1WI; H: Axial enhanced T1WI showing enhanced tumor margins and low internal enhancement.

outside the solid tumor, to predict the response of locally advanced rectal MAC to neoadjuvant therapy, since patients with mixed-type mucin pool showed a lower tumor response rate than those with separate type mucin pool following neoadjuvant chemotherapy (4.9% *vs* 25.5%, $P = 0.002$). However, using MRI to diagnose MAC can also produce false-positive results, possibly attributed to edema, congestion, abscess, or necrosis. False positives are especially important after treatment, as submucosal edema appears in the normal rectal wall after radiotherapy and chemotherapy[69]. More importantly, a few patients with CRC may form acellular mucin pools following adjuvant treatment, which is a manifestation of tumor response to treatment and is usually associated with a better prognosis[70,71]. However, due to the T2WI high signal on MRI, it is difficult to distinguish between persistent cell mucins (residual MAC tissue lacking response) and acellular mucin pools (therapeutic effect). There is currently no imaging technique to distinguish between the two[72], hence the comparison of MRI before and after treatment is particularly important.

Positron emission tomography (PET)/CT is an effective auxiliary test for patients with complicated conditions and cannot be clearly diagnosed by routine examination to determine the presence of distant metastases[73]. Although some studies have found no significant difference in the uptake of 18-fluorodeoxyglucose (FDG) between rectal MAC and NMAC in PET[74,75], it is not uncommon that MAC shows low uptake of 18-FDG on PET/CT and PET/MRI, and that the 18-FDG affinity of the tumor on a PET scan is inversely proportional to the total amount of mucins, which may lead to false-negative results[76].

Extracellular mucinous components > 50% are usually estimated by pathologists, while mucinous components vary in different pathological sections of the same tumor. In addition, Li *et al*[77] observed no significant difference in the distribution of mutations among the three adenocarcinoma subgroups with mucin characteristics (< 30%, 30%-50%, and > 50% mucinous components in tumor tissue)[77]. Furthermore, the more extracellular mucinous components of MAC tissue (50%-79%, 80%-89% and ≥ 90%), the worse the patient's OS and recurrence-free survival[78]. These findings suggest that more objective and standardized histopathological analysis and molecular data are warranted to update the classification of MAC and adenocarcinoma with mucinous components.

TREATMENT

The existing guidelines for the diagnosis and treatments of CRC are primarily based on TNM staging, biomarkers including *BRAF*, *RAS*, *HER2* and microsatellite status [73], and do not make recommendations based on the characteristics of MAC. Differences in histopathology and molecular characteristics between MAC and NMAC influence their treatment and prognosis, therefore, establishing standards for the diagnosis and treatments of MAC is essential.

Surgery, radiotherapy, and chemotherapy

Studies on patients with stage II or III colon cancer receiving adjuvant chemotherapy after radical resection have reported no significant difference in OS (HR = 1.05, 95%CI: 1.02-1.08, $P < 0.001$) between patients with stage II NMAC and MAC[79,80], whereas in patients with stage III colon cancer, compared to NMAC, the OS (HR = 1.05, 95%CI: 1.02-1.08, $P < 0.001$)[79], cancer-specific survival (CSS) (5-year CSS rate: MAC *vs* NMAC, 72.7% *vs* 67.9%, $P < 0.0001$)[81] and disease-free survival (HR = 1.82, 95%CI: 1.03-3.23, $P = 0.04$)[82] of MAC were significantly decreased. Studies on patients with stage IV CRC receiving palliative chemotherapy illustrated that despite the different chemotherapy regimens used in these trials [5-fluorouracil (5-FU) with oxaliplatin and/or CPT-11[83], FOLFOX-4 regimen[84], CAP + oxaliplatin + bevacizumab with or without cetuximab[85], 5-FU-based first-line chemotherapy[12]], the median OS of patients with MAC was shorter than that of patients with NMAC (MAC *vs* NMAC, 14.0 mo *vs* 23.4 mo, 8.0 mo *vs* 18.0 mo, 13.1 mo *vs* 21.5 mo, 11.8 mo *vs* 17.9 mo, respectively). However, although patients with stage III and IV MAC have poor responses to adjuvant or palliative chemotherapy, current evidence shows that adjuvant chemotherapy can effectively improve the survival rate of patients with stage II and III MAC[79,81].

A meta-analysis that included eight comparative series on the association between mucinous histology and response to neoadjuvant chemoradiotherapy in rectal cancer reported that MAC had a reduced rate of pathological complete response (pCR) (OR = 0.078, 95%CI: 0.015-0.397, $P = 0.002$) and tumor downstaging (OR = 0.318, 95%CI: 0.185-0.547, $P < 0.001$) following neoadjuvant chemoradiotherapy with an increased rate of positive resection margins (OR = 5.018, 95%CI: 3.224-7.810, $P < 0.001$) and poor OS (OR = 1.526, 95%CI: 1.060-2.198, $P = 0.023$) following resection, which suggests mucinous histology of rectal MAC as a biomarker for poor prognosis after neoadjuvant chemoradiotherapy[86,87]. Approximately 30% of patients with rectal cancer who received neoadjuvant therapy can have a clinical complete response. At this time, a watch-and-wait strategy can be adopted to provide patients with the opportunity to preserve the rectum and avoid surgery[88]. Tan *et al*[87] discovered that patients with NMAC (21%) were more likely to achieve pCR ($P < 0.001$) than those diagnosed with MAC (14%); in patients who achieved pCR, those with MAC had a poorer survival, with a 3-year OS rate of 67.5%, while the 3-year OS of patients with NMAC was 93.8% ($P < 0.001$)[87]. Therefore, the watch-and-wait strategy should be used more cautiously in patients with MAC. For patients with rectal MAC, preoperative treatment (short-term preoperative radiotherapy and preoperative chemoradiotherapy) plus total mesorectal resection (TME)[89] or adjuvant chemotherapy after TME[90] can be used to narrow the survival gap between rectal MAC and NMAC.

Hyperthermic intraperitoneal chemotherapy

The peritoneum is associated with treatment failure in patients with CRC. However, due to lack of clinical follow-up and available imaging technology, the diagnosis cannot be made in the early stages, resulting in an inaccurate assessment of the incidence of peritoneal metastasis. Sugarbaker[91] recommended a combination of cytoreductive surgery (CRS) to remove all visible peritoneal metastases and hyperthermic intraperitoneal chemotherapy (HIPEC) to remove minimal residual disease. Since the peritoneal metastatic rate of patients with colorectal MAC is higher than that of patients with NMAC[14], CRS combined with HIPEC is particularly important. Multiple studies have shown that the survival benefit of CRS and HIPEC in patients with peritoneal metastasis caused by CRC is better than that of systemic chemotherapy alone[92,93]. However, the results of a recent multicenter, randomized clinical trial showed that adding HIPEC to CRS did not benefit patients with peritoneal metastatic CRC (HR = 1.00, 95%CI: 0.63-1.58, $P = 0.99$), which resulted in more frequent postoperative late complications (CRS plus HIPEC group *vs* CRS group, 42% *vs* 32%, $P = 0.083$)[94]. Therefore, CRS alone should be the cornerstone of

therapeutic strategies with curative intent for colorectal peritoneal metastases. CRS plus HIPEC should be selected after a careful and individualized assessment including Eastern Cooperative Oncology Group performance status scores, peritoneal cancer index, and previous chemotherapy lines. Klempner and Ryan[95] suggested that future studies of peritoneal cancer should be attentive to the rich translational opportunities that CRS can supply for multiple avenues of investigation.

Targeted therapy

Traditional chemotherapy usually targets rapidly proliferating cancer cells by interfering with cell division. However, it also nonspecifically targets healthy cells that divide rapidly, such as bone marrow and hair cells, resulting in recognized chemotherapy side effects[96]. Therefore, the main goal of targeted therapy is to ensure that the drugs specifically act on tumor cells, while not affecting normal tissue cells. Currently, targeted drugs for CRC are primarily used in patients with advanced or metastatic CRC, including anti-epidermal growth factor receptor (EGFR) monoclonal antibody (cetuximab) and anti-vascular endothelial growth factor (VEGF) monoclonal antibody (bevacizumab). As previously mentioned, colorectal MAC has a higher frequency of *KRAS* and *BRAF* mutations, with the tumors being located more in the right hemicolon. De Roock *et al*[97] found that the median OS (32 wk *vs* 50 wk, HR = 1.75, 95%CI: 1.47-2.09, $P < 0.0001$) and median progression-free survival (PFS) (12 wk *vs* 24 wk, HR = 1.98, 95%CI: 1.66-2.36, $P < 0.0001$) of patients with *KRAS* mutations treated with cetuximab were lower than those of wild-type *KRAS* patients. In wild-type *KRAS* patients, the response rate of *BRAF* mutation carriers was significantly lower than that of *BRAF* wild-type-containing patients (8.3% *vs* 38.0%, OR = 0.15, 95%CI: 0.02-0.51, $P = 0.0012$). Studies have also reported that patients with metastatic CRC harboring a mutation in *KRAS* or *NRAS* do not respond to anti-EGFR therapy. Therefore, activating *RAS* mutations were regarded as negative predictive biomarkers for anti-EGFR therapy[98-100]. Research on bevacizumab has shown that FOLFOXIRI plus bevacizumab is a viable treatment option regardless of the mutation status of *RAS* or *BRAF*[101]. In addition, in patients with wild-type *RAS* and *BRAF*, the effect of bevacizumab combined with chemotherapy in right hemicolon cancer was better than that of cetuximab combined with chemotherapy[73]. Therefore, in addition to patients with wild-type *RAS* and *BRAF* and whose tumors are located in the left hemicolon or rectum considering anti-EGFR monoclonal antibody plus chemotherapy as the first-line treatment, anti-VEGF monoclonal antibody plus chemotherapy might be a better treatment option for patients with advanced MAC.

Drugs targeting mucins, one of the prominent features of MAC, are potential treatment strategies currently being investigated. Ahmad *et al*[37] found that the MUC1-C inhibitor, GO-203, could inhibit the growth of colon cancer cells *in vitro* and in nude mice, primarily by downregulating the expression of the TP53-inducible glycolysis and apoptosis regulator protein. In addition, since mucins are a class of O-glycosylated glycoproteins, the aberrant expression of O-glycan synthesis enzyme core 2 1,6 N-acetylglucosaminyltransferase (GCNT3/C2GnT-2) can lead to overexpression of mucins[102]. Therefore, targeting GCNT3 can inhibit mucin synthesis in MAC. At present, small-molecule GCNT3 inhibitors are under development[103].

Immunotherapy

The interaction of programmed cell death (PD)-1 on T cells and its interaction with its ligand, PD-L1, expressed on tumor cells and immune cells, including B cells, dendritic cells, and macrophages, plays an important role in immune checkpoint suppression [104]. The binding of PD-L1 on tumor cells to PD-1 on the surface of T cells inhibits T-cell-mediated antitumor immunity[105]. Immune checkpoint inhibitors have significantly improved the long-term outcomes of a few malignant tumors, such as melanoma, lung cancer, and renal cell carcinoma[106-108]. In MAC, the expression of PD-L1 in tumor cells and tumor-infiltrating immune cells is increased[109], which may be related to the high proportion of MSI-H in MAC. Studies have shown that compared to tumors with proficient mismatch repair (pMMR), tumors with deficient MMR (dMMR) highly express immune checkpoint proteins, including PD-1, PD-L1, and cytotoxic T-lymphocyte-associated protein (CTLA)-4[110]. MSI CRC has a higher tumor-infiltrating lymphocyte density and prominent Crohn's-like lymphoid reaction than MSS CRC[111,112]. It has been previously believed that the increased levels of neoantigens produced by frameshift mutations also increase T cell infiltration in MSI CRC. Recent findings have supported this hypothesis, linking the number of frameshift mutations directly to the density of tumor-infiltrating lymphocytes[113]. Based on these observations, several clinical trials are studying the application of PD-1 immunotherapy in MSI CRC. Le *et al*[110] found that the efficacy of pembrolizumab in

dMMR CRC was far better than that of pMMR CRC in terms of immune-related objective remission rate (40% *vs* 0%) and immune-related PFS rate within 20 wk (78% *vs* 11%)[110]. Therefore, pembrolizumab was the first drug that did not consider tumor types and only used biomarkers (dMMR/MSI-H) as treatment options based on overall response rates. Additional data also showed that nivolumab had benefits in advanced dMMR/MSI-H CRC where previous cytotoxic drugs had failed, with 31% of cases responding, and 69% of the overall disease control rate[114]. Therefore, the National Comprehensive Cancer Network guidelines have officially recommended pembrolizumab or nivolumab as second-line or third-line treatment for patients with MSI-H metastatic CRC since 2017[115]. Michael *et al*[116] reported that compared to anti-PD-1 monotherapy, nivolumab combined with ipilimumab had a higher response rate and better long-term clinical benefits, with controllable safety, and thus, should be considered as the first-line treatment for patients with metastatic dMMR/MSI-H CRC. The KEYNOTE-177 trial found that when pembrolizumab was used as the first-line treatment for metastatic dMMR/MSI-H CRC, patients had a significantly longer PFS (median, 16.5 *vs* 8.2 mo, HR = 0.60, 95%CI: 0.45-0.80, $P = 0.0002$) and fewer treatment-related adverse events (22% *vs* 66%) compared to those receiving chemotherapy[117]. Therefore, the US Food and Drug Administration approved pembrolizumab as a first-line treatment for unresectable or metastatic dMMR/MSI-H CRC in June 2020[118]. However, a subgroup analysis in the KEYNOTE-177 trial indicated that patients with metastatic dMMR/MSI-H CRC with *KRAS* or *NRAS* mutations could not benefit from pembrolizumab alone[117]. Whether adding chemotherapy or anti-CTLA-4 to PD-1 blockade could overcome this apparent resistance remains unknown.

PROGNOSIS

The prognosis of patients with colorectal MAC remains controversial, which may be due to the higher TNM stage at the time of diagnosis. Studies have found that the 5-year OS rate of patients with MAC was lower than that of patients with NMAC, whereas no difference in prognosis was found when comparing patients with the same TNM stage[11,24,27]. However, other studies have indicated that in stage III colon cancer, patients with MAC have a poor 5-year CSS rate (MAC *vs* NMAC, 67.9% *vs* 72.7%)[81]. Catalano *et al*[119] believed that the controversy over the prognosis of colorectal MAC was caused by the poor prognosis of rectal MAC, while there was no significant difference between colonic MAC and NMAC. The authors also found, for patients with stage II and III colon cancer who underwent radical surgery, there was no significant difference in prognosis between MAC and NMAC. In addition, MAC is more likely to have nodal metastases, be diagnosed at an advanced stage, and have lower resectability of tumors in the rectum than the colon, thus leading to a poor prognosis of rectal MAC[119].

Studies have also demonstrated that higher age (> 65 years), tumor grades including moderately, poorly, and undifferentiated tumors, tumor location in the rectum, preoperative CEA level (> 5 ng/mL), higher pathological T or N stage, intestinal obstruction, and perineural infiltration were all significantly associated with poor OS in MAC[7,120]. A greater number of lymph nodes examined (no fewer than 12) significantly increased OS (HR = 0.601, 95%CI: 0.537-0.673, $P < 0.001$) and CSS (HR = 0.582, 95%CI: 0.511 to -0.664, $P < 0.001$) in patients with colorectal MAC[120]. *BRAF* mutations were significantly associated with CRC-specific mortality (multivariate HR = 1.64, 95%CI: 1.18-2.27, $P = 0.003$), while MSI-H was associated with a statistically significant reduction in CRC-specific mortality (multivariate HR = 0.28, 95%CI: 0.17-0.46, $P < 0.001$). Considering both MSI-H and *BRAF*, the 5-year CSS rates were 79%, 73%, 65%, and 46%, respectively, in MSI-H/*BRAF*-wild-type, MSI-H/*BRAF*-mutant, MSS/*BRAF*-wild-type, MSS/*BRAF*-mutant[121], suggesting that the prognosis of patients with MAC could be stratified according to the status of MSI-H combined with *BRAF*. Notably, in metastatic CRC, dMMR corresponds to a poorer prognosis compared with pMMR[122]. Immunotherapies, including anti-PD-1 and CTLA-4, emerged in recent years are promising treatment strategy.

CONCLUSION

Colorectal MAC is a unique clinicopathological subtype of CRC. This review comprehensively describes the clinicopathological characteristics, molecular features, diagnosis, treatment, and prognosis of colorectal MAC. One of the most notable

features of MAC is the aberrant expression of multiple mucins, but the underlying mechanism remains unclear. The mucinous features of MAC suggest that it originates from cells expressing MUC2, with no clear understanding of the mechanism underlying mucus production by MAC against radiotherapy and chemotherapy. In the future, in-depth research is needed to clarify the role of mucus in MAC. Colorectal MAC has a higher frequency of *KRAS*, *BRAF* mutations, CIMP-H, and MSI-H, suggesting that the genetic origin of colorectal MAC is mainly related to the serrated pathway of CRC, namely the *BRAF*, MSI, and CIMP pathways, which also explains the high proportion of MSI-H in MAC. MSI-H indicates a better response to immunotherapy, which is hopeful for patients with MAC. The prognosis of patients with colorectal MAC remains controversial, which may be attributed to the poor prognosis of rectal MAC, while there is no significant difference in the prognosis of colonic MAC and NMAC.

In summary, MAC has various clinicopathological and molecular characteristics that differ from those of NMAC. Therefore, personalized diagnosis and treatment of MAC is beneficial. Further studies, such as targeted drugs for mucins, sensitization to chemoradiotherapy, and immunotherapy, are warranted to improve the prognosis of patients with MAC.

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2021 December 27; 13(12): 1584-1596

DOI: 10.4240/wjgs.v13.i12.1584

ISSN 1948-9366 (online)

MINIREVIEWS

Endoscopic therapy of weight regain after bariatric surgery

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Author contributions: Bulajic M and Vadalà di Prampero SF performed the study conceptualized the study and wrote and edited the paper; Boš koski I and Costamagna G reviewed and edited the paper; All authors have read and approve the final manuscript.

Conflict-of-interest statement: Dr Ivo Boskoski is a consultant for Apollo Endosurgery, Boston Scientific, research grant holder from Apollo Endosurgery, Scientific Board member EndoTools. Dr Guido Costamagna is a consultant for Cook Medical, Boston Scientific and Olympus.

Country/Territory of origin: Italy

Specialty type: Gastroenterology and hepatology

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

Peer-review report's scientific quality classification

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

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Abstract

Weight regain following primary bariatric surgery occurs in a significant proportion of patients and is attributed to epidemiological, anatomical and metabolic factors. Surgical revision of these patients has significant risks and limited benefits. Endoscopic revisions that reduce gastric pouch size and diameter of the gastrojejunal anastomosis may offer an effective, safe, less invasive and even reproducible treatment. We herein discuss the indication, selection and feasibility of different endoscopic techniques that could be used in the management of weight regain following primary bariatric surgery. Future research could optimize a personalized approach not only in the endoscopic management but also in combination with other therapeutic modalities for weight regain after bariatric surgery.

Key Words: Morbid obesity; Weight regain; Endoscopic sleeve gastroplasty; Transoral outlet reduction; Bariatric surgery; Full thickness suturing

Core Tip: Weight regain following primary bariatric surgery occurs in a significant proportion of patients and is attributed to epidemiological, anatomical and metabolic factors. Surgical revision of these patients has significant risks and limited benefits. Endoscopic revisions that reduce gastric pouch size and diameter of the gastrojejunal anastomosis may offer an effective and less invasive treatment. We herein discuss the indication, selection and feasibility of different endoscopic techniques that could be used in the management of weight regain following primary bariatric surgery.

Citation: Bulajic M, Vadalà di Prampero SF, Boškoski I, Costamagna G. Endoscopic therapy of

Grade E (Poor): 0

Received: February 9, 2021
Peer-review started: February 9, 2021
First decision: February 28, 2021
Revised: March 14, 2021
Accepted: August 2, 2021
Article in press: August 2, 2021
Published online: December 27, 2021

P-Reviewer: Ghannam WM, Xu PF, Richardson WS
S-Editor: Zhang H
L-Editor: Filipodia
P-Editor: Li JH

weight regain after bariatric surgery. *World J Gastrointest Surg* 2021; 13(12): 1584-1596
URL: https://www.wjgnet.com/1948-9366/full/v13/i12/1584.htm
DOI: https://dx.doi.org/10.4240/wjgs.v13.i12.1584

INTRODUCTION

The phenomenon of weight regain (WR) is a frequent issue in bariatric surgery and has been reported in many studies analyzing obesity recurrence, its related comorbidities and worsening of health-related quality of life[1-3]. The background of WR remains unknown and associated with high initial body mass index (BMI), insufficient lifestyle modification and lack of patient adherence to psychological support[2,4]. Many obese patients rarely change their eating habits and remain sedentary after surgery[1]. The bariatric procedures, independently from the WR phenomenon, could also be responsible for protein malnutrition, iron deficiency anemia, vitamin A deficiency, megaloblastic anemia and dumping syndrome[3].

Despite the complexity of this issue in modern medicine, there is still no consensus on the definition of WR[5]. Luckily, many options are available today ranging from behavioral interventions, drugs approved for weight loss (WL) to endoscopic procedures and revision surgery to overcome some of the factors contributing to WR [6]. It is very important to stress that all bariatric surgery treatments are temporary, and patients should be re-educated. Patient selection through a multidisciplinary approach is essential and a psychologic and/or psychiatric follow-up is necessary before and after treatment, regardless of the type of bariatric revision[7].

Furthermore, primary bariatric procedures are increasing rapidly. As stated in the recent global registry review provided from an international association[8], around 400000 of those interventions are performed annually, among which laparoscopic sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (RYGB) are the most frequent (46% and 38%, respectively)[8,9]. Nevertheless, not all patients undergoing primary bariatric interventions are able to maintain postoperative WL. In a recent prospective, long-term study of obese patients undergoing RYGB after 12 years of follow-up, 93% of them maintained a 10% WL from baseline, 70% maintained a 20% WL, while only 40% were able to maintain a 30% WL[10-12]. According to the same source, revision bariatric surgery in the United States accounts for 15.4% of all bariatric interventions, which is more than triple than in 2011[9]. Besides, up to one third of all patients undergoing LSG or RYGB will experience suboptimal WL and/or significant long-term WR, underscoring the chronic recurrent natural course of obesity and leading to an increased treatment risk and cost, especially when revision surgery is proposed without a specific personalized approach. In comparison with the primary bariatric surgery, both LSG and RYGB show inferior clinical outcomes in terms of morbidity and weight reduction due to an increased technical complexity and anatomical alterations[13,14]. Surgical revision is applied in a traditional manner in 3%–13% of cases, with a 15%-50% of adverse events, a more than double mortality rate compared to primary procedures and high medical costs[15]. A less invasive endoluminal approach, if safe and effective, could be a reasonable option offering a more favorable risk profile in these patients. Endoscopic revision is not only recommended for the WR treatment but also for the management of its complications, such as the dumping syndrome[16].

In this review, we discuss the indication, selection and feasibility of different endoscopic techniques that could be used in the treatment of WR after primary bariatric surgery.

ENDOSCOPIC OPTIONS FOR REVISION OF RYGB

Factors leading to WR after RYGB include dilation of the gastrojejunal anastomosis (GJA), mechanical dehiscence of the staples and patient-related factors like physical inactivity, psychiatric comorbidities and patient adherence to diet. According to the main United States bariatric society[17], the incidence of revisional bariatric surgery rapidly increased in the last decade, from 6% in 2011 to more than 15% in 2018. The management of revisional surgery following RYGB is not standardized yet[18]. Gastric banding revision, conversion to a distal RYGB with creation of a new ileal anastomosis and biliopancreatic diversion/duodenal switch revision represent the possible

management options, together with novel endoscopic procedures, such as suturing and plication, *e.g.*, transoral outlet reduction (TORe) or Revision Obesity Surgery Endoluminal (ROSE) and some other endoluminal procedures [*e.g.*, sclerotherapy, mucosal cryoablation, argon plasma coagulation (APC)].

Sclerotherapy

This type of injection therapy consists of an intramuscular sodium morrhuate application close to the GJA in order to narrow the anastomosis creating a circumferential edema[19]. The endoscopic procedure is performed using a needle catheter to inject 5% sodium morrhuate solution in 2 mL aliquots around the GJA. Vomiting, pain and early satiety are the main reported symptoms in the first 2 mo. A follow-up upper endoscopy is performed after this period to assess the size of GJA, and if needed the same intervention is repeated until a diameter of 10 mm is achieved[20].

The first results showed WL in 75% of the patients at 2 mo follow-up[21]. Another study of Spaulding *et al*[22] analyzed 32 obese subjects with a dilated GJA undergoing sclerotherapy, showing a monthly WL rate of almost 0.4 kg. Furthermore, around 56% of patients reported WL, one third maintained the same initial weight, while around 10% presented WR. The largest series included a retrospective analysis of 231 subjects undergoing one or more sessions of sclerotherapy and showed that those receiving two or three sessions reached higher rates of weight stabilization than the single session group (90% *vs* 60% at 12 mo; $P = 0.003$). The average WL at 6 mo from the previous sclerotherapy session was 10 lbs for the entire cohort, representing 18% of the weight regained after RYGB. A subset of 32% of patients of the same cohort had higher WL at 6 mo (26 lbs). Predictors of a favorable outcome were greater WR and higher number of sclerotherapy procedures with low complication rate[23]. A prospective comparative study from Jirapinyo *et al*[24] analyzed 43 RYGB patients with WR comparing endoscopic suturing (9/43) *vs* sclerotherapy (34/43). Many parameters, such as ghrelin level, BMI, GJA diameter and eating behavior were analyzed. Endoscopic suturing technique showed a significant WL, reduction of outlet diameter and eating behavior improvement compared to the sclerotherapy group. The most relevant point highlighted by this study was the direct correlation between the post-procedural GJA size and WL, establishing the outlet reduction as a significant predictor of WL.

Cryoablation

This novel endoscopic GJA reduction technique employs a cryoablation balloon to apply a circumferential ablation of the superficial mucosal layer by a cryogen, inducing fibrosis with a subsequent reduction of the GJA size and gastric pouch volume. A retrospective study at two university hospitals was performed on subjects with WR after RYGB[25]. Pouch length > 4 cm and/or outlet size > 15 mm were considered as inclusion criteria for cryoablation. Patients were extensively informed about APC *vs* cryoablation procedures and about the new indication of cryoablation [26], which was performed in the caudocranial direction starting from the GJA. In the outlet, ablations were applied circumferentially and clockwise, overlapping the consecutive ablation sites for about 20%-40%. Concerning the pouch, only the greater curvature was ablated. Technical success rate for the outlet ablation was almost 90%, while for the pouch ablation was 93%. At 8 wk follow-up, the GJA size decreased from 24 to 17 mm ($P < 0.001$), the pouch size decreased from 5 to 4 cm ($P < 0.05$) and a total body WL (TBWL) of 8.1% was achieved. In the short term this new approach appears to be safe, effective and feasible for the reduction of the GJA and the pouch, deserving to be analyzed in association with suturing and plication techniques in the future.

APC

APC represents one of the simplest endoscopic techniques for treatment of WR after RYGB. The first case of APC was made up of three separate sessions, every 6 wk[27]. A 2.0 L/min flow rate and a 70 W power were applied on each session. After a 45 d follow-up a 10 mm narrow stoma was observed, experiencing slight resistance while advancing the endoscope. Repeated radiological examinations showed a transient hold up of liquid contrast and a delay of solid contrast. The subject lost around 14 kg in 10 wk and 30 kg after 1 year (weight 67 kg, BMI 29). At 1 year follow-up endoscopy, a 10 mm stable outlet was detected.

APC settings could be different according to processor type, catheter shape and technique of application. However, a non-contact technique with 1.0 L/min and 50-80 W appeared to be quite effective[19]. Patients usually undergo procedures every 8–12 wk as required, until an optimal 8–10 mm outlet size and an effective WL are achieved

[28].

In order to propose the optimal APC settings for GJA thermoablation, a single-center retrospective study analyzed 217 RYGB patients treated by APC[29] for WR. Low-dose (45-55 W) *vs* high-dose (70-80 W) APC were compared: 53.5% patients underwent low-dose APC sessions (2.4 sessions/patient), and 46.5% patients underwent high-dose APC (1.4 sessions/patient). At 6 mo follow-up, the low- and high-dose groups reported 7.3% and 8.1% TBWL, respectively ($P = 0.41$). At 1 year, the low- and high-dose groups reported 5.1% and almost 10% TBWL, respectively ($P = 0.008$). The key point of this study reveals that the high-dose APC appears to be a valid predictor of a greater WL at 1 year follow-up.

Furthermore, a multicenter (eight obesity centers, one in the United States and seven in Brazil) retrospective study was conducted on 558 subjects undergoing APC for WR after RYGB[30]. The mean WL was considered statistically significant, being 6.5, 7.7 and 8.3 kg at 6, 12 and 24 mo, respectively ($P < 0.0001$). At a 1 and 2 year follow-up the group with BMI < 30 kg/m^2 had a greater TBWL than the group with BMI ≥ 30 kg/m^2.

Finally, a randomized controlled study was performed on patients with WR, comparing APC *vs* multidisciplinary approach only[31]. Two groups counting a total of 42 patients were analyzed (22 APC and 20 controls). At a 14 mo follow-up with a crossover at 6 mo, satiety and WL were significantly improved in the APC group and after crossover. A significant WL (9.73 *vs* + 1.38) in the APC group was observed as well as the reduction of the outlet size ($P < 0.001$), early satiation ($P < 0.001$) and improvement of quality of life ($P = 0.04$). However, concerning the total mean WL along the whole follow-up period almost the same WL was observed in both groups.

In terms of WL, early satiation and quality of life improvement, the management of the GJA with APC appears to be safe and effective. Many positive results in treatment of WR after RYGB gives APC the chance to be used as a dual therapy together with other restrictive endoscopic procedures.

Full-thickness suturing TORe

The introduction of full-thickness suturing technique has made an important breakthrough in the endoscopic treatment of obesity. A special role of this novel endoscopic technology, named suturing TORe (S-TORe), is reserved for the treatment of WR after RYGB. Many case reports, case series, prospective studies, systematic reviews and meta-analyses are establishing this procedure as the most frequent and commonly used.

Full-thickness tissue acquisition and suturing has been improved by a new OverStitch device (Apollo Endosurgery, Austin, TX) made up of an over-the-scope single or double-channel suturing device with a curved needle driver and a catheter type tissue screw (Helix) to ensure sequential full-thickness bites (Figure 1), using a non-absorbable 2.0 polypropylene filament to provide simple running stitches or more complex suture patterns (vest-over-pants or purse-string stitches)[32,33]. The suture reloading is performed during the procedure, without removing the device out of patient.

One of the main characteristics of this procedure is the possibility of its combination with APC[34] and other potentially GJA restrictive techniques, such as endoscopic submucosal dissection TORe[35]. The electrocautery injury inducing the subsequent mucosal scarring process plays a key role in GJA reduction. An enlarged GJA diameter has been demonstrated to be a significant risk factor for WR after RYGB[11], and therefore the measurement of the GJA and gastric pouch is mandatory before performing S-TORe.

The efficacy of S-TORe was highlighted in a multicenter randomized study that provided level I evidence that TORe reduces WR following RYGB[36]. Patients undergoing TORe showed a statistically significant WL from baseline (3.5%) than sham controls (0.4%). Patients undergoing TORe achieved a higher rate of WL or weight stabilization compared to controls (96% *vs* 78%, respectively; $P < 0.019$).

Some medium-term follow-up studies[37] showed safety, efficacy and durability of S-TORe in treatment of WR following RYGB[32,38]. In a study of Thompson *et al*[36], considering 331 RYGB subjects undergoing 342 TORe procedures, patients experienced 8.5%, 6.9% and 8.8% TBWL at 1, 3 and 5 years, respectively, with follow-up rates of 83.3%, 81.8% and 82.9%, respectively. Around 76%, 18%, 4% and 2% of all TORe procedures, were performed by single purse-string, interrupted, double purse-string and running suture patterns, respectively, with 9 ± 4 stitches per GJA on average. Reinforcement suturing of the pouch was performed with 3 ± 2 stitches on average in 57.3% of cases[32].

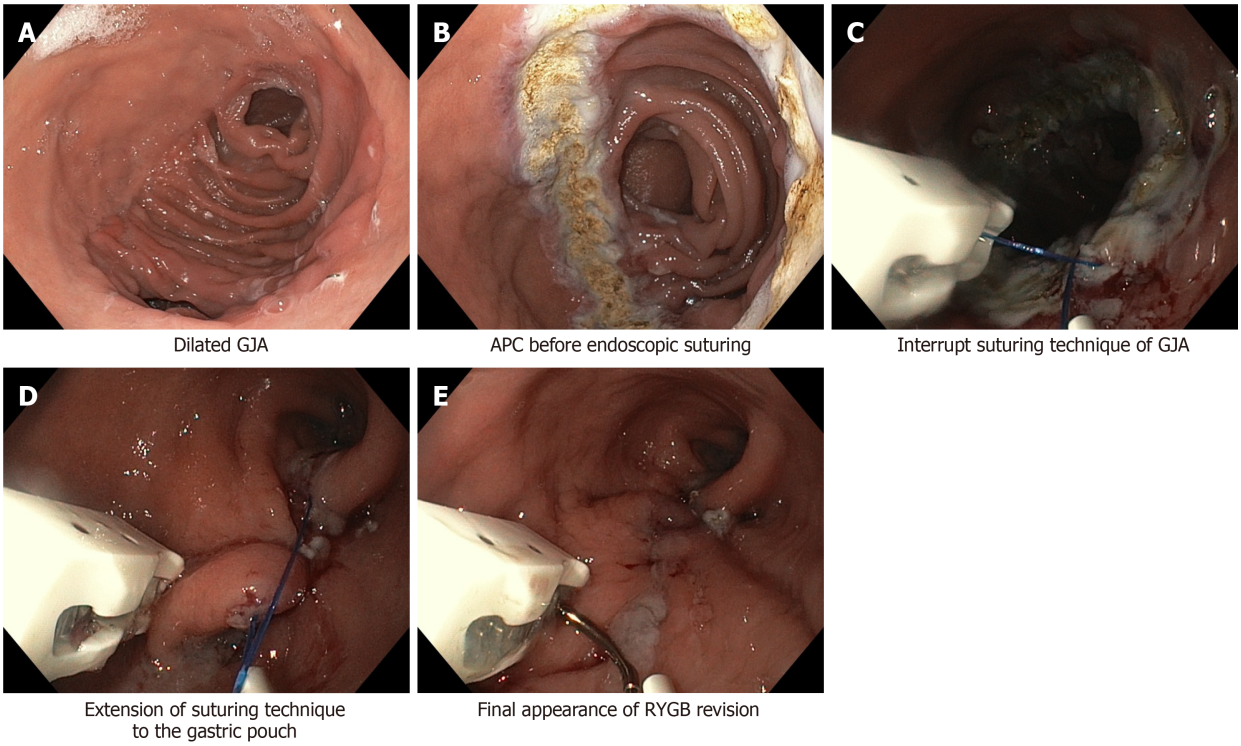

Figure 1 Suturing transoral outlet reduction. A: Dilated gastrojejunal anastomosis (GJA); B: Argon plasma coagulation (APC) before endoscopic suturing; C: Interrupt suturing technique of GJA; D: Extension of suturing technique to the gastric pouch; E: Final appearance of Roux-en-Y gastric bypass (RYGB) revision.

Another retrospective study analyzed 70 patients with WR after RYGB. On the day of S-TORe procedure, the average weight was 116 kg and BMI 42. The study showed that WL and percentage of excess WL (EWL) at follow-up were: 10.7 kg and 18.5% at 6 mo, 8.5 kg and 14.9% at 1 year, 6.9 kg and 12.2% at 2 years, 5.3 kg and 8.7% at 3 years, 3.1 kg and 3.2% at 4 years and 3.9 kg and 7.0% at 5 years. Subjects undergoing a purse-string suturing pattern or presenting a greater reduction in GJA size showed more significant %EWL[38].

In recent years, better quality data have been published in this area. A systematic review and meta-analysis[39] included in a qualitative manner 32 papers, among which 26 analyzed endoscopic full-thickness (FT) suturing, showing the following results in terms of absolute WL, EWL and TBWL: at 3 mo 8.5 kg, 21.6%, 7.3%; at 6 mo 8.6 kg, 23.7%, 8.0% and at 1 year 7.6 kg, 16.9%, 6.6%, respectively. A subgroup analysis highlighted that all these outcomes were superior in patients undergoing FT suturing combined with APC ($P < 0.0001$). The same meta-analysis considered 15 S-TORe studies confirming that the FT suturing was effective in treatment of WR following RYGB and showing better results in terms of WL when APC was performed prior to suturing.

Another systematic review[40] analyzed 26 studies involving all endoscopic bariatric procedures for WR and their combinations (endoscopic OverStitch device and sclerotherapy, APC or mucosal ablation). Endoscopic suturing systems showed best post-procedural results in terms of initial WL at 1 year, which were not confirmed at 18 mo. A greater sustained WL with a peak EWL of 19.9% after 18 mo follow-up was reported in only one study utilizing sclerotherapy. The greatest sustained EWL (36.4%) at 18 mo has been achieved by the combination therapy. Endoscopic suturing systems showed a better performance in terms of technical success (91.8%) and recurrence rate of WR (5%) compared to sclerotherapy or APC (46.8% and 21.5%, respectively)[40].

A further systematic review and meta-analysis[18] on S-TORe following RYGB extracted 13 studies involving 850 patients. The absolute WL at 3, 6 and 12 mo was 6.1 kg, 10.2 kg and 7.1 kg, respectively. The percent TBWL at 3, 6 and 12 mo was 6.7, 11.3 and 8.6, respectively. Among reported adverse events, abdominal pain was the most frequent (11.4%). At 1 year follow-up a significant inverse correlation between post-S-TORe GJA size and WL was observed (-0.11, $P < 0.001$). This study confirms safety and feasibility of S-TORe in patients with WR following RYGB.

Finally, the latest systematic review and meta-analysis was performed to summarize the two most common techniques in terms of efficacy and safety: FT suturing plus

mucosal APC (ft-TORe) and mucosal APC alone (APMC-TORe)[34]. Nine ft-TORe (n = 737) and seven APMC-TORe (n = 888) studies were considered. APMC-TORe was performed as a series of sessions (mean number from 1.2 to 3.0), while a single session was mostly performed in the ft-TORe group. At 3, 6 and 12 mo after ft-TORe the percentage of TBWL was 8.0%, 9.5% and 5.8%, while after APMC-TORe was 9.0%, 10.2% and 9.5%, respectively, with no difference at 3 and 6 mo in terms of WL (P > 0.05). Greater WL with APMC-TORe and numerical trends with ft-TORe correlated with a smaller GJA size after TORe and a greater modification in GJA size. The same meta-analysis demonstrated that significant and similar WL outcomes are provided by both procedures, with good and comparable results in terms of safety. This study highlights the role of APMC-TORe, emphasizing the need for multiple endoscopic sessions as its main disadvantage over ft-TORe.

Full-thickness plicating TORe

Another full-thickness technique proposed for WR following RYGB is the ROSE. This is the modified variant of the Primary Obesity Surgery Endoluminal procedure that uses the Incisionless Operating Platform (IOP; USGI, San Clemente, California). This technique is mostly focused on the management of enlarged pouch[41]. Full-thickness plications are placed by the IOP with the aim of reducing both pouch size and GJA diameter. A tissue approximator, a tissue grasper and a neonatal gastroscope are placed through the IOP. Tissue plication is performed by pulling the grasper into the approximator and aspirating the air to enlarge the plication surface. Then the needle deploys a pair of self-expanding tissue anchors, and the connecting suture is tightened (Figure 2).

A retrospective study analyzed the ROSE procedure's outcome in 27 patients with WR following RYGB from 2008 to 2013[42]. Preoperative average pouch length and GJA size were 6.8 and 2.1 cm, respectively. On average, 4 stitches were placed. Postoperative pouch length and GJA size were 3.4 and 0.86 cm with 50% and 61% reduction, respectively. A control upper endoscopy at 3 and 12 mo was performed in 12 (46%) and 7 (28%) patients. The mean pouch length and GJA size were 5 cm (26.5% reduction) and 1.2 cm (42.9% reduction) at 3 mo and 6.14 cm (10.0% reduction) and 2.2 cm (4.7% increase) at 12 mo, respectively. The %EWL was 8.9, 9.3, 8.0, 6.7, -10.7, -13.5, -5.8, -4.5 at 3, 6, 12, 24, 36, 48, 60 and 72 mo, respectively. Although endoscopic plication achieved the expected reduction in the pouch and stoma diameter at 3 mo, the patients regained the preoperative diameter at 12 mo.

A prospective multicenter study analyzed a total of 116 consecutive subjects with WR following RYGB undergoing ROSE. The procedure was technically successful in 97% of patients, with GJA size and pouch length reduction of 50% and 44% on average, respectively. More than 30% of WR following RYGB had been lost at 6 mo after the ROSE procedure, while EWL was 18% on average. At 1 year follow-up the anchors were still in place and tissue folds were stable[43]. A further report concluded that those patients with a dilated GJA (> 12 mm) who had a post-repair diameter of < 10 mm (30% of 66 patients) had more than doubled the EWL compared with the remaining cohort (24% *vs* 10%; P = 0.03)[44].

Other superficial and full-thickness restrictive procedures

The development of endoscopic suturing technology has led to the safe placement of full-thickness sutures in the gastrointestinal tract, which has created the space for novel endoscopic gastric restrictive procedures[45]. Some of these procedures were used primarily for other indications, such as EndoCinch Suturing System (C.R. Bard, Inc., Murray Hill, NJ) for gastro-esophageal reflux disease[46] or over-the-scope clip (OTSC; Ovesco Endoscopy AG, Tubingen, Germany) for fistula closure[47]. However, the chance to be applied in RYGB revision resulted in their further modification and improvement. In comparison to the previously mentioned major restrictive procedures, these techniques are not widely described in the literature.

StomaphyX (Endo Gastric Solutions) is another device that appeared on the market in the last decade as a gastric restrictive procedure. The first study to test the efficacy and safety of this device was a randomized controlled trial performed in patients with WR following RYGB in 2014[48]. One of the endpoints of this study was to achieve a significant WL in at least 50% of patients compared to a sham group. The gastroscope was introduced through the StomaphyX sheath. A vacuum was used to pull a large gastric fold of the pouch into the device shaft. The stylet, completely located inside the shaft, was advanced through aspirated gastric tissue, and the first polypropylene fastener was deployed forming a plication. Without device removal, 4-6 plications per 3-4 rows (12-24 total) were placed from the most distal portion of the pouch to the GJA, in a circumferential way. The aim was to reduce the gastric pouch and the GJA

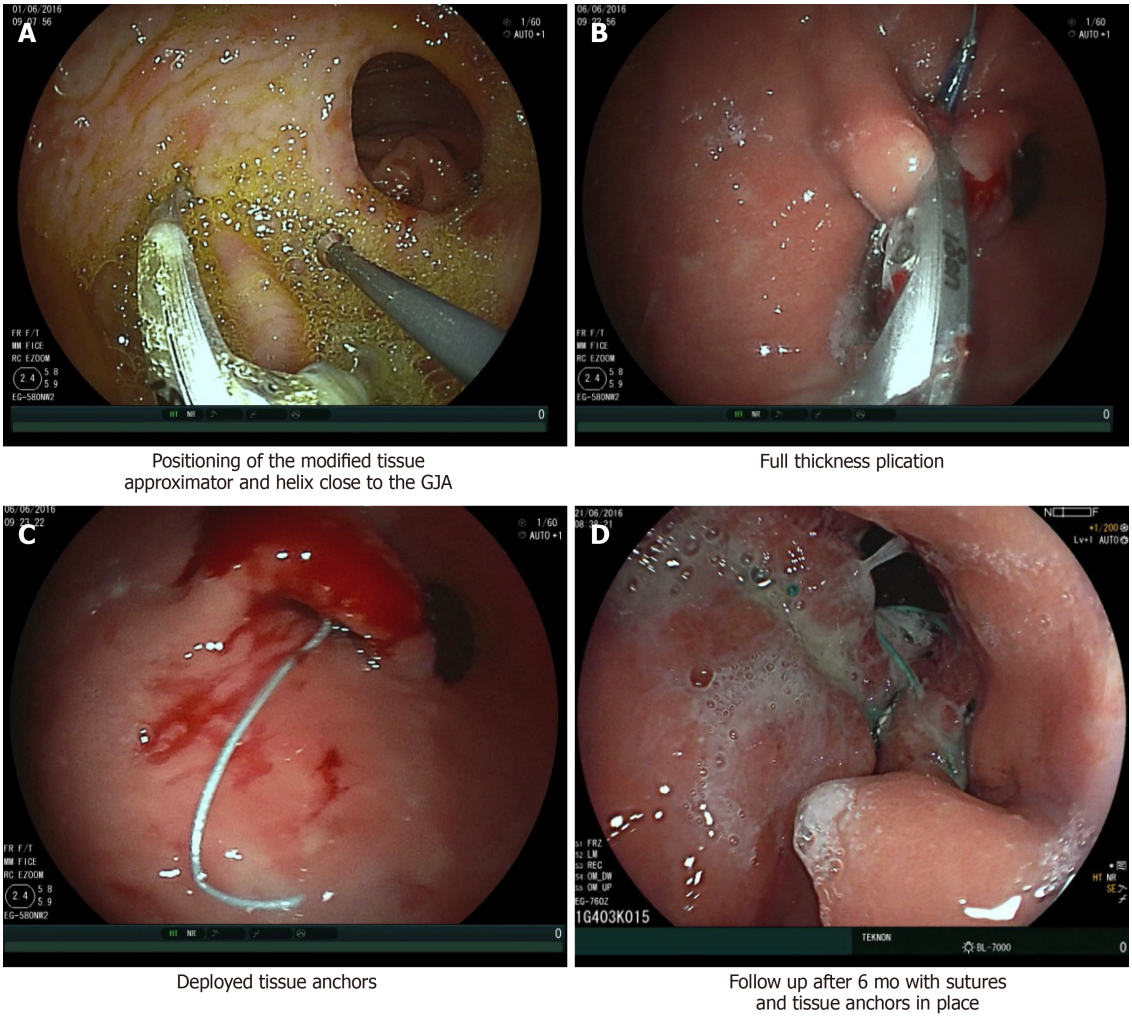

Figure 2 Revision obesity surgery endoscopic (Courtesy of Dr. Roman Turró). A: Positioning of the modified tissue approximator and helix close to the gastrojejunal anastomosis (GJA); B: Full thickness plication; C: Deployed tissue anchors; D: Follow up after 6 mo with sutures and tissue anchors in place.

diameter by at least 75% and 50%, respectively. Enrollment was interrupted earlier because preliminary results showed failure to meet the primary efficacy endpoint in at least 50% of study participants. However, at 3, 6 and 12 mo follow-up patients who successfully underwent this procedure had a significant WL and BMI reduction ($P \leq 0.05$).

Despite the promising initial results of the EndoCinch Suturing System, the success of the procedure was limited by its inability to obtain deeper tissue plications and the necessity to extract the EndoCinch for suture reloading[49]. The device was then modified to allow deeper gastric plications and to avoid the device withdrawal for suture reloading (RESTORe Suturing System, Bard). Furthermore, the technique was adjusted with a sequence of running sutures to embed the greater curvature, similarly to gastric surgical imbrication. This procedure can be considered as a precursor to endoscopic sleeve gastroplasty (ESG)[49]. In a pilot study the aim was to show the feasibility and procedural safety of transoral gastric volume reduction (TRIM procedure) using the Restore Suturing System in patients with a BMI of 30-45 kg/m^2. The TRIM procedure was successfully completed in all patients, with 4-8 plications per patient (6 on average)[50]. The mean EWL at 1 year was 27.7%[51]. The proportion of patients with an EWL of ≥ 20% or ≥ 30% was 57% and 50%, respectively. However, endoscopy at 1 year follow-up showed partial or complete dehiscence of plications in 13 patients.

The OTSC is made of super-elastic shape memory alloy (Nitinol) which re-takes its former unbent shape after the clip is released and thus exerts a constant compression on the tissue between the jaws of the clip. The material is biocompatible and can remain in the body even as a long-term implant, which represents at the same time its limitation for further removal or endoscopic re-intervention. In a series of 94 patients, the best clinical results were obtained by narrowing the GJA by placing two clips at

opposite sites, reducing the outlet by more than 80%[52]. Between surgery and OTSC application, the mean BMI dropped from 45.8 to 32.8. At 3 mo follow-up, the mean BMI was 29.7. At 1 year follow-up, the mean BMI was 27.4. OTSC for revisional endoscopy after RYGB is reliable and effective in treating WR due to dilated pouch outlet with favorable short- and medium-term results. The different types of the OTSC could be applied for the endoscopic closure of traumatic wall lesions of the digestive tract, which could be helpful as a rescue therapy after unsuccessful TORe as well[19,53,54].

ENDOSCOPIC OPTIONS IN REVISION OF SLEEVE GASTRECTOMY

Sleeve gastroplasty reduces gastric volume by 75%-80%. Weight regain seems to be common in LSG after 3 years[55]. If the patient is prone to a continuous WR, sleeve dilation may be a contributing factor that could benefit from additional WL procedures, such as gastric sleeve volume reduction with endoluminal plication[56]. Advances in endoluminal endoscopy and other minimally invasive bariatric procedures have inspired innovative techniques and produced reliable suture tools for gastric volume reduction[57].

One of the first attempts in terms of endoscopic sleeve plication for revision of sleeve gastrectomy reported an M-shaped pattern to ensure adequate plication of the folds and prevention of a secondary internal lumen[58]. Approximately eight sutures were placed in an interrupted sequential stitch, creating the central length of the sleeve. A second layer of two sutures was added to further reduce the gastric body. This was confirmed by an upper gastrointestinal series 1 d later. The patient lost 20 lbs.

A detailed description of 54Fr IOP plication platform was reported in a case report by Jirapinyo *et al*[59]. The procedure was described as a sleeve-in-sleeve procedure, focusing on the placement of the plications in the gastric body using a belt-and-suspenders pattern. First, the distal belt plications were placed perpendicular to the greater curvature in the distal body. Then, two rows of suspender plications were placed parallel to the greater curvature in the midbody. These suspender plications served to shorten the length of the sleeve. Finally, proximal belt plications were placed perpendicular to the greater curvature in the proximal body. No direct plications were placed in the fundus. The patient did well postoperatively and achieved an overall WL of 8% and an EWL of 21%.

A recent multicenter retrospective study analyzed 34 patients with WR after sleeve gastrectomy who had undergone ESG for WL[60]. The technical success was 100%. At 1 year, 82.4% and 100% of patients achieved ≥ 10% TBWL and ≥ 25% EWL, respectively. Median %TBWL was 13.2% and 18.3% and %EWL was 51.9% and 69.9% at 6 mo and 1 year, respectively. The mean %TBWL was 14.2%, 19.3%, 17.5% and 20.4%, and the %EWL was 88.5%, 84.4%, 55.4% and 47.8% for the BMI categories of overweight and obesity class I, II and III at 1 year, respectively. No predictors of outcome were identified in the multivariable regression analysis. This study concludes that ESG appears to be safe and effective in the treatment of WR after sleeve gastrectomy.

However, the trend of implementation of revisional ESG (R-ESG) is increasing, and more prospectively collected data are arriving. In a multicenter study, nine centers with 82 patients who underwent R-ESG for WR after LSG were treated using the OverStitch device[61]. The general purpose of R-ESG was to reduce the volume of the dilated gastric sleeve and shorten its length. R-ESG was performed with full-thickness endoscopic 2-0 prolene sutures applied in various suture patterns (predominantly U-shaped) to overlap the anterior/greater curvature/posterior gastric wall and create a tubular, restricted sleeve along the lesser curvature of the stomach. In a per-protocol analysis, ≥ 10% TBWL was achieved by 72.5% of patients at 6 mo and 81.0% of patients at 12 mo; ≥ 15% TBWL was achieved by 43.5% patients at 6 mo and 52.4% patients at 12 mo. The authors concluded that R-ESG is a safe and effective means of facilitating WL in those with WR after LSG. Future studies of R-ESG should evaluate improvement in obesity-related comorbidities, such as diabetes mellitus, hypertension, obstructive sleep apnea, nonalcoholic fatty liver disease and gastroesophageal reflux disease.

Unlike the LSG, the physiopathological pathways inducing WL and metabolic changes following ESG are still not well investigated. As ESG becomes more and more popular among bariatric procedures, comparison of endoscopic therapies for revision of LSG and ESG is mandatory. Anatomically, the main difference between ESG and endoscopic therapy for revision of LSG is that LSG resects ghrelin producing cells,

while ESG does not[62,63]. In the prospective pilot study, gastrointestinal hormone alterations following ESG and LSG were compared[64]. A significant decrease in leptin levels was observed at 6 mo after ESG. Insulin levels showed a decreasing trend, while insulin secretory pattern was improved. No change was observed in fasting ghrelin levels, glucagon-like peptide (GLP-1) and peptide Y-Y. However, peptide Y-Y, glucagon-like peptide and adiponectin levels were increased, while ghrelin and leptin levels were reduced significantly at 6 mo following LSG. At the same time, insulin levels were unchanged. At 6 mo, compared to ESG, a higher %TBWL (24.4 *vs* 13.3; $P < 0.001$) was obtained by LSG with a significant modification of peptide Y-Y, ghrelin and adiponectin levels. Changes in gut hormones followed different pathways between ESG and LSG. During WL a beneficial change in insulin secretion and a compensatory increase in ghrelin levels were promoted by ESG.

CONCLUSION

Management of WR following primary bariatric surgery is made of medical treatment and/or endoscopic or surgical revision and requires a multidisciplinary approach involving the surgeon (general and plastic), dietitian, endocrinologist, gastroenterologist, psychologist, psychiatrist and fitness trainer[3]. Endoscopic management offers several treatment options, ranging from less invasive approaches to the full-thickness endoscopic suture techniques. Traditionally, revisional surgery is an option in the setting of WR usually performed in patients who failed the medical treatment, but it is related to a significant postoperative morbidity and mortality[65]. Nowadays, revisional endoscopic bariatric therapy is a valid alternative for patients with WR unwilling to undergo surgical treatment again. All these options (surgery and endoscopy) should be considered in a multidisciplinary context[59], explaining and discussing with patients any possible advantage and disadvantage[66-68] in order to propose a "tailored therapy" for every single case.

Concerning the revisional endoscopic therapy, many aspects should be considered while managing patients with WR following primary bariatric surgery. Endobariatric techniques have different purposes according to the type of previously performed surgical procedure. That is to reduce the diameter of the GJA and pouch size in patients with prior RYGB, while reducing sleeve diameter in patients with prior LSG.

Concerning patients with RYGB, the first step preceding the endoscopic treatment is always the measurement of the GJA diameter and pouch. This data appears to be crucial in the decision of the type of restrictive technique, which can be individualized based on the patient's anatomy. Endoscopic TORe of the GJA is the only bariatric revision procedure with level 1 evidence[45]. For pouch > 5 cm, plicating TORe should be considered when GJA is < 30 mm, with S-TORe being performed when GJA is ≥ 30 mm. For pouch ≤ 5 cm, both APC and S-TORe may be considered for GJA < 18 mm, with S-TORe being preferred when GJA is ≥ 18 mm[69]. These latest data, together with expert opinion, could represent a crucial moment in personalizing the endoscopic management to offer each patient the most adequate solution.

Considering endotherapy in patients with previous LSG, the first step is to delineate the exact anatomy of the gastric sleeve, assessing for the dilated areas to plan the suture distribution[61]. Despite the OverStitch device appearing in the most published data in literature, the plication technique is showing promising results. However, a high level of safety, feasibility and efficacy has been reported by both these procedures.

Performing restrictive endoscopic bariatric procedures requires advanced skills in therapeutic endoscopy, including hemostasis and perforation management, other than knowledge of each device feature and performance. For example, it is more difficult to assemble the single operating channel suturing device than the double channel device. No specific, standardized and recognized certification in ESG is currently available by the international scientific societies[45]. However, training in ESG can be obtained as part of a comprehensive endoscopic suturing program through society- or industry-sponsored courses. Similarly, credentialing in ESG is institution specific. Proctoring in initial cases is recommended, although not mandatory, especially for operators with already recognized skills on the OverStitch device. Currently, there is limited data on the learning curve for ESG[70,71]. Those ESG learning curve studies are firstly focused on the number of cases necessary to achieve efficiency and later, mastery. The most recent study defined efficiency "as the point on the learning curve where the operator was able to make procedural improvements to decrease procedure time." Mastery was defined "as the point at which the procedure time became consistent by eliminating

outliers in terms of operating time." Following this analysis, 29–38 procedures were necessary to reach efficiency, while 55 procedures were needed to achieve mastery. Interestingly, the overall outcome of WL was not conditioned by the improvement in procedure time. The majority of endoscopists performing bariatric procedures are not familiar with endoscopic suturing techniques and devices, thus they need to acquire general skills on ESG while learning this complex procedure[45].

Nowadays another important issue is the global coronavirus disease 2019 (COVID-19) pandemic, which has left a strong impact on the management of obese patients, especially in the field of endoscopy, both primary and revisional. Many bariatric centers worldwide were transformed into COVID hospitals thus creating long lasting bariatric procedure waiting lists. Therefore, a position statement from the International Federation for the Surgery of Obesity and Metabolic Disorders was adopted on the practice of bariatric endoscopy during the COVID-19 pandemic[72] concluding that all elective bariatric endoscopy procedures should be delayed for more than 8 wk, both primary and revisional (*e.g.*, TORe, ROSE and R-ESG). In other words, the impact of the COVID-19 pandemic will inevitably bring a worldwide extension of bariatric surgery/endoscopy waiting lists with all possible consequences, both health-related and economic.

In conclusion, the causes of WR following primary bariatric surgery are multifactorial and join both pre- and postoperative parameters. Nowadays, there are several ways of managing WR, but this is still a challenge for both patients and professionals involved in the multidisciplinary team. Scientific societies and organizations should go on collaborating to develop a personalized approach that meets the needs of each individual patient.

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2021 December 27; 13(12): 1597-1614

DOI: 10.4240/wjgs.v13.i12.1597

ISSN 1948-9366 (online)

MINIREVIEWS

Patient-centered developments in colon- and rectal cancer with a multidisciplinary international team: From translational research to national guidelines

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Conflict-of-interest statement: The authors declare no conflict of interest.

Country/Territory of origin: Germany

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

Received: May 10, 2021
Peer-review started: May 10, 2021
First decision: June 24, 2021

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Abstract

Rarely, scientific developments centered around the patient as a whole are published. Our multidisciplinary group, headed by gastrointestinal surgeons, applied this research philosophy considering the most important aspects of the diseases "colon- and rectal cancer" in the long-term developments. Good expert cooperation/knowledge at the Comprehensive Cancer Center Ulm (CCCU) were applied in several phase III trials for multimodal treatments of primary tumors (MMT) and metastatic diseases (involving nearly 2000 patients and 64 centers), for treatment individualization of MMT and of metastatic disease, for psycho-oncology/quality of life involving the patients' wishes, and for disease prevention. Most of the targets initially were heavily rejected/discussed in the scientific communities, but now have become standards in treatments and national guidelines or are topics in modern translational research protocols involving molecular biology for *e.g.*, "patient centered individualized treatment". In this context we also describe the paths we had to tread in order to realize our new goals, which at the end were highly beneficial for the patients from many points of view. This description is also important for students and young researchers who, with an actual view on our recent developments, might want to know how medical progress was achieved.

Key Words: Colon- and rectal cancer; Translational research; Interdisciplinary treatment; Personalized treatment; National guidelines

Core Tip: Interdisciplinary innovative research projects centered on the needs of patients with either colon- or rectal cancer were initiated under the leadership of gastrointestinal-surgeons. Phase III- and translational research trials were applied. Quality of life and disease prevention were involved. The projects initially were heavily criticized, but now are routine methods of treatment or goals of modern translational research. The paths may be interesting for the scientific community, and for young researchers, even students.

Citation: Link KH, Kornmann M, Staib L, Kreuser ED, Gaus W, Röttinger E, Suhr P, Maulbecker-Armstrong C, Danenberg P, Danenberg K, Schatz M, Sander S, Ji ZL, Li JT, Peng SY, Bittner R, Beger HG, Traub B. Patient-centered developments in colon- and rectal cancer with a multidisciplinary international team: From translational research to national guidelines. *World J Gastrointest Surg* 2021; 13(12): 1597-1614
URL: https://www.wjgnet.com/1948-9366/full/v13/i12/1597.htm
DOI: https://dx.doi.org/10.4240/wjgs.v13.i12.1597

INTRODUCTION

Diagnosis and treatment of patients with colon- and rectal cancer has improved significantly in the last three decades. A multidisciplinary approach was the main driving force leading to higher cure rates[1]. In recent years treatment individualization/personalized medicine contributed to better treatment results in both adjuvant and palliative therapies, *e.g.*, respecting the mutational status of microsatellite stability (MSI), as outlined in current guidelines such as from the German Cancer Society[2]. Surgery of colon- and rectal cancer also has improved, avoiding local relapses[3,4]. Minimal invasive surgery in both tumor entities improved the quality of life[5-7]. The lethal fate of patients with metastasis, *e.g.*, to the liver[8,9] or to the peritoneum[10,11]

Revised: August 7, 2021
Accepted: November 24, 2021
Article in press: November 24, 2021
Published online: December 27, 2021

P-Reviewer: Ogino S
S-Editor: Gao CC
L-Editor: A
P-Editor: Gao CC

has been stepwise diminished, but not abolished. In the late 1980's surgery was the only treatment of choice for patients with primary colon- and rectal tumors in Germany. The 5-year survival rates of patients with advanced tumor stages, *e.g.*, in stage UICC III was 49% for colon cancer and 38% for rectal cancer at our university hospital[1,12,13], with the surgeon and hospital being significant prognostic factors for survival[13-15]. The local relapse rate for rectal cancer patients exceeded 30% at our hospital in a long-term review, despite them being originally operated on in curative attempt[16]. Only the minority of the patients with liver metastases were resected for cure[8], and patients with peritoneal carcinosis received palliative therapy only with 5-fluorouracil (5-FU) or 5-FU + folinic acid (FA) at median survival times below 15 mo [10,11]. Early detection of high-risk colon adenomas or early stage curable cancers by screening colonoscopy was not yet the standard to improve incidences and overall survival (OAS) rates of colon and rectal cancers. Psycho-oncology was unknown in cancer treating units and palliative homecare as well.

These unsatisfactory results encouraged us to seek significant improvement. The first author (Link KH), with grants from the German research foundation [Deutsche Forschungsgemeinschaft (DFG)], studied tumor biology at the department of basic research, USC Cancer Center in Los Angeles, as a postdoctoral student with the late Charles Heidelberger, who had developed 5-FU. International exchanges and the recommendation of Ch. Heidelberger led to the use of multimodal therapy for colon- and rectal cancer patients and to seek a possibility to individualize systemic treatment. The cooperation with the French group of the late Professor Jacquillat C and his successor, Professor Khayath D at Hospital Salpetrière, Univ.Paris, France initiated the idea to downstage advanced primarily nonresectable metastases by neoadjuvant chemotherapy. After suggestion of Link KH to P.V. and Danenberg K, then leading the "Fluoropyrimidine" laboratory of Ch. Heidelberger, they were able to show in cooperation with the medical oncologists at the USC cancer center that low expression of the thymidylate synthase (TS) in human metastatic tumor cells could predict a beneficial response to 5-FU (± FA)[17]. Previous work had already shown that the quantitative expression of TS correlates with the cytotoxicity of the 5-FU-anabolite FdUMP.

Subsequently, since 1987, under the leadership of Link KH, a multidisciplinary team at the Ulm University Cancer Center was established in cooperation with oncologic teams in 64 hospitals in Germany nationwide ["Forschungsgruppe Onkologie Gastrointestinale Tumoren" (FOGT) (= Multidisciplinary Study Group on Oncology of Gastrointestinal Tumors)]. At the Department of Surgery I (General and Visceral surgery) of the University Hospital of Ulm (Head: Professor Beger HG) a translational research project with a cell culture laboratory under continuous funding by research grants from the German Research Society "DFG" was established and integrated to modernize the traditional surgical treatment of primary tumors and metastases.

In addition, the demand for a better care for patients in the outpatient setting, either after curative surgery or in the palliative situation, became increasingly obvious. Psycho-oncologic expertise (MSch) was integrated into patient care. With the rising evidence of the significant benefit of screening colonoscopies, we initiated public awareness events on cancer prevention, including better nutritional habits (Maulbecker-Armstrong C, Link KH).

All efforts were initiated with a mindset of putting the patients in the center of our team´s efforts. With this we succeeded to establish many significant innovations in our country, with relevance worldwide.

During a time of eminence- and not evidence-based medicine, these provocative results were initially disregarded by many colleagues, but the significantly improved survival of patients with advanced colon- and rectal cancers prompted the field to integrate the new treatment concepts in their programs.

In this paper we want to summarize the results of our teamwork and therewith motivate research teams in oncology to perform multidisciplinary treatment approaches and to stimulate translational teams in basic and clinical research for the benefit of patients with colon- and rectal cancer. For example, an experienced biometrician is an essential member of the team.

The developments and results of multidisciplinary treatments included translational research with efforts towards a better outcome for patients with colon- and rectal cancer, including prevention of the disease.

PRIMARY TUMORS

We were trained in best quality procedures when operating on patients with primary tumors or metastases. We reported our results regularly and demanded quality control and benchmarking. We participated in corresponding expert groups and boards of the German Cancer Society and the Convent Leading Hospital Surgeons[1,12,14,18].

The team initiated the first nationwide multicenter phase III prospective controlled randomized trials for adjuvant chemotherapy of colon cancer patients with UICC stages II B (T4N0M0) and III (TxN1-2M0) (FOGT-1, 855 patients), and adjuvant radiochemotherapy of rectal cancer patients with UICC stages II + III (FOGT-2, 796 patients) involving three systemic treatment arms, after United States-research teams had shown that multimodal treatment improved the survival in both tumor entities and reduced local relapse rates in rectal cancer (reviewed in[13]). In both trials the patients received postoperative adjuvant systemic chemotherapy in the three arms: A: 5-FU, B: 5-FU + FA, C: 5-FU + interferon alpha (IFN-α). Rectal cancer patients were treated with radiochemotherapy (50.4 Gy + 5-FU) before the systemic chemotherapy arms were started with the same protocols as in FOGT-1. In FOGT-1, 5-year OAS was significantly improved by 11.5% from 60.5% (the control arm result corresponded to the results of the initiating United States trial of Ch. Moertel) to 72%; the 5-year OAS was not improved by adding IFN-α to 5-FU (61.7%)[19]. In rectal cancer stages UICC II + III, local relapse rates of 16.7%, 13.6%, and 17.1% in arms A, B, and C, respectively, were not differing in significance, but due to the radiochemotherapy and to the modern protocol-standardized (TME) surgery, turned out to be significantly lower than the 33% in historic controls[15,16]. Importantly, in FOGT-2 the 5-year overall survival rates showed no difference between treatment arms A (60.2%), B (60.3%), and C (59.9%)[20]. These findings were similar even after 7 years of observation. We were the first to show a lack of benefit in terms of OAS time improvement in rectal cancer patients in comparison to colon cancer patients treated with the same systemic chemotherapy[21]. In addition, we clearly demonstrated that the patient's age did not influence the outcome of colon cancer patients[22]. However, in rectal cancer, the 5-year OAS survival of aged patients was even reduced in the more intensive arm B (5-FU + FA)[21]. Regarding this and other differences between colon- and rectal cancer patients, we reviewed our FOGT data and the data from the literature and were among the first worldwide to make the statement that from many points of view (epidemiology, carcinogenesis, prevention, response to treatment *etc*.) colon cancer is different from rectal cancer, and the term "colorectal cancer" should be abandoned[13,23,24].

Adjuvant (and neoadjuvant) therapy can be a considerable overtreatment in a subset of patients that either never develop metastases or local relapses due to early tumor stages, or patients who progress despite of multimodal treatment (resistant micrometastases). Therefore, we searched for ways of predicting a patient's response towards 5-FU based multimodal treatment with molecular biology tests. Vital primary tumor biopsies were collected and then tested for the quantitative expression of the enzyme set TS and dihydropyrimidine dehydrogenase (DPDH), both involved in cell proliferation (TS) or 5-FU catabolism (DPDH). The analysis of samples from 295 patients was performed at the leading laboratory of Peter Danenberg at USC/Los Angeles. Most interestingly, and other than expected, patients with high TS had significantly higher survival rates than those with low TS; Low DPDH seemed to increase the survival rates[25-27].

With study groups from the universities of Heidelberg and Mainz we tested samples from the multimodal treatment study FOGT-4 for the predictive potency of the MSI status[28] and the VEGFR/EGFR expression[29]. It could be shown that expression of both in primary tumors correlates with survival under 5-FU based multimodal therapy. MSI meanwhile has been integrated into the national guidelines [13,23,24]. With this step towards personalization of multimodal treatment in colon- and rectal cancer patient, we were among the first three groups worldwide to start interdisciplinary research on this issue. In summary, reviewing our own experience and regarding the possibilities of treatment individualization in multimodal therapy, the 5-year survival rates was increased in colon cancer UICC III from 49% *via* 72% (FOGT-1 Arm B) to potentially > 85%[1,26].

In our team and in the FOGT protocols we always delineated the surgical procedures corresponding to the best standard (CME in colon cancer[3], TME in rectal cancer)[4,30], being in productive scientific exchange with Hohenberger *et al*[3] and Heald[4], who developed and propagated these techniques and attended several of the meetings of our International Colon- and Rectal Cancer Club (ICRCCs; *www.ICRCC.de*) (Figure 1). When we compared the FOGT-1 and -2 survival curves among hospitals,

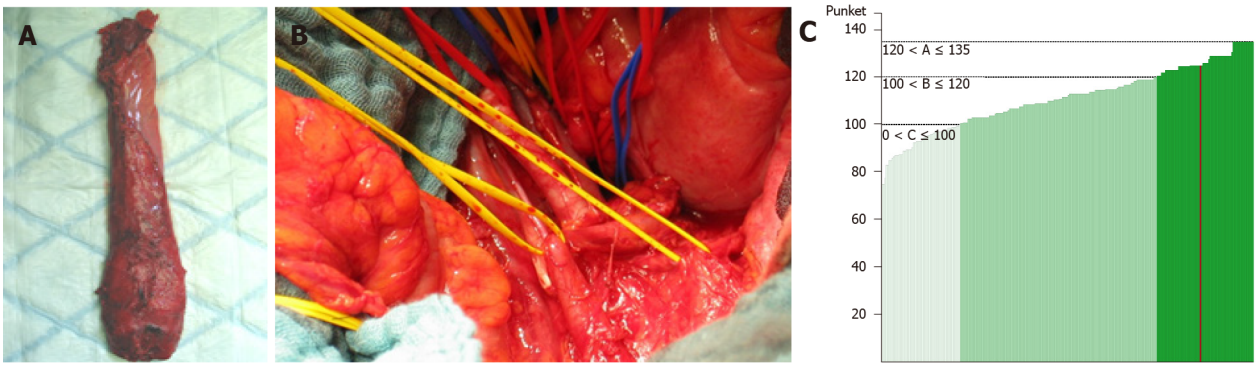

Figure 1 Examples for surgical treatment recommendations in the FOGT protocols and quality level of one participant´s surgical team applying these recommendations (Link KH) in the benchmarking of German Cancer Society Bowel Centers. A: The best standard-of-care in rectal resection was total mesorectal excision according to Heald RJ; B: Lateral nerve preserving lymph node dissection could be applied in cases with lateral LN-metastasis (diagnosed in the preoperative MRI) according to Mori T; C: The variation of results of quality control in German Bowel Centers is demonstrated [marked in red color is the position of APK Wiesbaden under leadership of the first author; dark green = bowel units that were rated as top groups (Link KH)].

we could not find significant differences in hospital volume categories — due to the strict surgical guidelines and repetitive discussion of those in study group- and ICRCC-meetings[13,23,24].

We also aimed at improving the standards of therapy in metastatic diseases. Our scientific strategy of involving translational research as consequently as possible, and the inherent initial difficulties in convincing surgical and medical oncologic colleagues at top level positions are described in the following.

METASTASES

Treatment individualization in colorectal liver metastases

At the time we started our multidisciplinary treatment concept, patients with liver metastases either were resectable according to standard indications[8] or they received palliative chemotherapy with 5-FU + FA either by systemic or by hepatic arterial infusion (HAI) chemotherapy. Systemic treatment with additional FA was even opposed by some medical oncologists at the Ulm Cancer Center at that time. HAI was performed due to the low effectivity of systemic 5-FU or 5-FU + FA, the therapeutic standard at our surgical department at that time in the late 1980s and early 1990s. Response and survival with HAI were twice as good as with systemic treatment[8,31].

Therefore, a rationally designed program for HAI in nonresectable "colorectal liver metastases" (CRLM) was developed with a translational research program. Two metastatic human colon cancer cell lines and individual cell suspensions from human metastatic tissue (mostly CRLM) in the human tumor colony assay (HTCA, first described by Hamburger A and Salmon S (for details see[32,33]) were established. Available drugs were tested for their concentration response behavior and for the optimal treatment time[34,35]. Similar approaches to find out best basic treatment conditions using patient-derived cell lines and *in vitro* cytotoxicity tests are standard practice today. These extensive *in vitro* experiments revealed a broad variability of cancer cell sensitivity between individual patients (as it is the factual dilemma *in vivo*) and offered first cues on how chemotherapeutic treatment may be optimized for the individual patient. We successfully translated these findings into clinical action by adding the *in vitro* active drugs, Mitomycin C and Mitoxantrone, to our primary HAI-protocol with 5-FU + FA according to their potential effectivity at the same conditions *in vivo* as tested *in vitro* (calculated drug kinetics in the arterial blood during infusion time was matched to the optimal *in vitro* conditions)[32,34-37]. The response rates and survival times achieved by these protocols increased from 45%/20 mo (HAI with 5-FU + FA) to 54%/26 mo (HAI with the combination of 5-FU + FA + Mitoxantrone + Mitomycin C (MFFM)[31,36,38]. The combination of Mitomycin C and Epirubicin, with high i*n vitro* phase II response rates at 10 μg/mL, was used for chemoembolization [39].

An important step in gaining confidence in our following study protocols using *in vitro* tests with assumed relevance for *in vivo* treatment was the *in vitro* confirmation of the immediate drug effects on tumor cell viability seen *in vivo* after isolated liver

perfusion (ILP) with high drug concentrations in a reconstruction experiment: For this experiment in CRLM patients, we did an incision biopsy of a metastasis and performed an HTCA drug cytotoxicity test as described above. After 1h of ILP (*e.g.*, with 5-FU + Mitomycin C), another metastasis was excised and the cell suspension was tested for its colony forming efficiency. To our great satisfaction, the colony growth inhibition rates after drug exposition *in vitro* correlated to those after *in vivo* treatment[33]. This made us hopeful to be able to individualize HAI by *in vitro* drug testing in the HTCA. First, being cautious, we correlated the *in vitro* results with the individual clinical responses to HAI, and then we used the drugs effective *in vitro* to add to 5-FU + FA for HAI *in vivo*[40,41]. After we had seen that patients with low TS responded very well to HAI with 5-FU[27,42] and that drug selection with the HTCA was possible[40] we finally added TS determination to our prospective *in vitro* individualization trial. With this strategy we were able to show an impressive response rate of 77% and median survival time of 32 mo in *in vitro* sensitive patients *vs* 9%/17 mo of the *in vitro* resistant patients receiving the standard MFFM protocol (Table 1)[42].

In the meantime, systemic chemotherapy had improved with major steps (FOLFIRI or FOLFOX). In a subsequent phase III decision aiding trial, supported by the European Organization for Research in Treatment of Cancer (EORTC), we tested if "TS-low" patients with multiple, unresectable metastases from colon and rectal cancer primaries could be selected to receive systemic i.v. chemotherapy with 5-FU-FA only without inferiority compared to the more toxic combination of 5-FU + FA + Irinotecan (FOLFIRI). TS quantitative expression was determined from diagnostic fresh biopsies by the Danenberg P and Danenberg K laboratories, and the results were reported timely to the treating center before the protocol assigned therapy was started. In this decision-aiding trial (FOGT-5), the TS-low patients treated with 5-FU + FA i.v. had nearly the same response rates as the (TS-low) FOLFIRI patients. Response towards FOLFIRI was comparable in TS-high and -low patients but significantly superior to 5-FU + FA in TS high patients, demonstrating the potential of TS in selecting patients that can profit from the more aggressive FOLFIRI protocol (Table 2)[27].

Downstaging and resection of CRLM

Since HAI with our stepwise concepts for personalized chemotherapy using cell culture and molecular biology methods resulted in higher response rates, and, compared to HAI with 5-FUDR, with only low hepatotoxicity[43], we started to resect patients with good responses ("downstaged CRLM's"). By this decision, we were able to achieve long term survivors (survival ≤ 81 mo, median survival 39.2 mo) in some cases exceeding 5-years and achieving even cures. Together with the Paris group of Professor Henry Bismuth we were the first worldwide with a major patient number reported to demonstrate that this treatment concept is possible and successful[38,44]. This treatment concept soon became standard for primarily nonresectable patients in our department in case of adequate responses and resectability, and meanwhile has become (the demanded) standard for systemic chemotherapy of CRLM in the national guidelines[2].

Split time resection of unresectable CRLM

The question of resectability sometimes was highly controversial and experts denied resectability of some patients, either at their first presentation or after relatively good responses. One young patient in the year 1992 was sent home from a renowned German liver transplantation unit judged to be nonresectable and recommended to have palliative chemotherapy at home with 5-FU + FA. According to our assessment, she was not suitable for primary HAI aiming at downstaging/resection. Since she was 35 years old and had two small children, we decided to resect the huge metastasis reaching into the pelvis by extensive right hepatectomy. Then we performed individualized HAI of the metastases remaining in the left liver segments. After 3 HAI cycles the patient had recovered well, the metastases had responded and the liver had regenerated as expected. The two metastases were resected for cure and the patient received additional HAI with the same protocol applied initially. She remained tumor free for seven years. Fatefully, she returned with jaundice due to lymphangiosis of the hepatoduodenal ligament, a noncurable situation. This split time liver resection with interim individual HAI was the first case reported worldwide (Figure 2)[8]. We (Link KH) applied this concept several times, even resulting in individual cures. One patient, received his second resection of a segment I metastasis by Link KH together with the top specialist for segment I resections from China, Professor Peng SY from the Department for Liver and Transplantation Surgery at Zhejiang University, Hangzhou, China, on occasion of his participation in an ICRCC-congress in Wiesbaden, and the

Table 1 Individualized response prediction in patients with hepatic artery infusion[42]

Response predictor	Clinical outcome		Median survival (mo, range)
	Beneficial response (%)	No response (%)	
HTCA			
Sensitive	58	42	28 (3-75)
Resistant	33	67	19 (5-48)
TS			
Sensitive	64	36	26 (6-48)
Resistant	20	80	26 (3-75)
HTCA + TS			
Sensitive	77	23	32 (5-75)
Resistant	9	91	17 (3-28)

HTCA: Human tumor colony assay; TS: Thymidylate synthase.

Table 2 Influence of quantitative thymidylate synthase expression in individual metastatic biopsies on response rates and median survival times in patients with metastatic colon- or rectal cancer[27]

	TS low		TS high	
	5-FU + FA	5-FU + FA + Irinotecan	5-FU + FA	5-FU + FA + Irinotecan
Patients (n = 119)	39	38	23	19
Median survival (95%CI)	18.4 (12.1-25.2)	18.8 (12.0-23.2)	19.2 (5.6-33.3)	15.2 (8.4-26.0)
Beneficial response[1] (%)	33	45	22	47, P = 0.077[3]
No response[2] (%)	67	55	78	53

[1]Complete and partial response.
[2]Stable and progressive disease.
[3]Fisher's exact test (one-sided).
TS: Thymidylate synthase; 5-FU: 5-Fluorouracil; FA: Folinic acid; CI: Confidence interval.

patient remained tumor free for the rest of his life exceeding 5 years. Split time resection thus was the precursor of TSH (Two Stage Hepatectomy) and ALPPS (Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy), both of which have become the treatment of choice in specialized surgical liver units[9,45,46].

Peritoneal carcinosis and malignant ascites

Peritoneal carcinosis at the time of our team formation was a death sentence to the patients. Sugarbaker P initiated the treatment "Peritonectomy with Hyperthermic Intraabdominal Chemotherapy" (HIPEC). The convincing data reported by several groups including a phase III trial and our own experience in Ulm, as one of the first teams in Germany and in Europe starting to apply this very extensive procedure, led us to propagate peritonectomy and HIPEC[10,11] on occasion of international meetings, actively involving Professor Sugarbaker P (*e.g.*, "ICACT"/Professor Khayath D/Paris, "ICRCC-meetings", *etc.*). After initial opposition, the procedure finally has been taken up into the S-3 guidelines of the German Cancer Society to be recommended as treatment in "isolated" peritoneal carcinosis in qualified patients[2] We used Mitoxantrone due to the excellent *in vitro* phase II results and applied the drug for HIPEC at the test concentration of our HTCA-tests with individual tumor cell suspensions from colon-, rectal-, and ovarian cancer metastases[32,47,48]. Later, Oxaliplatin was suggested by expert groups. Although qualified according to basic research experiments[49], we were reluctant to use oxaliplatin since the drug may exert severe systemic toxicity due to its significant peritoneal resorption, which did not occur with Mitoxantrone.

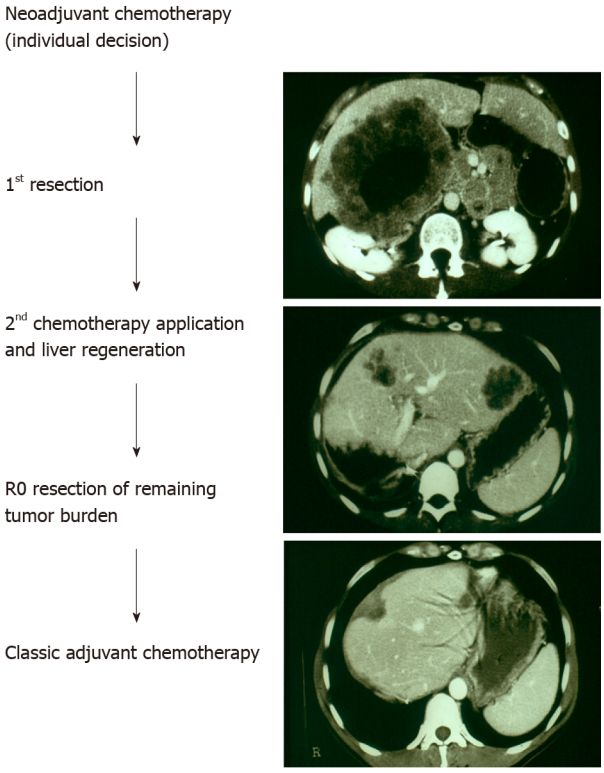

Figure 2 Individualized multistep treatment of a patient with primarily nonresectable isolated colorectal liver metastasis. A 35-yr-old woman with bi-lobal metastatic disease in the first step was partially resected by extended right hemihepatectomy, then treated with individualized hepatic artery infusion chemotherapy (HAI), then R0 resected by atypical resections on the left side. She then received three cycles of postoperative adjuvant chemotherapy applying the same HAI protocol. The resected metastases on the left side had shown nearly complete pathological responses. The patient lived tumor free for 7 yr and then presented with obstructive lymphangiosis in the hepatoduodenal ligament. She died due to disease progression after treatment with systemic chemotherapy.

Malignant ascites occurs in peritoneal carcinosis, and the palliative primary treatment option is diuretic therapy. Based on our *in vitro* phase II results, we used Mitoxantrone at 10 μg/mL for 1 h exposure as repeating intraperitoneal instillation therapy at 1-mo intervals as second line option after failure of diuretic drugs. Since this treatment was very effective and very well tolerated, we propagated it and then conducted a retrospective study on the effect of Mitoxantrone instillation therapy together with the gynecological department of the University Heidelberg. The data of the examination were convincing, and the treatment was approved by the German Drug Commission[32,47,50].

PREVENTION

Since Link KH at the Charles Heidelberger laboratory had a research project on carcinogenesis and tumor biology, we were interested on carcinogenesis and risk factors for colon- and rectal cancer. We were the first in Germany to organize a conference together with the CCCU on the topic "Nutrition and Cancer" in 1996 and the conference presentations were published in a book. At that time, we proposed a beneficial effect of a mediterranean diet. Although the idea was initially rejected by gastroenterologists, it was later approved by the European Prospective Investigation into Cancer and Nutrition (EPIC) with participation of the German Institute of Nutritional Science (Dr. Boeing HH). Now this primary preventive measure among others is recommended in the S3 guideline[2].

In parallel, we became very interested in the benefit of (secondary) preventive colonoscopy and continuously supported propagating initiatives, which have been actively conducted by Professor Riemann J, a participant of the ICRCC-meetings, who, as a most renowned gastroenterologist, has established the preventive colonoscopy to be recommended and paid for by the health insurances for all Germans (males at 50-year-old, females at 55-year-old, persons at risk earlier ages and in closer intervals). We (Maulbecker-Armstrong C and Link KH) co-founded the campaign "du bist kostbar" ("you are of great value") in Germany for the German Cancer Society and

others to promote prevention of various cancers, *e.g.*, involving Professor zur Hausen H, Nobel Prize Winner 2008 for his development of a vaccine against Human Papilloma Virus (HPV)/cervical cancer, and other preventive activities (Maulbecker-Armstrong C) together with Professor Riemann J (Mannheim) and Professor von Knebel-Doeberitz M, Director of the Department of Applied Tumor Biology at the University and German Cancer Center, Heidelberg. With "du bist kostbar" in 2013/2014 we conducted a wide initiative to improve the participation of male (in parallel, of course, also female) candidates for preventive colonoscopy, involving gastroenterologists, surgeons and prominent supporters from the field of sports such as a multiple Olympic gold medal winner and a soccer World Cup- and European Championship winner. The 1-year public initiative "1000 brave males" in Wiesbaden, the capital of the German state Hessen, convinced 1645 males and 1588 females to have a preventive colonoscopy. Regarding the usual frequency of high-risk adenomas and early cancers being detected and removed, potentially > 150 lives were saved by this 1-year campaign. The campaign gained political momentum and public interest initially in the state of Hessen and subsequently in Germany (German Cancer Society, *e.g.*, special session on the congress of the German Cancer Society 2018, organized by Link KH) (Figure 3).

But prevention measures shouldn't only include secondary preventive measures. Although thankfully preventive colonoscopies can detect and treat colon adenomas that might develop into invasive cancer, many colonoscopies without tumor symptoms still detect early stage lesions.

By understanding carcinogenic drivers in our everyday environment, we can take measures of primary prevention by reducing exposure and thus reducing the overall incidence of colon and rectal cancer.

Molecular pathologic epidemiology (MPE) is a novel approach in identifying those endogenous and exogenous exposures[51]. The computational integration of big-data consisting of potentially modifiable factors like dietary lifestyle, environment and also microbiome with pathological data of genome, transcriptome and metabolome of neoplasia can identify personal strategies for risk reduction[51,52].

Furthermore, MPE could identify patients with an increased stochastic risk tumor development and offer more intensive screening measures to this subpopulation.

Obviously, primary preventive measures are the most effective in reducing the threat that arises from neoplastic diseases, but the combination of both primary and secondary, yet even tertiary preventive measures offers the best chances in early stage detection of cancer.

PATIENT'S QUALITY OF LIFE

The patient's interests have always been in our focus, not only regarding the gain in their life expectancy by improving our therapeutic possibilities, but also with respect to their personal quality of life[53-55]. We early organized high-quality homecare by nurses from our Ulm University Hospital, including home parenteral nutrition (which in the beginning 1990's was not yet available from companies at that time). A psycho-oncologist (MSch) joined our team. We also involved the patient's wishes on the decision for multimodal therapy and received a national prize for this step[56]. Taking various high level and responsible positions in cancer societies and surgical societies in Hessen and in Germany, we (Link KH) also supported the psycho-oncological and social support of tumor patients and their families. With a 1 million Euro initial grant and then successive grants from the German Cancer Aid Fund (Deutsche Krebshilfe), we established 5 counseling units for patient support, accessible for free (Link KH).

Besides advocating for the patient's quality of life, we were also demanding surgical and oncological treatment quality with low morbidity/mortality in nationwide campaigns[14] and by participating in structure and S-3 guideline commissions of the German Cancer Society (Link KH: German Cancer Society S-3 guideline and structure commissions for "colorectal" cancer, pancreatic cancer, and for psycho-oncology). We took part in the benchmarking for treatment and structure quality of more than 260 "Bowel Centers", that had been certified by independent auditors according to the guidelines of the German Cancer Society (for a benchmarking result see Figure 1C). The patient's opinions towards neoadjuvant radiochemotherapy in rectal cancer were evaluated and disseminated by publications and oral presentations[57,58]. Quality of life was not diminished in our FOGT 1 + 2 Arms A and B chemotherapy protocols. By using the 2 h infusion of 5-FU, based on the cell culture experiment results, we soon recognized, that this treatment timing caused less toxicity than bolus injections. The

Figure 3 German action for secondary prevention of colon- and rectal cancers by colonoscopy/polyp excision. Public action "1000 brave men" (left, "1000 Mutige Männer") with support of public personalities in sports (left, Otto K, Olympic gold medal champion) and politics (right, Bouffier V, Hessian state prime minister).

toxicity in FOGT-1 + 2 were relatively low and the patients´ acceptance rates of the full protocol treatment, indicating a good quality of life in Arms A (5-FU) and B (5-FU + FA) for 1 year, was high; however, IFN-α in arm C (5-FU + IFN-α) had to be interrupted frequently[56].

DISCUSSION

The success of our team´s consistent multidisciplinary scientific work with several original innovations for the benefit of patients, together with our research philosophy, could be a model for young academic cooperative research teams. We always regarded the patient with the disease as a whole and were rewarded with good and satisfying results on all levels.

Our developments over many years are influenced by the available research- and clinical tools and processes. Nowadays the necessities and tools of prevention and personalization involving molecular diagnostics have become the major pacemakers to limit the lethal threat of the diseases colon- and rectal cancer. Recently one of the authors was elected to be "Ambassador of the year 2021" of "Stiftung Lebensblicke (SLB)", the German foundation that has established preventive colonoscopy as a routine examination. SLB, founded and headed by Professor Riemann J, aims to propagate the acceptance and the continuous improvement of prevention and early detection to reduce the burden of this type of cancer, with high incidences in the nations with western lifestyle such as dietary habits with fat and meat consumption, obesity, diabetes, and alcohol consumption.

The strategy of SLB aims both at achieving a high acceptance of the preventive colonoscopy and stool tests, as well as public information on the impact of lifestyle on polyp formation and cancer development in the colon and the rectum. Many environmental, dietary, and lifestyle factors, their influence on the microbiome and the immune system and on bowel habits contribute to the carcinogenesis in the colon and rectum. Cancer development is influenced by the consumption or intra-bowel formation of carcinogenic substances and their effect on molecular targets in the large bowel epithelium (gene-by-environment interactions). Patient exposures towards exogenous and endogenous factors like the gut microbiome and their influence on cancer development combined with pathological and epidemiological data is studied in molecular pathological epidemiology (MPE)[51,52]. These epidemiologic findings go hand in hand with molecular findings of personalized diagnostics in determining a patient's individual risk. Known genetic risk factors like loss of tumor suppressor genes and overexpression of tumor promotors might help to detect patients in need of more frequent preventive measures like colonoscopy or stool examinations. In the future, epidemiologists, nutritionists, molecular pathologists, human geneticists, immunologists should be integrated in the modern teams to reduce the still unnecessary high incidences of colon- and rectal cancers. Furthermore, treatment individualization by inclusion of nutritionists *etc.* should also be included in secondary and tertiary disease prevention to reduce the elevated risk for the development of second primary cancers in the colon or rectum.

With our group we initiated several new treatment options for patients with colon and rectal cancer in both primary tumors and metastases, and discussed our new developments continuously in oncological societies[59]. After recognizing the possibilities for multimodal therapy from a few trials[13], we introduced multimodal treatment of colon and rectal cancer patients in Germany in two nationwide trials

involving 64 hospitals and 1651 patients (FOGT-1: 855 pts., FOGT-2: 796 pts.). In these phase III trials, the 5-year-survival rates in colon cancer UICC IIB and UICC III were improved significantly. Unexpectedly, the same therapies led to no survival improvement in the stage II+III rectal cancer patients receiving postoperative adjuvant radiochemotherapy in FOGT-2. In FOGT-2 the local relapse rates in the three arms were similar, but significantly lower than after surgery only (13.8%, 10.7%, and 13.5% (in arms A, B, and C) *vs* > 30%, respectively)[20]. We regularly followed the possibilities of multimodal treatment in rectal cancers[60,61]. To our knowledge, neither modern combination protocols (*e.g.*, FOLFOX), nor neoadjuvant radiochemotherapy led to an increase of survival rates. In the comparison of preoperative vs. postoperative radiochemotherapy the local relapse rates were reduced by the preoperative (neoadjuvant) treatment, however with the insecurity of preoperative tumor staging and thus possible overtreatment. We established that colon- and rectal cancers are differing in response to chemotherapy besides many other parameters[21,23]. This had also been demonstrated by other groups[62]. We were the first to conduct a colon- and a rectal multimodal trial in parallel with identical adjuvant systemic treatment arms. The realization of the FOGT-1 and FOGT-2 trials helped, that multimodal therapy was included in national guidelines.

In case of metastatic disease, *e.g.*, nonresectable CRLM, 5-year survivors still are very rare with chemotherapy only[63]. Resection of primarily nonresectable CRLM after adequate response to systemic chemotherapy nowadays is demanded in the guidelines. Together with the group of Professor Henry Bismuth (Paris), we were among the first worldwide to show that downstaging and resection is possible in primarily nonresectable CRLM, improving median survival times significantly[38]. This later has been confirmed with large prospective controlled trials[64].

We were the first worldwide to perform "split time liver resections" in case of far advanced CRLM. TSH and ALPPS later followed our first report in 1993 (see in[13,23,24]) and is now routinely practiced in surgical liver units[9,45,46,65,66]. We have observed several patients who live > 5 years after this exceptional surgical treatment with added chemotherapy.

Our group successfully translated laboratory-based knowledge into clinical applications. We designed the optimal treatment timing of cytotoxic drugs by evaluating the impact of exposure concentration and time of 5-FU and other drugs[35], and applied this knowledge successfully in our clinical protocols for multimodal treatment of the primary tumors and for (regional) chemotherapy of metastases to the liver and peritoneum. By conducting dose response and *in vitro* phase II trials (testing the response rates of drugs tested in the HTCA with tumor cell suspensions deriving from *e.g.*, CRLM's of several patients) with individual metastatic tumor cell suspensions we identified active drugs for successful chemotherapeutic protocols of CRLM, peritoneal carcinosis, and malignant ascites. Response rates were high and exceeded the standard systemic treatment with 5-FU or 5-FU + FA at the corresponding time period. Meanwhile, to our great pleasure, systemic protocols were significantly improved by French oncological groups (FOLFIRI/FOLFOX ± MAB), so that we abandoned HAI, which can only be performed by surgical catheter implantation with high levels of special expertise. For chemoembolization we had established a combination protocol in Ulm [Mitomycin C + Epirubicin (+ Lipoidol)], based on our *in vitro* phase II results at the drug concentrations of 10 μg/mL, which are achievable by chemoembolization. Chemoembolization, in Germany promoted by a surgical friend, Professor Schultheis KH, is still standard in nonresectable liver tumors nonresponsive to the low concentration systemic i.v. chemotherapy, and applied as rescue therapy in CRLM[9].

Most importantly, we were the first group to show, that individual drug selection for (HAI-) chemotherapy of nonresectable CRLM is effective (this originally had been suggested to Link KH by Professor Charles Heidelberger, developer of 5-FU, in 1982). The individualized treatment of our patients, based on *in vitro* results (HTCA, TS-determination), induced significantly higher response rates and median survival times than the treatment with standard protocols or in the "*in vitro* resistant" patients. These results were published in "Cancer" and awarded "Best Paper of the Year 2000"[42]. With this paper we were able to show that personalization of chemotherapy in the HAI set-up is possible. Our success was based on the fact that we used exactly the same pharmacologic parameters (concentration and time of drug exposure) *in vitro* as those which had been either measured or calculated for the arterial blood concentrations. Our reconstruction experiment in ILP confirmed this hypothesis. Individual response, besides K-ras status and SMAD status is now also a prognosticator for the benefit of downstaging/resection, ALPPS or orthotopic liver transplantation in CRLM [9,64,67] . To our knowledge, up to now there is no test to individually select effective chemotherapeutic drugs for systemic chemotherapy, but research is ongoing[68,69].

The benefit of adding anti EGFR-monoclonal antibodies to chemotherapeutic combination protocols can be predicted by pathology immuno-assays.

We were one of the first three groups addressing the importance to select patients for multimodal therapy in resectable primary tumors to avoid a significant overtreatment. We retrospectively confirmed the usual prognostic parameters in our FOGT-1 + 2 trials and, as incidental information, showed that due to the outlined surgical standards in our FOGT protocols (which has not always been the case in other multimodal treatment protocols) the surgeons or hospitals were not prognostic factors [70]. Most importantly, in cooperation with Danenberg P and Danenberg K we obtained evidence, that TS- and DPDH-expressions seemed to be predictors of survival of the FOGT-1 + 2 patients[26]. In the meantime, we and many others have tried to define a reliable test of either single or a combination of parameters for personalization of multimodal therapy[68,69]. Up to now, only the MSI-status is influencing the decision for multimodal therapy in the S3 guidelines[2]. Most recently in adjuvant therapy of early node positive breast cancer, the large prospectively controlled trial RxPONDER successfully defined the benefit of chemotherapy by applying the Oncotype DX^{R} test. First results from the study conducted by the independent SWOG Cancer Research Network, and sponsored by the National Cancer Institute, identified the majority of women with 1-3 nodes who received no benefit from chemotherapy. The prospective randomized controlled phase III study at 632 sites has involved > 5000 women. The data was just recently presented at the 2020 San Antonio Breast Cancer Symposium (December 10, 2020)[71]. The Oncotype DX^{R} test, scheduled soon to be published (in 2021) in a peer reviewed journal, was said to have redefined personalized medicine by making genomics a critical part of cancer diagnosis and treatment. According to our findings, colon and rectal cancer patients differ in profiting from adjuvant chemotherapy, so that these tumor entities must be studied separately in future phase III trials similar to the RxPONDER trial in breast cancer.

Which are the principal conclusions for young (surgical) researchers and for translational research teams? First, you must be fully motivated to conduct research involving basic and clinical research. This can be described by the saying of Winston Churchill "We make a living by what we get-we make a life by what we give". The improvement of surgical techniques influenced the quality of life (*e.g.*, reducing local relapses by TME/Heald or applying minimally invasive- and robotic surgical techniques), but rarely improved overall survival. The findings of basic research must be translated earlier into clinical application. You must believe what you find *in vitro*, then cross check your hypothesis derived from the *in vitro* results, *e.g.*, with reconstruction experiments and then use these new findings in clinical applications. If you have new ideas, you have to reflect on them and then work on their realization. To recognize problems and deduct solutions is an individual intellectual process, as the German philosopher Kant I described in his major work "Kritik der reinen Vernunft" (philosophical reflections and discoveries on the process of getting a new own opinion/conviction)[72]. Popper K, the late contemporary Austrian/British philosopher (1902-1994) even demanded that you always have to proof your conviction by excluding the possibility of a truth with an opposite solution (*Popper 1994*). Kant, as cited by Popper said "Be brave and use your (scientific) sense"[73].

Your new strategy needs to be backed up by enough general experience so that you and your intentions are generally accepted. Broadening your research spectrum and applying these approaches can further increase the trust put into your research, *e.g.*, Link KH together with HGB also contributed to new developments in pancreatic cancer research[74]. We decided to translate the cell culture experiments into clinical practice, since we were convinced that the laboratory conditions are representative for the conditions *in vivo* in HAI of CRLM and HIPEC. Our reconstruction experiment (Popper: Is it really true?) fully supported our translational strategy and resulted in innovative findings to the benefit of the patients[33].

Once you have started your programs and generated first results that are better than the conventional practices, the way forward can get rocky, as Arthur Schopenhauer has described in his viewpoint on scientific developments: "First you are ridiculed, then you are heavily criticized, than your achievements are captured by others". When we initiated the multimodal FOGT-1 + 2 trials, we faced skepticism from both highly rated university surgeons ("In Ulm they cannot operate, they need additional chemotherapy and radiotherapy") and the medical oncologists, still stuck to 5-FU monotherapies for many GI-tumors ("Surgeons do not understand chemotherapy, they should perform surgery only"). Backed by the team at the CCCU and by the convinced head of the Department (HGB) (and by significant/protocol fixed support of companies (medac, Roche, Aventis, Sanofi, Pfizer, Baxter, Tyco), who also helped to generate interest in many German hospitals), we finally were able to finish the high

level FOGT-1, 2, 4 and 5 trials. After other groups confirmed the beneficial effects of multimodal therapies in colon and rectal cancer, these schemes were included into the German guidelines[8].

Similar critics were voiced after we promoted "downstaging and resection" in primarily nonresectable CRLM. Renowned liver surgeons were stating that "they (the Ulm group) can't operate on the liver". Most liver surgeons did not believe in our split time resection we originally performed in a young patient rejected for resection or transplantation at a top liver unit. International specialists for chemotherapy and surgery awarded the poster presentation with admiration and the poster prize at an international meeting in 1993. It took years and many oral presentations from our group (with increasing patient numbers), until another strategy, also taking liver regeneration into account, led to TSH/ALPPS[9,45].

So, Schopenhauer was right with his prediction on the fate of new scientific developments. However, sometimes findings, in spite of being significant, unfortunately are not accepted by *e.g.*, supporting companies or colleagues: Our published and addressed findings, that rectal cancer metastases/micrometastases seem to be less responsive to chemotherapy, so that adjuvant chemotherapy is less effective than in colon cancer (arm B FOGT-1 survival improvement, arm B FOGT-2 no survival improvement, or even harmful to patients > 70 years), are waiting to be included into clinical practice/guidelines. These findings relevant for the patient's benefit are not disputed: they are simply ignored, for whatever reason.

Besides our research we tried to perform the best possible surgery and to consider the guidance of the patients. We not only looked just at the organ to be operated/treated, but predominantly at the patient and his/her disease as a whole. We were continuously trying to improve the palliative situation at the patients' homes or to create professional psycho-oncological care and social advice to the patients and their families, not only during palliative care, but also after curative treatment. We and the patients, including their relatives, estimated this part of care also as "good treatment" [53,58,75].

CONCLUSION

What can be deducted from our "Patient-centered developments in colon and rectal cancer with a multidisciplinary international team converting translational research into national guidelines?" Surgery is important in modern human societies to promote the health of our peoples. Scientific developments are important to improve the medical armamentarium against diseases, also in surgery. New ideas and structures, with promise to achieve major achievements to fight diseases in terms of prevention, treatment, and posttreatment care — all to the benefit of the patient should be in the center of multidisciplinary efforts, avoiding the propagation of the status quo.

A surgeon participating or leading this kind of science in his academic profession can be assumed to be a good scientist but must not necessarily be a bad surgeon. A surgeon performing good studies on a surgical methodological or outcome question may be assumed to be a good surgeon, but isn't so necessarily. Young academic researchers should be accepted and supported by their older department colleagues and heads. Translational research is not always understood by doctors who prefer "surgery only". Basic and translational research should be regarded as equally important in the estimation of the surgeons/researchers. "Translational researchers" can also be good surgeons and even surgical academic department heads. Older experienced surgeons/department heads can take up molecular biology/translational research easily, if interested (like HGB). Thankfully, nowadays new developments from basic research areas are adopted more easily, and young surgeons are encouraged to also follow a research path.

Our research developments were clearly patient-centered and not oriented toward industrial or academic career interests. To our great amazement, some of our findings were rejected due to personal interests with withdrawn support of companies in cases when the presented data didn't match expectations. Treatment of rectal cancer patients > 70 years still includes intensified adjuvant schemes despite the findings of FOGT-2, and, additionally, of recent large randomized controlled trials that failed in showing positive effects of intensified adjuvant treatment[76,77]

The society of basic researchers in cancer research in Germany (SEK) was unreceptive towards our findings when we initially submitted abstracts on our translational research findings at their annual meeting in Heidelberg. The abstracts were accepted as posters but drew little attention from non-clinician basic scientists. This

thankfully has changed into a more constructive discourse between tumor biologists and clinicians leading to optimal cooperation without losing ideas and time to realize them. The US basic research association AACR was, in contrast, highly interested in our translational research, admitting several abstracts as oral presentations — and the posters were always well discussed. Even former presidents of the AACR and top basic researchers visited our regular "International Charles Heidelberger Symposiums on Cancer Research" to exchange ideas between clinicians and basic researchers (1997 and 2012 at the Cancer Center in Ulm with researchers like Professors Bertino J, former AACR president, and Curtis Harris (first description of p53 with relevance in colon- and rectal cancer tumor biology/carcinogenesis, National Cancer Institute/United States).

Besides conducting translational research, we were always highly interested in involving the patients in treatment decisions and monitoring/improvement of the quality of life which has been rewarding on a very personal level.

Young academic surgeons nowadays are sharing this opinion and will use these developments for their future work. Even established surgeons in surgical societies now are integrating such developments, which we had very early in our minds, into their research programs. Old-fashioned attitudes are gradually changing, as shown by the following statement (in this case, however, mainly relating to modern surgical management tasks): "Surgery is more than operating" (*H.Bauer, General Secretary em. of the German Surgical Society, 3/17*). We recommend to "See the problems of the patients as a whole, build up your philosophy and strategy for improvements, apply modern translational and interdisciplinary research, control your paths stepwise, take into account but not be frustrated by criticism, keeping your aim in mind and above all never give up".

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2021 December 27; 13(12): 1615-1627

DOI: 10.4240/wjgs.v13.i12.1615

ISSN 1948-9366 (online)

MINIREVIEWS

Advances in liver transplantation for unresectable colon cancer liver metastasis

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Author contributions: Cui X designed and wrote majority of the manuscript; Hou H designed and performed some parts of the manuscript; Geng XP made the revision; Zhou DC collected and analyzed the data; Yang MH collected and assembled the data.

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

Supported by Natural Science Foundation of the Higher Education Institutions of Anhui Province, No. KJ2017A825; and Natural Science Foundation of Anhui Province, No. 1808085MH270.

Country/Territory of origin: China

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

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Abstract

It is estimated that 50% of patients with colorectal cancer will develop liver metastasis. Surgical resection significantly improves survival and provides a chance of cure for patients with colorectal cancer liver metastasis (CRLM). Increasing the resectability of primary unresectable liver metastasis provides more survival benefit for those patients. Considerable surgical innovations have been made to increase the resection rate and decrease the potential risk of hepatic failure postoperation. Liver transplantation (LT) has been explored as a potential curative treatment for unresectable CRLM. However, candidate selection criteria, chemotherapy strategies, refined immunity regimens and resolution for the shortage of grafts are lacking. This manuscript discusses views on surgical indication, peritransplantation anti-tumor and anti-immunity therapy and updated advances in LT for unresectable CRLM. A literature review of published articles and registered clinical trials in PubMed, Google Scholar, and Clinicaltrials.gov was performed to identify studies related to LT for CRLM. Some research topics were identified, including indications for LT for CRLM, oncological risk, antitumor regimens, graft loss, administration of anti-immunity drugs and solutions for graft deficiency. The main candidate selection criteria are good patient performance, good tumor biological behavior and chemosensitivity. Chemotherapy should be administered before transplantation but is not commonly administered posttransplantation for preventive purposes. Mammalian target of rapamycin regimens are recommended for their potential oncological benefit, although there are limited cases. In addition to extended criterion grafts, living donor grafts and small grafts combined with two-stage hepatectomy are efficient means to resolve organ deficiency. LT has been proven to be an effective treatment for selected patients with liver-only CRLM. Due to limited donor grafts, high cost and poorly clarified oncological risks, LT for unresectable CRLM should be strictly performed under a well-organized study plan in selected patients. Some vital factors, like LT indication and anti-tumor and anti-immune treatment, remain to be confirmed. Ongoing clinical trials are

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: July 3, 2021
Peer-review started: July 3, 2021
First decision: September 5, 2021
Revised: September 19, 2021
Accepted: December 6, 2021
Article in press: December 6, 2021
Published online: December 27, 2021

P-Reviewer: Kim BS, Xu PF
S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

expected to delineate these topics.

Key Words: Liver transplantation; Colon cancer; Colorectal cancer liver metastasis; Transplant oncology

Core Tip: Liver transplantation (LT) for colorectal cancer liver metastasis (CRLM) has been explorally performed in the early stage of LT, but it was abandoned for its poorly oncological prognosis. Several newly released clinical studies showed the promising prospect of LT for CRLM. This review summarizes the history of LT for CRLM and lists the updated advancement in candidate selected criterion, potential immunosuppression and oncological safety balance strategies, surgical technique improvement and ongoing clinical trials.

Citation: Cui X, Geng XP, Zhou DC, Yang MH, Hou H. Advances in liver transplantation for unresectable colon cancer liver metastasis. *World J Gastrointest Surg* 2021; 13(12): 1615-1627
URL: https://www.wjgnet.com/1948-9366/full/v13/i12/1615.htm
DOI: https://dx.doi.org/10.4240/wjgs.v13.i12.1615

INTRODUCTION

In 2020, over 1.8 million new colorectal cancer (CRC) patients were diagnosed, while approximately 915880 deaths were caused by CRC worldwide[1]. Twenty percent of CRC patients are estimated to have developed metastatic disease at the time of diagnosis[2]. The liver is the second most common metastatic site for CRC following the lung[3]. The management of metastatic colon and rectal cancer has significantly progressed over the last few decades. Owing to advancements in surgery, modern chemotherapy and perioperative care, the 5-year overall survival (OS) rate of patients with CRC liver metastasis (CRLM) has approached 35%–40%. In well-selected patients, the 5-year OS has reached over 50%[4-6].

Although early recurrence is mostly unavoidable, patients who are treated with curative-intent liver resection for CRLM have favorable survival outcomes[7]. However, despite advances in preoperative portal vein embolization, two-stage liver resection and systemic treatment, more than 70% of CRLM patients are not suitable for liver resection[8]. Complete removal of the tumor mass by liver transplantation (LT) has been explored, but this approach has received little attention in recent decades.

In the first cohort study of LT for CRLM conducted in Austria between the 1980s and 1990s, the 5-year survival rate was less than 20%[9]. No clear enrollment criteria were defined in this study. The early attempt was soon abandoned after the data were published in the 1990s. Due to advances in the understanding of oncology mechanisms, surgical techniques, immunosuppression therapy and refined systemic treatment regimens, exploratory studies have been reinitiated in the last decade. Secondary cancer (SECA) serial studies showed that the 5-year OS of patients with unresectable CRLM treated with LT was up to 60%-83%[10,11]. The selection criteria for LT for unresectable CRLM, neoadjuvant therapy and postoperative immunity suppression regimens have not been clearly delineated. Here, we have reviewed this field.

THE SELECTION CRITERIA FOR LT IN CANDIDATES WITH UNRESECTABLE CRLM

There are no widely accepted criteria for an ideal candidate to date due to the limited number of study. The first LT for patients with CRLM was performed in Boston, 1963 [12]. The patients soon died of pneumonitis and hepatic failure 11 d postoperation (Table 1). As an experimental procedure, CRLM used to be an indication for LT in the early exploration stage of LT surgery. Fifty cases were recorded between 1968 and

Table 1 Published data on liver transplantation for colorectal cancer liver metastasis

Ref.	Year	Center	Period	Patients number	Survival time
Moore *et al* [12]	1964	Peter Bent Brigham Hospital, United States	September, 1963	1	11 d
Demirleau *et al*[58]	1964	Hospital St. Antonie, France	January, 1964	1	0 d (died of bleeding)
Andersen *et al* [59]	2012	Oslo University Hospital, Norway	1970	1	24 d (died of fuminating sepsis)
Penn[13]	1991	Cincinnati Medical Center, United States	September 1968-March 1991	8	Mortality 11% recurrence rate 70%
Pichlmayr *et al*[60]	1997	Hannover Medical School, German	1972-1995	4	11 mo, 8 d, 33 mo
Honoré *et al* [61]	2003	University of Liege, Belgium	1992	1	10 yr
Kappel *et al*[9]	2006	Medical University of Vienna, Austria	1983-1994	24	5-yr OS rate 12%-18%
Hoti *et al*[14]	2008	European Liver Transplant Registy	1968-1995	50 (including 24 above)	1- and 5-yr OS rate were 62% and 18%
Uskudar *et al* [62]	2011	The Mount Sinai Hospital, United States	2005, 2008	2	5 yr (no recurrence); 2 yr (no recurrence)
Kocman *et al* [63]	2011	University Hospital Mekur (Croatia)	2006	1	5 yr (no recurrence)
Hrehoreț *et al* [64]	2013	University of Medicine and Phamarcy Caro Davila, Romania	January, 2012	1	20 mo post-operation (lung recurrence)
Line *et al*[46]	2015	Oslo University Hospital, Norway	2014-2017	3	40 d (died of complications); 5.5 yr (no recurrence); 2 yr (recurrent at 12 mo)
Caicedo *et al* [65]	2016	ICESI University, Colombia	November, 2014	1	19 mo (no recurrence)
Toso *et al*[66]	2017	Portugal, Paris, Geneva	1995-2015	12	5-yr OS 50% ± 16%, 5-yr PFS 38% ± 15%
Dueland *et al* [10]	2020	Olso University Hospital, Norway	2006-2012	23	5-yr OS 60%
Yang *et al*[67]	2019	Zhongnan Hospital of Wuhan University, China	2016	1	34 mo (recurrent at 4 mo)
Lerut *et al*[68]	2019	University Hospital Saint-Luc, Belgium	1985-2016	4	17 mo (recurrent at 6 mo), 64 mo (recurrent at 47 mo), 32 mo (no), 28 mo (recurrent at 4 mo)
Fernandes *et al*[69]	2019	Rio de Janeiro Federal University, Brazil	December, 2018	1	No prognosis information
Dueland *et al* [10]	2019	Oslo University Hospital, Norway	2012-2016	15	5-yr OS 83%
Smedman *et al* [25]	2019	Oslo University Hospital, Norway	2014-2018	10	Median OS 18 mo. Median DFS 4 mo
Coubeau *et al* [52]	2020	Cliniques Unviersitaires Saint-Luc	2019	1	180 d (no recurrence)

OS: Overall survival; DFS: Disease-free survival; PFS: Progression-free survival.

1995 in the European Liver Transplant Registry (ELTR), and their 1- and 5-year survival rates were 62% and 18%, respectively, which is in accordance with the data from 8 cases in a North American cohort reported in 1991[13,14]. Due to this unsurprisingly poor survival compared to that achieved by R0 liver resection and the deficiency of organs for transplantation, the initial exploration was abandoned. Risk factors predicting a survival benefit were identified *via* a retrospective analysis of a 25-case cohorts from Vienna[9]. Three patients in this cohort with lymph node negativity and no p53 or K-RAS mutations showed a significantly longer OS than patients with positive lymph nodes and p53 or K-RAS mutations.

Hagness *et al*[11] performed the first prospective pilot study, SECA-I, to evaluate the possibility of LT for CRLM in Oslo University Hospital[11]. The work of Hagness showed a potential curative effect of LT for CRLM. The 1- and 5-year OS rates were 95% and 60%, respectively, although the patients enrolled in this study were diverse. This study identified independent risk factors for OS: CEA > 80 μg/L, tumor size > 5.5 cm, interval time between primary resection and LT less than 2 years, and failure to respond to chemotherapy[11]. These risk factors had also been identified previously for hepatectomy and are defined as the Oslo score here.

In the SECA II trial, clearer characteristic selection criteria that showed a better benefit on prognosis [lower number of metastatic masses, smaller size of the largest lesion, lower CEA levels, Oslo score < 2, and Fong Clinical Risk Score (FCRS) < 2] were summarized based on data from the SECA I trial, which included the following factors: Primary tumor with positive nodes, disease-free survival less than 12 mo, more than 1 metastasis, CEA levels greater than 200 ng/mL, and diameter of the largest metastasis greater than 5 cm. The 5-year OS rate was surprisingly 83% among the 15 patients selected according to the criteria[10]. The SECA I and SECA II trials explored stringent criteria for LT, suggesting that patients with good tumor performance could be candidates.

Although transplantation is a successful treatment, recurrence is mostly unavoidable. The 2-year recurrence was 100% for SECA I, while the 3-year recurrence was 75% in SECA II. In addition to these completed studies, there are several ongoing prospective clinical studies led by different groups exploring stricter inclusion criteria to optimize oncological outcomes and delineate the benefits of LT in CRLM. These inclusion criteria are summarized in Table 2.

The common inclusion criteria are as follows: Good performance status as indicated by Eastern Cooperative Oncology Group (ECOG) score 0–1, confirmed primary tumor R0 resection, completion of at least 2 mo or several cycles of chemotherapy with a stable or partial response based on Response Evaluation Criteria in Solid Tumors (RECIST) at 8 wk or beyond, and no recurrence at the primary tumor location or at extrahepatic sites as confirmed by coloscopy and positron emission tomography/computed tomography (PET/CT).

The role of PET/CT in precisely evaluating disease progression and stage was strongly emphasized in the inclusion criteria. The metabolic tumor volume and total lesion glycolysis value before transplant are both correlated with OS[15]. With the increasing number of trials whose outcomes are awaited, clearer selection criteria based on larger cohorts of patients will become available.

PERITRANSPLANTATION CHEMOTHERAPY FOR UNRESECTABLE CRLM

Chemotherapy is commonly used as the first choice in treating patients with unresectable CRLM. It is expected to inhibit tumor progression and convert unresectable CRLM into potentially resectable disease. If conversion therapy is not successful, maintaining disease stability is acceptable (Table 3).

The efficacy of LT and chemotherapy in treating unresectable CRLM was compared between the cohorts from the SECA I and NORDIC VII trials[16]. Three different first-line regimens based on fluorouracil/folinic acid and oxaliplatin (FLOX), FLOX combined with cetuximab, and intermittent FLOX with cetuximab were included in NORDIC VII trials[17]. The 5-year survival rate in the SECA I trial was 56%, while it was 19% in the chemotherapy groups. Similar disease-free survival (DFS) times wereobserved in the transplantation group and chemotherapy group (8 mo *vs* 10 mo). The postrecurrence 5-year OS rate in the SECA I group was significantly superior to that in the chemotherapy group (53% *vs* 6%). It is also notable that current first-line regimens were not available at that time: FOLFIRINOX or mFOLOX-6 combined with bevacizumabpromoted conversion, with resection rates of 61% and 49%, and the tumor response rates were 81% and 62%, respectively[18-20]. In the SECA I trial, no chemotherapy response was a required inclusion criterion, and progression occurred under treatment with 1st- and 2nd-line chemotherapy[11].

Given the early experience of transplantation in the CRLM and SECA serial trials, recurrence is considered inevitable. Although tumor progression could not be preoperatively inhibited under 1st-, 2nd-, or even 3rd-line chemotherapy, transplantation showed a survival benefit over standard chemotherapy. In SECA II, a response to chemotherapy of at least 10% according to the standard RECIST was required as a major inclusion criterion and was a good biological behavior predictor. Due to advances in chemotherapeutic regimens and the hepatic artery infusion technique, a

Table 2 Inclusion criteria in some prospective studies on liver transplantation for colorectal cancer liver metastasis

Study	SECA I	SECA II	LIVERTWOHEAL	TRANSMET	Toronto NCT02864485
Inclusion criteria	Primary tumor R0 resected; ECOG 0-1; More than 6 wk chemotherapy; No extrahepatic metastasis or recurrence confirmed by PET/CT, bone scan	Addition standard: No signs of extra hepatic metastatic disease (except resectable lung metastasis) or local recurrence according to coloscopy, CT or MRI within 12 mo; Chemotherapy response > 10%, If not, TACE or Y-90 response > 20%; More than 12 mo from diagnosis or adjuvant therapy	Unresectable CRLM without extrahepatic tumor burden, except resectable pulmonary metastases; Disease regresses or keeps stable after more than 8 wk chemotherapy	ECOG 0-1; BRAF wild type; Primary tumor R0 resected; No primary recurrence within 12 mo confirmed by coloscopy. Disease stable or regress more than 3 mo with chemotherapy; CEA < 80 ng/mL or decrease ≥ 50%; No extrahepatic metastasis confirmed by CT or PET-CT	ECOG 0-1; Primary tumor stage is ≤ T4a; More than 6 mo since liver resection; No major vascular invasion; More than 3 mo chemotherapy; Disease regression or stable more than 3 mo; Stable CEA value or decease at all time prior to LT
Outcome	OS	OS 10 yr	OS 3 yr	OS 5 yr	OS 5 yr; PFS 5 yr

TACE: Transcatheter arterial chemoembolization; Y-90: Yttrium; PET/CT: Positron emission tomography/computed tomography; MRI: Magnetic resonance imaging.

promising oncological benefit could be expected for candidates who undergo LT for unresectable CRLM.

Adjuvant chemotherapy is not commonly employed posttransplantation and is instead only used when recurrence is confirmed (Table 4). There are some differing views on this issue: (1) Complete resection of a liver metastasis with a margin-negative edge offers great benefit for long-term survival. No high-level evidence of a survival benefit of adjuvant therapy for CRLM postoperation exists[21,22]; (2) Adjuvant chemotherapy combined with immune checkpoint inhibitors or without combination might cause graft loss or an increase in the failure rate[23,24]; and (3) After tumor progression posttransplantation, chemotherapy can be administered safely, and it improved survival relative to nonchemotherapytreatment[25].

POSTTRANSPLANTATION IMMUNOSUPPRESSION AND ONCOLOGICAL SAFETY

Long-term immunosuppression promotes secondary malignancy, primary tumor recurrence and subclinical micrometastasis progression posttransplantation. Chronic immunosuppression directly related to malignancy is expected to be the leading cause of death in transplant recipients[26-28]. From the data reported, the estimated standardized incidence ratio of de novo malignancies after LT in CRC ranges from 1.2–12.5-fold to 3.3-fold for anal cancer[26,28,29]. Among United States transplant societies, the guidelines suggest that the common malignancy-free period before transplantation for patients with CRC should be more than 2 years (0–5 years, depending on the TNM stage). In European guidelines, this delay period has been extended to more than 5 years[30].

Immunosuppression increases *de novo* malignancy occurrence and cancer recurrence *via* several mechanisms: (1) Negative modulation of immune surveillance that increases the risk of oncovirus-driven malignancy and tumor cell escape from immunity[31]; and (2) A nonspecific mode of action induced by immunosuppressive drugs that promotes insulin resistance, inhibits DNA damage repair and enhances tumor angiogenesis and invasiveness[32]. Calcineurin inhibitors (CNIs), such as tacrolimus and cyclosporine, are the most commonly used immunosuppressive drugs, and they work by inhibiting calcineurin and downregulating nuclear factor of activated T cells, which is related to the gene expression of IL-2, IFN-γ, and GM-CSF [33,34]. CNIs promote the activation of oncogenes and tumor progression, and they are positively correlated with the incidence of malignancy in a dose-dependent manner [35]. Compared to continuation of CNIs, a change to mycophenolate mofetil significantly reduced the occurrence of de novo malignancies[36]. Mammalian target of rapamycin (mTOR) inhibitors exert antitumor effects in experimental studies and protective effects in reducing malignancy posttransplantation, especially within the first year[37]. Although all immunosuppressive drugs, including mTOR inhibitors and mycophenolate mofetil, increase the risk of malignancy based on SRTR data analysis, it is highly recommended to switch from CNIs to mTOR inhibitors when there is a risk of malignancy or a malignancy diagnosis has been made posttransplantation[38].

Table 3 Treatment for unresectable colorectal cancer liver metastasis prior to transplantation

Ref.	Year	Treatment prior to liver transplantation		
		Liver resection	Local therapy	Systemic therapy
Moore *et al*[12]	1964	NR	NR	NR
Demirleau *et al*[58]	1964	NR	NR	NR
Andersen *et al*[59]	2012	NR	NR	NR
Penn[13]	1991	NR	NR	NR
Pichlmayr *et al*[60]	1997	NR	NR	NR
Honoré *et al*[61]	2003	Yes	No	No
Kappel *et al*[9]; Hoti *et al*[14]	2006; 2008	NR	NR	NR
Uskudar *et al*[62]	2011	Yes	Yes, TACE, HAI. Yes, HAI (causing liver failure)	Yes
Kocman *et al*[63]	2011	Yes (Two times)	No	Yes, 1/1
Hrehoreț *et al*[64]	20I3	Yes (ALPPS one stage)	Yes, radio therapy	Yes, FOLFOX AND bevacizumab
Line *et al*[46]	2015	No; NR	No; NR	Yes, 3/3, FLIRI/cetuximab
Caicedo *et al*[65]	2016	No	Yes, 1/1 RFA	Yes, 1/1, FOFIRI + cetuximab
Toso *et al*[66]	2017	Yes, 10/12	1/12 RFA	11/12, irinotecan, oxaliplatin, cetuximab, bevacizumab
Dueland *et al*[10]	2020	Yes, 4/23	2/23	Yes, 23 (1st line, 10 patients; 2nd line, 9 patients; 3rd line, 4 patients)
Yang *et al*[67]	2019	No	Yes, 1/1; TACE + RFA	Yes, 1/1, mFOLFOX6 + bevacizumab
Lerut *et al*[68]	2019	No	No	Yes, 4/4, 5-FU, Oxaliplatin irinotecan, bevacizumab,
Fernandes *et al*[69]	2019	Yes	Yes	FOLFOX/FOLFIRI
Dueland *et al*[10]	2020	4/15	NR	Yes, 15/15
Smedman *et al*[25]	2019	2/10	2/10 RFA	Yes, 10 patients (1st line), 10 (2nd line), 3 (3rd line)
Coubeau *et al*[52]	2020	NAR	NAR	Yes, 1/1

NR: Not report; RFA: Radiofrequency ablation; mFOLFOX-6: Modified 5-fluorouracil/folinic acid and oxaliplatin; FOLFIRI: Fluorouracil, folinic acid, and irinotecan.

The data on the administration of immunosuppressive drugs to patients with CRLM posttransplantation come from a few case reports and only limited clinical trials. The patients with pulmonary metastasis posttransplantation in the SECA I study were compared to the nontransplantation patients with pulmonary metastasis. Neither a worse oncological prognosis nor a correlation between sirolimus concentration and DFS was observed in the transplantation group[39]. No other published data are available.

Experience from patients with HCC who underwent LT might provide some evidence: (1) Elevated CNI levels in the early posttransplantation period were correlated with an increased rate of recurrence of HCC[40]; (2) mTOR inhibitor-based regimens showed significantly lower recurrence of HCC after LT and 5-year survival advantages relative to CNI-based regimens[41,42]; and (3) A multicenter randomized clinical trial (RCT) showed that incorporating mTOR inhibitor regimens after six weeks of non-mTOR regimens could benefit 1- and 3-year disease-free survival in patients with HCC in contrast to continuation of non-mTOR regimens[43].

In the limited case series, the most commonly used regimens are mTOR inhibitors, including everolimus or sirolimus, prednisolone, mycophenolate mofetil, and basiliximab. The use of relatively low CNI levels in the early posttransplantation period keeps the balance between antiproliferative and rejection effects, and transitioning to mTOR inhibitors at a reasonably early stage might be a safe strategy, but more evidence is needed.

Table 4 Adjuvant therapy for recurrence after liver transplantation for unresectable colorectal cancer liver metastasis

Ref.	Overall survival (months)	Die/alive	Recurrence	Adjuvant therapy post recurrence after LT
Yang *et al*[67]	34	0/1	Yes	Chemotherapy
Lerut *et al*[68]	28	3/1	Yes, 4, 6, 47 mo	Chemotherapy
Toso *et al*[66]		6/6	Median DFS 6 mo	5 chemotherapy; 1 radiotherapy
Hagness[39]	27	6/15	Median DFS 19 mo	11 Chemotherapy; 1 TACE; 7 Radiation therapy; 11 Re-resection
Smedman *et al*[25]	18	5/5	Median DFS 8 mo	3 Chemotherapy combined radiation therapy; 2 Chemotherapy; 1 Radiation; 1 Surgery
Dueland *et al*[10]	36	2/13	Median DFS 8 mo	6 Surgery; 2 Surgery combined Radiation therapy; 2 Chemotherapy
Hrehoreț *et al*[64]	20	0/1	Yes, 6 wk	Chemotherapy

LT: Liver transplantation.

ADVANCES IN LT SURGERY FOR CRLM

The scarcity of liver grafts is the most common reality worldwide, in contrast to the relatively plentiful liver graft pool in Norway. The challenge of obtaining liver grafts for those with end-stage liver disease is inevitably brought to mind when allocating the limited livers to those patients with CRLM, who fall beyond the existing indications. Living liver donors and extended criteria donors might be a potential resolution. In SECA II arm D, the authors utilized extended criteria livers for 10 patients who had exceeded the inclusion criteria. Their outcome was inferior to that of patients from the other arms, which was mainly due to oncological progression. No dysfunction of the grafts occurred[44]. Three prospective trials using partial livers from living or deceased donors for CRLM were initiated. One is from Toronto University (NCT02864485), and the other two are from Europe, Oslo University (NCT02215889) and Tubingen and Jena University (NCT03488953); these trials introduced a new surgical technique and concept, the RAPID technique (resection and partial liver segment 2–3 transplantation with delayed total hepatectomy)[45]. This technique is derived from the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) technique, which efficiently increasesthe volume of future liver remnants and improves surgery safety and curability in patients with potentially resectable CRLM[46].

In traditional deceased donor split LT, donor grafts are divided into two sections according to the clinical needs of the recipients. Donor livers that are suitable for splitting are not plentiful. Functional liver remnants are also not sufficient for some recipients. The basic principle of RAPID is as follows: In the first stage, left hemihepatectomy is performed in the recipients, and transplantation with segmental grafts (segments 2 and 3) and ligation of the right portal vein are performed. During the waiting time, the remnant hemiliver is supposed to support body requirements while the transplant graft becomes established. In the second stage, the right hemiliver is removed when the transplant graft has grown to a sufficient size. The remaining donor extended right liver graft can then safely be transplanted to another recipient, which does not carry a significantly increased risk compared to using a whole liver graft[47].

The physical background for this surgical procedure is based on two points. (1) RAPID is considered an advanced variant of ALPPS. The ALPPS technique enhances future remnant liver (FRL) regeneration by diverting portal vein inflow into the FRL. In RAPID, ligation of the right portal vein and removal of the left hemiliver totally divert the main portal vein inflow into the transplant graft, which induces fast regeneration of liver volume and functional capacity[48]; and (2) Immunosuppressive regimens posttransplantation do not increase CRLM recurrence in comparison with no immunosuppressive regimens[16,49]. Relatively good tumor biological behavior is required for candidates according to the inclusion criteria. A sufficient length of the interval stage could be expected for liver graft regeneration before second-stage surgery.

As a common risk for all small transplant grafts, the RAPID technique also needs to resolve PV hyperperfusion, which causes arterial vascular structure damage, inhibits

liver regeneration and causes graft dysfunction[50]. Based on ALPPS andhepatectomy experience, higher portal vein inflow pressure is associated with an increased incidence of morbidity and mortality. High portal vein pressure is not very common in CRLM. The suggested resolution for PV hyperperfusion is to monitor the PV; if PV pressure > 15 mmHg, an inflow shunt should be considered[51].

Eleven patients with unresectable CRLM, specifically eight patients with LD-RAPID (five in Germany, two in Italy, and one in Belgium), had undergone RAPID surgery using deceased donor (DD) grafts and living donor (LD) grafts by the end of 2019[52]. Of the German patients, three patients were alive without tumor recurrence within 6 to 18 mo of follow-up; one patient died of pulmonary embolism at 24 mo post transplantation, with tumor recurrence in the thoracic vertebral body, skull and bilateral lung but not the liver at the fifth month[53]. No recurrence or death occurred at 180 d according to published data[52]. In the Oslo group, 3 patients underwent DD-RAPID transplantation, and one died of hepatic artery thrombosis and sepsis 40 d post operation. The first patient survived for 5.5 years without recurrence, and the other patient survived for 2 years but experienced recurrence in the 12th month.

CONCLUSION

When treating unresectable CRLM with standard chemotherapy, the 2- and 5-year OS have been found to be 10%[54,55]. If unresectable CRLM patients cannot tolerate second- and third-line chemotherapy after disease progression, the median survival period is only 5 to 7 mo[56,57]. Based on the present clinical outcome and previous data, LT has promise for treating unresectable CRLM, with a 5-year survival rate of over 50%. However, the scarcity of grafts worldwide and lack of clear indications challenge the implementation of LT for unresectable CRLM.

Resolution of these challenges requires two approaches: (1) Developing stringent selection criteria that can identify the candidates who can most benefit from LT; and (2) Increasing the suitable graft pool or extending donor graft criteria for unresectable CRLM. Good biological tumor behavior identifications have been explored to establish better criteria. Most patients experience recurrence after LT, but the median survival time from relapse of such patients is better than that of a cohort of patients with HCC. Recurrence does not shorten their survival time. DFS and its related factors are not considered an appropriate indicator for LT for CRLM.

The prognostic biological factors associated with survival were extrahepatic metastasis status confirmed by 18-FDG/PET scans, CEA level, the period between diagnosis confirmation and LT, chemotherapy response, and clinical risk scores (FCRS and Oslo scores). In well-selected patients with the above good behavior characteristics, the 5-year survival rate was 100%[10]. There are also some common risk factors for chemotherapy and liver resection in CRLM that have been found to be closely correlated with a poor survival rate. The location of the primary tumor significantly affects the survival prognosis. A K-RAS mutation in the tumor could be a powerful prognostic factor based on early studies of LT for unresectable CRLM. With more data from ongoing trials, the definite pathological characteristics of the group of patients who can benefit the most from LT will become clearer (Table 5).

Another strategy to overcome the lack of organs is to extend the present transplantation indications. This solution includes two parts: Showing superiority in survival of patients under stringent criteria or using small grafts with the RAPID technique or extended-criteria grafts to expand the donor pool. The fear of wasting valuable grafts can be re-evaluated and overcome by a better understanding of the biological outcomes based on up-to-date data on LT for CRLM. The RAPID concept provides a better resolution for the shortage of organ grafts. Segment transplantation, especially through LDLT,could balance the risks of living donors and the needs of recipients. The difficulty of the RAPID surgical technique will be more challenging for surgeons than standard split LT.

There are also some other techniques and oncological questions that need to be further explored: (1) Defining suitable second surgical indications that both ensure sufficient graft function and lower the risk of tumor dissemination; and (2) Determining the suitable graft-to-recipient weight ratio for the recipients when a standard or extended left hemihepatectomy is performed to ensure the patient is tumor-free.

The current ongoing trials will further advance the insights into the oncological behavior of CRLM post-LT and better define the transplantation indications. Due to the need for solid evidence, this promising treatment option should be carefully

Table 5 Ongoing clinical trials on liver transplantation for colorectal cancer liver metastasis

NCT number	Study name	Year	Type	Patients	Unit, country	Study aims
03494946	SECA III	2016-2027	RCT	25	Oslo University hospital, Norway	LT *vs* chemotherapy
02215889	No	2014-2028	Intervention	20	Oslo University hospital, Norway	Single arm (segment 2, 3 partial LT)
03488953	LIVERTWOHEAL	2018-2023	Intervention	40	Jena University Hospital, German	Single arm (Living donor liver transplantation with two-staged hepatectomy)
02597348	TRASMET	2015-2027	RCT	90	Hôpitaux de Paris, France	LT plus chemotherapy *vs* chemotherapy
03231722	COLT	2019-2024	Multi-center non-RCT		Fondazione IRCCS Istituto Nazionale dei Tumori, Italy	LT *vs* chemotherapy (parallel arm in TRIPLETE trial)
04161092	SOULMATE	2020-2030	Multi-center RCT	45	Vastra Gotaland Region, Sweden	LT (extended criteria graft) *vs* best alternative therapy

RCT: Randomized clinical trial; LT: Liver transplantation.

implemented.

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2021 December 27; 13(12): 1628-1637

DOI: 10.4240/wjgs.v13.i12.1628

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Pediatric T-tube in adult liver transplantation: Technical refinements of insertion and removal

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Institutional review board statement: The Institutional

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Abstract

BACKGROUND

With the increasing use of extended-criteria donor organs, the interest around T-tubes in liver transplantation (LT) was restored whilst concerns regarding T-tube-related complications persist.

AIM

To describe insertion and removal protocols implemented at our institution to safely use pediatric rubber 5-French T-tubes and subsequent outcomes in a consecutive series of adult patients.

METHODS

Data of consecutive adult LT patients from brain-dead donors, treated from March 2017 to December 2019, were collected (*i.e.*, biliary complications, adverse events, treatment after T-Tube removal). Patients with upfront hepatico-jejunostomy, endoscopically removed T-tubes, those who died or received retransplantation before T-tube removal were excluded.

RESULTS

Seventy-two patients were included in this study; T-tubes were removed 158 d (median; IQR 128-206 d) after LT. In four (5.6%) patients accidental T-tube removal occurred requiring monitoring only; in 68 (94.4%) patients Nelaton drain insertion was performed according to our protocol, resulting in 18 (25%) patients

Review Board of Fondazione Policlinico Universitario A Gemelli IRCCS provided approval for this study (IRB No. 3796).

Conflict-of-interest statement: The authors declare no conflicts of interest.

Data sharing statement: No additional data are available.

Country/Territory of origin: Italy

Specialty type: Transplantation

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

Peer-review report's scientific quality classification

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

Received: March 17, 2021
Peer-review started: March 17, 2021
First decision: May 4, 2021
Revised: May 17, 2021
Accepted: November 24, 2021
Article in press: November 24, 2021
Published online: December 27, 2021

P-Reviewer: Perisetti A
S-Editor: Zhang H
L-Editor: A
P-Editor: Zhang H

with a biliary output, subsequently removed after 2 d (median; IQR 1-4 d). Three (4%) patients required endoscopic retrograde cholangiopancreatography (ERCP) due to persistent Nelaton drain output. Three (4%) patients developed suspected biliary peritonitis, requiring ERCP with sphincterotomy and nasobiliary drain insertion (only one revealing contrast extravasation); no patient required percutaneous drainage or emergency surgery.

CONCLUSION
The use of pediatric rubber 5-French T-tubes in LT proved safe in our series after insertion and removal procedure refinements.

Key Words: Liver transplantation; T-tube; Kehr; Biliary fistula; Endoscopic retrograde cholangio-pancreatography; Biliary drainage

Core Tip: The use of small caliber T-tubes and a peculiar insertion technique minimize the size of the choledochotomy and reduce the chance of T-tube related adverse events; a careful T-tube removal procedure with the insertion of a temporary Nelaton drain mitigates the risk of uncontrolled biliary fistula and the need for emergency procedures.

Citation: Spoletini G, Bianco G, Franco A, Frongillo F, Nure E, Giovinazzo F, Galiandro F, Tringali A, Perri V, Costamagna G, Avolio AW, Agnes S. Pediatric T-tube in adult liver transplantation: Technical refinements of insertion and removal. *World J Gastrointest Surg* 2021; 13(12): 1628-1637
URL: https://www.wjgnet.com/1948-9366/full/v13/i12/1628.htm
DOI: https://dx.doi.org/10.4240/wjgs.v13.i12.1628

INTRODUCTION

Duct-to-duct biliary anastomosis is the most common technique of biliary reconstruction in deceased-donor liver transplantation (LT). In the past, T-tubes have been routinely used during biliary anastomoses in LT because it provides easy access to the biliary tree, and maintains lower pressure inside the biliary system. Furthermore, quality and quantity of bile production can be monitored and the occurrence of anastomotic strictures and early bile leaks can be reduced. However, in the 90's, many centers stopped using T-tubes based on growing evidence of safe duct-to-duct biliary reconstruction without biliary splinting, and randomized trials demonstrated non-inferior results without the use of T-tubes[1,2]. In addition, concerns regarding the risk of biliary fistulae, major adverse events following T-tube removal and reduced cost-effectiveness were reported[3,4]. Since nowadays more marginal organs are accepted (*e.g.*, steatotic livers, liver donation after cardiac death, and reconditioned grafts) the usefulness of T-tubes in LT is newly discussed. Two single-center randomized trials showed improved results using T-tubes; in particular, a reduced incidence and severity of biliary complications and anastomotic strictures were reported[5,6]. The risk of biliary peritonitis after T-tube removal seems to be attenuated using rubber instead of silicone-coated T-tubes. No consensus around the benefits of T-tube use in LT has been achieved yet, even though evidences were reassessed with several meta-analyses[7-10].

Our center continued to use T-tubes in LT, and the insertion technique, removal protocol and device types were continuously modified and updated over the years with the intent to minimize the risk of T-tube-related adverse events. In particular, a pediatric T-tube in adult patients was implemented to minimize the size of the necessary choledochothomy and possibly post-removal complications. In this study, we describe insertion and removal protocols implemented at our institution for the safe use of pediatric rubber 5-French T-tubes and subsequent outcomes in a consecutive series of adult patients.

MATERIALS AND METHODS

Consecutive adult patients who underwent LT, between March 2017 and December 2019, after the introduction of a pediatric 5-French rubber T-tube at our unit, were included in this retrospective analysis; enrollment was limited to December 2019 to allow a minimum follow-up of 6 mo.

Perioperative and follow-up data were collected including: recipients, donors and intraoperative assessment, early bile leaks (defined as bile leakage from surgical drains or wounds within 30 d from LT), accidental T-tube removal, endoscopic and interventional radiology procedures on the bile ducts, time to T-tube removal, biliary fistulae after T-tube removal, episodes of biliary peritonitis and need for surgical intervention. Biliary fistulae were divided in uncontrolled and controlled depending whether the patients developed biliary peritonitis or not.

The primary objective of our study was to investigate the safety profile of T-tube insertion and removal techniques in LT recipients defined as the incidence of T-tube removal related biliary complications. We analyzed the incidence of biliary complications after T-tube removal in patients who received a duct-to-duct biliary anastomosis over a 5-French pediatric rubber T-tube, which was subsequently removed without instrumental aid [*e.g.*, endoscopic retrograde cholangiopancreatography (ERCP)-assisted or during surgery]. In particular, we focused on the need for endoscopic, interventional radiology or surgical treatment after T-tube removal. Even patients with an accidental T-tube removal were included in our analysis to evaluate whether our insertion technique is protective against bile leaks in such circumstance. Patients who had the T-tube removed during endoscopic interventions on the bile ducts were excluded and summarized separately. Patients with an up-front bilio-enteric anastomosis, those who died or received retransplantation before T-tube removal were excluded.

The study protocol was approved by the Ethics Committee of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS (protocol No. 3796).

T-tube insertion protocol

The policy of our hospital foresees routine placement of T-tubes in all liver transplants except for bilio-enteric anastomoses. Our standard biliary reconstruction technique is an end-to-end duct-to-duct anastomosis with interrupted Vicryl 6/0 stitches and extraluminal knots. Recipient's and graft bile duct ends are trimmed short enough to obtain a straight, non-redundant bile duct to avoid kinking after minimizing liver cephalad and duodenum caudal retraction. Firstly, the posterior half of the anastomosis is sewn with interrupted stitches. Then, a T-tube is inserted through a small choledochotomy approximately 2 cm caudal to the anastomosis. In March 2017, we adopted pediatric 5-French rubber T-tubes (Bard Medical, GA) as our standard device. Main steps of T-tube insertion are shown in Figure 1. The smallest right-angle dissector in our DDLT set (6¼ inches Mixter forceps, Aesculap, DE) is advanced inside the recipient bile duct through the open anterior half of the anastomosis; the tip of the instrument is pushed against the anterior wall of the choledochus; the resulting bulge on the choledochus is incised with a no. 11 scalpel (Figure 1A). This allows creating a choledochotomy < 2 mm in size which is necessary to advance the tip of the right-angle dissector. Grabbing and pulling the T-tube is avoided as this would require opening the jaws of the right-angle and inevitably expand the size of the choledochotomy. Instead, a 3/0 silk tie is pulled through the choledochotomy (Figure 1B) and stitched to the horizontal end of the T-tube (Figure 1C). Only then the silk tie is completely pulled through, which allows the T-tube to slide through the choledochotomy to obtain a perfect fit of the T-tube (Figure 1D). The lower branch of the vertical portion of the T-tube usually self-allocates inside the distal choledochus (Figure 1E) while the upper branch is placed with forceps. The anterior wall of the anastomosis is completed (Figure 1F) with interrupted stitches and the T-tube is externalized through the right upper quadrant, cranial to the transverse skin incision. A video of the insertion technique is provided separately (see supplementary material).

T-tube management

During the first week after LT, bile output is collected daily for quantitative and qualitative assessment to aid postoperative patient management. Before discharge, a T-tube cholangiogram is performed and, in absence of biliary anomalies, the T-tube is capped and secured underneath a wound dressing, which is kept in place for approximately 3 mo. T-tube cholangiograms are performed on demand. In order to insure

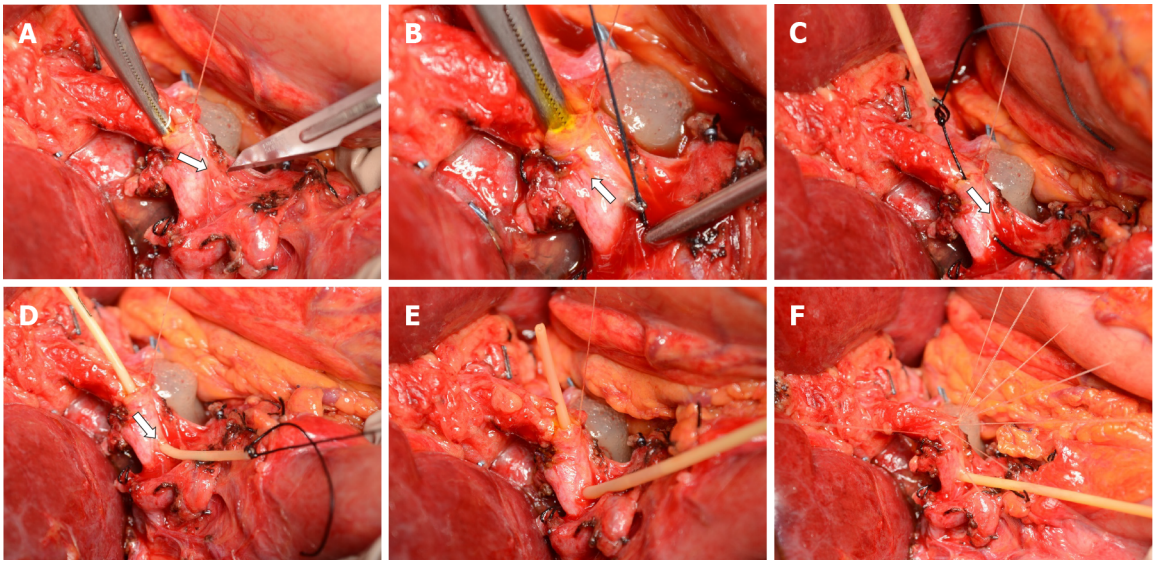

Figure 1 T-tube insertion protocol. A: The right-angle is advanced through the open anterior layer of the duct-to-duct anastomosis and a choledochotomy is created with a no. 11 scalpel; B-D: A silk tie is grabbed and pulled through the choledochotomy after being stitched to the horizontal end of the T-tube; E: the T-tube is allocated inside the bile duct; F: the anastomosis is completed with interrupted Vicryl 6/0 stitches.

adequate T-tube management after discharge at home, patients receive care instructions. During outpatient visits, T-tubes are evaluated by dedicated transplant staff.

T-tube removal protocol

T-tube removal is planned approximately 90 d after LT as an in-patient procedure. Directly after admitting the patients, history and examination are taken and transplant records are reviewed in search of details that could predict a higher risk of biliary complications from T-tube removal (*e.g.*, discrepancy in ducts caliber graft > recipient, complex arterial reconstruction, arterial thrombosis). Patients without evidence of increased risk proceed directly with the removal after the administration of a smooth-muscle relaxant and antibiotic prophylaxis. Patients with increased risk of biliary complications receive a T-tube cholangiogram to detail biliary anatomy and to anticipate critical anatomical conditions to insure safe T-tube removal. If the cholangiogram reveals anatomical problems, the bile duct is prophylactically stented during ERCP or the removal proceeds under fluoroscopic guidance and a stent is inserted on demand. An abdominal ultrasound is also performed in high-risk patients to acquire baseline information before the T-tube is removed.

Figure 2 shows a bedside, standard removal procedure. After informed consent, the patient's abdomen is prepped and draped and local anesthetic is administered around the T-tube exit site. The T-tube is removed and the length between the exit site and the end of the T-tube is measured (Figure 2A and B). Through the exit site of the T-tube, a flexible 8-French Nelaton drain (Teleflex Medical, PA) is advanced 2-3 cm shorter than the length measured on the T-tube with the aim to reach the space near the choledochotomy without entering it accidentally. The drain is secured to the skin with a stitch and connected to a drain bag. The insertion of a Nelaton drain aims at draining possible bile leaks from the choledochotomy. An abdominal ultrasound is performed in search of intrabdominal fluid collections when clinically indicated. The following day, the Nelaton drain is removed, if no bile leak was present, or retracted by approximately 2 cm in case of bile output. The same process is repeated on the following day until the drain is clear of bile and the patient can be discharged.

RESULTS

During the study period, 96 patients received 97 Liver transplants in our center: 92 had an end-to-end duct-to-duct anastomosis over a 5 French T-tube and 5 received an up-front hepaticojejunostomy. Seven patients (five with biliary complications from ischemic cholangiopathy) required endoscopic intervention and removal of the T-tube together with endoscopic biliary stenting: One patient with a bile leak on day 28 post-

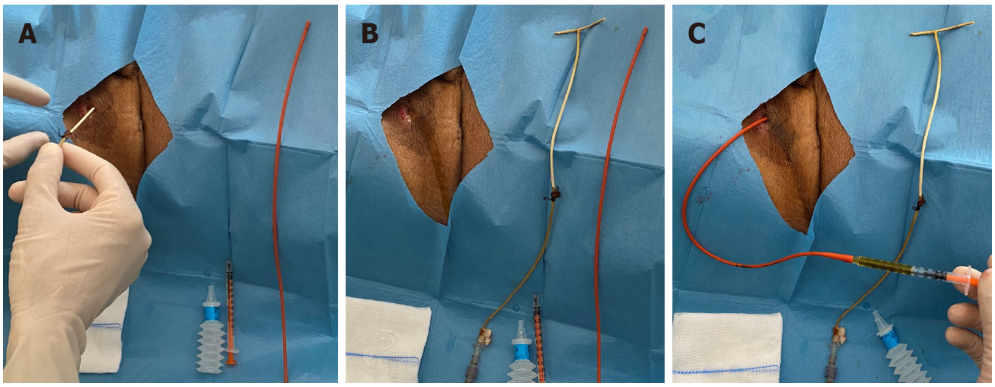

Figure 2 Bedside, standard T-tube removal procedure. A: The T-tube is removed; B: A Nelaton drain is kept aside to measure the length of the T-tube internal tract (whiter portion of the T-tube); C: The Nelaton drain is inserted approximately 2 cm shorter than the measured length.

LT required hepaticojejunostomy after failed endoscopic management attempts due to bile duct end necrosis; four patients had non-anastomotic biliary strictures, and two had biliary stones. After applying the exclusion criteria, 72 patients were included in the study. The characteristics of the study population are reported in Table 1.

Accidental T-tube removal occurred in four (5.6%) cases, on days 11, 13, 87 and 122 post-LT, respectively, and none required active treatment (abdominal ultrasound showing no signs of bile leak).

T-tube cholangiograms were performed in all patients before capping the T-tube. Removal of the T-tube took place as an in-patient procedure, after a median of 158 d (IQR 128-206 d) post-LT. Twenty-five (34.7%) patients received a T-tube cholangiogram before removal, because of deranged liver function tests (n = 14) followed by a history of complex anatomy or complications with the hepatic artery (n = 11). There were no cases of incomplete T-tube removal (*i.e.*, no retained broken pieces after extraction). In 68 (94.6%) cases it was possible to insert a Nelaton drain through the exit site of the T-tube. Of these, 18 (25%) patients had a biliary output from the Nelaton drain, which was removed after a median of 2 d (IQR 1-4 d) from insertion. Table 2 summarizes management details of the study population. Three (4%) patients had persistent output from the Nelaton drain despite the progressive retraction on a daily basis, as described in the protocol. Therefore, the patients underwent ERCP with endoscopic sphincterotomy and temporary naso-biliary drain (n = 1), endoscopic stenting (n = 1), while one patient required hepatico-jejunostomy due to a tight bile duct stenosis. Three (4%) patients without output from the Nelaton drain developed symptoms of biliary peritonitis, and underwent ERCP. Of note, ERCP revealed contrast extravasation from the bile duct only in one patient; nevertheless, all three patients received sphincterotomy and temporary naso-biliary drain insertion, which was removed after symptom resolution. Altogether, biliary fistula after T-tube removal occurred in 6 patients (4% controlled and 4% uncontrolled fistula respectively). T-tube-related events are shown in Table 3.

No patient required percutaneous drainage of bile collections or emergency surgery after T-tube removal. No patient death occurred or was related to T-tube removal.

DISCUSSION

Biliary complications from T-tube use are within the most feared and disappointing events after LT. Minimizing the risk of such complications is pivotal for maintaining positive outcomes in LT recipients. With this intent, we refined our insertion technique and removal protocol. Suspected biliary peritonitis after T-tube removal occurred only in 4% of our patients. Of these, only one patient had confirmed contrast extravasation at the time of ERCP, and, therefore, the remaining two had probably a self-limiting bile leak. Remarkably, no patient developed biliary peritonitis or bile collections requiring emergency interventional radiology procedures or surgery. Compared with a systematic review, reporting the incidence of biliary peritonitis of 5% to 33% after T-tube removal, our experience demonstrates that the attention to the insertion and removal technique is essential to preserve LT recipients' safety[11]. As shown in clinical and animal studies, rubber have been preferred over silicone T-tubes in general surgery owing to their ability to induce a stronger fibrogenic reaction forming a

Table 1 Patients' characteristics and surgical data

Variable	Study population *n* = 72, median (IQR)/*n*
Male sex	61 (84.7%)
Recipient age (yr)	57 (50-61)
Body mass index (kg/m^2)	27 (23-29)
Underlying liver disease	
Hepatitis C virus	21 (29.2%)
Hepatitis B virus	7 (9.7%)
Alcohol-related liver disease	25 (34.7%)
Primary biliary cirrhosis	2 (2.8%)
Polycystic liver disease	2 (2.8%)
Acute liver failure	4 (5.6%)
Other	11 (15.3%)
HCC	41 (56.9%)
MELD score	17 (12-22)
Donor age (yr)	62 (45-73)
Use of temporary porto-caval shunt	29 (40.3%)
Use of veno-venous bypass	6 (8.3%)
Total ischemia time (min)	435 (390-488)

HCC: Hepatocellular carcinoma; MELD: Model for end-stage liver disease.

Table 2 T-tube management in the study population

Variable	Study population *n* = 72, median (IQR)/*n*
Time to removal of T-tube (d)	158 (128-206)
T-tube cholangiogram before removal	25 (35%)
Nelaton drain successful insertion	68 (94%)
Nelaton drain with bile output	18 (25%)
Time to removal of Nelaton drain	2 (2-4)
Active treatment required	
ERCP	6 (8%)
Hepatico-jejunostomy	1 (1%)
Emergency surgery	0

ERCP: Endoscopic retrograde cholangiopancreatography.

pseudo-channel that conveys the bile externally after the tube is removed[12]. Keeping the choledochotomy small using a pediatric 5-French T-tube supposedly increases chances that the surrounding tissues can fold the hole in the choledochus after the T-tube is removed; this may explain our low incidence of uncontrolled post-removal biliary fistula. Furthermore, developed fistulae seemed smaller, requiring endoscopic intervention only in a few cases and emergency surgery in no cases. In addition, no bile leak from choledochotomy occurred during cholangiogram in controls, probably owing to the exact fit achieved keeping the choledochotomy the size of the T-tube.

Biliary peritonitis is a surgical emergency that can lead to sepsis and multiorgan failure, especially in the vulnerable LT population[13]. By inserting a Nelaton drain through the T-tube exit site, our removal protocol minimizes consequences of bile

Table 3 Summary of events and treatment required in the study population after T-tube removal

	Events	First-line treatment	Definitive treatment
Accidental T-tube removal	4	4 monitoring	
Post T-tube removal bile leak			
Controlled fistula (through Nelaton drain)	18	15 onitoring	-
		3 ERCP	2 stent; 1 HJ
Biliary peritonitis	3 suspected	3 ERCP (1 confirmed)	3 NBD

ERCP: Endoscopic retrograde cholangiopancreatography; HJ: Hepatico-jejunostomy; NBD: Naso-biliary drain.

leaks. The placement of a straight drain by interventional radiologists, with the aim to reduce the occurrence of biliary peritonitis, has been already described in 1998[14]. Similarly, we use a Nelaton drain, which is inserted at the bedside as soon as the T-tube is removed. Some patients with biliary output from the Nelaton drain (controlled biliary fistula) could be considered as potentially saved from developing biliary peritonitis (uncontrolled fistula).

Several alternatives to conventional T-tube placement have been described. A tunneled retroperitoneal route has been proposed with the rationale to support T-tube tract development allowing to control fistula after removal[15]. Intraductal stent placement has been adopted to overcome the side effects of external T-tubes in 20 patients with a bile duct caliber < 5 mm. The downside with this approach is the need for endoscopic removal 4 to 6 mo after placement and the reported complication rate was still significant in 4 patients[16]. A randomized clinical trial is ongoing in which custom-made 2 cm-segment of an 8 French T-tube are inserted in the biliary duct without suture fixation, which is removed *via* ERCP and sphincterotomy 4 to 6 mo after LT[17]. Resorbable internal biliary stents for LT have been tested *in vitro* and have been already employed to treat refractory anastomotic strictures in LT recipients[18, 19]. In a matched case–control study, a transcystic straight drain has been used with improved results compared with T-tube placement; however, the technique is not applicable in bile ducts with a low cystic duct confluence [20].

Concerns over the lack of fibrous tract formation around the T-tube have been addressed by delaying the time of removal (transplant recipients might have impaired healing processes due to the steroidal treatment and ascites formation). On the other hand, a higher rate of biliary stricture have been observed, supposedly because of the prolonged permanence of the T-tube inside the bile duct and increased risk of microbial contamination[21].

In our center, we maintained our T-tube policy, which is a limitation of our study as we have no comparative group (no-T-tube group). Moreover, our LT recipients are inevitably subjected to an extra hospital admission to remove the T-tube. The need to hospitalize patients for the removal procedure can also cause delays due to limited bed capacities, as shown in our time to T-tube removal, which is often longer than 3 mo. A relevant proportion of patients had the T-Tube removed during interventional ERCP for biliary complications mainly related to ischemic cholangiopathy, if T-tubes aggravate such complications remains unclear. The long-lasting presence of a foreign body could contaminate ischemic bile ducts and contribute to damage[22].

CONCLUSION

We managed to mitigate the risk of complications related to T-tube insertion and removal, which partly explains the reason why we did not change our policy. Altogether, we demonstrated safety, and our outcomes are not inferior to those reported in literature. With our study, we provide insight on LT management of patients who received a T-tube, which we believe could be of interest in the contemporary context of increased donor risk and regained attention around the use of T-tubes.

ARTICLE HIGHLIGHTS

Research background

The use of T-tube in liver transplantation (LT) remains controversial despite being the objective of randomized trials and meta-analyses. Since the 90's many centers stopped using T-tubes in LT. More recently, the increasing use of extended-criteria organs has revived the interest around the usefulness of T-tube in LT.

Research motivation

In our center, we maintained our T-tube policy refining the T-tube insertion and removal techniques continuously. Since March 2017, we have adopted a pediatric rubber 5-French T-tube for splinting the biliary duct-to-duct anastomosis in adult LT recipients.

Research objectives

To describe the insertion and removal protocols implemented at our institution for the safe use of pediatric rubber 5-French T-tubes and the subsequent outcomes in a consecutive series of adult patients.

Research methods

We retrospectively analyzed data of consecutive adult LT recipients from brain-dead-donors, treated from March 2017 to December 2019, regarding biliary complications, adverse events, and treatment required after T-tube removal. Patients with upfront hepatico-jejunostomy, endoscopically removed T-tubes, those who died or received retransplantation before T-tube removal were excluded.

Research results

Out of 72 patients who had the T-tube removed, 68 (94.4%) had per-protocol Nelaton drain insertion through the T-tube exit site. Of these, biliary output was observed in 18 (25%) patients. The Nelaton drain was removed after 2 d (median; IQR 1-4 d). Three (4%) patients required endoscopic retrograde cholangiopancreatography (ERCP) due to persistent Nelaton drain biliary output. Three (4%) patients developed suspected biliary peritonitis, requiring ERCP with sphincterotomy and nasobiliary drain insertion (only one revealing contrast extravasation). No patients required percutaneous drainage of bile collections or emergency surgery after T-tube removal. In four (5.6%) patients accidental T-tube removal occurred, none requiring active treatment. There was no mortality associated with T-tube removal.

Research conclusions

In our series of adult LT recipients, the use of a pediatric T-tube was safe with insertion and removal technique refinements, resulting in minor morbidity and no mortality after T-tube removal.

Research perspectives

With the increasing use of extended-criteria donor grafts in LT, the use of T-tubes is regaining interest, regarding bile output and quality measure and for bile duct protection purposes to reduce the risk of stenosis and leaks. In this perspective, refined insertion and removal techniques are pivotal to ensure low morbidity associated with the use of the T-tube.

ACKNOWLEDGEMENTS

We would like to thank Franziska M Lohmeyer, PhD, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, for her support revising our manuscript.

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2021 December 27; 13(12): 1638-1650

DOI: 10.4240/wjgs.v13.i12.1638

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Preoperative calculation of angles of vision and working area in laparoscopic surgery to treat a giant hiatal hernia

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Author contributions: Lara FJP made a substantial contribution to the concept and design; Lara FJP and Zubizarreta Jimenez R drafted the article, revised it critically for important intellectual content and approved the version to be published; Moya Donoso FJ, Hernández Gonzalez JM, Prieto-Puga Arjona T, del Rey Moreno A, Pitarch Martinez M approved the version to be published.

Institutional review board statement: The study was approved by the Antequera Hospital.

Informed consent statement: Due to the retrospective design of the study, the requirement of informed consent was waived.

Conflict-of-interest statement: Authors have no conflict of interest.

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Abstract

BACKGROUND

Giant hiatal hernias still pose a major challenge to digestive surgeons, and their repair is sometimes a highly complex task. This is usually performed by laparoscopy, while the role of the thoracoscopic approach has yet to be clearly defined.

AIM

To preoperatively detect patients with a giant hiatal hernia in whom it would not be safe to perform laparoscopic surgery and who, therefore, would be candidates for a thoracoscopic approach.

METHODS

In the present study, using imaging test we preoperatively simulate the field of vision of the camera and the working area (instrumental access) that can be obtained in each patient when the laparoscopic approach is used.

RESULTS

From data obtained, we can calculate the access angles that will be obtained in a preoperative computerised axial tomography coronal section, according to the location of the trocar. We also provide the formula for performing the angle calculations If the trocars are placed in loss common situations, thus enabling us to determine the visibility and manoeuvrability for any position of the trocars.

CONCLUSION

The working area determines the cases in which we can operate safely and those in which certain areas of the hernia cannot be accessed, which is when the

Data sharing statement: No additional data are available.

Country/Territory of origin: Spain

Specialty type: Surgery

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

Peer-review model: Single blind

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

Received: March 27, 2021
Peer-review started: March 27, 2021
First decision: June 14, 2021
Revised: June 21, 2021
Accepted: November 26, 2021
Article in press: November 26, 2021
Published online: December 27, 2021

P-Reviewer: Shah OJ
S-Editor: Liu M
L-Editor: A
P-Editor: Liu M

thoracoscopic approach would be safer.

Key Words: Hiatal hernia; Angles; Approach; Laparoscopy; Thoracoscopy

Core Tip: This study was conducted to determine the accessibility obtained when the laparoscopic approach is applied to the repair of a giant hiatal hernia. The main study aim is to detect cases in which full access to all areas of the hernial sac is not possible, and in which, therefore, the thoracoscopic approach would be safer.

Citation: Lara FJP, Zubizarreta Jimenez R, Moya Donoso FJ, Hernández Gonzalez JM, Prieto-Puga Arjona T, del Rey Moreno A, Pitarch Martinez M. Preoperative calculation of angles of vision and working area in laparoscopic surgery to treat a giant hiatal hernia. *World J Gastrointest Surg* 2021; 13(12): 1638-1650
URL: https://www.wjgnet.com/1948-9366/full/v13/i12/1638.htm
DOI: https://dx.doi.org/10.4240/wjgs.v13.i12.1638

INTRODUCTION

A hiatal hernia is the protrusion of abdominal contents into the mediastinum through the diaphragmatic hiatus. It is a common condition in the general population and, due to the progressive aging of the population, is expected to become more so[1].

Hiatal hernias are classified into four types according to their anatomical characteristics[2-7]. Type 1 ("Sliding"), the most common, is a herniation of the oesophagogastric junction above the diaphragm, propelling the stomach into the abdomen. Type 2 ("Pure para-oesophageal") is the thoracic migration of the gastric fundus while the oesophagogastric junction remains in the correct position. Type 3 ("Mixed") combines the components of Types 1 and 2. Type 4 ("Giant"), occurs when the hernia affects the entire stomach and other abdominal viscera, including the colon, omentum, small intestine, liver and spleen[8].

However, the term "Giant para-oesophageal hernia" is imprecise. The term "giant" is subject to interpretation, and although there is no consensus as to what percentage of the stomach should rise into the thorax for the hernia to be defined as "giant", most authors agree that this category represents 5%-10% of all hiatal hernias[9].

The standard treatment for a hiatal hernia is to reduce the capacity of the abdominal cavity, to close the defect and to perform an anti-reflux procedure, usually by means of 360º (Nissen) fundoplication.

When the hernia is large, it is sometimes difficult to dissect the sac to reduce the hernia, and so 'dark' areas may remain, which cannot be accessed through the abdominal approach, due either to an insufficient angle of vision or to an insufficient instrument working angle (the apparatus cannot reach the operative site). In the present article, we derive the information necessary to assess visual (camera) and working (instrumental) access to all parts of the intrathoracic hernial sac, making it possible to confirm whether the laparoscopic approach is safe and reliable, or on the contrary, whether a thoracic approach would be necessary.

MATERIALS AND METHODS

As observed above, with giant hernias, it is sometimes not possible to achieve full visibility of all areas of the sac using the laparoscopic approach. For this reason, we describe a procedure by which the angles of vision and the instrument working angle needed during the intervention can be preoperatively assessed by simulation in a computerised axial tomography (CAT) scan. The information thus obtained will reveal whether it is safe to use a laparoscopic approach or whether a thoracoscopic approach is needed.

By determining certain parameters – the camera angle aperture, the diameter of the hernial orifice and the positioning of the trocars with respect to this orifice – we can calculate the angle of vision and the instrument working angle available during the intervention. The angle of vision is defined as the visual field of the intrathoracic content into which the optical instrument must be inserted through the hernial orifice. The instrument working angle is the available access to the different parts of the intrathoracic hernial content by means of which the instruments can be delivered through the hiatal hernial orifice.

The procedure consists in performing a simulation with a preoperative thoraco-abdominal CAT scan of all patients with a giant hiatal hernia. In the coronal plane, we evaluate the angles of vision and the instrument working angles that will be obtained, according to where the trocars are located. This will reveal whether there are any hidden areas that are inaccessible visually or with surgical instruments.

The following methods are used to calculate these angles.

RESULTS

Assessing the angle of vision

To evaluate the angle of vision, consider the geometry shown in Figure 1, regarding a laparoscopic intervention. The entry point for the instruments is marked with point O, which for simplicity is assumed to be centred with respect to the hernial orifice within the cavity, of diameter D. The distance between point O and the centre of the hernial orifice is labelled X, and b is the angle from the vertical, from point O to the maximum point of entry of the instruments.

The greatest angle of view that the camera can achieve is obtained when the camera inserted *via* the entry point reaches the hernial orifice. From here, the camera's angle of vision (a) can be projected.

Considering the geometric relationship between the distances and the angles, the angle q can be calculated as follows, from the camera's angle of vision (data supplied by the manufacturer), distance X and the diameter of circle D.

$$\text{TAN}\,\beta = \frac{D/2}{X}. \quad \rightarrow \quad \beta = \text{ATAN}\left(\frac{D/2}{X}\right)$$

$$\theta = \alpha/2 + \beta = \alpha/2 + \text{ATAN}\left(\frac{D/2}{X}\right)$$

The camera can sometimes be bevelled to increase the angle of vision, rotating it through the angle d. Figure 2 shows how the bevel arrangement expands the angle of vision. When a bevel angle of d is introduced, the equation then becomes:

$$\theta = \alpha/2 + \beta + \delta = \alpha/2 + \text{ATAN}\left(\frac{D/2}{X}\right) + \delta$$

These expressions allow us to evaluate the cone of vision for the instrument working area. Figure 3 shows the projection of this cone on the CAT scan, to illustrate the geometric concept.

Determining the instrument working angle

Figure 4 shows the geometric model for the laparoscopy instruments.

In this case, the additional angles a and d cannot be applied to the operating instruments since the heads cannot be rotated. The maximum angle that can be achieved with the stipulated geometry is then calculated as follows:

$$\theta = \beta = \text{ATAN}\left(\frac{D/2}{X}\right)$$

Tables of angles of vision and instrument working angles

From the above expressions, the maximum viewing and working angles can be calculated, using the corresponding dimensions for each patient. By way of example, and to facilitate the evaluation, Figure 5 shows the CAT image, from which the dimensions for the D and X values can be taken to calculate the angle q.

Tables 1, 2 and 3 detail the values of angle q for the different geometric values observed in the intervention, with a camera angle of vision of a = 60º and a bevel angle d of 0º or 30º.

Determining the angle of the working area with lateral displacement at the entrance

The lateral access trocars increase the instrument working angle, since they are located on either side of point O, thus forming a second entry point, called O'. This point is displaced by distance b from point O. Figure 6 shows the model overlain on the CAT scan.

Table 1 Camera angles of vision 0º (δ = 0º and δ = 60º) (x = trocar-hiatus cm, D = hernia- hiatus diameter)

	D (cm)								
X (cm)	2	3	4	5	6	7	8	9	10
10	35.71	38.53	41.31	44.04	46.70	49.29	51.80	54.23	56.57
11	35.19	37.77	40.30	42.80	45.26	47.65	49.98	52.25	54.44
12	34.76	37.13	39.46	41.77	44.04	46.26	48.43	50.56	52.62
13	34.40	36.58	38.75	40.89	42.99	45.07	47.10	49.09	51.04
14	34.09	36.12	38.13	40.12	42.09	44.04	45.95	47.82	49.65
15	33.81	35.71	37.59	39.46	41.31	43.13	44.93	46.70	48.43
16	33.58	35.36	37.13	38.88	40.62	42.34	44.04	45.71	47.35
17	33.37	35.04	36.71	38.37	40.01	41.63	43.24	44.83	46.39
18	33.18	34.76	36.34	37.91	39.46	41.00	42.53	44.04	45.52
19	33.01	34.51	36.01	37.50	38.97	40.44	41.89	43.32	44.74
20	32.86	34.29	35.71	37.13	38.53	39.93	41.31	42.68	44.04
21	32.73	34.09	35.44	36.79	38.13	39.46	40.78	42.09	43.39
22	32.60	33.90	35.19	36.48	37.77	39.04	40.30	41.56	42.80
23	32.49	33.73	34.97	36.20	37.43	38.65	39.87	41.07	42.26
24	32.39	33.58	34.76	35.95	37.13	38.30	39.46	40.62	41.77
25	32.29	33.43	34.57	35.71	36.84	37.97	39.09	40.20	41.31

Table 2 Angles of vision with camera angle bevelled 30º (x = trocar-hiatus cm, D = hernia- hiatus diameter)

	D (cm)								
X (cm)	2	3	4	5	6	7	8	9	10
10	65.71	68.53	71.31	74.04	76.70	79.29	81.80	84.23	86.57
11	65.19	67.77	70.30	72.80	75.26	77.65	79.98	82.25	84.44
12	64.76	67.13	69.46	71.77	74.04	76.26	78.43	80.56	82.62
13	64.40	66.58	68.75	70.89	72.99	75.07	77.10	79.09	81.04
14	64.09	66.12	68.13	70.12	72.09	74.04	75.95	77.82	79.65
15	63.81	65.71	67.59	69.46	71.31	73.13	74.93	76.70	78.43
16	63.58	65.36	67.13	68.88	70.62	72.34	74.04	75.71	77.35
17	63.37	65.04	66.71	68.37	70.01	71.63	73.24	74.83	76.39
18	63.18	64.76	66.34	67.91	69.46	71.00	72.53	74.04	75.52
19	63.01	64.51	66.01	67.50	68.97	70.44	71.89	73.32	74.74
20	62.86	64.29	65.71	67.13	68.53	69.93	71.31	72.68	74.04
21	62.73	64.09	65.44	66.79	68.13	69.46	70.78	72.09	73.39
22	62.60	63.90	65.19	66.48	67.77	69.04	70.30	71.56	72.80
23	62.49	63.73	64.97	66.20	67.43	68.65	69.87	71.07	72.26
24	62.39	63.58	64.76	65.95	67.13	68.30	69.46	70.62	71.77
25	62.29	63.43	64.57	65.71	66.84	67.97	69.09	70.20	71.31

The following equations are used to calculate the maximum instrument working angle:

$$\theta = \beta' = \text{ATAN}\left(\frac{\frac{D}{2}+b}{X}\right)$$

Table 3 Working angles with laparoscopic instruments

	D (cm)								
X (cm)	2	3	4	5	6	7	8	9	10
10	5.71	8.53	11.31	14.04	16.70	19.29	21.80	24.23	26.57
11	5.19	7.77	10.30	12.80	15.26	17.65	19.98	22.25	24.44
12	4.76	7.13	9.46	11.77	14.04	16.26	18.43	20.56	22.62
13	4.40	6.58	8.75	10.89	12.99	15.07	17.10	19.09	21.04
14	4.09	6.12	8.13	10.12	12.09	14.04	15.95	17.82	19.65
15	3.81	5.71	7.59	9.46	11.31	13.13	14.93	16.70	18.43
16	3.58	5.36	7.13	8.88	10.62	12.34	14.04	15.71	17.35
17	3.37	5.04	6.71	8.37	10.01	11.63	13.24	14.83	16.39
18	3.18	4.76	6.34	7.91	9.46	11.00	12.53	14.04	15.52
19	3.01	4.51	6.01	7.50	8.97	10.44	11.89	13.32	14.74
20	2.86	4.29	5.71	7.13	8.53	9.93	11.31	12.68	14.04
21	2.73	4.09	5.44	6.79	8.13	9.46	10.78	12.09	13.39
22	2.60	3.90	5.19	6.48	7.77	9.04	10.30	11.56	12.80
23	2.49	3.73	4.97	6.20	7.43	8.65	9.87	11.07	12.26
24	2.39	3.58	4.76	5.95	7.13	8.30	9.46	10.62	11.77
25	2.29	3.43	4.57	5.71	6.84	7.97	9.09	10.20	11.31

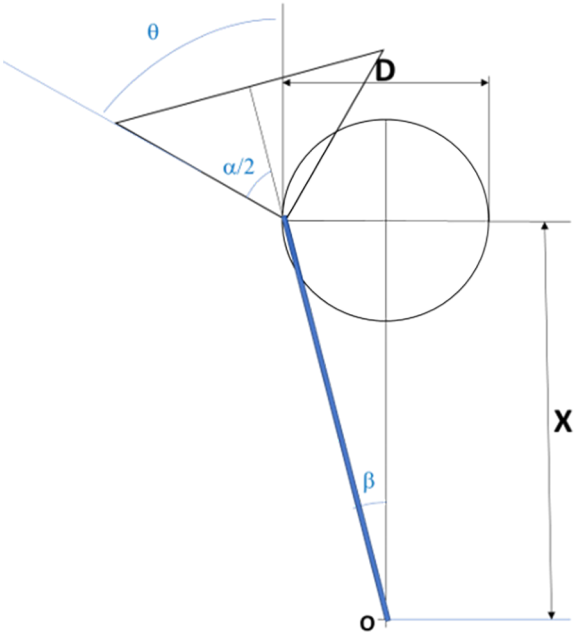

Figure 1 Geometric model for laparoscopy camera field of vision, 0º.

Table 4 shows the q (º) values for b = 6 cm, which is the estimated mean location of the lateral trocars normally employed for laparoscopic hiatal hernia surgery.

Determining the angle of vision with lateral displacement at the entrance

The field of vision can be expanded by inserting the camera through one of the trocars with lateral displacement (Figure 7). The resulting field of vision is then calculated by the following expression:

$$\theta = \alpha/2 + \beta + \delta = \alpha/2 + \text{ATAN}\left(\frac{\frac{D}{2}+b}{X}\right) + \delta$$

Table 4 Operative angles with standard trocars located 6 cm right or left from the midline

	D (cm)								
X (cm)	2	3	4	5	6	7	8	9	10
10	34.99	36.87	38.66	40.36	41.99	43.53	45.00	46.40	47.73
11	32.47	34.29	36.03	37.69	39.29	40.82	42.27	43.67	45.00
12	30.26	32.01	33.69	35.31	36.87	38.37	39.81	41.19	42.51
13	28.30	29.98	31.61	33.18	34.70	36.16	37.57	38.93	40.24
14	26.57	28.18	29.74	31.26	32.74	34.16	35.54	36.87	38.16
15	25.02	26.57	28.07	29.54	30.96	32.35	33.69	34.99	36.25
16	23.63	25.11	26.57	27.98	29.36	30.70	32.01	33.27	34.51
17	22.38	23.81	25.20	26.57	27.90	29.20	30.47	31.70	32.91
18	21.25	22.62	23.96	25.28	26.57	27.82	29.05	30.26	31.43
19	20.22	21.54	22.83	24.10	25.35	26.57	27.76	28.93	30.07
20	19.29	20.56	21.80	23.03	24.23	25.41	26.57	27.70	28.81
21	18.43	19.65	20.85	22.04	23.20	24.34	25.46	26.57	27.65
22	17.65	18.82	19.98	21.12	22.25	23.36	24.44	25.51	26.57
23	16.93	18.06	19.18	20.28	21.37	22.44	23.50	24.54	25.56
24	16.26	17.35	18.43	19.50	20.56	21.60	22.62	23.63	24.62
25	15.64	16.70	17.74	18.78	19.80	20.81	21.80	22.78	23.75

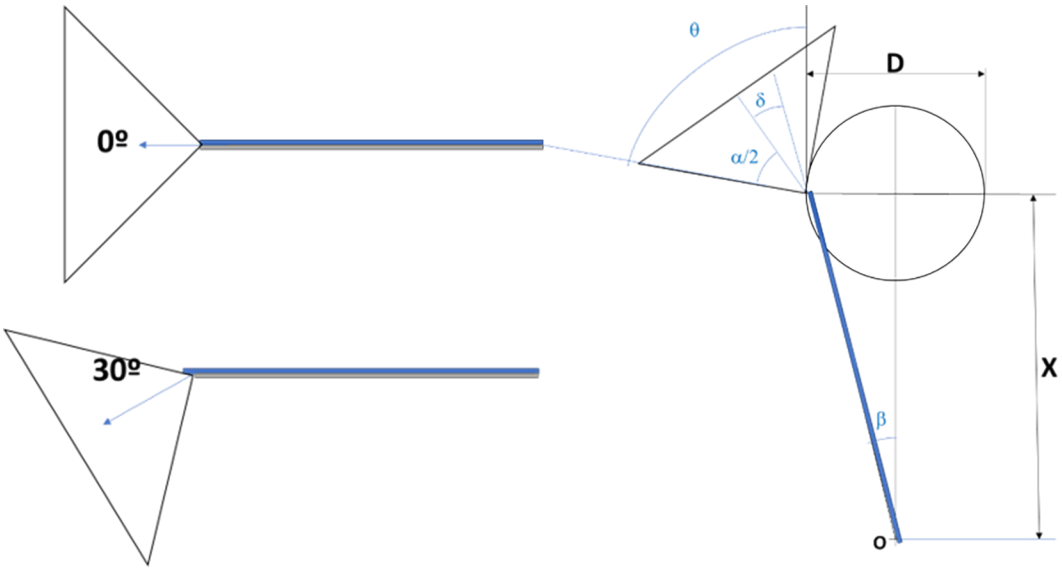

Figure 2 Angle of vision for 0º and 30º camera and geometric model (30º).

Tables 5 and 6 show the values obtained for the field of vision after applying the following values: lateral displacement, b = 6 cm; camera viewing angle = 60º; bevel angle d = 0º or 30º.

DISCUSSION

In 1919, Soresi performed the first operation to reduce a hiatal hernia and to achieve closure of the diaphragmatic pillars[10]. Since then, Skinner *et al*[2], Nissen[11], Collis [12], have advanced the state of the art with their conceptual and technical innovations. The first completely laparoscopic operation with Collis gastroplasty and

Table 5 Angles of vision with the camera at 0º located 6 cm right or left from the midline

	D (cm)								
X (cm)	2	3	4	5	6	7	8	9	10
10	64.99	66.87	68.66	70.36	71.99	73.53	75.00	76.40	77.73
11	62.47	64.29	66.03	67.69	69.29	70.82	72.27	73.67	75.00
12	60.26	62.01	63.69	65.31	66.87	68.37	69.81	71.19	72.51
13	58.30	59.98	61.61	63.18	64.70	66.16	67.57	68.93	70.24
14	56.57	58.18	59.74	61.26	62.74	64.16	65.54	66.87	68.16
15	55.02	56.57	58.07	59.54	60.96	62.35	63.69	64.99	66.25
16	53.63	55.11	56.57	57.98	59.36	60.70	62.01	63.27	64.51
17	52.38	53.81	55.20	56.57	57.90	59.20	60.47	61.70	62.91
18	51.25	52.62	53.96	55.28	56.57	57.82	59.05	60.26	61.43
19	50.22	51.54	52.83	54.10	55.35	56.57	57.76	58.93	60.07
20	49.29	50.56	51.80	53.03	54.23	55.41	56.57	57.70	58.81
21	48.43	49.65	50.85	52.04	53.20	54.34	55.46	56.57	57.65
22	47.65	48.82	49.98	51.12	52.25	53.36	54.44	55.51	56.57
23	46.93	48.06	49.18	50.28	51.37	52.44	53.50	54.54	55.56
24	46.26	47.35	48.43	49.50	50.56	51.60	52.62	53.63	54.62
25	45.64	46.70	47.74	48.78	49.80	50.81	51.80	52.78	53.75

Table 6 Angles of vision with the camera at 30º located 6 cm right or left from the midline

	D (cm)								
X (cm)	2	3	4	5	6	7	8	9	10
10	94.99	96.87	98.66	100.36	101.99	103.53	105.00	106.40	107.73
11	92.47	94.29	96.03	97.69	99.29	100.82	102.27	103.67	105.00
12	90.26	92.01	93.69	95.31	96.87	98.37	99.81	101.19	102.51
13	88.30	89.98	91.61	93.18	94.70	96.16	97.57	98.93	100.24
14	86.57	88.18	89.74	91.26	92.74	94.16	95.54	96.87	98.16
15	85.02	86.57	88.07	89.54	90.96	92.35	93.69	94.99	96.25
16	83.63	85.11	86.57	87.98	89.36	90.70	92.01	93.27	94.51
17	82.38	83.81	85.20	86.57	87.90	89.20	90.47	91.70	92.91
18	81.25	82.62	83.96	85.28	86.57	87.82	89.05	90.26	91.43
19	80.22	81.54	82.83	84.10	85.35	86.57	87.76	88.93	90.07
20	79.29	80.56	81.80	83.03	84.23	85.41	86.57	87.70	88.81
21	78.43	79.65	80.85	82.04	83.20	84.34	85.46	86.57	87.65
22	77.65	78.82	79.98	81.12	82.25	83.36	84.44	85.51	86.57
23	76.93	78.06	79.18	80.28	81.37	82.44	83.50	84.54	85.56
24	76.26	77.35	78.43	79.50	80.56	81.60	82.62	83.63	84.62
25	75.64	76.70	77.74	78.78	79.80	80.81	81.80	82.78	83.75

Nissen fundoplication was described in 1998[13].

The essential steps of the procedure are the complete reduction of the hiatal hernia, excision of the hernial sac, extensive mediastinal mobilisation of the oesophagus, tension-free femoral closure and the construction of an anti-reflux mechanism. The

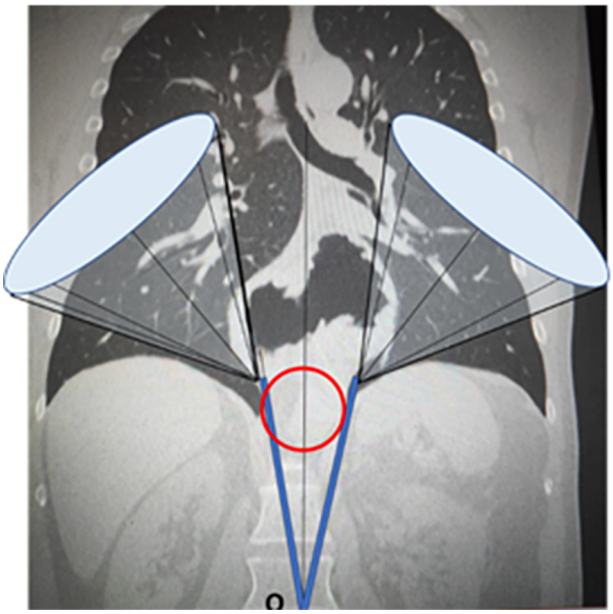

Figure 3 Projections of the operating field cones of vision.

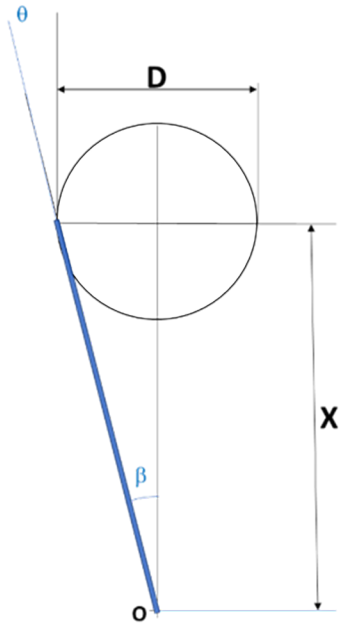

Figure 4 Geometric model of working area with laparoscopic operative instruments.

first step is to reduce the hiatal hernia content by gentle traction of the hernial sac, gradually proceeding with extensive mediastinal mobilisation of the oesophagus (with blunt dissection) to obtain at least 2-2.5 cm of intra-abdominal oesophageal length[14]. During the dissection of the hernial sac, care must be taken to avoid lesions of the vagal nerves on the anterior and posterior surfaces of the oesophagus, the pleura and the adjacent vascular structures. Evidently, this manoeuvre could be very dangerous without visual control of certain areas of adhesions to the sac, or even with visual control if we cannot access the necessary areas with the laparoscopic instrument. These circumstances sometimes lead to blind dissections and traction that may damage vital structures[15].

The minimally invasive approach generally provides an excellent view of the hiatal region, far superior to that obtained by laparotomy, and is associated with low rates of morbidity and mortality, a short hospital stay and excellent patient compliance. From the technical point of view, during hernia reduction, the laparoscopic approach allows

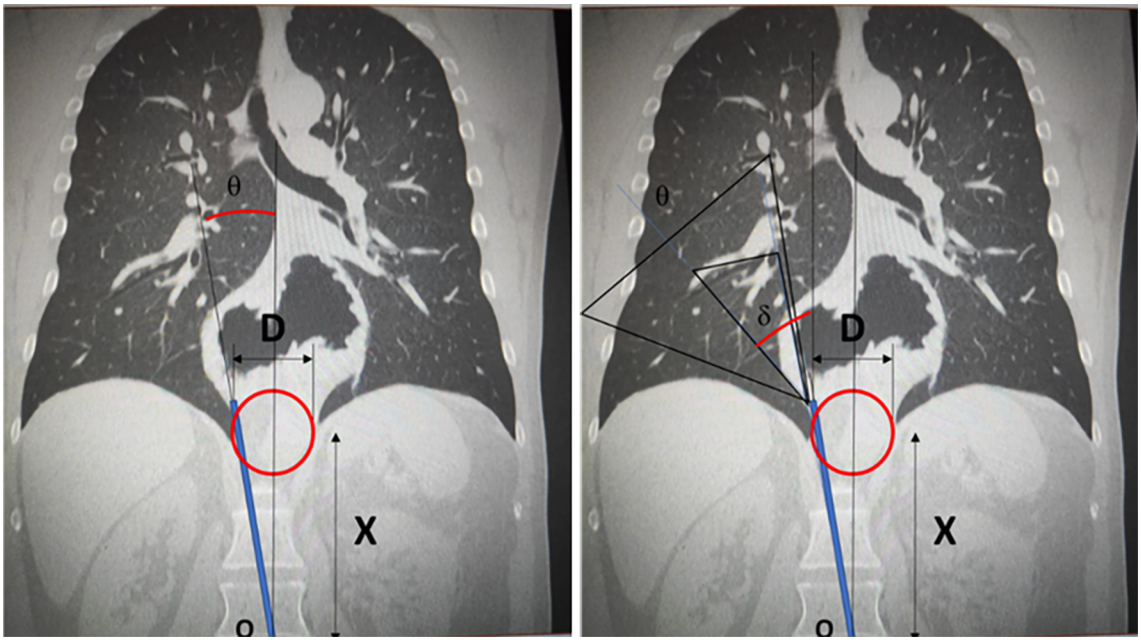

Figure 5 Model superimposed on image: Working area and field of vision with central trocar.

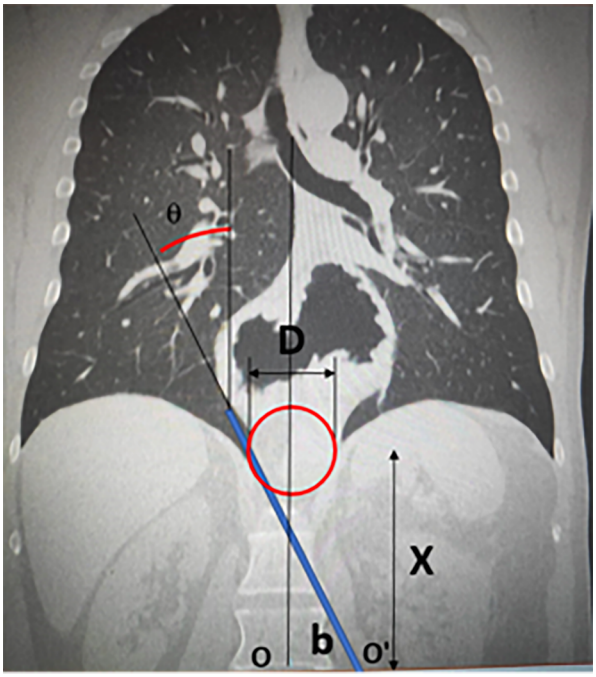

Figure 6 Working area with lateral displacement of the trocar.

precise identification of the anatomical structure (vagus nerves, parietal pleura, distal oesophagus, *etc.*). Moreover, the dissection is facilitated by pneumoperitoneum[16-18].

Laparoscopic para-oesophageal hernia repair can be safely performed, by expert practitioners, with mortality rates of 1.3% in elective settings and 8% in emergencies [19,20]. However, major surgical complications can sometimes occur following iatrogenic lesions of the pleura, aorta or pericardium[21]. In addition, traction on the gastric fundus, the oesophagus-gastric junction and the lower oesophagus can provoke immediate or delayed visceral perforation, with life-threatening consequences[22].

These problems are usually due to a lack of direct vision of the working area. Moreover, in giant hernias the surgeon must overcome a 'bottleneck' effect; the hernial sac and content must be accessed through a relatively narrow hiatal hernial orifice, which limits the manoeuvrability of the instruments and the laparoscopic camera. With larger hernias, this situation can make it impossible to access certain areas of the

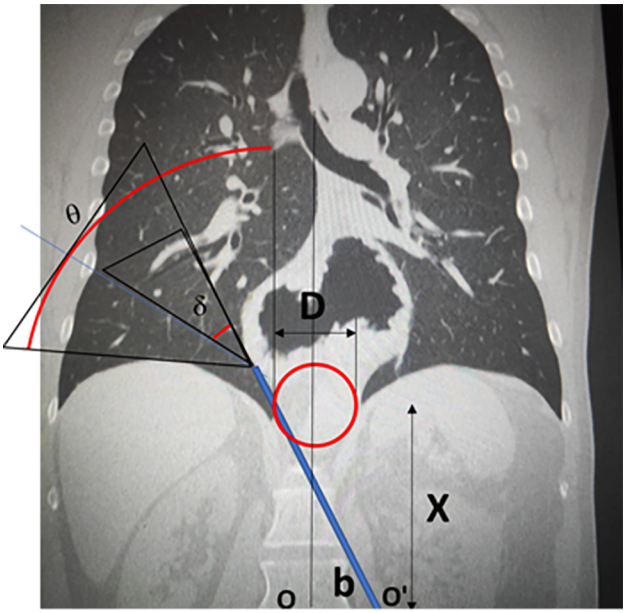

Figure 7 Field of vision with lateral displacement of the trocar and camera at 30º.

intrathoracic hernial content.

Clearly, preoperative awareness of these circumstances is of great importance. If the field of vision or the instrument accessibility is limited, we could opt for a thoracic approach that would provide a good field of vision and an adequate working area in which to intervene safely.

The tables below show the angles of vision and the working angles obtained, according to the distance from the trocar to the hiatal orifice and according to its diameter. Tables 1, 2 and 3 show the results with the camera trocar in the usual, midline, position. Tables 4, 5 and 6 then show the angle of vision and the working angles obtained with the trocar located 6 cm to the left or right of the midline (the usual position for instrument trocars). From these data, we can calculate the access angles that will be obtained in a preoperative CAT coronal section, according to the location of the trocar. We also provide the formula for performing the angle calculations If the trocars are placed in less common situations, thus enabling us to determine the visibility and manoeuvrability for any position of the trocars.

From the study results obtained, it is apparent that the field of vision (with the 30º camera) spans almost all areas of expansion of a giant hiatal hernia. However, the working area is more limited and this factor, ultimately, determines the cases in which we can operate safely and those in which certain areas of the hernia cannot be accessed, which is when the thoracoscopic approach would be safer.

The optimal surgical approach for the repair of giant hiatal hernias has long been debated. Traditionally, this process required a laparotomy or thoracotomy, with their associated rates of morbidity. Conventional thinking used to be that the formation of adhesions, which often occur with laparotomy, might lessen the risk of hernia recurrence by helping retain the reduced structures within the abdomen.

However, the laparoscopic repair of hiatal hernias has provided a valuable surgical alternative since its introduction in 1992[23], in many cases offering better postoperative results and reducing costs[24,25]. For this reason, and especially since 2007, laparoscopic and thoracoscopic procedures have increasingly been employed to treat hiatal hernias.

To date, no randomised controlled trials have been performed to determine whether the thoracoscopic or laparoscopic approach is better, and so the choice remains highly dependent on the preferences and skills of the surgeon in question. Proponents of the laparoscopic approach refer to the easier manipulation of instruments and the ability to visualise the reduced viscera, thus avoiding inadvertent injury. On the other hand, supporters of the thoracoscopic method emphasise that it helps avoid adhesions (if there has been previous abdominal surgery) and that abdominal viscera are easily reduced with CO2 insufflated into the thorax[26].

Surgeons who advocate thoracoscopic repair point out that this method achieves a better visualisation of herniated structures, thus facilitating the dissection and resection of the sac. Accordingly, this approach would be indicated when preoperative

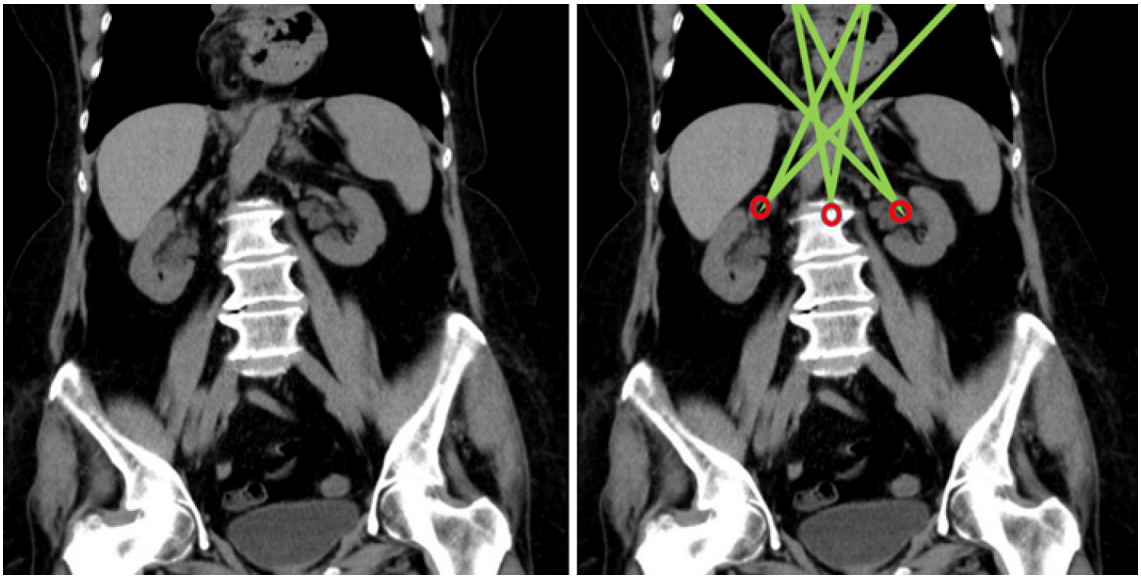

Figure 8 Simulation of the working area with different entry trocars, in a laparoscopically accessible giant hiatal hernia.

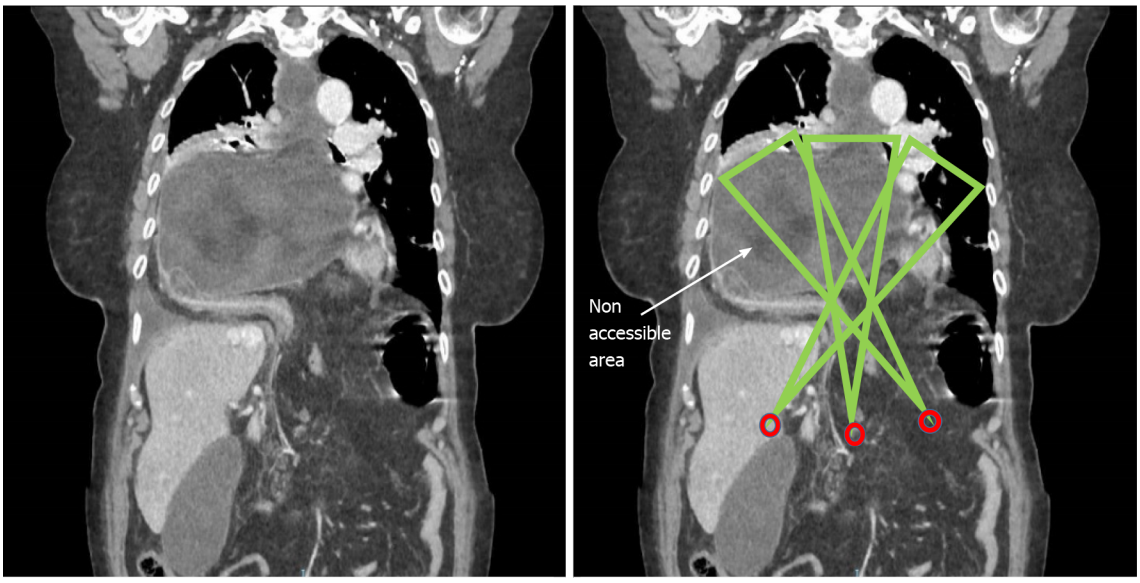

Figure 9 Simulation of the working area with different entry trocars, in a giant hiatal hernia for which the laparoscopic approach is impractical (the arrow shows the area non-accessible to instruments).

simulation detects the presence of 'dark' areas that cannot be accessed visually or instrumentally *via* laparoscopy.

Nowadays, the vast majority of surgeons use the laparoscopic approach for hiatal hernias, and so laparoscopic fundoplication is performed almost universally[27].

Recurrence rates after primary laparoscopic hiatal repair range from 1% to 7%, but can reach 50% with large hiatal hernias[28]. This increase is probably influenced by the fact that in these types of hernias there may be dark areas that cannot be accessed, which prevents the correct dissection of the sac (Figures 8 and 9). In fact, we performed a retrospective calculation of the angles of vision and the working angles in patients operated on with giant hernias, and found four cases in which the content of the hernia was not fully accessible. One of these cases could not be completed laparoscopically. Of the other three, two suffered a recurrence. For these patients, the outcomes would probably have been better if the thoracoscopic approach had been taken.

Despite its long history, the surgical management of giant hiatal hernias continues to evolve, and several questions remain to be clarified. For example, how should we define a giant hernia? Is mesh repair always appropriate? What are the indications

determining the most suitable approach? Our study helps clarify the latter issue by providing objective data on visibility and manoeuvrability, thus informing the surgical team of the indications for the approach which is safest and produces the best results.

CONCLUSION

In short, we believe that full use should be made of the complementary imaging tests that are now available, so that before undertaking any laparoscopic intervention for a giant hiatal hernia we can calculate exactly what can be seen and how far we can go with the surgical instruments. This information, in turn, will enable the most suitable approach to be taken and thus optimise the results of the intervention.

ARTICLE HIGHLIGHTS

Research background

This study was conducted to determine the accessibility obtained when the laparoscopic approach is applied to the repair of a giant hiatal hernia.

Research motivation

In patients with giant hernias, it is sometimes not possible to achieve full visibility of all areas of the sac using the laparoscopic approach.

Research objectives

The main study aim is to detect cases in which full access to all areas of the hernial sac is not possible, and so the thoracoscopic approach would be safer.

Research methods

Our study helps clarify the latter issue by providing objective data on visibility and manoeuvrability, thus informing the surgical team of the indications for the approach which is safest and produces the best results.

Research results

Information of complementary imaging tests will enable us to adopt the most suitable approach and thus optimise the results of the intervention in patients with giant hiatal hernia.

Research conclusions

From the study results obtained, the working area determines the cases in which we can operate safely and those in which certain areas of the hernia cannot be accessed, which is when the thoracoscopic approach would be safer.

Research perspectives

By determining certain parameters – the camera angle aperture, the diameter of the hernial orifice and the positioning of the trocars with respect to this orifice – we can calculate the angle of vision and the instrument working angle available during the intervention.

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2021 December 27; 13(12): 1651-1659

DOI: 10.4240/wjgs.v13.i12.1651

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Effect of aluminum phosphate gel on prevention of early rebleeding after ligation of esophageal variceal hemorrhage

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Author contributions: Xu ZL conceived the idea for the study; Zhang ZL, Peng MS, Chen ZM, Long T, and Xu ZL collected the case data and drafted the manuscript; Wang LS reviewed and revised the manuscript.

Institutional review board statement: The study was reviewed and approved by the ethics committee of Shenzhen People's Hospital.

Informed consent statement: This study has received informed consent from all patients.

Conflict-of-interest statement: The authors declare no conflict of interest for this article.

Data sharing statement: Dataset available from the corresponding author at 78249073@qq.com.

Supported by Natural Science Foundation of Guangdong Province of China, No. 2018A0303130278.

Country/Territory of origin: China

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Abstract

BACKGROUND

Liver cirrhosis is the main cause of portal hypertension. The leading cause of death in patients with liver cirrhosis is its most common complication, esophageal variceal bleeding (EVB). Endoscopic variceal ligation (EVL) is recommended by many guidelines to treat EVB and prevent rebleeding; however, esophageal ulcers occur after treatment. Delayed healing of ulcers and unhealed ulcers lead to high rebleeding and mortality rates. Thus, the prevention of early postoperative rebleeding is of great significance in improving the quality of life and prognosis of patients.

AIM

To evaluate the efficacy of aluminum phosphate gel (APG) plus a proton pump inhibitor (PPI) in the prevention of early rebleeding after EVL in patients with EVB.

METHODS

The medical records of 792 patients who were diagnosed with EVB and in whom bleeding was successfully stopped by EVL at Shenzhen People's Hospital, Guangdong Province, China from January 2015 to December 2020 were collected. According to the study inclusion and exclusion criteria, 401 cases were included in a PPI-monotherapy group (PPI group), and 377 cases were included in a PPI and APG combination therapy (PPI + APG) group. We compared the incidence rates of early rebleeding and other complications within 6 wk after treatment

Specialty type: Gastroenterology and hepatology

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

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

Received: April 27, 2021
Peer-review started: April 27, 2021
First decision: July 14, 2021
Revised: July 14, 2021
Accepted: November 14, 2021
Article in press: November 14, 2021
Published online: December 27, 2021

P-Reviewer: Estremera-Arevalo F, Savarino V
S-Editor: Wu YXJ
L-Editor: Wang TQ
P-Editor: Wu YXJ

between the two groups. The two-sample *t*-test, Wilcoxon rank-sum test, and chi-squared test were adopted for statistical analyses.

RESULTS
No significant differences in age, sex, model for end-stage liver disease score, coagulation function, serum albumin level, or hemoglobin level were found between the two groups. The incidence of early rebleeding in the PPI + APG group (9/337; 2.39%) was significantly lower than that in the PPI group (30/401; 7.48%) (P = 0.001). Causes of early rebleeding in the PPI group were esophageal ulcer (3.99%, 16/401) and esophageal varices (3.49%, 14/401), while those in the PPI + APG group were also esophageal ulcers (5/377; 1.33%) and esophageal varices (4/377; 1.06%); such causes were significantly less frequent in the PPI + APG group than in the PPI group (P = 0.022 and 0.024, respectively). The early mortality rate within 6 wk in both groups was 0%, which was correlated with the timely rehospitalization of all patients with rebleeding and the conduct of emergency endoscopic therapy. The incidence of adverse events other than early bleeding in the PPI + APG group (28/377; 7.43%) was significantly lower than that in the PPI group (63/401; 15.71%) (P < 0.001). The incidence of chest pain in the PPI + APG group (9/377; 2.39%) was significantly lower than that in the PPI group (56/401; 13.97%) (P < 0.001). The incidence of constipation in the PPI + APG group (16/377; 4.24%) was significantly higher than that in the PPI group (3/401; 0.75%) (P = 0.002) but constipation was relieved after patients drank more water or took lactulose. In the PPI and PPI + APG groups, the incidence rates of spontaneous peritonitis within 6 wk after discharge were 0.50% (2/401) and 0.53% (2/377), respectively, and those of hepatic encephalopathy were 0.50% (2/401) and 0.27% (1/377), respectively, presenting no significant difference (P > 0.999).

CONCLUSION
PPI + APG combination therapy significantly reduces the incidence of early rebleeding and chest pain in patients with EVB after EVL.

Key Words: Esophageal variceal bleeding; Esophageal variceal ligation; Proton pump inhibitor; Endoscopic variceal ligation; Aluminum phosphate gel

Core Tip: Esophageal variceal bleeding (EVB) is a common disease with a high mortality rate. Esophageal variceal ligation (EVL) is an effective means of hemostasis; however, ulcer foci of the esophagus can form after treatment. Patients with delayed healing of ulcers and unhealed ulcers are prone to experiencing early rebleeding. No studies have reported on the promotion of ulcer healing or prevention of rebleeding in EVB patients after EVL. This study showed that the application of aluminum phosphate gel in combination with a proton pump inhibitor after EVL significantly reduced the incidence of early rebleeding following endoscopic surgery in EVB patients.

Citation: Zhang ZL, Peng MS, Chen ZM, Long T, Wang LS, Xu ZL. Effect of aluminum phosphate gel on prevention of early rebleeding after ligation of esophageal variceal hemorrhage. *World J Gastrointest Surg* 2021; 13(12): 1651-1659
URL: https://www.wjgnet.com/1948-9366/full/v13/i12/1651.htm
DOI: https://dx.doi.org/10.4240/wjgs.v13.i12.1651

INTRODUCTION

Rupture and bleeding of esophageal gastric varices is a common complication in patients with liver cirrhosis, with an annual incidence of approximately 10% to 15% [1]. Some research has found that the mortality of esophageal gastric variceal bleeding within 6 wk after treatment is 15% to 25%[2-4]. Esophageal variceal bleeding (EVB) is

more common than gastric variceal bleeding, and taking steps to prevent early rebleeding after treating EVB is of significant importance.

Many guidelines suggest endoscopic variceal ligation (EVL) as an effective means to treat EVB and prevent rebleeding[5-8]. EVL ligates varicose veins to form fibrosis after venous ischemia, stenosis, and vascular occlusion at the ligation site to achieve a hemostatic effect. The ulcer surface left by the ligation usually takes 2 to 3 wk to fully heal[9]. Necrosis of the mucosa and submucosa occurs 24 h after EVL, while the onset of acute inflammation usually happens 3 to 7 d after the operation. On postoperative day 7, the local tissues that have been ligated evolve from a necrotic state to one of crusting and shedding to form ulcers. This process is the main period in which postoperative bleeding may occur and a key window during which to prevent early bleeding. Early rebleeding after EVL often occurs within 3-14 d after endoscopic surgery[10]. During the healing window, high-risk factors, such as consumption of an improper diet by the patient, may cause early rebleeding of varicose veins, with an incidence rate of 4.6% to 5.1% and a mortality rate as high as 22% to 23.8%[11,12]. The possible causes of rebleeding after EVL include the presence of varicose veins that have not completely disappeared during the operation; ulcers caused by ischemia after EVL; the presence of portal hypertension, rupturing the fragile ulcers; the ferrule falling off prematurely; and the existence of tissue fibrosis that is not firm enough[13].

Proton pump inhibitors (PPIs) inhibit gastric acid secretion, increase the gastric pH value, mitigate damage to the mucosa from gastric acid, and promote postoperative ulcer healing. A randomized controlled clinical trial has shown that PPIs reduce the size of esophageal ulcers after EVL and the incidence of rebleeding[14]. Studies have also found that treatment with PPIs for 10 d to 30 d after EVL is safe and reduces the incidence of early postoperative bleeding[15,16]. Aluminum phosphate gel (APG) is usually used as a protective agent for the mucous membrane of the digestive tract. It has a specific viscosity, forming a large contact area with the ulcer[17]; thus, it is closely integrated with the ulcer surface formed after EVL, exhibiting a protective effect at the wound's surface. This study retrospectively analyzed the efficacy of APG combined with PPI to prevent early rebleeding after EVL in patients with EVB.

MATERIALS AND METHODS

Data collection

This retrospective analysis selected a total of 792 patients who were diagnosed with EVB at Shenzhen People's Hospital, Guangdong Province, China from January 2015 to December 2020 and included 778 patients for final analysis according to the screening criteria. These 778 patients were stratified into a PPI-monotherapy group (PPI group) and a PPI and APG combination therapy (PPI + APG) group according to their treatment plans, and their medical records were collected for the analysis. This study was reviewed and approved by the ethics committee of Shenzhen People's Hospital. All study participants provided informed consent.

Inclusion criteria

Male or female patients aged 18 to 75 years old, diagnosed with EVB by gastroscopy and treated with EVL, were eligible for inclusion in this study.

Exclusion criteria

Patients with the following were excluded from this study: (1) Incomplete clinical data or (2) other serious diseases, such as coronary heart disease, chronic renal insufficiency, or advanced liver cancers, at the time of hospital admission that may affect the patient's prognosis.

Endoscopic surgery and postoperative follow-up

In the PPI group, patients after endoscopic therapy were treated with a conventional dose of PPI (20 mg rabeprazole, 40 mg pantoprazole, or 40 mg esomeprazole daily) for 4 consecutive weeks. In the PPI + APG group, in addition to the same PPI treatment, patients were given 20 g of APG administered orally three times daily (Boryung Pharmaceutical Co., Ltd., Seoul, South Korea) for 2 consecutive weeks, starting on the same day after endoscopic therapy. All patients were evaluated, and those with no contraindications were given nonselective beta-blocker therapy (propranolol) to prevent rebleeding[5-8]. All patients were closely followed, and those with suspected rebleeding were rehospitalized and immediately underwent endoscopy and treatment.

Outcome indicators

Early postoperative rebleeding in the EVB patients was identified based on the occurrence[8] of active bleeding events (*i.e.*, hematemesis, melena, or hematochezia; reduction in systolic blood pressure > 20 mmHg or increase in the heart rate > 20 beats/min; or > 30 g/L of hemoglobin in the absence of blood transfusion) at 72 h to 6 wk after the first bleeding was under control. Rebleeding was the main outcome indicator of this study; secondary outcome indicators included deaths, infection, and other adverse events.

Statistical analysis

The Statistical Package for the Social Sciences version 25.0 software (IBM Corporation, Armonk, NY, United States) was used for statistical analyses in this study. Normally distributed measurement data were presented as the mean ± SD and were compared between the two groups using a two-sample *t*-test. Skewed measurement data were presented as the median (lower quartile, upper quartile) and were compared between the two groups using the Wilcoxon rank-sum test. Count data are presented as the number of cases and percentages and were compared between the two groups using the chi-squared test. *P* values of less than 0.05 were considered statistically significant.

RESULTS

General data at discharge

Table 1 summarizes the statistical analysis of the general data of the two groups of study participants recorded at the time of hospital discharge. No significant differences in age, sex, model for end-stage liver disease score, prothrombin activity, fibrinogen, platelet count, serum albumin level, or hemoglobin level were found between the two groups.

Occurrence of early rebleeding

Table 2 summarizes the incidence of early rebleeding in the two groups. The incidence of early rebleeding in the PPI + APG group (2.39%, 9/337) was significantly lower than that in the PPI group (30/401; 7.48%) (P = 0.001). Considering the causes of early rebleeding, the incidence rates of esophageal ulcers (6/377; 1.33%) and esophageal varices (1.06%, 4/377) in the PPI + APG group were significantly lower than those in the PPI group (16/401; 3.99%; P = 0.022 and 14/401; 3.49%; P = 0.024, respectively). PPI + APG combination therapy reduced the early incidence rates of esophageal ulcer and bleeding as well as esophageal varices and bleeding after EVL. The early mortality rate within 6 wk after surgery was 0% in both groups; this low rate of mortality was related to the timely rehospitalization of all patients with rebleeding and the conduct of emergency endoscopic therapy.

Occurrence of other complications and adverse events except for bleeding

Table 3 summarizes the statistical analysis of other complications and events except for bleeding that occurred in the two groups of patients. In the PPI + APG group, the incidence of other complications was 7.43% (28/377), which was significantly lower than that in the PPI group (63/401; 15.71%; P < 0.001), while the incidence of chest pain in the PPI + APG group was 2.39% (9/377), which was also significantly lower than that in the PPI group (56/401; 13.97%; P < 0.001). In contrast, the incidence of constipation in the PPI + APG group was 4.24% (16/377), which was significantly higher than that in the PPI group (3/401; 0.75%; P = 0.002). Nevertheless, all cases of constipation in the PPI + APG group were relieved after drinking water for hydration and the oral administration of lactulose. The incidence rates of spontaneous peritonitis within 6 wk after discharge were 0.50% (2/401) and 0.53% (2/377), respectively, and those of hepatic encephalopathy were 0.50% (2/401) and 0.27% (1/377), respectively, showing no significant difference between the two groups (P > 0.999).

DISCUSSION

Rebleeding frequently occurs in patients with EVB after EVL treatment. The cause of early rebleeding is currently considered to primarily relate to postoperative ulcer formation and varicose veins (Figure 1). However, no relevant clinical guidelines offering a definition or treatment advice are currently available. One study reported

Table 1 Baseline data of the two groups

Characteristic	PPI group (*n* = 401)	PPI + APG group (*n* = 377)	*P* value
Age (yr)	53.55 ± 12.55	52.73 ± 13.35	0.376
Female/Male	83/318	73/304	0.642
MELD score	14.94 ± 3.05	15.19 ± 3.30	0.275
Prothrombin activity (%)	65.30 ± 15.26	65.70 ± 16.94	0.731
Fibrinogen (g/dL)	1.94 ± 0.68	2.00 ± 0.73	0.211
Platelet (10^9/L)	104.43 ± 69.88	97.67 ± 70.20	0.179
Albumin (g/dL)	3.39 ± 0.51	3.40 ± 0.52	0.682
Hemoglobin (g/dL)	8.92 ± 0.68	8.86 ± 0.69	0.229

PPI: Proton pump inhibitor; APG: Aluminum phosphate gel; MELD: Model for end-stage liver disease.

Table 2 Main outcomes in the two groups, *n* (%)

Characteristic	PPI group (*n* = 401)	PPI + APG group (*n* = 377)	*P* value
Early rebleeding	30 (7.48)	9 (2.39)	0.001
Source of rebleeding			
Esophageal ulcer	16 (3.99)	5 (1.33)	0.022
Esophageal varices	14 (3.49)	4 (1.06)	0.024
6-wk mortality	0	0	1.000

PPI: Proton pump inhibitor; APG: Aluminum phosphate gel.

Table 3 Other adverse events of the two groups

Characteristic	PPI group (*n* = 401)	PPI + APG group (*n* = 377)	*P* value
Total complications	63 (15.71)	28 (7.43)	< 0.001
Chest pain	56 (13.97)	9 (2.39)	< 0.001
Constipation	3 (0.75)	16 (4.24)	0.002
Spontaneous peritonitis	2	2	1.000
Hepatic encephalopathy	2	1	1.000

PPI: Proton pump inhibitor; APG: Aluminum phosphate gel.

that the polyps formed by banding began to exhibit mucosal and submucosal necrosis and dissolution of the bands 5 to 7 d after EVL, following which the necrotic tissues were shed and ulcers were formed[18]. As compared with ordinary peptic ulcers, patients with portal hypertension experience a poorer esophageal mucosal blood supply and a lower mucosal regeneration rate and self-defense ability, and their ulcer wounds are more susceptible to gastric acid damage, resulting in bleeding. In our study, early esophageal ulcer bleeding was found in 16 cases in the PPI group and 5 cases in the PPI + APG group, accounting for 53.85% (21/39) of the early rebleeding cases.

PPIs inactivate NA^+-K^+-ATPase, thereby inhibiting gastric acid secretion, reducing the injury caused by gastric acid to the mucosa, and promoting postoperative ulcer healing[19]. Although reports have suggested that long-term application of PPIs might increase the occurrence of spontaneous peritonitis and hepatic encephalopathy in patients with liver cirrhosis[20-22], a recent clinical study determined that routine application of PPIs for 30 d after EVL was safe and could significantly reduce the upper gastrointestinal rebleeding and mortality rates of patients within 30 d of hospit-

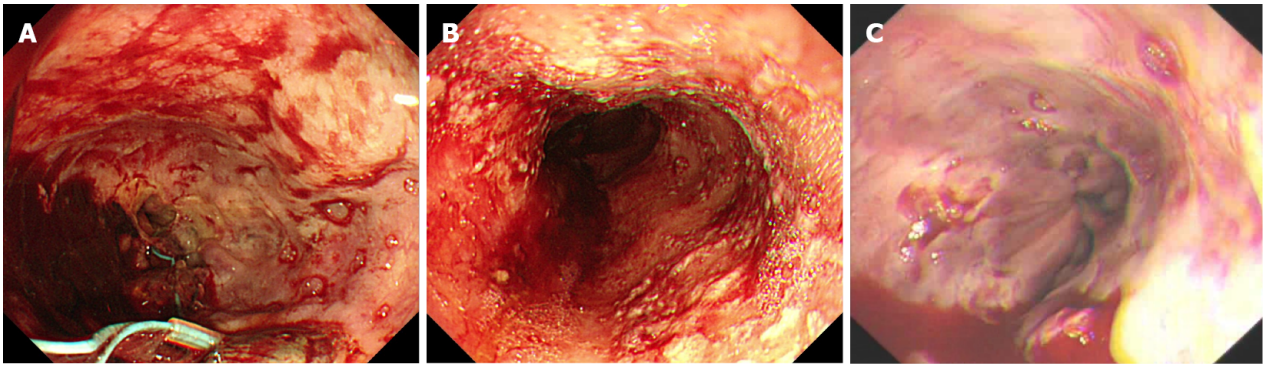

Figure 1 Early rebleeding after endoscopic variceal ligation treatment in esophageal variceal bleeding patients. A: Esophageal varices developed ulceration and bleeding on day 7 after treatment; B: Esophageal varices developed ulceration and bleeding on day 10 after treatment; C: Ulceration of the esophageal variceal vein 14 d after treatment led to rebleeding of the variceal vein.

alization[16]. Meanwhile, a recent meta-analysis also showed that PPI reduced the rebleeding rate of patients with liver cirrhosis and esophagogastric variceal bleeding by nearly 50% after endoscopic therapy. This meta-analysis recommended treating patients with bleeding from esophageal varices with PPIs for at least 4 wk after endoscopic therapy. As a mucosal-protection agent, APG boasts the capabilities to neutralize and buffer gastric acid; it increases the pH value in the upper gastrointestinal tract, promotes the formation of blood clots, and forms a colloidal protective film to closely combine with the ulcer formed after the operation. Thus, APG blocks the invasion of stomach acid, stimulates mucosal epithelial cells to secrete mucus, and promotes the self-repair of epithelial cells. The formed protective film also provides good drug-attachment sites for orally administered PPIs to facilitate drug absorption. Theoretically, therefore, APG has a complementary effect with PPI preparations. The viscous nature of APG facilitates its attachment to the surface of esophageal ulcers. Recently, several studies on the treatment of postoperative esophageal stenosis using APG as an adhesive for the esophagus demonstrated a good therapeutic effect[17,23,24].

The present retrospective study revealed that the incidence of early rebleeding after EVL in EVB patients in the PPI + APG group was 2.39% (9/377), which was significantly lower than that in the PPI group (30/401; 7.48%; $P = 0.001$). In addition, PPI + APG combination therapy decreased the early rebleeding rate of esophageal ulcer and esophageal varices after EVL and significantly reduced the incidence of chest pain after EVL (2.39% *vs* 13.97%; $P < 0.001$). Although APG triggered a significant increase in the incidence of constipation (4.24% *vs* 0.75%; $P = 0.002$), the patients who experienced this complication achieved relief after drinking more water or consuming lactulose, without serious adverse consequences. Cases of spontaneous peritonitis and hepatic encephalopathy within 6 wk after EVL occurred after early rebleeding in both groups of patients. However, after 4 wk of PPI therapy in combination with 2 wk of APG administration, no significant increase in the number of cases of spontaneous peritonitis or hepatic encephalopathy was found. There was also no significant difference in the mortality between the two groups of patients within 6 wk of EVL, possibly due to the close follow-up performed by physicians, that is, all patients with suspected early rebleeding were hospitalized in time and subjected to emergency endoscopic therapy.

However, this study still has certain limitations. First, although the inclusion and exclusion criteria of this retrospective study were formulated, this study lacked good control over some related variables (patient's diet, movement, some chronic medication, *etc.*), so the level of evidence is not high. Second, this single-center study only included residents of the hospital's service region, thus lacking representativeness and thereby limiting the applicability of the experimental results. In addition, the follow-up period of this study was 6 wk, and only the incidence rates of early rebleeding and related secondary outcome indicators were studied. Some clinical data and long-term indicators, such as mortality, survival, and the number of hospitalizations, were not further examined in this study. Also, no reports on whether double-dose PPI therapy can reduce the incidence of early rebleeding after EVL endoscopic therapy in EVB patients are available, and this study similarly did not test this theory. All bleeding and rebleeding patients achieved the goal of hemostasis through endoscopy and drug therapy, and no cases required transjugular intrahepatic

portosystemic shunt treatment in this study. Further research *via* prospective, multicenter, large-sample, long-term follow-up randomized controlled clinical trials is necessary.

CONCLUSION

In conclusion, the application of APG in combination with PPI therapy for the treatment of EVP after endoscopic EVL promotes the rapid healing of postoperative esophageal ulcers and relieves chest pain symptoms in the patients. Importantly, this combination therapy regimen significantly reduces the incidence of early rebleeding from postoperative esophageal ulcer and esophageal varices, with relatively few adverse reactions.

ARTICLE HIGHLIGHTS

Research background

Endoscopic variceal ligation (EVL) is a common treatment for esophageal variceal bleeding (EVB), but early rebleeding may occur after endoscopic therapy. And most patients are released from the hospital by the time they bleed again, which can be life-threatening.

Research motivation

How to reduce the early rebleeding after EVL is very important. Oral medication is accessible and convenient for patients. Therefore, we wanted to study oral drugs to reduce the rate of early rebleeding after EVL.

Research objectives

This study aimed to investigate oral medications to reduce early rebleeding after EVL. It was found that the combination of proton pump inhibitor (PPI) and aluminum phosphate gel (APG) could significantly reduce the incidence of early rebleeding. This oral treatment regimen is clinically worthwhile.

Research methods

The patients were divided into two groups. One group was treated with oral PPI after EVL. The other group was treated with oral PPI combined with APG. A retrospective study was conducted to compare and analyze the therapeutic effects of the two groups of patients.

Research results

We found that PPI combined with APG therapy could significantly reduce the rate of early rebleeding after EVL, and reduce the incidence of chest pain after EVL. But this is a retrospective study and it would be nice to do a prospective multicenter study.

Research conclusions

To prevent early rebleeding after EVL, the combination of PPI and APG can be considered.

Research perspectives

Oral medications are used to reduce the risk of postoperative rebleeding in EVL patients.

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2021 December 27; 13(12): 1660-1672

DOI: 10.4240/wjgs.v13.i12.1660

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Postoperative complications after robotic resection of colorectal cancer: An analysis based on 5-year experience at a large-scale center

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Author contributions: Huang ZX and Ye SP wrote and revised the paper; Ye SP, Li TY designed and proofread the manuscript; Huang ZX, Ye SP, Zhou Z and Shi HR collected the data and conducted the analysis of pooled data.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

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Abstract

BACKGROUND

As a common gastrointestinal malignancy, colorectal cancer (CRC) poses a serious health threat globally. Robotic surgery is one of the future trends in surgical treatment of CRC. Robotic surgery has several technical advantages over laparoscopic surgery, including 3D visualization, elimination of the fulcrum effect, and better ergonomic positioning, which together lead to better surgical outcomes and faster recovery. However, analysis of independent factors of postoperative complications after robotic surgery is still insufficient.

AIM

To analyze the incidence and risk factors for postoperative complications after robotic surgery in patients with CRC.

METHODS

In total, 1040 patients who had undergone robotic surgical resection for CRC between May 2015 and May 2020 were analyzed retrospectively. Postoperative complications were categorized according to the Clavien-Dindo (C-D) classification, and possible risk factors were evaluated.

RESULTS

Among 1040 patients who had undergone robotic surgery for CRC, the overall, severe, local, and systemic complication rates were 12.2%, 2.4%, 8.8%, and 3.5%, respectively. Multivariate analysis revealed that multiple organ resection ($P < 0.001$) and level III American Society of Anesthesiologists (ASA) score ($P = 0.006$) were independent risk factors for overall complications. Multivariate analysis

Country/Territory of origin: China

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: May 21, 2021
Peer-review started: May 21, 2021
First decision: June 22, 2021
Revised: July 16, 2021
Accepted: December 2, 2021
Article in press: December 2, 2021
Published online: December 27, 2021

P-Reviewer: Caycedo-Marulanda A, Cianci P, Hashida H
S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

identified multiple organ resection ($P < 0.001$) and comorbidities ($P = 0.029$) as independent risk factors for severe complications (C-D grade III or higher). Regarding local complications, multiple organ resection ($P = 0.002$) and multiple bowel resection ($P = 0.027$) were independent risk factors. Multiple organ resection ($P < 0.001$) and level III ASA score ($P = 0.007$) were independent risk factors for systemic complications. Additionally, sigmoid colectomy had a lower incidence of overall complications (6.4%; $P = 0.006$) and local complications (4.7%; $P = 0.028$) than other types of colorectal surgery.

CONCLUSION
Multiple organ resection, level III ASA score, comorbidities, and multiple bowel resection were risk factors for postoperative complications, with multiple organ resection being the most likely.

Key Words: Colorectal neoplasms; Surgery; Robot; Complication; Postoperative; Classification; Retrospective studies

Core Tip: This retrospective study of 1040 cases was performed to analyze the incidence and risk factors for postoperative complications after robotic colorectal cancer surgery. The postoperative complications were defined into four types: Overall, severe, local, and systemic complications, and their rates were 12.2%, 2.4%, 8.8%, and 3.5%, respectively. Their independent risk factors were as follows: (1) Overall complications: Multiple organ resection and a level III American Society of Anesthesiologists (ASA) score; (2) Severe complications: Multiple organ resection and comorbidities; (3) Local complications: Multiple organ resection and multiple bowel resection; and (4) Systemic complications: Multiple organ resection and a level III ASA score.

Citation: Huang ZX, Zhou Z, Shi HR, Li TY, Ye SP. Postoperative complications after robotic resection of colorectal cancer: An analysis based on 5-year experience at a large-scale center. *World J Gastrointest Surg* 2021; 13(12): 1660-1672
URL: https://www.wjgnet.com/1948-9366/full/v13/i12/1660.htm
DOI: https://dx.doi.org/10.4240/wjgs.v13.i12.1660

INTRODUCTION

As a common malignant tumor of the digestive tract, colorectal cancer (CRC) poses a serious health threat globally. According to the global tumor epidemiology statistics[1,2] released in 2020 by the International Agency for Research on Cancer of the World Health Organization, approximately 1931600 new cases of CRC and 935200 deaths occurred worldwide in 2020. The incidence and mortality of CRC are ranked third and second among all malignant tumors, respectively[3,4]. Overall, compared with the trend of stabilization or decline in developed countries, the incidence and mortality of CRC in developing countries have been rising slowly in recent years[5,6]. China accounts for 31% of the total number of patients with CRC globally, and 83% of patients in China are at an advanced stage when first diagnosed[1,7].

Surgical resection is the cornerstone of radical intent treatment[3]. Ensuring surgical operation quality is crucial because it is directly related to the patient's survival and quality of life. With the emergence and development of laparoscopy and robotics, minimally invasive surgery (MIS) for CRC can substitute for conventional open surgery with similar or better perioperative and oncologic outcomes[8-10]. However, during laparoscopic surgery, surgeons are faced with challenging conditions, such as a narrow pelvic cavity, anatomical complexity, and restricted surgical view[11]. The da Vinci surgical system, which has several technical advantages, including 3D visualization, elimination of the fulcrum effect, and better ergonomic positioning, overcomes these limitations and is very likely leading to better surgical outcomes and faster recovery than laparoscopic surgery[12,13]. However, because of the lack of high-

quality randomized controlled studies, analysis of independent factors of postoperative complications after robotic surgery is still insufficient[14,15].

Considering the limitations of previous studies and lack of large-scale studies, we analyzed retrospectively more than 1040 cases of short-term postoperative complications after robotic surgery for CRC to assess related risk factors.

MATERIALS AND METHODS

Study population and data collection

In this retrospective clinical study, we gathered and analyzed the information of 1302 patients who underwent robotic surgery for CRC between May 2015 and May 2020 at the First Affiliated Hospital of Nanchang University, a large-scale center. The inclusion criteria were as follows: (1) Age older than 18 and younger than 80 years; (2) Primary colonic adenocarcinoma confirmed pathologically by endoscopic biopsy; (3) Pathological T1-4N0-2M0 (T: Primary tumor, T1-T4; N: Regional lymph nodes, N0-N2; M: Distant metastasis, M0) at postoperative evaluation according to the 8th American Joint Committee on Cancer Cancer Staging Manual[16]; (4) A performance status of 0 or 1 on the Eastern Cooperative Oncology Group scale; (5) American Society of Anesthesiologists (ASA) score I, II, or III; and (6) Written informed consent. The exclusion criteria were as follows: (1) Pregnancy or breastfeeding; (2) Palliative surgery; (3) Emergency surgery due to a complication (bleeding, obstruction, or perforation) caused by CRC; (4) Previous neoadjuvant chemotherapy or radiotherapy; or (5) Recurrence surgery.

Patients who met the diagnostic criteria of related diseases were all subjected to routine preoperative chest X-ray, abdominal ultrasound, tumor markers, abdominal computed tomography, colonoscopy, magnetic resonance imaging, and other examinations to improve the evaluation of the patient's staging and condition. All the patients' medical records were extracted from the prospectively maintained database at the Department of Gastrointestinal Surgery of the First Affiliated Hospital of Nanchang University. This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University.

Surgical treatment

For information regarding surgical principles and procedures, the Chinese expert consensus on robotic surgery for CRC[15] should be referenced. In all cases, the surgical approach was to remove the colon and mesocolon of adjacent organs within the range of resection, cut the tumor-bearing segment, and ligate the origin of the aorta to maximize lymph node dissection (LND) without damaging the visceral fascia layer. The surgeon attempted to secure 10 cm or more for the proximal and distal resection margins (over 5 cm distal margin for rectosigmoid lesions). For colon resection and rectal resection, we followed D3 LND (D3) + complete mesocolic excision principles [17-19] and total mesorectal excision (TME) principles[20-22], respectively.

Different surgical methods were applied to tumors in different areas of invasion, and they have different characteristics (Figure 1). Right hemicolectomy or extended right hemicolectomy cases were included in group A (right colon resection). LND was performed along the superior mesenteric pedicle, including its front side, with high ligation of the ileocolic vessels, middle colic vessels (for hepatic flexure and proximal transverse colon lesion), or right branch of the middle colic vessels (for lesions proximal to hepatic flexure colon). Left hemicolectomy or extended left hemicolectomy cases were included in group B (left colon resection). LND was performed on the origin site of the middle colic vessels (left branch of the middle colic vessels for left hemicolectomy) and the origin site of the left colic artery for complete removal of the mesocolon. Full splenic flexure mobilization was also required for all patients in these cases. For transverse colectomy (group C), LND was only performed on the origin site of the middle colic vessels, and the gastroepiploic vessels were only meticulously dissected, instead of routinely ligated. Sigmoid colectomy (group D) cases required LND only around the inferior mesenteric artery (IMA). The surgical treatment of rectal cancer mainly included low anterior resection (LAR) of rectal cancer (group E) and abdominoperineal resection (group F). Although the scope of resection is different, the scope of LND involves the origin site of IMA. All of the above procedures only involve resection of one bowel segment of the primary tumor, hereinafter referred to as single bowel resection. When at least two primary tumor lesions invaded different parts of the intestine, multiple bowel resection (group G), simultaneous resections of multiple bowel segments of primary tumors, or even (sub-) total colectomy was applied.

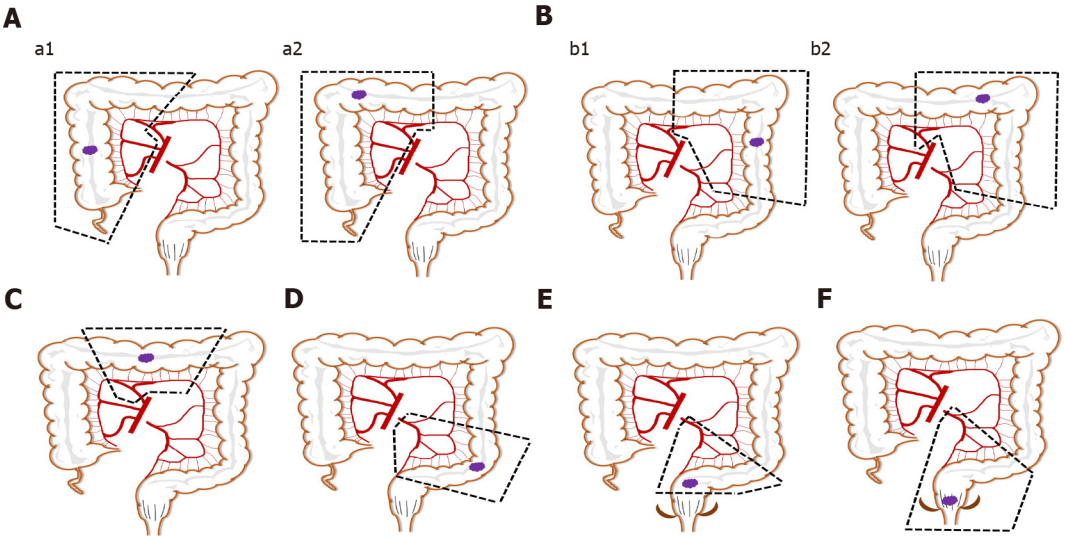


Figure 1 Illustrations describing specific procedures in the lymph node dissection area of six groups. A: Right colon resection; a1: Right hemicolectomy; a2: Extended right hemicolectomy; B: Left colon resection; b1: Left hemicolectomy; b2: Extended left hemicolectomy; C: Transverse colectomy; D: Sigmoid colectomy; E: Low anterior resection; F: Abdominoperineal resection.

Multiple organ resection was performed in cases with peripheral organ tumor invasion or organ diseases requiring surgery.

In our center, there are two types of robotic surgery for CRC: Totally robotic surgery and robot-assisted surgery. Totally robotic surgery uses robotic arms to complete the process of naked intestine, anastomosis, cutting, reinforcement, and removal in the abdominal cavity under the field of endoscopy. Robot-assisted surgery is used to pull out the intestine segment from an additional auxiliary incision after dissection and nakedness by robotic arms in the abdominal cavity, and to complete the process of anastomosis, cutting and reinforcing under direct vision. Surgical procedures for totally robotic CRC resection or robotic-assisted resection have been previously described in detail[6,23]. All robotic surgery procedures were performed by surgeons experienced in laparoscopic surgery for CRC.

Observation and evaluation parameters

The patients' general demographics data were as follows: Age, sex, body mass index (BMI), history of abdominal surgery, smoking and drinking history, comorbidity (*e.g.*, diabetes, cardiopathy, hypertension, and other basic diseases). The surgical parameters of the patients were as follows: ASA-class, operation time, intraoperative evaluated blood loss, types of colorectal surgery (*e.g.*, right resection, left resection, sigmoid colectomy, rectal resection and multiple bowel resection), types of robotic surgery (*e.g.*, totally robotic or robotic-assisted), number of retrieved lymph nodes, multiple organ resection (cases with peripheral organs tumor invasion or organ diseases requiring surgery), operation number per year. The pathology parameters were as follows: Diameter of the neoplasm, histological type, pathological tumor, node and metastasis (TNM) stage, number of metastatic lymph nodes, lymphovascular invasion, resection margin. The postoperative complications were recorded using the Clavien-Dindo (C-D) classification and divided into local and systemic complications[24,25].

The primary outcomes of the study were postoperative complications. When complications were associated with surgical techniques near the field of operation, such as wounds or anastomosis, they were considered local complications. Complications were classified as systemic when they were not associated with the field of operation, such as pulmonary or hepatic complications. We reviewed morbidity and mortality that occurred during hospitalization after surgery.

Statistical analysis

All statistical analyses were performed using SPSS, ver.26.0 (IBM Corp., Armonk, NY, United States). Categorical variables were presented as counts and percentages. Normally distributed continuous variables were expressed as mean ± SD. Variables with *P* values less than 0.05 in univariate analysis were included in the multivariate analysis. Multivariate analysis was conducted using the logistic regression model to identify independent risk factors for postoperative complications. *P* values less than

0.05 were considered statistically significant.

RESULTS

Patients and surgical outcomes

Table 1 shows the patient demographics, baseline pathologic characteristics and perioperative outcomes. Of the 1040 patients, 133 had a history of abdominal surgery, and 239 had other comorbidities, such as diabetes, hypertension, and heart disease. Regarding operative parameters, approximately 12.4% of surgical patients were rated as class III by anesthesiologists using the ASA classification standard. The mean operation time and evaluated blood loss were 173.6 ± 51.1 min and 108.4 ± 87.3 mL, respectively. In total, 235 right colon resections, 88 left colon resections, 11 transverse colectomies, 234 sigmoid colectomies, 369 LARs, and 79 abdominoperineal resections were performed. Multiple bowel resection was applied to 24 cases (2.3%) with multiple cancer foci inside the intestinal tube. The number of totally robotic (507 cases) and robotic-assisted (533 cases) surgeries performed was similar. Thirty-six cases (3.5%) involved multiple organ resection, including seven cases with partial small bowel enterectomy, six cases of oophorocystectomy, four cases of cholecystectomy, three cases of cystectomy, three cases of gastrectomy, three cases of hysterectomy, two cases of pneumonectomy, two cases of adnexectomy, two cases of splenectomy, two cases of nephrectomy, one case of partial hepatectomy, and one case of appendectomy.

Regarding the in-hospital outcomes, the overall complication rate was 12.2%, the severe complication rate was 2.4%, and the mortality rate was 0.4%.

Postoperative complications

The local and systemic complications classified by C-D are shown in Table 2. The incidence of local complication was 8.8%, among which anastomotic leakage was the most common, followed by wound problems, intra-abdominal infection, and effusion. Three cases of anastomosis leakage and one case of intra-abdominal bleeding required reoperation under intravenous or inhalation anesthesia. The systemic complication rate was 3.5%, among which hematologic complications were the most common, with severe anemia (13 cases) accounting for the majority, followed by coagulation abnormalities (2 cases). Four patients died after surgery: Three from severe infection leading to shock and one from severe pneumonia resulting in respiratory failure.

Overall complication rates among the five different age groups were similar (P = 0.766), as well as when broken down for minor (P = 0.750), severe (P = 0.091), local (P = 0.847), and systemic (P = 0.066) complications (Figure 2). Considering the trend of the broken line in Figure 2, the severe and systemic complication rates generally increased with age, and significant differences were found between the group aged older than 70 years and the other age groups (Supplementary Table 1). Postoperative complication rates in subgroups of CRC surgery approaches are outlined in Figure 3. The differences in the complication rates were significant among the seven types of colorectal surgery, including the overall (P = 0.006 < 0.10) and local (P = 0.031 < 0.10) complication rates. These differences may be caused by sigmoid colectomy (P = 0.002 for overall complications and P = 0.013 for local complications) or multiple bowel resection (P = 0.020 for overall complications and P = 0.013 for local complications) (Supplementary Table 2). Therefore, in multivariate analysis, we divided the types of colorectal surgery into three categories for comparison — multiple bowel resection, sigmoid colectomy and the other surgery types.

Risk factors for complications

Univariate analyses for overall and severe complications are demonstrated in Supplementary Table 3. Multivariate analysis revealed that multiple organ resection (P < 0.001) and a level III ASA score (P = 0.006) were independent risk factors for overall complications, and multiple organ resection (P < 0.001) and comorbidities (P = 0.029) were independent risk factors for severe complications (C-D grade III or higher) (Supplementary Table 4).

Univariate analyses for local and systemic complications are outlined in Supplementary Table 5. For local complications, multiple organ resection (P = 0.002) and multiple bowel resection (P = 0.027) were identified as independent risk factors. Multiple organ resection (P < 0.001) and a level III ASA score (P = 0.007) were identified as independent risk factors for systemic complications. Additionally, sigmoid colectomy was identified as an independent protective factor for overall (P = 0.006) and local (P = 0.028) complications (Supplementary Table 6).

Table 1 Baseline clinicopathologic characteristics and surgical outcomes

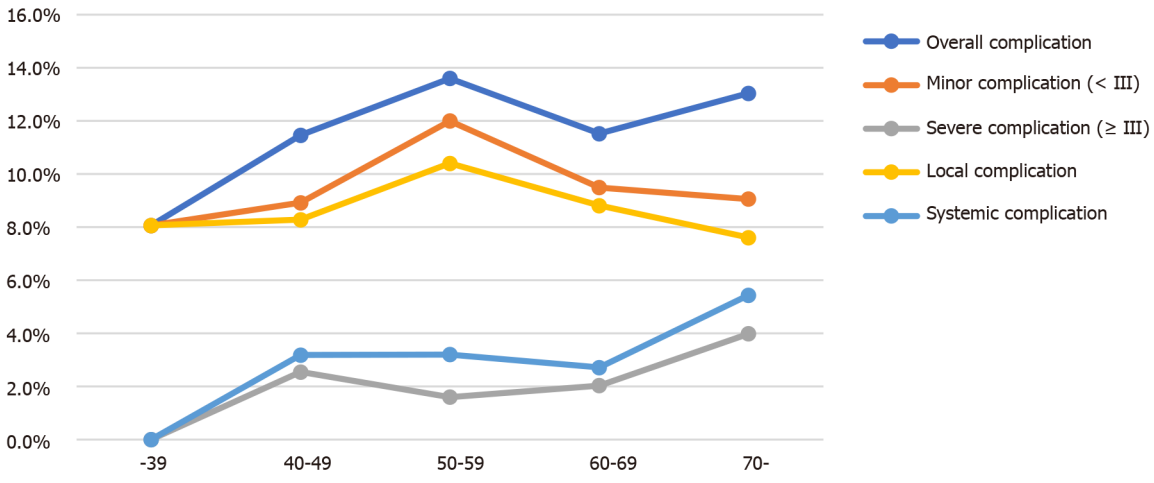
Variables	Total (*n* = 1040)
Patient demographics	
Age (yr)	60.4 ± 12.4
Sex (male/female)	611/429
BMI (kg/m^2)	22.5 ± 3.2
With previous abdominal surgery, no. (%)	133 (12.8)
Smoking and drinking history, no. (%)	426 (41.0)
Comorbidity, no. (no/one or more)	239 (23.0%)
Operative parameters	
ASA class, no. (I/II/III)	593/518/129
Operation time (min)	173.6 ± 51.1
Evaluated blood loss (mL)	108.4 ± 87.3
Types of colorectal surgery, no. (right-/left-/transverse-/sigmoid-/LAR/abdominoperineal-/multiple-)	235/88/11/234/369/79/24
Types of robotic surgery, no. (totally robotic/robotic-assisted)	507/533
No. lymph nodes retrieved	17.8 ± 7.5
Multiple organ resection, no. (%)	36(3.5)
Operation number, no. (yr)	
2015/5-2016/5	226 (21.7%)
2016/5-2017/5	226 (21.7%)
2017/5-2018/5	259 (24.9%)
2018/5-2019/5	280 (26.9%)
2019/5-2020/5	311 (29.9%)
Pathology results	
Neoplasm longest diameter, cm	4.5 ± 2.3
Histological type, no. (well or moderately/poorly or undifferentiated)	947/93
pT stage, no. (T1/T2/T3/T4)	107/126/218/589
pN stage, no. (0/1/2)	659/252/129
pTNM stage, no. (I/II/III)	197/462/381
With lymph node metastasis, no. (%)	381 (36.6)
With lymphovascular invasion, no. (%)	423 (40.7)
With positive resection margin, no. (%)	8 (0.8)
In-hospital outcomes	
Time to 1st bowel movement, h	25.4 ± 6.3
Time to 1st first flatus, h	58.6 ± 8.9
Time to 1st liquid diet, h	71.5 ± 9.3
Overall complications, no. (%)	127 (12.2)
Complications, no. (II/III/IV/V)	20/82/15/6/4
Severe complication, no. (C-D grade ≥ III, %)	25 (2.4)
Local complications, no. (%)	91 (8.8)
Systemic complication, no. (%)	36 (3.5)
Mortality, no. (%)	4 (0.4)

Postoperative hospital stay of all patients (d)	7.4 ± 2.3
Postoperative hospital stay of patients without complications (d)	6.5 ± 1.1
Postoperative hospital stay of patients with complications (d)	14.1 ± 5.2

BMI: Body mass index; ASA: American Society of Anesthesiologists; right-, Right colon resection; left-: Left colon resection; transverse-: Transverse colectomy; sigmoid-: Sigmoid colectomy; LAR: Low anterior resection; abdominoperineal-: Abdominoperineal resection; multiple-: Multiple bowel resection; C-D grade: Clavien-Dindo grade; T: Primary tumor; N: Regional lymph nodes; M: Distant metastasis.

Table 2 Local and systemic complications clarified by Clavien-Dindo classification

Local complication	Total *n* (%)	Grade ≥ III	Systemic complication	Total *n* (%)	Grade ≥ III
Wound problem	14 (1.3)	0 (0.0)	Pulmonary	9 (0.9)	2 (0.2)
Anastomosis leakage	43 (4.1)	9 (0.9)	Hepatic	0 (0.0)	0 (0.0)
Intra-abdominal infection and effusion	12 (1.2)	3 (0.3)	Cardiovascular	2 (0.2)	1 (0.1)
Intra-abdominal bleeding	2 (0.2)	1 (0.1)	Urinary	2 (0.2)	0 (0.0)
Anastomosis bleeding	3 (0.3)	0 (0.0)	Central nervous	2 (0.2)	2 (0.2)
Ileus/motility disorder	9 (0.9)	2 (0.2)	Hematologic	15 (1.4)	0 (0.0)
Infection of presacral space	4 (0.4)	0 (0.0)	Infection	6 (0.6)	5 (0.5)
Others	4 (0.4)	0 (0.0)	Endocrine	0 (0.0)	0 (0.0)

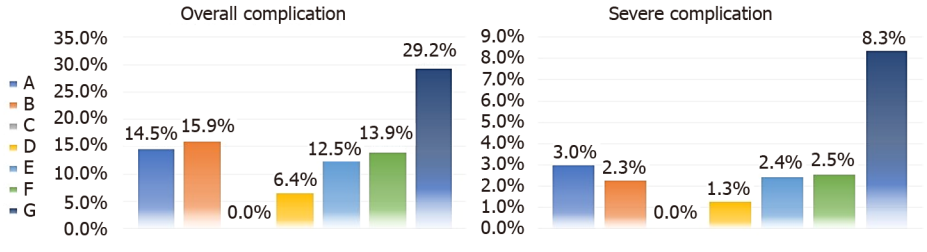


No. of patients	62	157	250	295	276	Total	*P*
Overall complication	5 (8.1%)	18 (11.5%)	34 (13.6%)	34 (11.5%)	36 (13.0%)	127 (12.2%)	0.766
Minor complication (< III)	5 (8.1%)	14 (8.9%)	30 (12.0%)	28 (9.5%)	25 (9.1%)	102 (9.8%)	0.750
Severe complication (≥III)	0 (0.0%)	4 (2.5%)	4 (1.6%)	6 (2.0%)	11 (4.0%)	25 (2.4%)	0.091
Local complication	5 (8.1%)	13 (8.3%)	26 (10.4%)	26 (8.8%)	21 (7.6%)	91 (8.8%)	0.847
Systemic complication	0 (0.0%)	5 (3.2%)	8 (3.2%)	8 (2.7%)	15 (5.4%)	36 (3.5%)	0.066

Figure 2 Postoperative complication rates in different age groups.

DISCUSSION

For CRC, MIS is now increasingly accepted and applied. Many clinical trials have shown that short-term outcomes after robotic surgery for CRC are better than those after laparoscopic surgery[26-29]. Robotic surgery is considered more accurate and reliable, reducing trauma and improving the quality of life while ensuring radical resection of the tumor[30,31]. However, the Jayne *et al*[14]'s study, a multicenter randomized clinical trial, found that robotic surgery performed by surgeons with varying robotic experience did not provide clinically important benefits over conventional laparoscopic surgery in the short term. In our study, which only included



	A	B	C	D	E	F	G	
No. of patients	235	88	11	234	369	79	24	*P*
Overall complication	34 (14.5)	14 (15.9)	0 (0.0)	15 (6.4)	46 (12.5)	11 (13.9)	7 (29.2)	0.006
Severe complication	7 (3.0)	2 (2.3)	0 (0.0)	3 (1.3)	9 (2.4)	2 (2.5)	2 (8.3)	0.438
Local complication	21 (8.9)	9 (10.2)	0 (0.0)	11 (4.7)	36 (9.8)	8 (10.1)	6 (25.0)	0.031
Systemic complication	13 (5.5)	5 (5.7)	0 (0.0)	4 (1.7)	10 (2.7)	3 (3.8)	1 (4.2)	0.216

Figure 3 Postoperative complication rates in subgroups of colorectal cancer surgery approaches. A: Right colon resection; B: Left colon resection; C: Transverse colectomy; D: Sigmoid colectomy; E: Low anterior resection; F: Abdominoperineal resection; G: Multiple bowel resection.

patients with malignant disease who had undergone robotic surgery at a single institution, the quality of the surgical procedures was consistently high and the data were sufficiently reliable. Additionally, chief surgeons had completed an initial phase of more than 30 cases[32] before 2015 and could master operations proficiently. Comparing the above two studies, we found that some in-hospital outcomes were numerically superior in our study, such as the mean length of stay (7.3 d *vs* 8.0 d), overall complications (12.2% *vs* 33.1%), and incidence of anastomotic fistula (4.1% *vs* 12.2%). Regarding the huge gap between the two studies, potential reasons may be responsible, such as the limited case volume and inadequate surgical experience that may compromise the quality of surgery[33,34]. A retrospective study[35] of robot-assisted colorectal surgery with the largest sample size worldwide verified the safety and efficacy of robotic techniques and confirmed its clinical advantages, particularly in reducing anastomotic fistulas. The short-term outcomes of our study, a low incidence of anastomoses (approximately 4%), and a short recovery time, were similar to those of this retrospective study except for mortality (0.1%, 6/5389 cases *vs* 0.4%, 4/1040 cases) and morbidity (9%, 487/5389 cases *vs* 12.2%, 127/1040 cases). Analysis of its data found that the incidence of complications that are C-D III or above accounted for 2.4% (129/5389 cases *vs* 25/1040 cases, 2.4%) in all patients. Among patients with CRC suitable for curative resection, compared with conventional laparoscopic surgery, the robotic procedure performed at an experienced medical unit resulted in more favorable clinical outcomes[14,35].

Many researchers have begun to analyze the different significant factors associated with complications after colorectal surgery. Manilich *et al*[33] examined the records of 3552 patients who had undergone colorectal surgery and concluded that BMI, operative time, and chief surgeon were the three most important factors influencing the re-admission rates, rates of transfusions, and surgical site infection. Kirchhoff *et al* [36] found that, of the 20 general background factors analyzed, the following 5 were significant factors for complications following laparoscopic colorectal procedures as an initial report: The surgeon's level of experience, patient age, patient sex, ASA class, and neoplasia. The real world data of 1145 consecutive cases in China[37] revealed that male sex, tumors located in the mid-low rectum, combined organ resection, and clinical T category (cT3-4) were independent risk factors for robotic surgical complications.

In the present study, 21 general background variables were analyzed by univariate analysis, among which 5 were identified as significant factors: Age, comorbidity, ASA class, type of colorectal surgery, and multiple organ resection. Finally, age was excluded from the multivariate analysis of risk factors for all complications. Generally, elderly patients are considered a high-risk population for major abdominal surgery

because of reduced functional reserve and increased comorbidities[38,39]. Some studies[40-43] have confirmed that aging is an independent risk factor for postoperative complications. Additionally, systemic complications are related to the increase in preoperative adverse conditions and comorbidities. We found that only severe and systemic complication rates increased mildly with age. Additionally, postoperative complications in elderly patients (age ≥ 70) tend to be more severe than those in nonelderly patients. Therefore, during preoperative assessment and postoperative management, medical personnel must focus more on patients aged 70 years and older. The incidence and severity of postoperative complications among elderly patients who had undergone robotic surgery were similar to those who had undergone laparoscopic surgery[44-46].

In our study, multiple organ resection was considered to be a primary independent risk factor for overall, severe, local, and systemic complications after robotic surgery. Chang *et al*[37] reported that combined organ resection was confirmed as an independent risk factor for surgical complications and significantly increased the risk of anastomotic fistula. The conclusions of other studies[47,48] were similar. The complex procedure of intraperitoneal surgery not only poses a challenge to the surgeon but is also a potential risk factor for postoperative complications. Additionally, the complexity of multiple bowel resection makes it an independent risk factor for overall and local complications. Xu *et al*[35] explained that the postoperative complication rate was 8.6% (434/5063 cases) for patients with only primary resection and 16.3% (53/326 cases) for patients with multiple resections. Different types of surgery caused by different tumor locations have different risk degrees for different complications. In a multivariate analysis, we selected sigmoid colectomy as a covariate to further analyze the role of sigmoid colectomy in complications. As expected, sigmoid colectomy was a protective factor for overall and local complications because of clear anatomy and simple operation. Proctectomy was a risk factor for ureteral injuries, but transverse colectomy and right colectomy were protective factors[49]. Therefore, we should focus on different types of complications after different surgeries.

This study has several limitations. First, this retrospective study involved only one single center where experienced surgeons operated on patients. This would limit the promotion to the population of physicians with less experience in robotic resection. Second, this study excluded patients with neoadjuvant therapy, which would limit the universality of our research results. Additionally, selection bias might influence the results, and the follow-up period was relatively short. Thus, the factors identified in this study require confirmation in future research.

CONCLUSION

The present study demonstrated, in detail, the postoperative complications of robotic surgery treating patients with CRC and identified several independent and significant predictors of the complication rate after robotic CRC surgery. Among them, multiple organ resection was the greatest independent risk factor for complications. We recommend that complex surgical procedures are best performed by experienced surgeons. Additionally, patients' comorbidities should be improved preoperatively, and more attention should be given to follow-up to prevent postoperative complications related to different surgical types.

ARTICLE HIGHLIGHTS

Research background

As a common malignant tumor of the digestive tract, colorectal cancer (CRC) poses a serious health threat globally. Robotic surgery for the treatment of CRC is one of the future trends in surgical treatment. With several technical advantages of 3D visualization, elimination of the fulcrum effect, and better ergonomic positioning, the da Vinci surgical system is better than laparoscope and these technical benefits lead to better surgical outcomes and faster recovery. However, it is impossible to accurately explain which factors will affect the complications of robotic surgery because of the lack of high-quality randomized controlled studies.

Research motivation

To provide new ideas and directions for reducing complications, through the analysis of incidence and risk factors for postoperative complications after robotic surgery in patients with CRC.

Research objectives

To analyze the incidence and risk factors for postoperative complications after robotic surgery in patients with CRC.

Research methods

In total, 1040 patients who had undergone robotic surgical resection for CRC between May 2015 and May 2020 were analyzed retrospectively. Postoperative complications were classified as minor complications, severe complications, local complications, and systemic complications, and their possible risk factors were assessed. Variables that were statistically significant ($P < 0.05$) in univariate analysis were included in multivariate analysis. To identify independent risk factors for postoperative complications, the logistic regression model was used in multivariate analysis.

Research results

Among 1040 patients who had undergone robotic surgery for CRC, the overall, severe, local, and systemic complication rates were 12.2%, 2.4%, 8.8%, and 3.5%, respectively. Multivariate analysis revealed that multiple organ resection ($P < 0.001$) and a level III American Society of Anesthesiologists (ASA) score ($P = 0.006$) were independent risk factors for overall complications. Multivariate analysis identified multiple organ resection ($P < 0.001$) and comorbidities ($P = 0.029$) as independent risk factors for severe complications (Clavien-Dindo grade III or higher). Regarding local complications, multiple organ resection ($P = 0.002$) and multiple bowel resection ($P = 0.027$) were identified as independent risk factors. Multiple organ resection ($P < 0.001$) and a level III ASA score ($P = 0.007$) were identified as independent risk factors for systemic complications. Additionally, sigmoid colectomy had a lower incidence of overall complications (6.4%; $P = 0.006$) and local complications (4.7%; $P = 0.028$) than other types of colorectal surgery.

Research conclusions

The present study demonstrated, in detail, the postoperative complications of robotic procedure to treating patients with CRC, and identified several factors that were independent and significant predictors of the complication rate after robotic CRC surgery. Among them, multiple organ resection was the greatest independent risk factor for complications.

Research perspectives

The development of robotic surgery is unstoppable, and the application of robotic surgery to CRC will become more and more widespread. Therefore, research on the risk factors of complications is essential. It will not only provide the possibility to reduce complications in the future but also promote the development of robotic surgery.

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2021 December 27; 13(12): 1673-1684

DOI: 10.4240/wjgs.v13.i12.1673

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

'Short' pancreaticojejunostomy might be a valid option for treatment of chronic pancreatitis in many cases

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Author contributions: Murruste M, Kirsimägi Ü, Kase K, Veršinina T, Talving P and Lepner U designed the study; Murruste M, Kirsimägi Ü, Kase K and Veršinina T performed the study; Murruste M and Kirsimägi Ü produced statistics and wrote the paper.

Institutional review board statement: The Research Ethics Committee of the University of Tartu approved this study (approval No. N 291/T-1).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Data sharing statement: No additional data are available.

Country/Territory of origin: Estonia

Specialty type: Gastroenterology and hepatology

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Abstract

BACKGROUND

The Partington-Rochelle pancreaticojejunostomy (PJ) is an essential management option for patients with chronic pancreatitis (CP) associated with intractable pain and a dilated pancreatic duct (PD). Wide ductotomy and long PJ (L-PJ) have been advocated as the standard of care to ensure full PD decompression. However, the role of short PJ (S-PJ) in a uniformly dilated PD has not yet been evaluated.

AIM

To evaluate the possible advantages and disadvantages of S-PJ and L-PJ and to interpret the perspective of S-PJ in the treatment of CP.

METHODS

A retrospective review of prospectively collected cohort data was conducted on surgically treated CP patients subjected to side-to-side PJ. The length of the PJ was adapted to anatomical alterations in PD. A comparison was made of S-PJ (< 50 mm) for uniformly dilated PD and L-PJ (50-100 mm) in the setting of multiple PD strictures, calcifications and dilatations. We hypothesized that S-PJ and L-PJ ensure comparable clinical outcomes. The primary outcomes were pain relief and quality of life (QOL); the secondary outcomes were perioperative characteristics, body weight, patients' satisfaction with treatment, and readmission rate due to CP.

RESULTS

Overall, 91 patients underwent side-to-side PJ for CP, including S-PJ in 46 patients and L-PJ in 45 patients. S-PJ resulted in better perioperative outcomes:

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

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

Received: May 28, 2021
Peer-review started: May 28, 2021
First decision: June 26, 2021
Revised: July 7, 2021
Accepted: November 3, 2021
Article in press: November 3, 2021
Published online: December 27, 2021

P-Reviewer: Zhao CF
S-Editor: Gao CC
L-Editor: Webster JR
P-Editor: Gao CC

Significantly shorter operative time (107.5 min *vs* 134 min), lower need for intraoperative (0% *vs* 15.6%) and total (2.2% *vs* 31.1%) blood transfusions, and lower rate of perioperative complications (6.5% *vs* 17.8%). We noted no significant difference in pain relief, improvement in QOL, body weight gain, patients' satisfaction with surgical treatment, or readmission rate due to CP.

CONCLUSION
Based on our data, in the setting of a uniformly dilated PD, S-PJ provides adequate decompression of the PD. As the clinical outcomes following S-PJ are not inferior to those of L-PJ, S-PJ should be preferred as a surgical option in the case of a uniformly dilated PD.

Key Words: Chronic pancreatitis; Surgical treatment; Pancreaticojejunostomy; Partington-Rochelle; Length of anastomosis

Core Tip: Pancreaticojejunostomy (PJ) is an essential management option in patients with chronic pancreatitis associated with intractable pain and a dilated pancreatic duct (PD). Our retrospective study demonstrated that in the setting of a uniformly dilated PD, short PJ provides adequate decompression of the PD. As the clinical outcomes following short PJ are not inferior to those of long PJ, short PJ should be preferred as a surgical option in the case of a uniformly dilated PD. The use of short PJ is beneficial to patients due to shorter operating time, lower need for blood transfusion and lower rate of surgical complications.

Citation: Murruste M, Kirsimägi Ü, Kase K, Veršinina T, Talving P, Lepner U. 'Short' pancreaticojejunostomy might be a valid option for treatment of chronic pancreatitis in many cases. *World J Gastrointest Surg* 2021; 13(12): 1673-1684
URL: https://www.wjgnet.com/1948-9366/full/v13/i12/1673.htm
DOI: https://dx.doi.org/10.4240/wjgs.v13.i12.1673

INTRODUCTION

Chronic pancreatitis (CP) is a benign chronic inflammatory disease of the pancreatic gland, which is characterized by irreversible morphologic changes resulting in progressive scarring and atrophy of the pancreatic tissue, ductal strictures and dilatations, calcifications, impairment of exocrine and endocrine functions, and chronic pain[1]. The main indication for surgical treatment is chronic intractable pain, but in up to one third of cases pain is combined with local complications[2]. Previous systematic reviews have noted that surgery remains the best option for the management of pain in these settings[3,4]. Although there are several controversies in the surgical treatment of CP, the basic options are: Drainage operations, most commonly decompression of the pancreatic duct (PD) through side-to-side pancreaticojejunostomy (PJ), resection of the chronically inflamed, painful and functionally impaired pancreatic mass ('pseudotumor'), and in some cases, a combination of these approaches[4].

The indication for decompressive PJ is enlargement of the PD without pancreatic pseudotumor[5]. Various surgical drainage procedures have been employed during more than 60 years of the history of drainage operations. The Partington-Rochelle modification is the most widely used method owing to its safety and feasibility. Although there are dozens of reports on the surgical technique, morbidity, mortality and clinical effects of this modification on PJ, no comparative studies are available on the impact of the anastomotic length of PJ on the outcome of surgical treatment, especially regarding pain relief and quality of life (QOL). It has often been emphasized that the 'standard' Partington-Rochelle PJ has to achieve complete drainage of the Wirsung duct along the whole pancreas and has to be at least 10 cm long[6-9]. However, Partington and Rochelle[10] have stated in their original paper that 'sacculations of the PD should be opened if possible, but a uniformly dilated duct need

not be opened so extensively'. Thus, the accepted 'standard' anastomosis and the recommendations given by Partington and Rochelle[10] are somewhat contradictory.

Since the launch of our program of surgical treatment for CP at Tartu University Hospital in 1997, we have applied the basic treatment principle of the 'large duct disease': The goal of PD drainage has to be full decompression of the PD. However, the ways to achieve this can be variable, since the anatomical changes in the PD are variable. Therefore, a large, even total, opening of the PD using a long PJ (L-PJ) is reasonable and wholly justified in cases of multiple PD strictures, calcifications and dilatations. However, there is a large subgroup of patients whose situation is different; instead, they have a quite homogeneously dilated PD and significant strictures or calcifications only in a single region. In these cases, effective decompression of the PD can be achieved through its limited opening in the affected region, followed by a relatively short anastomosis. Additional opening of an almost uniformly dilated PD can hardly be beneficial.

The above considerations served as the basis for defining the indications for the use of short PJ (S-PJ) or L-PJ, depending on local anatomical changes in PD.

In this study, we report comparative data regarding the two above described groups. The aim was to evaluate the possible advantages and disadvantages of S-PJ and L-PJ and to interpret the perspective of S-PJ in the treatment of CP.

MATERIALS AND METHODS

Patients

Following approval of the Research Ethics Committee of the University of Tartu, all consecutive adult patients (≥ 18 years of age) who were suffering from CP and were subjected to side-to-side PJ were reviewed within this single-center, retrospective study of prospectively collected data, comparing the outcomes following S-PJ and L-PJ.

We hypothesized that S-PJ and L-PJ ensure comparable clinical outcomes. The primary outcomes were pain relief and QOL, the secondary outcomes were perioperative characteristics, body weight, patients' satisfaction with treatment, and readmission rate due to CP.

Baseline data

Data on the patients' demographics and co-morbidities according to Charlson's comorbidity index[11], CP associated data, and data of pancreatic function, as well as the characteristics of pain and QOL were recorded at baseline. CP associated data included duration and etiology of CP, number of hospital admissions due to CP (from onset of chronic pain) and local changes in the pancreatic gland (PD diameter, calcifications, pseudocysts). These data were obtained from routine CT scan in all cases; further information was obtained and recorded during surgery.

For assessment of pancreatic exocrine insufficiency (PEI), we introduced a set of five simple signs (weight loss, diarrhea, steatorrhea, flatulence and foul-smelling stool) that the patients assessed in a questionnaire. PEI was defined as the presence of two or more of the above-mentioned symptoms or as the need for supplementary treatment with pancreatic enzymes. Additionally, we recorded patients' loss of body weight during one year before surgical treatment and body mass index (BMI) as possible markers for PEI. Pancreatic endocrine function was evaluated by the presence of diabetes mellitus.

Surgical methods

Choice of the surgical method (S-PJ or L-PJ) was based on the anatomical characteristics of PD. Patients with a uniformly dilated PD and significant strictures or calcifications in only a single location of the duct were treated using S-PJ. For patients with multiple PD strictures, calcifications and dilatations, L-PJ was performed. S-PJ was defined as the anastomosis with a length of 30 up to 50 mm; in the case of L-PJ, the length of the anastomosis was 50 mm or more (up to 100 mm).

As a standardized approach, the dilated PD was opened distal to strictures or calcifications, usually in the region of the pancreatic body, after which ductotomy was extended proximally to overcome the stricture and/or to remove calcifications. The initial length of the ductotomy was usually 35-40 mm. All discovered calcifications were removed with graspers. This was followed by testing the adequacy of the drainage of the entire PD. For this, we used a 3 mm (9 Fr) metallic probe and a length of 100 mm of successful probing (proximal and distal duct together) was judged

sufficient to ensure free outflow of pancreatic juice (Figure 1). If probing was successful (there were no more strictures or calcifications), a single-layer continuous PJ anastomosis with slowly absorbable suture material (4-0 polydiaxanone) was performed, involving a small portion of the transected parenchyma.

If probing was unsuccessful due to multiple PD strictures, initial ductotomy was extended beyond the last detected stricture. All calcifications were removed with graspers, and when necessary, additional ductotomy was carried out. The total length of L-PJ was dependent on the number and location of strictures and was somewhat variable (50 mm to 100 mm). However, the basic principle was the same: ductotomy has to be long enough to ensure complete decompression of the PD, which was tested by probing.

Data of surgical treatment

The recorded characteristics of the surgical treatment of CP were as follows: Duration of operation, intraoperative and total need for PRC (packed red cells) transfusion, morbidity, mortality and length of hospital stay. For assessment of morbidity, the Clavien-Dindo classification and comprehensive complication index (CCI) were used [12,13].

Assessment of the clinical effects of surgical treatment

We evaluated the clinical effects of the two types of PJ by comparing the preoperative and 1-year follow-up data for both groups: QOL, intensity of chronic pancreatic pain, pain-associated role limitations, changes in pain treatment, BMI, hospital admissions due to CP, and patients' satisfaction with surgical treatment.

Data on the QOL and characteristics of pain before and after surgery were obtained from the questionnaires completed by the patients. QOL was evaluated using the RAND 36-item Short Form Health Survey (SF-36, *RAND Corporation*)[14]. For assessment of pain, we used an 11-point numerical rating scale (NRS) ranging from 0 (no pain at all) to 10 (worst imaginable pain)[15]. Pain-associated role limitations were assessed using the pain disability index (PDI). The PDI reflects the degree of interference with normal role functioning caused by chronic pain, based on an 11-point scale ranging from 0 to 10, in seven areas of activities, with a maximum score of 70[16]. Complete pain relief was defined as freedom of chronic abdominal pain and absence of the need for pain medications, and partial pain relief was defined as pain reduction by 50% or more according to NRS.

To highlight the surgical effect of pain treatment, we made a comparative analysis of preoperative and 1-year follow-up use of pain medications. The patients were divided into three groups: Opioid users, users of non-opioid painkillers, and patients without the need for any pain medications.

The magnitude of the effect of surgical treatment on the exacerbations of CP requiring hospital admission was calculated as the number of admissions per patient year (PY). Preoperative PY was calculated as the period from the first admission due to CP to the time of surgery. These data were compared with the data of admissions during follow-up.

For evaluation of the patients' satisfaction with surgical treatment, we used Likert's five-level scale (from 1 — not satisfied at all, to 5 — very much satisfied, and from 1 — much worse, to 5 — much better, as appropriate)[17]. We asked all patients to evaluate satisfaction with the results of surgical treatment in general, changes in pain characteristics after surgical treatment, and changes in QOL after surgery.

Statistical analysis

All collected data were entered in a computerized database (Microsoft Access 2016, Microsoft Inc., WA, United States). The main characteristics are presented as means with SD, or medians with the interquartile range as appropriate. Comparisons between the groups were made using the following tests: Fisher's exact test in the case of percentages, unpaired *t*-test in the case of samples' means for independent groups, paired *t*-test in the case of samples' means when the samples included the same subjects, the Mann-Whitney test in the case of medians for non-parametric unpaired data groups, and Fisher's exact test with the 95%CI in the case of PY. The software package Statistica version 13.3 (TIBCO Software, CA, United States) was employed for statistical calculations.

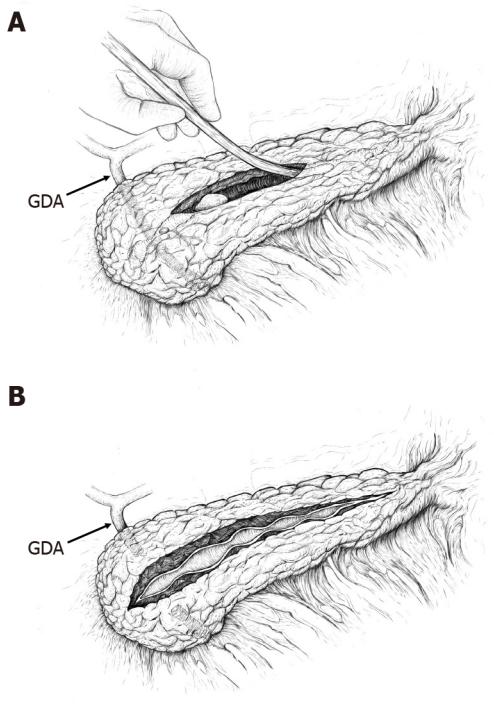

Figure 1 Two surgical options: 'Short' and 'long' ductotomy. A: 'Short' ductotomy (median length 40 mm), probing of the pancreatic duct; B: 'Long' ductotomy (length up to 100 mm). GDA: Gastroduodenal artery.

RESULTS

Baseline data

Between 10/1997 and 12/2020, 91 patients underwent side-to-side PJ: S-PJ in 46 patients and L-PJ in 45 patients.

A comparison of the preoperative data in these two groups revealed some anatomical and clinical differences (Table 1). The most important anatomical characteristic of the L-PJ group was the presence of multiple strictures or calcifications in the PD: the outflow of pancreatic juice was compromised in several locations, which was decisive for carrying out L-PJ.

Patients in the L-PJ group, compared to those in the S-PJ group, were significantly younger (45.6 years *vs* 52.6 years), had more previous admissions due to CP (5 *vs* 4), and had a larger main PD (8.0 mm *vs* 6.0 mm); the proportion of disabled persons was higher (73.3% *vs* 45.7%), as well as the proportion of patients with ≥ 2 symptoms of PEI (73.3% *vs* 47.8%). Also, the proportion of patients with alcoholic etiology (95.6% *vs* 82.6%) and pancreatic calcifications (77.8% *vs* 58.7%) was higher in this group, but these differences were statistically nonsignificant.

There were no differences between the groups regarding patients' gender, time from onset of chronic pain, endocrine insufficiency, BMI, loss of body weight or proportion of patients with pancreatic pseudocysts. Pain characteristics (NRS and PDI) did not differ between the groups before surgery (Figures 2 and 3). Approximately half of the patients required pain treatment with opioids (45.7% in the S-PJ group and 57.8% in the L-PJ group, Figure 4). The preoperative characteristics of QOL were similar for both groups (Figure 5).

The indications for surgical treatment were chronic intractable pain in 79 cases (86.8%) and complications of CP associated with intraductal hypertension in 12 cases (13.2%). There were no differences in the indications between the groups.

Characteristics of surgery

Assessment of the surgical characteristics of PJ revealed significantly shorter operating time (107.5 min *vs* 134.0 min), lower need for intraoperative PRC transfusion (0% *vs* 15.6%), as well as for total PRC transfusion in the perioperative period (2.2% *vs* 31.1%) in the S-PJ group (Table 1).

In addition, morbidity was lower in the S-PJ group (6.5% *vs* 17.8%), but this difference was statistically nonsignificant. The total number of complications was 11;

Table 1 Comparison of the short pancreaticojejunostomy and long pancreaticojejunostomy patients

Characteristics	S-PJ (*n* = 46)	L-PJ (*n* = 45)	*P* value
Preoperative data			
Age (yr)	52.6 ± 9.7	45.6 ± 7.6	**< 0.001**
Male (%)	73.9	88.9	0.116
Co-morbidity (Charlson's index)	2 (1-3)	1 (1-3)	0.066
Disabled persons (%)	45.6	73.3	0.013
Chronic pancreatitis			
Alcoholic etiology (%)	82.6	95.6	0.096
Time from onset of pain (mo)	18 (6-36)	24 (10-36)	0.420
N^0 of admissions due to CP	4 (2-5)	5 (3-7)	**0.002**
Rate of admissions per PY[1]	1.8 (1.5-2.1)	2.0 (1.8-2.3)	0.240
Anatomical changes in CP			
PD diameter (mm)	6 (5-7)	8 (7-9)	**0.002**
Pancreatic calcifications (%)	58.7	77.8	0.082
Pseudocysts (%)	58.7	53.3	0.760
Pancreatic endo- and exocrine function			
DM (%)	28.3	28.9	0.999
BMI (kg/m^2)	23.6 ± 5.0	22.3 ± 3.3	0.161
Loss of body weight (kg)[2]	9 (6-12)	9 (5-17)	0.366
≥ 2 symptoms of PEI (%)	47.8	73.3	**0.022**
Characteristics of surgery			
Length of anastomosis (mm)	40 (35-45)	65 (60-70)	**< 0.0001**
Duration of surgery (min)	107.5 (85.0-139.0)	134.0 (110.0-155.0)	**0.006**
IO PRC transfusion (%)	0	15.6	**0.011**
PRC transfusion in total (%)	2.2	31.1	**0.001**
Length of stay (d)	8.5 (8.0-11.0)	9.0 (8.0-11.0)	0.668
Morbidity (%)	6.5	17.8	0.182
CCI[3]	26.6 (20.9-29.6)	20.9 (20.9-34.6)	0.919
Mortality (%)	0	0	

Preoperative characteristics and characteristics of surgery (mean ± SD or median values with IQR or percentages as appropriate, *P* values).
[1]Preoperative patient year was defined as the time from onset of chronic pain requiring first admission.
[2]During one year before surgery.
[3]Median comprehensive complications index for complicated cases (short pancreaticojejunostomy *n* = 3, long pancreaticojejunostomy *n* = 8).
S-PJ: Short pancreaticojejunostomy; L-PJ: Long pancreaticojejunostomy; IQR: Interquartile range; CP: Chronic pancreatitis; PY: Patient year; PD: Pancreatic duct; DM: Diabetes mellitus; BMI: Body mass index; PEI: Pancreatic exocrine insufficiency; IO: Intraoperative; PRC: Packed red cells; CCI: Comprehensive complications index.

most of them were mild according to the Clavien-Dindo classification (grades I-II). There were only three grade III complications: in the S-PJ group there was one case of peripancreatic fluid collection (grade IIIa), which was percutaneously drained. In the L-PJ group there were two cases of postoperative intra-abdominal hemorrhage (associated with pancreatic ductotomy) both of which required relaparotomy (grade IIIb). Use of CCI for evaluation of severity of complicated cases revealed no difference between the groups: median CCI was 26.6 for the S-PJ group and 20.9 for the L-PJ group. Perioperative mortality was zero in both groups.

There was no difference in the median length of hospital stay between the groups (8.5 d for S-PJ and 9.0 d for L-PJ).

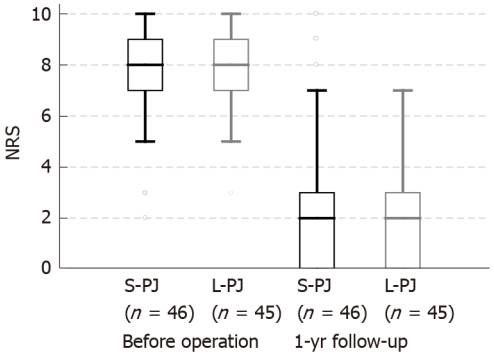

Figure 2 Box plot of the intensity of pain according to the numerical rating scale (0-10) before surgery and 1 yr after surgical treatment of chronic pancreatitis. NRS: Numerical rating scale; S-PJ: Short pancreaticojejunostomy; L-PJ: Long pancreaticojejunostomy.

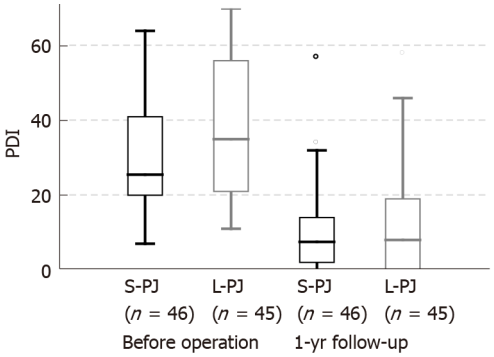

Figure 3 Box plot of the pain disability index (0-70) before surgery and 1 yr after surgical treatment of chronic pancreatitis. PDI: Pain disability index; S-PJ: Short pancreaticojejunostomy; L-PJ: Long pancreaticojejunostomy.

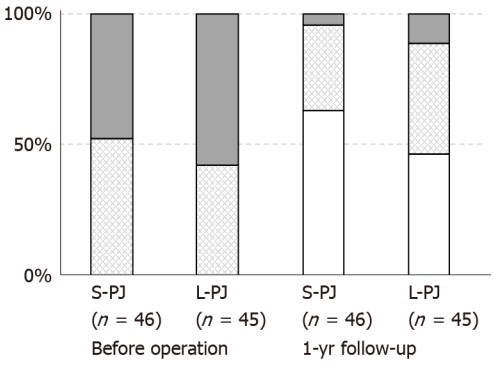

Figure 4 Data on pain treatment before surgery and 1 yr after surgical treatment of chronic pancreatitis. Gray bars, opioid users; diamond-filled bars, users of non-opioid painkillers; white bars, non-users of any painkillers. S-PJ: Short pancreaticojejunostomy; L-PJ: Long pancreaticojejunostomy.

Clinical effects of surgical treatment

All clinical effects were assessed before surgery and one year after surgery. Pain assessment revealed significant pain reduction in both study groups without differences between them. Median NRS decrease was 6 points (8 to 2) in both groups (Figure 2). Analogously, a significant decrease in the median PDI was seen in both groups, without a significant difference between them: 18.0 points (25.5 to 7.5) in the S-PJ group and 27.0 points (35.0 to 8.0) in the L-PJ group (Figure 3). Complete or partial pain relief was then 84.8% and 88.9%, respectively.

Pain relief was correlated with marked changes in pain treatment: when before surgery all patients needed some kind of pain treatment, then one year after surgery almost two thirds of the patients in the S-PJ group (63.0%) and almost half of the patients in the L-PJ group (46.7%) did not need any pain treatment (Figure 4). The proportion of patients with the occasional need for opioids was 4.4% (two patients) in

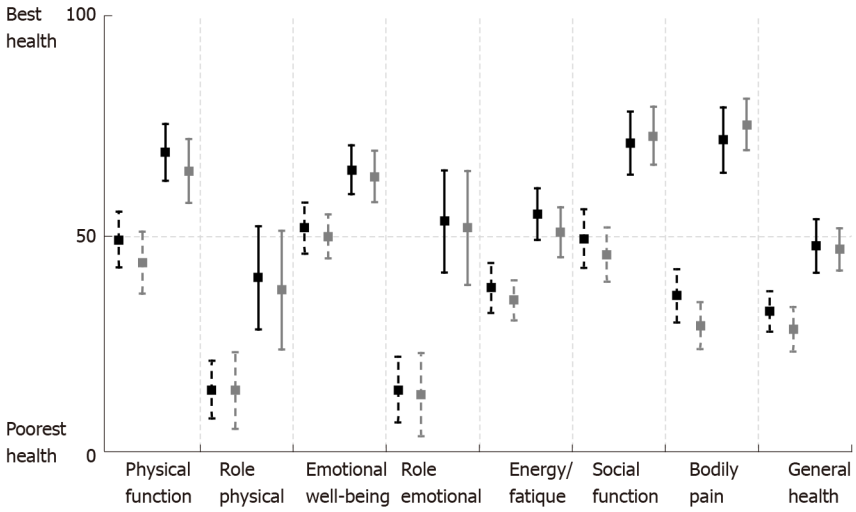

Figure 5 Quality of life RAND SF-36 mean scores, with 95% confidence interval, before surgery and 1 yr after surgical treatment of chronic pancreatitis. Black, short pancreaticojejunostomy (n = 46), gray, long pancreaticojejunostomy (n = 45); dashed lines, before surgery; solid lines, 1 yr after surgical treatment of chronic pancreatitis.

the S-PJ group and 11.1% (5 patients) in the L-PJ group; the difference between the groups was nonsignificant.

Changes in QOL were measured using the RAND SF-36 scale. All eight assessed aspects of QOL showed significant improvement in both study groups, with the most notable positive effect regarding the impact of pain on QOL and role limitations due to emotional problems (Figure 5).

Patients' BMI increased during the first year after surgery in most cases: 75.6% in the S-PJ group and 55.8% in the L-PJ group. However, despite the high proportion of patients with weight gain, the average increase in BMI was modest, being only 1.1 and 0.4 kg/m^2, respectively.

PJ showed high effectiveness in preventing new hospital admissions due to exacerbations or complications of CP in both groups. There were 1.8 (S-PJ group) and 2.0 (L-PJ group) hospital admissions because of CP per PY before surgery, which dropped to 0.1 admissions per PY in both groups after surgery.

Patients' general satisfaction with the results of the surgical treatment of CP according to the Likert 5-point scale (1 — not satisfied at all, to 5 — very much satisfied) was very high: 4.7 in the S-PJ group and 4.9 in the L-PJ group. Changes in chronic abdominal pain were rated as much less intense, at 4.9 points compared to the baseline in both groups (1 — much more intense, to 5 — much less intense).

DISCUSSION

This retrospective study provides comparative data on aspects of the surgical treatment of CP and the clinical effects of surgery, using either S-PJ or traditional L-PJ. The S-PJ was applied in cases of an almost uniformly dilated PD and L-PJ was applied in cases with multiple ductal changes: strictures, dilatations and calcifications. According to our study, S-PJ showed better perioperative results: shorter operating time, lower need for PRC transfusion and lower rate of perioperative complications. We observed no significant difference in the clinical results regarding pain relief, improvement in QOL, weight gain, patients' satisfaction with surgical treatment, and decrease in the rate of postoperative hospital admissions per PY due to CP.

Thus, the main outcome of our study is that for patients with a uniformly dilated PD and strictures or calcifications in a single region, S-PJ shows better operative characteristics, while the subsequent clinical effects are not inferior to those of L-PJ.

Study groups

Assessment of the preoperative data showed that our study groups were similar regarding the patients' main complaints (intensity of pain, time from onset of pain, pain medications) and QOL. At the same time, the groups were dissimilar regarding some other important aspects. The L-PJ group was characterized by a higher rate of

alcoholic CP, and the patients in this group had more admissions due to CP in the history of the disease. Several studies (Hao *et al*[18], Dancour *et al*[19], and Miyake *et al*[20]) have shown that alcoholic CP is associated with a more aggressive disease course and a higher rate of complications compared to other etiologies. In support of these findings, the patients in the L-PJ group had more pronounced local changes in the pancreatic gland: multiple ductal changes (strictures, dilatations and calcifications) and a larger diameter of PD.

Length of the PJ anastomosis

According to the predominant statement, 'standard' PJ necessitates the full-length anastomosis with total opening of the PD. Indeed, the obvious advantage of this approach is easy clearance of the entire PD of calcifications and full decompression of the duct[21,22]. However, variable suggestions concerning the length of PJ have been proposed. Bradley[23] stated in his review, that the length of the PJ should be at least 6 cm to gain long-term success in pain treatment; Yeo *et al*[24] reported having attempted to obtain a minimum of 8 cm ductotomy; Prinz *et al*[25] suggested that ductotomy should be carried out to within 1 cm of the ampulla of Vater and to within 1 cm of the tip of the pancreatic tail on the left side[23-25]. Regarding the extent of ductotomy, the pioneers of the method, Partington and Rochelle[10], stated in 1960: 'uniformly dilated duct need not be opened extensively', 'PD split should continue somewhat right to mesenteric vessels' and 'it is rarely necessary to split distal portion in the tail'[10]. Some authors admit that the extent of the ductal incision does not have a fixed length; rather, ductotomy has to ensure full PD decompression. Thus, instead of the widely accepted 'standard', there exist slightly different practices and up to the present no comparative data have been available on the effectiveness of the shorter or longer PJ.

Despite the obvious advantages, total ductotomy has also some disadvantages and surgical risks. Unroofing of the PD is especially challenging in the region of the pancreatic head: The gastroduodenal artery (GDA) is usually located in the proximal 1.5-3 cm of the pancreatic head and has to be suture ligated superiorly and inferiorly in front of the ductotomy (Figure 1). Nevertheless, despite ligation of the GDA, the pancreatic head is still very well vascularized and ductotomy in this region is associated with a considerable risk of bleeding. Therefore, some surgeons have suggested performing partial resection of the pancreatic head in this situation (as described by Frey) as a less risky procedure compared to ductotomy[26,27].

One of the options to avoid wide ductotomy is to replace it with intraoperative instrumental exploration of the PD. We used intraoperative probing and in case we found additional calcifications or strictures, further ductotomy was performed. An alternative would be endoscopic visualization of the PD, which has been pioneered mainly by laparoscopic surgeons. Kurian and Gagner[28] used a choledochoscope for visualization of PD and Fogarty catheters for ductal clearance of calcifications; Tantia *et al*[29] used a 30° laparoscope to visualize the lumen of the PD and cleared the unopened part of the pancreatic head of calcifications using graspers — a procedure which the authors called 'pancreaticodochoscopy'. Bhandarwar *et al*[30] suggested using a 5 mm zero-degree laparoscope to confirm ductal clearance beyond the ductotomy, while Sahoo and Kumar[31] used a cystoscope for this purpose[30,31].

The value of ductotomy in the region of the pancreatic tail is also debatable: in the splenic hilum PD is not well accessible and is narrowing anyway, so the effect of the extensive distal PD incision (up to within 1 cm of the tip of the pancreatic tail) for allowing better pancreatic juice drainage can be quite modest. Considering the above mentioned aspects, several surgeons have abandoned opening the PD in the region of the pancreatic tail (*e.g.*, Sahoo and Kumar[31], Ceppa and Pappas[32]) and have replaced it with intraoperative exploration of the PD.

According to our study, avoiding total ductotomy provided significant benefits in terms of operating time, need for PRC transfusion, and morbidity. However, the rate of severe complications was low in both groups: only two patients in the L-PJ group needed relaparotomy due to postoperative hemorrhage, both cases being due to ductotomy in the region of the pancreatic head.

The clinical effects of the two types of PJ were evaluated one year after surgery. Both surgical options, S-PJ in the treatment of patients with a uniformly dilated PD and L-PJ in the treatment of patients with multiple ductal changes (strictures, dilatations and calcifications), were effective in resolving the main clinical problems without significant differences in the results.

The proportion of patients with pain relief was comparable to that reported in previous studies (D'Haese *et al*[33], Tian *et al*[34]). Interestingly, despite the fact that 4.4% (S-PJ) and 11.1% (L-PJ) of the patients occasionally used opioids, they rated

(according to the Likert 5-point scale) abdominal pain as much less intense compared to the baseline. Some patients reported that 'they were used to take opioids even in the case of mild pain because of effectiveness of this medication'. Patients' general satisfaction with the results of the surgical treatment of CP was high, being on average 4.7 in the S-PJ group and 4.9 in the L-PJ group (Likert scale).

Significant improvement in QOL was evident in all eight aspects of the SF-36 tool. The most marked changes were seen in pain associated QOL and in role limitations because of emotional problems. The importance of pain in predicting QOL is well known[35]. Hence, a greater than 30-point improvement in pain associated QOL was to be expected.

One of the anticipated effects of the surgical treatment of CP is prevention of new admissions due to pain and exacerbations or complications of CP[10,36]. In this study, the effectiveness of surgical treatment in preventing new admissions was higher than 95%: there were 1.8 (in the S-PJ group) and 2.0 (in the L-PJ group) hospital admissions because of CP per PY before surgery; after surgery this indicator dropped to 0.1 admissions per PY in both groups. This effect cannot be underestimated, as it translates into a decrease of the health care burden for patients with CP. Hall *et al*[37] found in their systematic review that most treatment costs for patients with CP are associated with pain management. Hence effective surgical pain treatment leads to a considerable economic effect.

Limitations

This study has some limitations. Firstly, as the choice of the surgical method was based on the anatomical characteristics of the PD, the study groups were dissimilar. Secondly, lack of randomization: it would be important to randomly compare patients with a uniformly dilated PD, using either S-PJ or L-PJ. Thirdly, as surgeons specialized in pancreatic surgery operated on all enrolled patients, the obtained results (zero mortality and relatively low morbidity) may not be generalizable to outcomes at hospitals that have less expertise. It has been shown that centralization of pancreatic surgery is important and its beneficial effect is associated in particular with better short-term results after surgery[38].

CONCLUSION

Based on our data, in the setting of a uniformly dilated PD, S-PJ provides adequate decompression of PD. As the clinical outcomes following S-PJ are not inferior to those of L-PJ, S-PJ should be preferred as a surgical option in the case of a uniformly dilated PD.

ARTICLE HIGHLIGHTS

Research background

The Partington-Rochelle pancreaticojejunostomy (PJ) is an essential management option in patients with chronic pancreatitis (CP) associated with intractable pain and a dilated pancreatic duct (PD). Wide ductotomy and long PJ (L-PJ) have been advocated as the standard of care to ensure full PD decompression. Nevertheless, the role of short PJ (S-PJ) in uniformly dilated PD has not yet been evaluated.

Research motivation

The aim of this study was to evaluate the possible advantages and disadvantages of S-PJ and L-PJ and to interpret the perspective of S-PJ in the treatment of CP.

Research objectives

We hypothesized that S-PJ and L-PJ ensure comparable clinical outcomes. The primary outcomes were pain relief and quality of life, secondary outcomes were perioperative characteristics, body weight, patients' satisfaction with treatment, and readmissions rate due to CP.

Research methods

A retrospective review of prospectively collected cohort data was conducted on surgically treated CP patients subjected to side-to-side PJ. The length of PJ adapted to

anatomical alterations in PD: A S-PJ (< 50 mm) in uniformly dilated PD, and a L-PJ (50-100 mm), in the setting of multiple PD strictures, calcifications and dilatation were compared.

Research results

S-PJ resulted in improved perioperative outcomes: significantly shorter operative time (107.5 min *vs* 134 min), lower need for intraoperative (0% *vs* 15.6%) and total (2.2% *vs* 31.1%) blood transfusions, and lower rate of perioperative complications (6.5% *vs* 17.8%). We noted no significant difference in pain relief, improvement in quality of life, body weight gain, patients' satisfaction with surgical treatment, and readmission rate due to CP.

Research conclusions

Based on our data, in the setting of a uniformly dilated PD, the S-PJ provides adequate decompression of the PD. As the clinical outcomes following S-PJ are not inferior to those of L-PJ, S-PJ should be preferred as a surgical option in a uniformly dilated PD.

Research perspectives

It would be important to compare randomly selected patients with uniformly dilated PD using either S-PJ or L-PJ.

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2021 December 27; 13(12): 1685-1695

DOI: 10.4240/wjgs.v13.i12.1685

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Risk factors for perioperative complications in laparoscopic surgeries of retrorectal cystic lesions

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Author contributions: Wu B designed and revise the review; Wang PP collected clinical data, follow up the patients and wrote the manuscript; Lin C contributed to the analysis and statistics section; Wu B, Zhou JL and Qiu HZ carried out the operation; Xu KW modified the article format; all authors have read and approved the final version to be published.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Peking Union Medical College Hospital.

Informed consent statement: The analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

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Abstract

BACKGROUND

The incidence of retrorectal lesions is low, and no consensus has been reached regarding the most optimal surgical approach. Laparoscopic approach has the advantage of minimally invasive. The risk factors influencing perioperative complications of laparoscopic surgery are rarely discussed.

AIM

To investigate the risk factors for perioperative complications in laparoscopic surgeries of retrorectal cystic lesions.

METHODS

We retrospectively reviewed the medical records of patients who underwent laparoscopic excision of retrorectal cystic lesions between August 2012 and May 2020 at our hospital. All surgeries were performed in the general surgery department. Patients were divided into groups based on the lesion location and diameter. We analysed the risk factors like type 2 diabetes mellitus, hypertension, the history of abdominal surgery, previous treatment, clinical manifestation, operation duration, blood loss, perioperative complications, and readmission rate within 90 d retrospectively.

RESULTS

Severe perioperative complications occurred in seven patients. Prophylactic transverse colostomy was performed in four patients with suspected rectal injury. Two patients underwent puncture drainage due to postoperative pelvic infection. One patient underwent debridement in the operating room due to incision infection. The massive-lesion group had a significantly longer surgery duration, higher blood loss, higher incidence of perioperative complications, and higher readmission rate within 90 d ($P < 0.05$). Univariate analysis, multivariate analysis,

Country/Territory of origin: China

Specialty type: Gastroenterology and hepatology

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

Peer-review report's scientific quality classification

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

Received: July 19, 2021
Peer-review started: July 19, 2021
First decision: September 5, 2021
Revised: September 14, 2021
Accepted: October 27, 2021
Article in press: October 27, 2021
Published online: December 27, 2021

P-Reviewer: Navarrete Arellano M, Ortmann O, Reiter M
S-Editor: Wang LL
L-Editor: A
P-Editor: Wang LL

and logistic regression showed that lesion diameter was an independent risk factor for the development of perioperative complications in patients who underwent laparoscopic excision of retrorectal cystic lesions.

CONCLUSION

The diameter of the lesion is an independent risk factor for perioperative complications in patients who undergo laparoscopic excision of retrorectal cystic lesions. The location of the lesion was not a determining factor of the surgical approach. Laparoscopic surgery is minimally invasive, high-resolution, and flexible, and its use in retrorectal cystic lesions is safe and feasible, also for lesions below the S3 level.

Key Words: Laparoscopic excision; Retrorectal cystic lesions; Minimally invasive; Risk factors; Perioperative complications

Core Tip: The incidence of retrorectal tumors is low, and no consensus has been reached regarding the most optimal surgical approach. Advantages of laparoscopic approach has been demonstrated in this field. We retrospectively reviewed the patients who underwent laparoscopic excision of retrorectal cystic lesions in our center. This study aimed to investigate the risk factors for perioperative complications in laparoscopic surgeries of retrorectal cystic lesions. We also evaluated the feasibility and safety of laparoscopic excision of retrorectal cystic lesions below the S3 Level.

Citation: Wang PP, Lin C, Zhou JL, Xu KW, Qiu HZ, Wu B. Risk factors for perioperative complications in laparoscopic surgeries of retrorectal cystic lesions. *World J Gastrointest Surg* 2021; 13(12): 1685-1695
URL: https://www.wjgnet.com/1948-9366/full/v13/i12/1685.htm
DOI: https://dx.doi.org/10.4240/wjgs.v13.i12.1685

INTRODUCTION

Retrorectal cystic lesions are located in the space between the sacrum and the rectum, also called presacral cysts. The incidence of these lesions is 1/40000[1]. Common lesions include epidermoid/dermoid cysts, tailgut cysts, and cystic teratomas. Most lesions are benign, but teratomas have a 5%-10% risk of malignant transformation[2-4]. Treatment of retrorectal lesions is surgical. The surgical approach was chosen based on the tumor's location, size, and relationship with the surrounding viscera. Common approaches include transsacral (posterior), abdominal (anterior), and combined abdominosacral approaches[5,6].

The incidence of retrorectal lesions is low, and no consensus has been reached regarding the surgical approach. Retrospective investigations at some medical centers reported that most operations adopted the transabdominal or transsacral approach[5,7,8]. It was proposed that the surgical approach should be determined based on the anatomical relationship between the tumor and the 3rd sacral vertebra level(S3). Specifically, tumors under the S3 Level should be accessed *via* the transsacral approach and those above the S3 Level *via* the abdominal approach[9]. However, strong evidence is still lacking to support this empirical preference.

In the mid-1990s, laparoscopic excision of retrorectal cystic lesions was first reported [10]. To date, most studies on laparoscopy in this disease have been case reports, except for some small retrospective studies[11-13]. We used the experience of the literatures of retrospective studies with large sample size on risk factors related to perioperative complications of retrorectal tumor[14-16]. Factors included the general condition of the patient such as age, body mass index (BMI) and American Society of Anesthesiologists (ASA) classification. Factors associated with surgery included surgical approach, tumor size, and tumor location. We aimed to investigate the risk factors for perioperative complications in laparoscopic surgeries of retrorectal cystic lesions. We can also evaluate the feasibility and safety of laparoscopic excision of

retrorectal cystic lesions below the S3 Level.

MATERIALS AND METHODS

Patient characteristics

We retrospectively reviewed the medical records of patients who underwent laparoscopic excision of retrorectal cystic lesions between August 2012 and May 2020 at our hospital. The inclusion criteria were as follows: (1) Diagnosis of retrorectal cystic lesion before surgery; and (2) Underwent laparoscopic excision of the retrorectal cystic lesion with or without the combined use of the transsacral approach. The exclusion criteria were as follows: (1) Open abdominal or transsacral operations; and (2) Surgical pathology report revealed solid tumors such as lipoma, fibroma, gastrointestinal stromal tumors, and neuroendocrine tumors.

We divided the patients into two groups based on the relative position of the upper margin of the lesion to the level at the lower margin of the S3 vertebra. The two groups were named under and above-S3 groups. We also grouped patients based on whether the diameter of the lesion reached 10 cm. Patients were divided into smaller lesion ($d < 10$ cm) and massive-lesion ($d \geq 10$ cm) groups. In both pairs of groups, we compared the patients' age, BMI, type 2 diabetes mellitus, systemic arterial hypertension, ASA classification, history of abdominal surgery, previous management at other hospitals, clinical manifestation, rectal examination, operation duration, blood loss, perioperative complications, postoperative length of hospital stay, and readmission rate within 90 d. The ASA classification reflected comorbidities that some patients presented. Perioperative complications were reported using the Clavien-Dindo (CD) classification. Severe complications were defined by a CD classification of 3a or higher.

After discharge, patients were scheduled for regular follow-ups (every 6 mo in the first 2 years, every 1 year thereafter). Additional information was collected *via* telephone interviews conducted by a specific researcher.

Surgical procedures

After anesthesia induction, the patient was placed in the lithotomy position. Usually, 4-5 trocars were used, which were placed in the anterior resection of rectal cancer. Based on the location of the tumor, an incision was made on the left (or right) side of the mesorectum, exposing the retrorectal space (Figure 1A). The hypogastric plexus was protected. To find the lesion, we dissected the retrorectal space and mobilized the rectum and mesorectum to the front (Figure 1B). The capsule of the lesion was exposed and dissected along the capsule. In most cases, we first dissected the top of the lesion and then dissected the lateral wall, reaching the attachment points of the pelvic floor muscles (Figure 1C). When dissecting the medial wall and base of the lesion, the rectal wall was carefully protected. The rectum could be pushed to the other side to achieve en bloc excision. Throughout the operation, the pelvic autonomous nerves and the presacral venous plexus should be carefully protected (Figure 1D). The fascia of the levator ani muscle was sometimes resected for lesions extending to the pelvic floor. For very large cysts, after dissecting the pelvic floor, the cystic fluid was intentionally aspirated to reduce tension, facilitating en bloc excision. The specimens were removed using a retrieval bag. After irrigation and bleeding control, a drainage tube was placed on the pelvic floor.

Statistical analysis

SPSS statistical software (version 26.0, for Windows) was used for data analysis. Variables following a normal distribution were reported as median or mean ± SD. The *t*-test and rank-sum test were used to analyze quantitative data. Enumeration data were analyzed using χ^2 and Fisher tests and are reported as numbers or percentages. Statistical significance was set at $P < 0.05$. Statistically significant variables in the univariate analyses were included in the multivariate analysis using the logistic regression of ordinal categorical variables. Statistical significance was set at $P < 0.05$.

RESULTS

A total of 62 patients were included in this study. Five of them were men and 57 were women, with a male to female ratio of 1:11.4. The age at surgery was 15 to 70 years, with a mean age of 37.6 ± 12.9 years. The range of body mass index (BMI) was 17.6 to

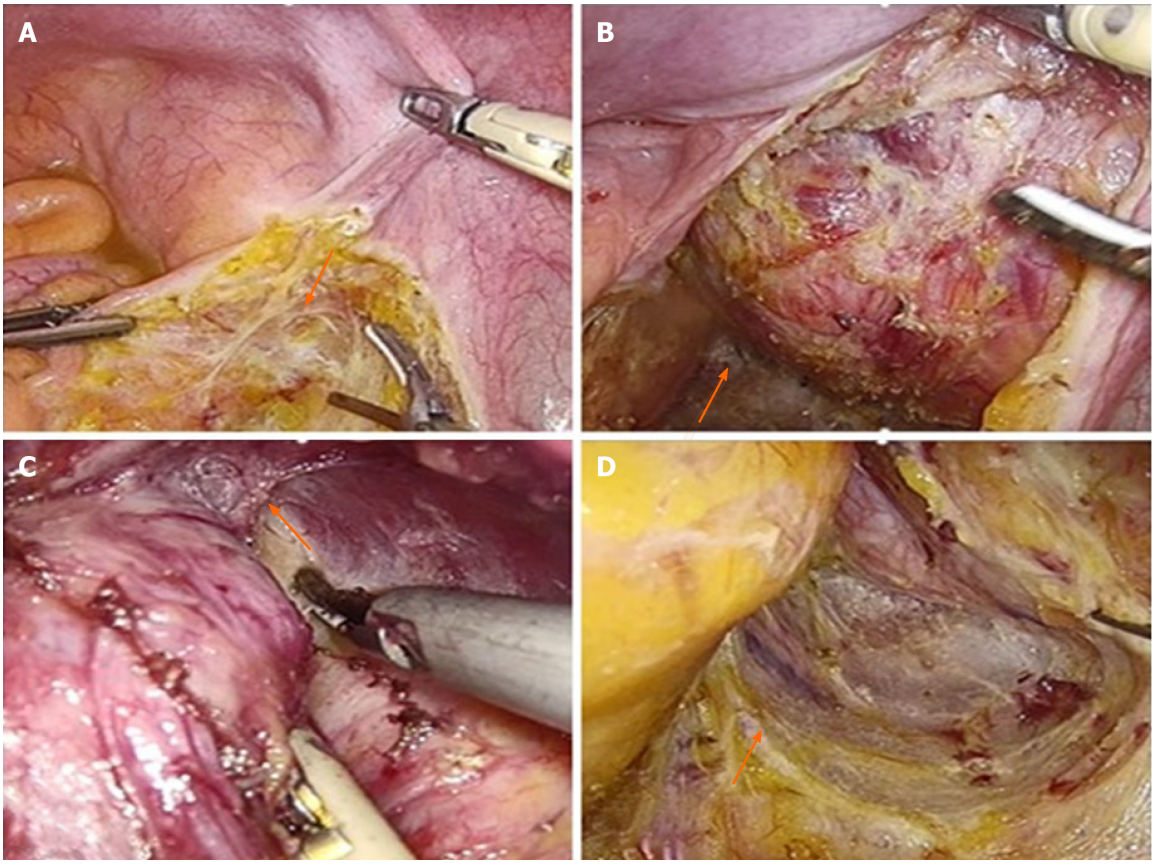

Figure 1 Important steps in the laparoscopic excision technique of retrorectal lesions. A: An incision was made on the left side of the mesorectum; B: Dissection the retrorectal space and mobilized the rectum and mesorectum to the front; C: Dissection the top of the lesion and then dissected the lateral wall, reaching the attachment points of the pelvic floor muscles; D: Protection of the pelvic autonomous nerves and the presacral venous plexus.

35.3 kg/m^2, with a mean of 24.5 ± 3.8 kg/m^2. Severe perioperative complications occurred in seven patients. Severe complications were defined by a CD classification of 3a or higher. Prophylactic transverse colostomy was performed in four patients with suspected rectal injury. Two patients underwent puncture drainage due to postoperative pelvic infection. One patient underwent debridement in the operating room due to incision infection.

Under- and above-S3 groups

Twenty-three patients were included in the under-S3 group and 39 patients in the above-S3 group. Patient characteristics are detailed in Table 1. No significant differences were observed in baseline characteristics such as age, BMI, and ASA class ($P > 0.05$). There was no significant difference in the size of lesions between the two groups (above-S3, 8.3 ± 3.5 cm; under-S3, 8.2 ± 2.8 cm; $P > 0.05$). There was also no significant difference in operation duration (above-S3, 132.9 ± 66.2 min; under-S3, 139.4 ± 56.9 min; $P > 0.05$) and blood loss (above-S3, 61.8 ± 130.0 mL; under-S3, 67.4 ± 101.8 mL, $P > 0.05$). No significant differences in perioperative complications or postoperative length of hospital stay were observed. Three patients in the above-S3 group and one in the under-S3 group were readmitted within 90 d of discharge.

Smaller- and massive-lesion groups

The smaller-lesion group included 24 patients with a lesion diameter of less than 10 cm. The massive-lesion group included 38 patients whose lesion diameters were equal to or larger than 10 cm. Patient characteristics are detailed in Table 2. There were no significant differences in baseline characteristics, such as age, BMI, and ASA class ($P > 0.05$). The mean lesion diameter was 11.5 ± 2.3 cm in the massive-lesion group and 6.2 ± 1.5 cm in the smaller-lesion group. No significant difference was observed in the operation duration, blood loss, or complications of CD ≥ 2. A significant difference was observed in complications of CD 3a or higher. Six patients in the massive lesion group and one in the small lesion group had such complications ($P < 0.05$). The postoperative length of hospital stay was not significantly different between the groups. Three

Table 1 Comparisons of the perioperative variables between two groups (*n* = 62)

Variables	No. (%) or mean ± SD		
	Above-S3, *n* = 39	Under-S3, *n* = 23	*P* value
Age, yr	38.7 ± 12.4	35.8 ± 13.8	0.387
BMI, kg/m^2	23.5 ± 3.5	23.5 ± 4.2	0.963
Type 2 diabetes mellitus			0.623
Yes	2 (5.1)	2 (8.7)	
No	37 (94.9)	21 (91.3)	
Hypertension			0.356
Yes	5 (12.8)	5 (21.7)	
No	34 (87.2)	18 (78.3)	
ASA classification			0.744
Class I	27 (69.2)	15 (65.2)	
Class II	12 (30.8)	8 (34.8)	
Previous abdominal surgery			0.838
Yes	21 (53.8)	13 (56.5)	
No	18 (46.2)	10 (43.5)	
Previous treatment			0.836
Yes	6 (15.4)	4 (17.4)	
No	33 (84.6)	19 (82.6)	
Symptomatic			0.602
Yes	16 (41.0)	11 (47.8)	
No	23 (59.0)	12 (52.2)	
Digital rectal examination			0.764
Positive	31 (79.5)	19 (82.6)	
Negative	8 (20.5)	4 (17.4)	
Tumor size, cm	8.3 ± 3.5	8.2 ± 2.8	0.882
Operation duration, min	132.9 ± 66.2	139.4 ± 56.9	0.694
Blood loss, mL	61.8 ± 130.0	67.4 ± 101.8	0.860
Perioperative complications			0.146
Yes	18 (46.2)	15 (65.2)	
No	21 (53.8)	8 (34.8)	
Severe complications[1]			0.520
Yes	4 (10.3)	3 (13.0)	
No	35 (89.7)	20 (87.0)	
Postoperative length of hospital stay,d	6.5 ± 3.1	7.5 ± 4.4	0.296
Readmission within 90 d			0.524
Yes	3 (7.7)	1 (4.3)	
No	36 (92.3)	22 (95.7)	

[1]Severe complications are defined as perioperative complications of Clavien-Dindo grade 3a or higher.

patients in the massive-lesion group and one in the smaller tumor group were readmitted within 90 d of discharge.

Table 2 Comparisons of the perioperative variables between two groups (*n* = 62)

Variables	No. (%) or mean ± SD		
	Massive-lesion, *n* = 24	Smaller-lesion, *n* = 38	*P* value
Age, yr	36.6 ± 13.5	39.3 ± 11.8	0.426
BMI, kg/m^2	22.8 ± 3.1	22.7 ± 2.8	0.07
Type 2 diabetes mellitus			0.289
Yes	3 (12.5)	1 (2.6)	
No	21 (87.5)	37 (97.4)	
Hypertension			0.927
Yes	4 (16.7)	6 (15.8)	
No	20 (83.3)	32 (84.2)	
ASA classification			0.678
Class I	17 (70.8)	25 (65.8)	
Class II	7 (29.1)	13 (34.2)	
Previous abdominal surgery			0.660
Yes	14 (58.3)	20 (52.6)	
No	10 (41.7)	18 (47.4)	
Previous treatment			0.027[a]
Yes	7 (29.2)	3 (7.9)	
No	17 (70.8)	35 (92.1)	
Symptomatic			0.416
Yes	12 (50.0)	15 (39.5)	
No	12 (50.0)	23 (60.5)	
Digital rectal examination			0.924
Positive	20 (83.3)	30 (78.9)	
Negative	4 (16.6)	8 (21.1)	
Tumor location			0.258
Above-S3	13 (54.2)	26 (68.4)	
Under-S3	11 (45.8)	12 (31.6)	
Tumor size, cm	11.5 ± 2.3	6.2 ± 1.5	0.000[a]
Operation duration, min	183.6 ± 57.5	104.7 ± 43.7	0.000[a]
Blood loss, mL	117.1 ± 175.7	30.3 ± 36.7	0.004[a]
Perioperative complications			0.027[a]
Yes	17 (70.8)	16 (42.1)	
No	7 (29.2)	22 (57.9)	
Severe complications[a]			0.022[a]
Yes	6 (25.0)	1 (2.6)	
No	18 (75.0)	37 (97.4)	
Postoperative length of hospital stay,d	7.7 ± 4.6	6.3 ± 2.9	0.111
Readmission within 90 d			0.019[a]
Yes	4 (16.6)	0 (0.0)	
No	20 (83.3)	38 (100.0)	

[1]Severe complications are defined as perioperative complications of Clavien-Dindo grade 3a or higher.
[a]*P* value < 0.05 indicates the statistical difference.

Risk factor for perioperative complications

All 62 patients underwent laparoscopic excision of the retrorectal cystic lesions. In 5 patients, a combined transsacral approach was used for laparoscopic surgery. Univariate logistic regression showed that lesion diameter was a risk factor for perioperative complications. In multivariate analysis, we included factors that could potentially affect complications, such as lesion location, history of abdominal surgery, and previous treatment at other hospitals. The diameter of the cyst was an independent risk factor for complications ($P < 0.05$). The data are presented in Table 3.

Surgical pathology and follow-up

Final surgical pathology reports showed that 20 patients had teratoma, of which 2 patients had mature teratoma with mucinous adenocarcinoma and one patient had mature teratoma with neuroendocrine carcinoma. There were 29 cases of epidermoid cysts, 11 cases of dermoid cysts, and 2 cases of tailgut cysts.

Sixty-one (98.4%) patients were followed up. Follow-up ranged from 10 to 103 mo, with a median follow-up of 58 months. During follow-up, a subcutaneous cyst was found in 1 patient 8 mo postoperatively, who underwent local excision of the cyst. In another patient, magnetic resonance imaging (MRI) at the 6-month follow-up showed recurrence of small presacral cysts. The cysts had not grown by March 2021, and the patient is still followed up. Recurrence was not observed in the remaining 59 patients.

DISCUSSION

Traditionally, low retrorectal cystic lesions are accessed *via* the posterior transsacral approach, which provides a good surgical view and facilitates en bloc excision[17,18]. However, the coccyx and part of the sacrum were removed when using this approach. This leads to more tissue damage and a higher rate of fluid accumulation and wound infection[19]. When the upper border of the cyst is high, dissection of the top can be difficult *via* the posterior approach, which can lead to incomplete excision and presacral bleeding[20]. Our center performed the first laparoscopic excision of retrorectal cystic lesions in 2012[21,22]. The surgical field can be better exposed through high-resolution cameras and flexible tools. Therefore, we can explore the area from the inlet of the true pelvis to the levator hiatus, which cannot be achieved using traditional laparotomy or the transsacral approach. In the 62 patients reported, there was no conversion from laparoscopy to an open approach. The traditional abdominal approach had a higher recurrence rate than the posterior approach because of the difficulty in exposing and dissecting deep sacrococcygeal lesions. Even with laparoscopy, a combined transsacral approach is sometimes needed for some massive lesions that penetrate the pelvic floor to the gluteal subcutaneous tissue. Under these circumstances, the laparoscopic approach is first used to dissect the lesion as much as possible, reaching beyond the pelvic floor. The patient was then switched to the prone jackknife position, and the lesion was resected en bloc *via* the transsacral approach. Of the 62 patients reported in this study, five underwent combined laparoscopic and transsacral surgery.

Retrorectal cystic lesions grow slowly in the pelvis, leading to silent onset. Most patients present with non-specific or non-specific clinical characteristics[23,24]. Some patients show symptoms suggestive of compression by large tumors, including lower back or sacrococcygeal pain, constipation, urinary frequency, and dysuria. Very large retrorectal cysts surround the posterior and lateral sides of the rectum. They can also penetrate the pelvic floor muscles, protrude into the gluteal subcutaneous tissue, and even ulcerate. Of the 62 patients included in this study, 33 (53.2%) were asymptomatic and diagnosed by routine health checkups. Two patients (3.2%) experienced recurrence after previous surgery at other hospitals. Twenty-seven (43.6%) patients presented with symptoms such as changes in bowel habits (14 cases), abdominal pain (6 cases), urinary frequency (2 cases), dysuria (1 case), and sacrococcygeal pain (4 cases).

Imaging examinations used for the assessment of retrorectal cystic lesions include B ultrasonography, enhanced computed tomography (CT), and pelvic magnetic resonance imaging (MRI)[25]. MRI has been reported to be the most accurate

Table 3 Univariate and multivariate analyses of factors associated with perioperative complication in all patients (*n* = 62)

Variates	Univariate analysis			Multivariate analysis		
	OR	95%CI	*P*	OR	95%CI	*P* value
Sex						
Male	Reference					
Female	5.125	0.538-48.718	0.155			
Age, yr						
≤ 60	Reference					
> 60	0.559	0.087-3.605	0.541			
BMI, kg/m^2						
≤ 23	Reference					
> 23	1.700	0.621-4.657	0.302			
ASA						
Class I	Reference					
Class II	0.826	0.284-2.400	0.726			
Type 2 diabetes mellitus						
No	Reference					
Yes	3.954	0.306-51.098	0.292			
Hypertension	Reference					
No						
Yes	0.591	0.126-2.774	0.505			
Tumor diameter, cm						
< 10	Reference			Reference		
≥ 10	3.339	1.122-9.938	0.030[a]	3.286	1.020-10.587	0.046[a]
Tumor location						
S3↑	Reference			Reference		
S3↓	2.187	0.755-6.341	0.149	1.991	0.655-6.054	0.225
Operation duration, min						
< 121 min	Reference					
≥ 121 min	1.670	0.611-4.568	0.318			
Blood loss, ml						
< 25 mL	Reference					
≥ 25 mL	1.923	0.699-5.285	0.205			
Previous abdominal surgery						
No	Reference			Reference		
Yes	0.750	0.274-2.051	0.575	0.667	0.227-1.963	0.462
Previous treatment						
No	Reference			Reference		
Yes	1.389	0.350-5.505	0.640	0.938	0.208-4.226	0.933

[a]*P* value < 0.05 indicates the statistical difference.

diagnostic tool, which can effectively detect solid components and assess the relationship between the lesion and surrounding structures[26,27]. In this study, 56 patients underwent pelvic MRI before excision, while 6 patients underwent both

ultrasound and enhanced CT. The decision of the surgical approach was based on the location, size, possibility of malignancy, and relationship with the surrounding tissues. Retrorectal cystic lesions are often polycystic lesions with septa. Our review of patient imaging examinations showed that approximately two-thirds of the tumors were polycystic. We suggest that surgeons review imaging examinations carefully before the operation to facilitate thorough exploration and complete excision of all lesions.

We analyzed the differences between postoperative patients with lesions above and below the S3 Level[28]. General conditions such as age, BMI, and ASA class were similar between the groups, with no significant differences observed. Some patients were treated in other hospitals. Procedures such as needle biopsy and exploratory laparotomy can aggravate adhesion in the surgical area, adding to the difficulty and risk of the operation. However, there was no significant difference in previous treatment between the two groups. Additionally, no significant difference was observed in the size of the lesion between the groups (above-S3, 8.3 ± 3.5 cm; under-S3, 8.2 ± 2.8 cm; $P > 0.05$). Therefore, the baseline characteristics of the patients before surgery were similar. Blood loss, operation duration, and postoperative length of hospital stay were not significantly different between the groups. Perioperative complications ≥ CD grade II or ≥ CD grade IIIa also showed no significant difference. The readmission rate within 90 d of discharge was also similar between the groups. These results suggest that the location of the lesion relative to the S3 Level might not be a determinant of the proper surgical approach. For lesions under the S3 Level, laparoscopic surgery is feasible after a thorough review of the imaging examinations.

Based on our experience, we defined lesions with diameters ≥ 10 cm as massive lesions. The baseline characteristics of the massive- and smaller-lesion groups were not significantly different. As expected, the massive-lesion group showed significantly longer operation duration and larger blood loss. The massive-lesion group also had higher rates of complications ≥ CD grade II and ≥ CD grade IIIa ($P < 0.05$). For larger retrorectal lesions, there was a higher risk of perioperative complications such as damage to the rectum and rectal fistula, and we usually performed a temporary transverse colostomy for patients with rectal damage during surgery. The same procedure was also performed in patients who did not respond to conservative treatment. After recovery, the ostomy reversal procedure contributed to a longer length of hospital stay ($P < 0.05$).

Univariate and multivariate analyses showed that lesion diameter might be a risk factor for complications in laparoscopic excision of retrorectal lesions. Larger lesions tended to have a longer operation duration, larger blood loss, and a higher risk of severe complications. Larger cysts interfere with dissection into the deeper parts of the pelvis. Therefore, after dissecting as much as possible towards the pelvic floor, we sometimes puncture the cyst and aspirate the cyst fluid to create a space for the en bloc excision. With sufficient irrigation in the direct view of the laparoscope, such cyst decompression procedures will not increase the risk of complications, as Abe *et al* showed in their study[29].

This study has certain limitations. First, it was a retrospective study, and selection bias should be considered. Second, to evaluate the use of laparoscopy in lesions under the S3 Level, we compared laparoscopy and the combined use of laparoscopic and transsacral approaches. In future research, larger multi-center, prospective studies can be used to better evaluate the use of laparoscopy in retrorectal lesions at the S3 Level or larger than 10 cm in diameter.

CONCLUSION

This is the largest single-center report of laparoscopic excision of retrorectal cystic lesions, with a mean follow-up period of more than 4 years[12,16]. Comparison between the groups and univariate or multivariate analyses showed that the diameter of the lesion was an independent risk factor for perioperative complications. However, the location of the lesion is not necessarily a determinant of the surgical approach. Laparoscopic surgery is minimally invasive, high-resolution, and flexible, and its use in retrorectal cystic lesions is safe and feasible, also for lesions below the S3 Level. It can better expose the surgical area and play an important role in the treatment of retrorectal cystic lesions.

ARTICLE HIGHLIGHTS

Research background

The incidence of retrorectal lesions is low. Advantages of laparoscopic approach has been demonstrated in this field. Surgeons should minimize the incidence of perioperative complications.

Research motivation

Laparoscopic surgery of retrorectal cystic lesions have been widely used. The risk factors influencing perioperative complications of laparoscopic surgery should be discussed.

Research objectives

To investigate the risk factors for perioperative complications in laparoscopic surgeries of retrorectal cystic lesions.

Research methods

We retrospectively collected patient data as detailed as possible. Besides univariate analysis and multivariate analysis, patients were divided into groups based on the lesion location related to the 3rd sacral vertebra(S3) and diameter to investigate the possible risk factors.

Research results

Tumor diameter larger than 10 cm could be an independent risk factor. No significant differences in perioperative complications between the under-S3 group and the above-S3 group.

Research conclusions

Laparoscopic excision of retrorectal cystic lesions below the S3 Level is safe and feasible. Lesion diameter was an independent risk factor for the development of perioperative complications.

Research perspectives

Larger multi-center, prospective studies can be conducted to verify whether tumors larger than 10 cm in diameter could be the risk factor.

ACKNOWLEDGEMENTS

First of all, we sincerely thank the patient for his cooperation. Secondly, we thank the surgeons, physician, nurses, technical staff, and hospital administration of contributions to this study. Moreover, we thank Dr Wu for advice and support. Finally, the authors have declared that no competing interests exist.

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2021 December 27; 13(12): 1696-1707

DOI: 10.4240/wjgs.v13.i12.1696

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Liver resection *vs* radiofrequency ablation in single hepatocellular carcinoma of posterosuperior segments in elderly patients

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Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

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statement: This study was reviewed and approved by the Ethics Committee of "F. Miulli" General Regional Hospital.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All the authors are aware of the content of the manuscript and have no conflict of interest.

Data sharing statement: No additional data are available.

Country/Territory of origin: Italy

Specialty type: Surgery

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

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

Received: July 22, 2021
Peer-review started: July 22, 2021
First decision: August 19, 2021
Revised: August 30, 2021
Accepted: November 1, 2021
Article in press: November 1, 2021
Published online: December 27,

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Abstract

BACKGROUND
Liver resection and radiofrequency ablation are considered curative options for hepatocellular carcinoma. The choice between these techniques is still controversial especially in cases of hepatocellular carcinoma affecting posterosuperior segments in elderly patients.

AIM
To compare post-operative outcomes between liver resection and radiofrequency ablation in elderly with single hepatocellular carcinoma located in posterosuperior segments.

METHODS
A retrospective multicentric study was performed enrolling 77 patients age ≥ 70-years-old with single hepatocellular carcinoma (≤ 30 mm), located in posterosuperior segments (4a, 7, 8). Patients were divided into liver resection and radiofrequency ablation groups and preoperative, peri-operative and long-term outcomes were retrospectively analyzed and compared using a 1:1 propensity score matching.

RESULTS
After propensity score matching, twenty-six patients were included in each group. Operative time and overall postoperative complications were higher in the resection group compared to the ablation group (165 min *vs* 20 min, $P < 0.01$; 54% *vs* 19% $P = 0.02$ respectively). A median hospital stay was significantly longer in the resection group than in the ablation group (7.5 d *vs* 3 d, $P < 0.01$). Ninety-day mortality was comparable between the two groups. There were no significant differences between resection and ablation group in terms of overall survival and disease free survival at 1, 3, and 5 years.

CONCLUSION
Radiofrequency ablation in posterosuperior segments in elderly is safe and feasible and ensures a short hospital stay, better quality of life and does not modify the overall and disease-free survival.

Key Words: Elderly; Hepatocellular carcinoma; Posterosuperior segments; Liver resection; Radiofrequency ablation; Multicentric study

Core Tip: A retrospective multicentric study was performed enrolling 77 patients with ≥ 70 years of age and a single hepatocellular carcinoma (≤ 30 mm), located in the posterosuperior segments (4a, 7, 8). Patients were divided into two groups: liver resection and radiofrequency ablation. Peri-operative and long-term outcomes were analyzed and compared using a 1:1 propensity score matching. The study results show that radiofrequency ablation in posterosuperior segments in elderly patients is safe and feasible and ensures a short hospital stay, reduces overall postoperative complications, increases the quality of life and does not modify the overall and disease-free survival.

2021

P-Reviewer: Kim JH
S-Editor: Wang LL
L-Editor: Filipodia
P-Editor: Wang LL

Citation: Delvecchio A, Inchingolo R, Laforgia R, Ratti F, Gelli M, Anelli MF, Laurent A, Vitali G, Magistri P, Assirati G, Felli E, Wakabayashi T, Pessaux P, Piardi T, di Benedetto F, de'Angelis N, Briceño J, Rampoldi A, Adam R, Cherqui D, Aldrighetti LA, Memeo R. Liver resection *vs* radiofrequency ablation in single hepatocellular carcinoma of posterosuperior segments in elderly patients. *World J Gastrointest Surg* 2021; 13(12): 1696-1707
URL: https://www.wjgnet.com/1948-9366/full/v13/i12/1696.htm
DOI: https://dx.doi.org/10.4240/wjgs.v13.i12.1696

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide and the fifth most common cancer[1]. According to Barcelona Clinic Liver Cancer (BCLC) staging system, ablation, resection and liver transplantation (LT) are considered the best treatment for patients affected by HCC very early and early stage [2]. Considering the increasing number of elderly patients in our population, LT could not be considered as a valid therapeutic option in these patients, due to the limit of age that is contraindicated in many liver transplantation centers[3]. Nevertheless, for elderly patients, liver resection (LR) and radiofrequency ablation (RFA) remains a valid alternative. LR guarantees a complete removal of the tumor with a wide margin either in anatomical and non-anatomical resection. Even if in recent periods the use of minimally invasive approaches, laparoscopic and robotic, has been increasing, they still remain invasive procedures performed under general anesthesia[4]. On the contrary, RFA has very low invasiveness and morbidity but literature is still unclear in terms of disease free and overall survival compared to liver resection[5,6].

The choice between LR and RFA is still controversial, especially in cases of HCC affecting posterosuperior segments (PSS).

PSS are more difficult to access than the anterolateral ones for the anatomical position and are technically complex for the bleeding control and poor liver field visualization. Open liver resection (OLR) is widely considered as preferred procedure for HCC located in PSS[7], instead, laparoscopic liver resection (LLR) in PSS is challenging and needs to be approached by experienced surgeons in major centers. LLR presents important benefits with less invasiveness, less postoperative pain, early discharge and similar mortality and morbidity compared to OLR according to 2017 Southampton Consensus Guidelines[8].

In the literature there are few studies with focus on surgical treatments in elderly patients with HCC especially in PSS[9]. The aim of our study is to compare short and long-term outcomes between LR and RFA in elderly patients with single HCC located in PSS.

MATERIALS AND METHODS

Patient data

A multicentric retrospective study was performed enrolling 77 patients with ≥ 70 years of age, from January 2009 to January 2019 in the following European hospital centers: IRCCS San Raffaele Hospital, Milan, Italy; Paul Brousse University Hospital, Villejuif, France; University Hospital Reina Sofía, Córdoba, Spain; Henri Mondor University Hospital, Créteil, France; University Hospital Policlinico of Modena, Modena, Italy; Miulli Hospital, Bari, Italy; Hospital Niguarda, Milan, Italy; Strasbourg University Hospital, IRCAD, Strasbourg, France; Robert Debré University Hospital, Reims, France; University Hospital Geneva, Switzerland.

Inclusion criteria were elderly patients (age ≥ 70) with single HCC ≤ 30 mm, located in PSS, treated with RFA or LR. Exclusion criteria are multiple HCC or single > 30mm, patients younger than 70 years and American Society of Anesthesiologists (ASA) score > IV.

Patients were divided into two groups according to the treatment, LR or RFA. LR group included open liver resection and laparoscopic liver resection.

The choice of treatment was generally based on the tumor location, the history of previous upper abdominal surgery and each center experience.

Preoperative, peri-operative data and long term outcomes were retrospectively analyzed and compared in both groups before propensity score matching (b-PSM) and after propensity score matching (a-PSM).

Preoperative data

Patient demographic data and preoperative variables were collected: blood tests, *i.e.* serum α-fetoprotein (AFP), platelets, bilirubin and coagulation; American Society of Anesthesiologists (ASA) score; comorbidities; cause of cirrhosis; Child-Pugh and the model for end-stage liver disease (MELD) scores.

All patients were staged preoperatively following computer tomography of the chest-abdomen-pelvis and/or abdominal magnetic resonance.

Tumor involving segments 4a, 7, 8 or between them were defined as located in PSS. HCC location and size were recorded and the type of treatment was discussed in multidisciplinary teams including surgeons, hepatologists, oncologists, interventional radiologists and pathologists.

Diagnosis was based on non-invasive criteria according to European Association for the Study of the Liver (EASL) and biopsy was used in case of inconclusive diagnosis [10].

Perioperative data

The procedure was performed by expert surgeons and interventional radiologists with a minimum consolidated experience of 10 years.

An intraoperative Doppler Ultrasound was systematically achieved to confirm the procedure to be performed.

Percutaneous RFA was performed using a single internally cooled electrode under a continuous sonographic guidance with local anesthesia and intravenous sedation. Post-RFA ultrasound was performed to control that there were no immediate complications such as hemorrhage or hematoma. On the 1st post-op day, an ultrasound was performed to assess the quality of the ablation in terms of necrotic area.

The Couinaud classification was used to define liver segmentation and the Brisbane 2000 terminology was used to define liver resections[11,12]. During surgical resection, attempts were made to maintain an adequate parenchymal margin of at least 1 cm.

The Pringle maneuver was routinely prepared for surgical resection and used according to the experience of each center. Perioperative variables included operative time, rate of blood transfusion, complications and length of hospital stay which were recorded. Clavien-Dindo grading system was used to classify postoperative complications.

Ninety-day mortality was defined as any deaths occurring 90 d from surgery or RFA.

Long-term outcomes

Patients undergoing RFA were given a CT scan 1 mo after ablation, in order to evaluate the results of the treatment according to mRECIST (modified Response Evaluation Criteria in Solid Tumors) criteria[13].

A standardized follow-up was adopted, every 2 mo for the first 2 years and then every 4 mo. During such follow-up, the patients were subjected to blood testing including alpha-fetoprotein, liver function and imaging, such as abdominal ultrasonography, CT, or MRI. Recurrence treatment included repeat resection or RFA, transarterial chemo-embolization, chemotherapy or supportive care according to the EASL clinical practice guidelines[10].

All HCC-related deaths and recurrences were estimated and used to calculate the overall survival (OS) and disease-free survival (DFS) in both groups.

Statistical analysis

A propensity score-based analysis was performed to minimize selection bias and limit confusion in the retrospective study. The propensity score was estimated using a 1:1 Logistical regression regarding the following variables: ASA score, MELD score and the tumors size.

Continuous variables, expressed as median with range, were compared using Mann-Whitney U test. Instead, categorical variables, expressed as numbers with percentages, were compared using chi-square test.

Overall survival and disease-free survival were estimated using the Kaplan-Meier method and compared using a log-rank test. A P value of < 0.05 was considered to indicate statistical significance. Statistical analyses were performed using SPSS software version 20.

RESULTS

Preoperative outcome b-psm and a-psm

The preoperative characteristics, before and after propensity score matching of RFA and LR groups are presented in Table 1.

During the study period, 77 patients were enrolled and divided into two groups according to the procedure performed: 40 patients in the RFA group and 37 patients in the LR group. After a 1:1 PSM, 52 patients were enrolled: 26 patients for each group.

The rate of F4 cirrhosis was lower in LR group than in the RFA group both before (51% *vs* 82%, $P = 0.01$) and after PSM (46% *vs* 85%, $P = 0.01$). ASA scores and MELD scores were lower in liver resection group b-PSM than in the RFA group ($P = 0.05$, $P = 0.01$, respectively) and equal between the two groups a-PSM ($P = 0.35$, $P = 0.23$, respectively). Tumor size was higher in the LR group than in the RFA group b-PSM (median, 29 mm *vs* 23 mm, $P = 0.02$) and comparable between two groups a-PSM (median, 23 mm *vs* 20.5 mm, $P = 0.08$).

Perioperative outcomes b-psm and a-psm

The perioperative characteristics, before and after propensity score matching of the RFA and LR groups are presented in Table 2.

Operative time was higher in the LR group than in the RFA group b-PSM (260 min *vs* 23.5 min, $P < 0.01$) and this was confirmed also after restricting the analysis to propensity score matching (165 min *vs* 20 min, $P < 0.01$). Intraoperative blood transfusion was comparable between the LR group and the RFA group both before (19% *vs* 7%, $P = 0.20$) and after PSM (19% *vs* 12%, $P = 0.70$). There were no differences in overall postoperative complications between the LR group and the RFA group b-PSM (43% *vs* 22%, $P = 0.09$), conversely, for a-PSM were significantly higher in the LR group than in the RFA group (54% *vs* 19%, $P = 0.02$). A median hospital stay was significantly longer in the LR group than in the RFA group both before and after PSM (6 d *vs* 2 d, $P < 0.01$; 7.5 d *vs* 3 d, $P < 0.01$, respectively). There was no difference in the 90-d mortality between the LR and the RFA groups both before (5% *vs* 5%, $P = 1.0$) and after PSM (8% *vs* 8%, $P = 1.0$).

Long-term outcomes b-psm and a-psm

OS and DFS were calculated before and after the propensity score matching according to the procedure performed and are presented in Figure 1.

There were no statistically significant differences between each group in terms of OS (b-PSM $P = 0.50$; a-PSM $P = 0.91$) and DFS (b-PSM $P = 0.17$; a-PSM $P = 0.70$).

The estimated 1-, 3-, and 5-year OS rates b-PSM were 9%, 72%, and 59% for the RFA group and 88, 74, and 74% for the LR group respectively.

The estimated 1-, 3- and 5-year OS rates a-PSM were 92%, 73%, and 63% for the RFA group and 84, 71, and 71% in the LR group respectively.

DFS b-PSM at 1-, 3- and 5-years was 66%, 48%, and 38% in the RFA group as compared to 84, 59, and 35% in the LR group respectively.

DFS a-PSM at 1-, 3- and 5-years was 72%, 54%, and 54% in the RFA group as compared to 87, 59 and 34% in the LR group respectively.

DISCUSSION

To our knowledge, our retrospective multicentric study is one of the few series reported in literature comparing short and long-term outcomes between RFA and LR in elderly patients and it is the first considering the HCC located in PSS.

The number of elderly patients is constantly growing thanks to improved medical care and an increase in life expectancy; therefore, the cut-off age to define the elderly has moved from > 65 years to 70 years[14].

Elderly patients should be treated with RFA or LR for a curative intent because they are unsuitable for LT due to advanced age [3]. Elderly are considered fragile as a result of the accumulation of chronic diseases, the gradual loss of reserve capacity and the increase in the tumor's rate including HCC[15].

HCC located in PSS still represent a surgical challenge and the best therapeutic option is still controversial. PSS segments are difficult to access, located in the posterior part of the abdominal cavity where exposure is not ideal[16,17].

The resections of lesions located in PSS are technically complex and should be performed by experienced surgeons in open and laparoscopic surgery and in a high-volume centers, as recommended by Southampton Guidelines[18]. Experience is

Table 1 Preoperative characteristics before and after propensity score matching, according to the procedure

	Before PSM (*n*: 77)			After PSM (*n*: 52)		
	RFA (*n*: 40)	Surgery (*n*: 37)	*P* value	RFA (*n*: 26)	Surgery (*n*: 26)	*P* value
Male, *n* (%)	28 (70)	27 (73)	0.80	17 (65)	16 (62)	1.0
Age (yr) median (range)	74.5 (70-87)	74.98 (70-83)	0.80	75 (70-81)	74.26 (70-81)	0.43
BMI (kg/cm²) median (range)	26.7 (19-51)	26.7 (22-36)	0.90	26.7 (19-51)	26.7 (22-36)	0.48
Comorbidity ≥ 2, *n* (%)	23 (57)	14 (38)	0.10	12 (46)	10 (40)	0.78
Cause of cirrhosis, *n* (%)			0.30			0.71
Hepatitis C virus, *n* (%)	21 (53)	19 (50)		16 (61)	16 (61)	
Hepatitis B virus, *n* (%)	5 (12)	10 (27)		4 (15)	6 (23)	
Alcohol, *n* (%)	6 (15)	4 (12)		3 (12)	1 (4)	
Others, *n* (%)	8 (20)	4 (11)		3 (12)	3 (12)	
F4 cirrhosis, *n* (%)	33 (82)	19 (51)	0.01	22 (85)	12 (46)	0.01
ASA score, *n* (%)			0.05			0.35
I/II, *n* (%)	11 (28)	19 (51)		10 (40)	11 (42)	
III/IV, *n* (%)	29 (72)	18 (49)		16 (61)	15 (58)	
Preoperative blood tests median (range)						
Bilirubin (μmol/L) median (range)	1 (1-1.1)	1 (1-2)	0.55	1 (1-1.1)	1 (1-1)	0.90
Platelet count × 10^9/L median (range)	118 (52-380)	173 (55-387)	0.01	137 (69-380)	183 (55-340)	0.06
INR median (range)	1 (1-2)	1 (1-2)	0.40	1 (1-1.2)	1 (1-2)	0.06
AFP (mg/mL) median (range)	5 (1-1988)	12.5 (2-3900)	0.14	6.5 (1-1988)	7 (2-3900)	0.64
Child-Pugh, *n* (%)			0.20			0.06
A	37 (93)	30 (81)		26 (100)	21 (81)	
B	3 (7)	7 (19)		0 (0)	5 (19)	
MELD median (range)	8 (6-15)	6 (6-16)	0.01	8 (6-15)	7 (6-16)	0.23
Tumors size (mm) median (range)	23 (10-30)	29 (12-30)	0.02	20.5 (10-30)	23 (15-30)	0.08
Tumor locations, *n* (%)			0.10			0.45
4a	3 (7)	3 (8)		2 (8)	2 (8)	
7	8 (20)	17 (46)		4 (15)	9 (34)	
8	23 (58)	14 (38)		17 (65)	13 (50)	
7-8	6 (15)	3 (8)		3 (12)	2 (8)	
Histological proven, *n* (%)	7 (17)	8 (22)	0.80	6 (23)	8 (31)	0.75

AFP: α-fetoprotein; ASA: American Society of Anaesthesiology; BMI: Body mass index; INR: International normalized ratio; MELD: Model of end-stage liver disease; PSM: Propensity score matching; RFA: Radiofrequency ablation.

essential to ensure success without compromise to oncological outcomes and surgical safety. Laparoscopic approach was considered difficult for these kind of lesions and also the anatomical landmarks are not clear as in anterior segments of the liver[8,19]. In complex cases including major hepatectomy, biliary reconstruction and difficult segmentectomy of the PSS, robotic surgery improved intra-operative and short-term postoperative outcomes[20].

In recent years RFA has been increasingly used for the treatment of small HCC as first line curative treatment when patients are not candidates for LR or LT and also as bridging treatment for patients on the waiting list for liver transplantation[21].

Table 2 Perioperative characteristics before and after propensity score matching, according to the procedure

	Before PSM (*n*: 77)			After PSM (*n*: 52)		
	RFA (*n*: 40)	Surgery (*n*: 37)	*P* value	RFA (*n*: 26)	Surgery (*n*: 26)	*P* value
Operative time (min) median (range)	23.5 (5-55)	260 (120-600)	< 0.01	20 (5-26)	165 (120-383)	< 0.01
Blood transfusion, *n* (%)	3 (7)	7 (19)	0.20	3 (12)	5 (19)	0.70
Postoperative complications, *n* (%)	9 (22)	16 (43)	0.09	5 (19)	14 (54)	0.02
Dindo-Clavien classification, *n* (%)						
I-II	9 (22)	11 (30)	0.60	5 (19)	10 (40)	0.20
III-IV	0 (0)	5 (13)	0.02	0 (0)	2 (8)	0.50
Type of complications, *n* (%)						
Liver failure	0 (0)	2 (5)	0.22	0 (0)	2 (8)	0.50
Ascites	0 (0)	4 (11)	0.05	0 (0)	4 (15)	0.11
Biliary leakage	0 (0)	1 (3)	0.50	0 (0)	1 (4)	1
Hemorrhage	1 (2)	2 (5)	0.60	1 (4)	1 (4)	1.0
Systemic infection	0 (0)	4 (11)	0.05	0 (0)	4 (15)	0.11
Intra-abdominal abscess	0 (0)	2 (5)	0.23	0 (0)	1 (4)	1.0
Wound infection	0 (0)	0 (0)		0 (0)	0 (0)	
Portal thrombosis	0 (0)	0 (0)		0 (0)	0 (0)	
Pulmonary	3 (7)	3 (8)	1	1 (4)	3 (12)	0.61
Cardiac	1 (2)	2 (5)	0.60	0 (0)	2 (8)	0.50
Renal	1 (2)	3 (8)	0.35	1 (4)	2 (8)	1.0
Reoperation, *n* (%)	0 (0)	0 (0)		0 (0)	0 (0)	
Postoperative treatment, *n* (%)	0 (0)	2 (5)	0.23	0 (0)	1 (4)	1.0
Length of hospital stay (d) median (range)	2 (1-15)	6 (2-203)	< 0.01	3 (1-9)	7.5 (2-203)	< 0.01
90 d mortality, *n* (%)	2 (5)	2 (5)	1.0	2 (8)	2 (8)	1.0
Recurrence, *n* (%)	21 (52)	15 (40)	0.40	12 (46)	11 (42)	1.0

PSM: Propensity score matching; RFA: Radiofrequency ablation.

Technological improvements have increased effectiveness of RFA characterized by less invasiveness and morbidity and better tolerability compared to LR; on the other hand, liver resection guarantees removal of the tumor-bearing portal and hepatic veins territory affected by micro metastases and microscopic vascular tumor invasions[5,22-24].

The choice between percutaneous RFA and LR is still controversial because many randomized prospective studies and meta-analyses were not conclusive[6,25-27]. Several aspects must be considered for choosing the best procedure including patient's age, HCC characteristics, oncological outcome, periprocedural risks, length of hospitalization and costs[22].

According to Asian Pacific Association for the Study of the Liver(APASL) HCC guidelines[28], RFA is recommended as first line treatment for HCC ≤ 2 cm because it showed similar results in terms of OS compared to LR. Instead, American Association for the Study of Liver Diseases (AASLD) highlight that surgical resection remains the first therapeutic option in small size HCC, leaving RFA for patients not eligible for surgery[29]. In cases of a single HCC > 2 cm, all guidelines recommend LR as the first approach when feasible. RFA has the advantage of cost effectiveness, feasibility, minimal invasiveness, short hospital stay, excellent efficacy and is particularly suitable for older patients and tumors located in deep positions in the liver, also in PSS.

Our retrospective multicentric study showed better short-term outcomes and similar long-term outcomes for RFA compared to LR in elderly patients with HCC ≤ 30 mm located in PSS.

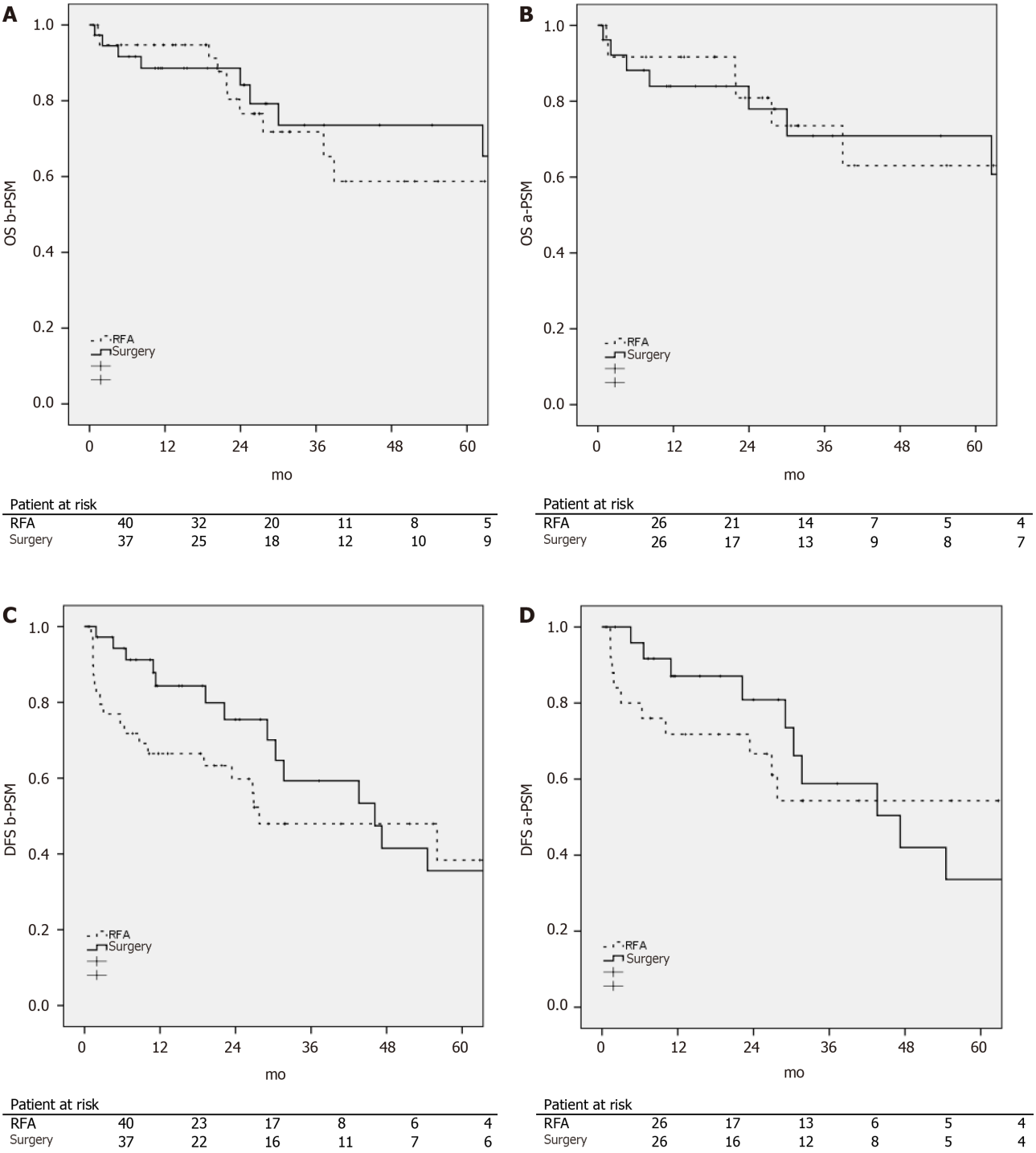

Figure 1 Overall and disease-free survival after surgery *vs* radiofrequency ablation in elderly patients for hepatocellular carcinoma before and after propensity score matching. A: Overall survival before propensity score matching, Log Rank (Mantel Cox) = 0.50; B: Overall survival after propensity score matching, Log Rank (Mantel Cox) = 0.91; C: Disease free survival before propensity score matching, Log Rank (Mantel Cox) = 0.17; D: Disease free survival after propensity score matching, Log Rank (Mantel Cox) = 0.70. OS: Overall survival; DFS: Disease-free survival.

In our work, operative time and hospital stay were shorter in the RFA group compared to the LR group. This highlights the less invasive nature of the ablative treatment and is corroborated by randomized controlled trials[6,25,27].

According to the literature data, overall postoperative complications were significantly lower in the RFA group than in the LR group. These data emphasize the minimally invasiveness and improved post-operative quality of life of percutaneous treatment, necessary features especially for elderly patients[30,31].

In our study, OS and DFS had no significant difference between the RFA and LR group and this is confirmed by Chen *et al*[25] Conversely, many articles reported a decreased recurrence risk and improvement in OS of LR compared to the RFA group

[32-35], but we would underline that there was no specificity regarding patient's age.

LR has been associated with less HCC recurrences due to complete eradication of the tumor and venous tumor thrombi, and could therefore result in better long-term survival compared to RFA[36]. In addition, RFA may be associated with an increased risk of neoplastic dissemination after treatment due to repeated puncture and temperature-related intratumoral explosion[37].

Compared to LR, it is clear from numerous reports that percutaneous RFA treating liver tumors ≥ 40-50 mm in diameter or located in difficult sites of the liver (subcapsular, adjacent gallbladder or diaphragm) is associated with an increased rate of incomplete treatment, which is usually reported erroneously as a local recurrence [37,38].

Liver resection should be considered for patients with better liver function and longer life expectation in order to balance the postoperative risk of treatment with the benefits in long-term survival.

It is evident that most of the studies and guidelines comparing LR with RFA do not consider the patient's age and the tumors locations, hence the need for additional prospective randomized studies focusing on elderly patients with HCC located in PSS.

CONCLUSION

RFA in PSS segments in elderly patients is safe and feasible, ensures a short hospital stay, increases the quality of life and does not modify the overall success rate. This technique should be recommended mainly in elderly patients because it allows a reduction of postoperative complications and a fast discharge to home.

ARTICLE HIGHLIGHTS

Research background

Liver resection and radiofrequency ablation are considered curative options for hepatocellular carcinoma, but the choice among them is still controversial, especially in cases of hepatocellular carcinoma affecting posterosuperior segments in elderly.

Research motivation

In literature there are few studies which focus on surgical treatments in elderly patients with hepatocellular carcinoma especially in posterosuperior segments.

Research objectives

To compare short and long-term outcomes between liver resection and radiofrequency ablation in elderly patients with single hepatocellular carcinoma located in posterosuperior segments.

Research methods

We performed a multicentric retrospective study enrolling 77 patients with ≥ 70 years of age, from January 2009 to January 2019 in 10 European hospital centers. Patients were divided into two groups according to the treatment, liver resection or radiofrequency ablation. Preoperative, peri-operative data and long term outcomes were retrospectively analyzed and compared in both groups before propensity score matching and after propensity score matching.

Research results

After propensity score matching, 26 patients were included in each group. Operative time and overall postoperative complications were higher in the resection group compared to the ablation group. A median hospital stay was significantly longer in the resection group than in the ablation group. There was no significant differences between resection and ablation groups in terms of overall survival and disease free survival at 1, 3 and 5 years.

Research conclusions

Radiofrequency ablation in posterosuperior segments in elderly is safe and feasible and ensures a short hospital stay, better quality of life and does not modify the overall and disease-free survival.

Research perspectives

Radiofrequency ablation can be considered a gold standard for the treatment of single hepatocellular carcinoma located in posterosuperior segments in elderly. These results must be a starting point for future research and to ensure a higher level of evidence in clinical practice.

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2021 December 27; 13(12): 1708-1720

DOI: 10.4240/wjgs.v13.i12.1708

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Observational Study

Expression of adipokine ghrelin and ghrelin receptor in human colorectal adenoma and correlation with the grade of dysplasia

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Author contributions: Stojsavljevic-Shapeski S, Virovic-Jukic L and Tomas D designed the study; Stojsavljevic-Shapeski S, Tomasic V, Kralj D, Barsic N, Budimir I and Hrabar D participated in the acquisition of data; Stojsavljevic-Shapeski S, Virovic-Jukic L and Tomas D participated in the analysis and interpretation of the data; Stojsavljevic-Shapeski S and Virovic-Jukic L drafted the initial manuscript; Hrabar D, Duvnjak M and Ljubicic N revised the article critically for important intellectual content.

Institutional review board statement: The study and all its documents as well as the informed consent form were reviewed and approved by the Ethical committee of «Sestre Milosrdnice» University Hospital Center, 10000 Zagreb, Croatia in December 2013.

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Abstract

BACKGROUND

Ghrelin is an adipokine that plays an important role in energy balance. Expression of ghrelin and ghrelin receptor has been investigated in different tissues and tumors. Studies regarding expression of ghrelin and ghrelin receptor in colorectal tumors are scarce and no data on expression of ghrelin and its receptor in colorectal adenomas has been published. Ghrelin and ghrelin receptor were highly expressed in colon carcinoma cells while expression was decreased in less differentiated tumors, presuming that ghrelin might be important in early phases of tumorigenesis.

AIM

To investigate the expression of ghrelin and ghrelin receptor in human colorectal adenomas and adjacent colorectal tissue.

METHODS

In this prospective study (conducted from June 2015 until May 2019) we included 92 patients (64 male and 28 female) who underwent polypectomy for colorectal adenomas in the Department of Gastroenterology and Hepatology, "Sestre

Informed consent statement: All study participants, or their legal guardian, provided after extensive written and communicated information an informed written consent prior to study enrollment.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No additional data are available.

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

Country/Territory of origin: Croatia

Specialty type: Gastroenterology and hepatology

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

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: June 28, 2021
Peer-review started: June 28, 2021
First decision: July 27, 2021
Revised: August 20, 2021
Accepted: November 3, 2021
Article in press: November 3, 2021

milosrdnice" Clinical Hospital Center in Zagreb, Croatia. After endoscopic removal of colorectal adenoma, an additional sample of colon mucosa in the proximity of the adenoma was collected for pathohistological analysis. Adenomas were graded according to the stage of dysplasia, and ghrelin and ghrelin receptor expression were determined immunohistochemically in both adenoma and adjacent colon tissue using the polyclonal antibody for ghrelin (ab150514, ABCAM Inc, Cambridge, United States) and ghrelin receptor (ab48285, ABCAM Inc, Cambridge, United States). Categorical and nominal variables were described through frequencies and proportions and the difference between specific groups were analyzed with Fisher's and Fisher-Freeman-Halton's method respectively. Spearman's rank correlation coefficient was determined for correlation of expression of ghrelin and ghrelin receptor in adenoma and adjacent colon tissue with the grade of adenoma dysplasia.

RESULTS

Among 92 patients with colorectal adenoma 43 had adenomas with high-grade dysplasia (46.7%). High expression of ghrelin was 7 times more common in high-grade adenoma compared to low-grade adenomas (13.95% to 2.04%, $P = 0.048$), while the expression of ghrelin in adjacent colon tissue was low. We found no correlation between ghrelin receptor expression in adenoma and adjacent colon tissue and the grade of colorectal adenoma dysplasia. The most significant correlation was found between ghrelin and ghrelin receptor expression in adenomas with high-grade dysplasia (rho = 0.519, $P < 0.001$).

CONCLUSION

Ghrelin and ghrelin receptor are expressed in colorectal adenoma and adjacent tissue with ghrelin expression being more pronounced in high grade dysplasia as a possible consequence of increased local synthesis.

Key Words: Ghrelin; Ghrelin receptor; Adipokines; Colorectal adenoma; Colorectal adenoma dysplasia; Large intestine

Core Tip: Colorectal adenomas are benign, but premalignant lesions of the large intestine, as dysplasia may progress over time and result in the occurrence of colorectal carcinoma. The risk of progression is increased in adenomas with high-grade dysplasia. There are several risk factors for adenomas with high-grade dysplasia, of which energy imbalance and metabolic syndrome are increasing in importance because of their rising prevalence. Ghrelin is an adipokine important in energy balance and its expression was investigated in different tumors and tissues. With this prospective observational study we gained new insight on the expression and role of ghrelin and ghrelin receptor in colorectal adenomas.

Citation: Stojsavljevic-Shapeski S, Virovic-Jukic L, Tomas D, Duvnjak M, Tomasic V, Hrabar D, Kralj D, Budimir I, Barsic N, Ljubicic N. Expression of adipokine ghrelin and ghrelin receptor in human colorectal adenoma and correlation with the grade of dysplasia. *World J Gastrointest Surg* 2021; 13(12): 1708-1720
URL: https://www.wjgnet.com/1948-9366/full/v13/i12/1708.htm
DOI: https://dx.doi.org/10.4240/wjgs.v13.i12.1708

INTRODUCTION

Ghrelin is an adipokine, an endogenous ligand of growth hormone (GH) secretagogue receptor (GHS-R), which was first isolated in 1999 by Kojima *et al*[1] from rat gastric cells. Ghrelin stimulates the release of GH through activation of its receptors and for some time it was though that its main and only function was the regulation of energy and appetite[1]. However, ghrelin stimulates the release of other pituitary hormones,

Published online: December 27, 2021

P-Reviewer: Abdalla MMI, Mori H, Tan X
S-Editor: Gao CC
L-Editor: A
P-Editor: Gao CC

influences gastric motility and secretion of gastric acid, modulates pancreatic endocrine function and influences glucose metabolism, insulin resistance and cell proliferation[2]. Apart from its production by gastric cells, it is expressed and produced in almost all tissues of the gastrointestinal tract and body in general[3,4]. Serum concentrations of total ghrelin were found to be lower in obese individuals on the account of decreased levels of deacylated ghrelin, while acylated ghrelin levels were mostly constant[5]. Ghrelin receptor was found to be highly expressed in adipose tissue where its activation induced the differentiation and proliferation of adipocyes and decreased their apoptosis which is mediated through MAP/PIP 3/Akt pathway [6]. Since ghrelin influences the release of GH and is a regulator of the GH/insulin like GH (IGF)-1 pathway, it has been also linked to tumor progression[7]. Gastric carcinoma cells exposed to ghrelin showed increased migratory and invasion abilities while their apoptosis was reduced[8]. This was shown to be also mediated through the PI3K/Akt pathway[8].

Ghrelin receptor expression varies among different types of tumors. Two types of ghrelin receptor forms have been described, type GHS-R1a and GHS-R1b, with GHS-R1a recognized as predominant and therefore responsible for ghrelin activity[9]. However, one study found GHS-R1b more expressed in tumor cells with advancing colorectal carcinoma stage while GHS-R1a expression was decreased[10]. Ghrelin has been investigated in different tumor tissues and although not all results concurred, most were consistent in tumor expression of ghrelin and in favor of its proliferative and anti-apoptotic role[11-16].

Colorectal adenomas are premalignant lesions that are differentiated among other characteristics on the grade of dysplasia in high and low-grade dysplasia adenomas [17]. With time, progression of dysplasia leads to a well-known adenoma-carcinoma sequence. Various risk factors have been associated with high-grade dysplasia adenoma, including genetic predisposition, inflammatory bowel diseases, age, male sex, smoking, poor dietary habits, obesity and metabolic syndrome[18,19]. Since metabolic syndrome is experiencing a worldwide epidemic-like rise in incidence, its clinical consequences such as tumors, with colorectal adenomas and carcinomas among others, are also experiencing a dramatic rise[20,21]. Although the influence of insulin resistance and hyperinsulinemia in colorectal carcinoma formation and progression has been well established, the role of adipokines connected to the metabolic syndrome such as ghrelin has still not been completely clarified[22]. Researching the published data regarding influence of ghrelin and its receptor in colorectal carcinoma and colorectal adenoma progression, we realized that there is a need for further insight on this subject. Current data are not sufficient for complete understanding of all ghrelin effects, and there are missing data from large cohort studies, tissue expression, genetic and plasma level studies which was also emphasized in a recently published review on ghrelin role in gastrointestinal tract tumors[23]. In this study we aimed to investigate the expression of ghrelin and ghrelin receptor in colorectal adenoma and adjacent healthy tissue, and to our knowledge this is the first study dealing with this issue. New information on this subject could influence the current recommendations for colorectal adenoma and carcinoma screening, giving more attention to patients burdened with metabolic syndrome features as well as influence postpolypectomy surveillance guidelines. Current guidelines rely on conventional adenoma characteristics such as number, size, histology and presence of dysplasia, but the burden imposed on patients and health services by surveillance colonoscopies encourages research of novel genomic and immunohistochemical markers for identifying risk of metachronous polyp development[24]. Understanding the complex involvement of adipokines in the pathways responsible in adenoma to carcinoma progression could influence potential management strategies[25]. Ghrelin as an important adipokine is in this respect still insufficiently investigated and further studies are needed.

MATERIALS AND METHODS

Patients

In this prospective observational study we included 92 patients who underwent endoscopic polypectomy for colorectal adenoma at the Department of Gastroenterology, "Sestre milosrdnice" University Hospital Center in Zagreb, Croatia. The participants were included in the study in the period from June 2015 until May 2019. All participants were prior to recruitment informed of the nature of the study and gave their informed consent for participation. Exclusion criteria were an active or prior

malignant disease, history of inflammatory bowel disease or any abdominal surgical procedure, prior removal of colorectal adenoma and a lack of informed consent.

All patients underwent a total colonoscopy with the removal of colorectal adenoma or adenomas. During the procedure, an additional biopsy of adjacent, "healthy" tissue was taken 5 cm proximally or distally from the removed adenoma. In cases where more adenomas were removed, only the largest adenoma and the tissue adjacent to it were used in further immunohistochemical analysis. Adenoma sample and the adjacent tissue sample underwent pathohistological analysis for dysplasia that was graded either high or low, and immunohistochemical analysis for expression of ghrelin and ghrelin receptor. We used tissue fixation technique with solution of 40 g/L formaldehyde (10% neutral buffered formalin) and the samples were embedded in paraffin blocks and cut into 5 μm slices. A power analysis was done in a pilot study to determine the number of participants needed to reach statistical significance.

Immunohistochemical analysis

For immunohistochemical analysis we used a polyclonal antibody for the ghrelin receptor (ab150514, ABCAM Inc, Cambrige, United States) and a polyclonal antibody for ghrelin (ab48285 ABCAM Inc, Cambrige, United States), both in concentrations of 5 mg/mL. The analysis for both antibodies was performed on a Dako Autostainer automated slide processing system (Dako, Copenhagen, Denmark) by EnVision FLEX-PTL method. The results of the immunohistochemical analysis were expressed semi-quantitatively by determination of the immunohistochemical staining index (ISI), taking in account the intensity of the reaction (IR) and the percentage of the immunoreactive cells (PC). Two experienced pathologists independently performed the interpretation of the IR and the percentage of immunoreactive cells. In cases of discordant results a third pathologist was consulted to reach an agreement. Intensity of the staining was classified as 0 for no reaction, 1 for a poor cytoplasmic reaction, 2 for a moderate one and 3 for an intense cytoplasmic reaction. The percentage of immunoreactive cells was classified as 0 for no reaction, 1 for reaction in ≤ 33 percent of cells, 2 for reaction in more that 33 percent and ≤ 66 percent, and 3 for a reaction in more that 66 percent of cells. Each sample was in that way assigned a grade for the percentage of immunoreactiove cells and a grade for the intensity of staining. ISI was determined as a multiplication of the IR and the percentage of reactive cells. We distinguished two groups of specimens: those with the ISI value of 9, which represents the strong reaction and the group with ISI values less than 9 representing no, poor or slight reaction.

Statistical analysis

Categorical and nominal variables were described through frequencies and proportions and the difference between specific groups were analyzed with Fisher's and Fisher-Freeman-Halton's method respectively. Spearman's rank correlation coefficient was determined for correlation of expression of ghrelin and ghrelin receptor in adenoma and adjacent colon tissue with the grade of adenoma dysplasia. *P* values less than 0.05 were considered significant and in the analysis we used the licensed program support IBM SPSS Statistics, version 25.0 (https://www.ibm.com/analytics/spss-statistics-software).

RESULTS

From 123 screened, 92 patients were included in the study (due to later drop out), 64 male (69.9%) and 28 female (30.4%). The youngest patient was 29 and the oldest 83 years old, age median was 66. Forty-nine patients (53.3%) had a low-grade dysplasia adenoma and 43 patients (46.7%) high-grade dysplasia adenoma. Adenomas were categorized according to size in larger than 5 mm and smaller than 5 mm, and adenomas larger than 5 mm were according to type categorized in sessile, subpeduncular, peduncular and flat. The descriptive statistics regarding the localization, size and type of adenomas is presented in Table 1.

All adenomas as well as adjacent tissue were immunohistochemically stained to evaluate ghrelin and ghrelin receptor expression. Figure 1 shows different intensities of immunohistochemical staining for ghrelin in adenoma and adjacent tissue (Figure 1A-C). Figure 2 shows different intensities of immunohistochemical staining for ghrelin receptor in adenoma and adjacent tissue (Figure 2A-C). Figure 3 shows the statistical distribution of ISI values for ghrelin and ghrelin receptor among adenomas depending on dysplasia grade, and Figure 4 the statistical distribution of ISI values for

Table 1 Descriptive statistics regarding adenoma size, localization and type (sessile, peduncular, subpeduncular, flat)

	n	%
Adenoma < 5 mm in ascending colon		
Not found	65	70.7
Found	27	29.3
Adenoma > 5 mm in ascending colon		
Not found	62	67.4
Found	30	32.6
Type of adenoma > 5 mm in ascending colon		
Sessile	24	54.6
Peduncular	3	6.8
Subpeduncular	7	15.9
Flat	10	22.7
Adenoma < 5 mm in transverse and descending colon		
Not found	75	81.5
Found	17	18.5
Adenoma > 5 mm in transverse and descending colon		
Not found	69	75.0
Found	23	25.0
Type of adenoma > 5 mm in transverse and descending colon		
Sessile	15	51.7
Peduncular	7	24.1
Subpeduncular	4	13.8
Flat	3	10.4
Adenoma < 5 mm in sigmoid colon		
Not found	68	73.9
Found	24	26.1
Adenoma > 5 mm in sigmoid colon		
Not found	43	46.7
Found	49	53.3
Type of adenoma > 5 mm in sigmoid colon		
Sessile	18	31.1
Peduncular	26	44.8
Subpeduncular	12	20.7
Flat	2	3.4
Adenoma < 5 mm in rectum		
Not found	75	81.5
Found	17	18.5
Adenoma > 5 mm in rectum		
Not found	73	79.3
Found	19	20.7
Type of adenoma > 5 mm in rectum		
Sessile	14	73.7

Peduncular	4	21.1
Subpeduncular	1	5.2
Flat	0	0.0

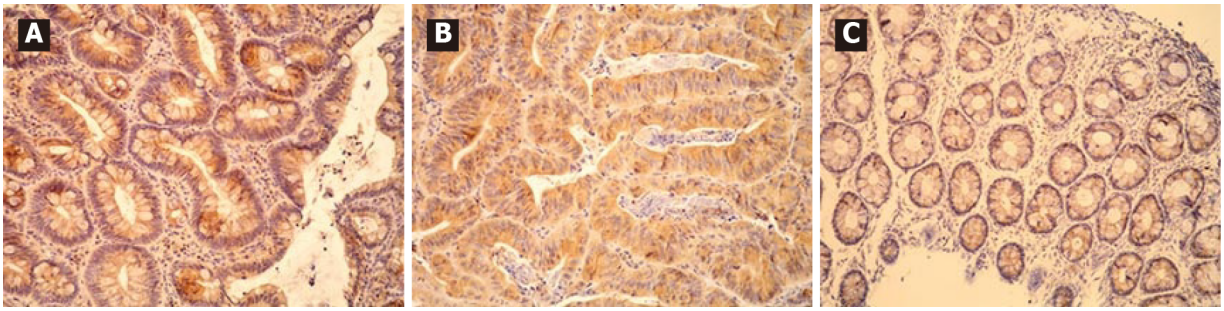

Figure 1 Immunohistochemical expression of ghrelin in adenoma and adjacent tissue. A: Representative image of strong immunohistochemical expression of ghrelin in adenoma with low grade dysplasia (200 × magnification); B: Representative image of strong immunohistochemical expression of ghrelin in adenoma with high grade dysplasia (200 × magnification); C: Representative image of moderate immunohistochemical expression of ghrelin in adjacent tissue (200 × magnification).

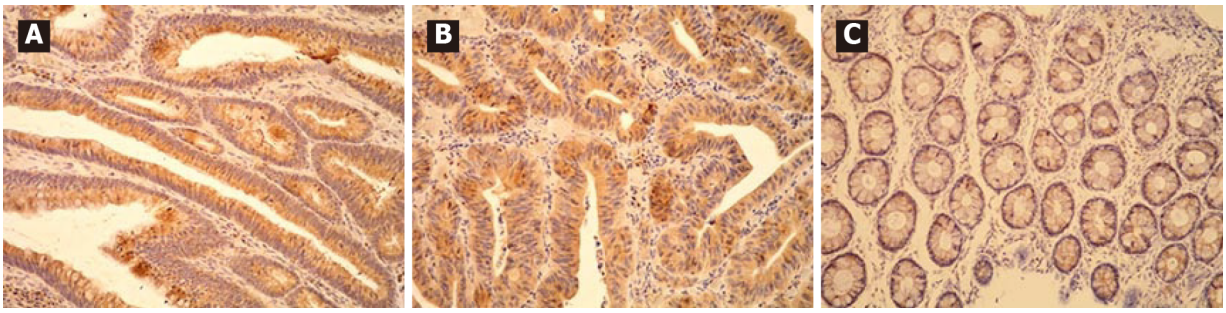

Figure 2 Immunohistochemical expression of ghrelin receptor in adenoma and adjacent tissue. A: Representative image of strong immunohistochemical expression of ghrelin receptor in adenoma with low grade dysplasia (200 × magnification); B: Representative image of strong immunohistochemical expression of ghrelin receptor in adenoma with high grade dysplasia (200 × magnification); C: Representative image of moderate immunohistochemical expression of ghrelin receptor in adjacent tissue (200 × magnification).

ghrelin and ghrelin receptor in adjacent tissue (Figures 3 and 4).

We found that ghrelin was in different intensities expressed in 98.8% of all adenomas, and 79.3% of adjacent tissue samples, while ghrelin receptor was expressed in 98.9% of adenoma and 94.6% of adjacent tissue samples.

In Table 2 we showed the correlation of immunohistochemical expression of ghrelin and ghrelin receptor based on two groups of ISI values in adenoma and adjacent tissue to the stage of adenoma dysplasia (Table 2). In adenomas with high-grade dysplasia strong expression of ghrelin was 7 times more frequent than in adenomas with low-grade dysplasia ($P = 0.048$). We found no correlation between immunohistochemical expression of ghrelin receptor in adenoma and adjacent tissue to the stage of adenoma dysplasia ($P > 0.05$).

The results of Spearman's rank correlation coefficient (rho) analysis for correlation between immunohistochemical expression (value of ISI index) of ghrelin and ghrelin receptor in adenoma (and adjacent colon tissue) and grade of adenoma dysplasia are shown in Table 3.

In adenomas with high-grade dysplasia there is a positive correlation between immunohistochemical expression of ghrelin in adenoma and the immunohistochemical expression of ghrelin receptor in adenoma (rho = 0.519; $P < 0.001$) and expression of ghrelin in adjacent tissue (rho = 0.467; $P = 0.002$). In adenomas with low-grade dysplasia we have not found a positive correlation between immunohistochemical expression of ghrelin and the ghrelin receptor but we found a positive correlation between expression of ghrelin receptor in adenoma and the expression of ghrelin receptor in adjacent tissue (rho = 0.567; $P < 0.001$). Regardless of the stage of adenoma dysplasia in adjacent colon tissue we found a positive correlation between

Table 2 Correlation of immunohistochemical expression of ghrelin and ghrelin receptor based on two groups of immunohistochemical staining index value in adenoma and adjacent tissue to the stage of adenoma dysplasia

	Dysplasia grade				*P* value
	Low dysplasia		High dysplasia		
	n	%	*n*	%	
ISI for ghrelin in adenoma					0.048[a]
ISI < 9	48	98.0	37	86.0	
ISI 9-strong reaction	1	2.0	6	14.0	
ISI for ghrelin in adjacent tissue					1.000
ISI 0 < 6	42	85.7	37	86.0	
ISI 6-moderate reaction	7	14.3	6	14.0	
ISI for ghrelin receptor in adenoma					0.114
ISI < 9	43	87.8	32	74.4	
ISI 9-strong reaction	6	12.2	11	25.6	
ISI for ghrelin receptor in adjacent tissue					0.664
ISI < 9	30	61.2	29	67.4	
ISI 9-strong reaction	19	38.8	14	32.6	

[a]P = 0.048 for strong ghrelin expression in adenoma with high *vs* low grade dysplasia.
ISI: Immunohistochemical staining index.

expression of ghrelin and ghrelin receptor (rho = 0.367; P = 0.009 in low dysplasia group and rho = 0.409; P = 0.002 for high-grade dysplasia group respectively). For interpretation of this correlation it is important to note that regardless of the dysplasia grade in adenoma we have not found in any obtained sample of adjacent colon tissue a high expression of ghrelin, and in more than 75% of adjacent tissue samples ISI index was ≤ 3 which marked poor to none ghrelin expression.

DISCUSSION

To our knowledge there have been no studies regarding the expression of ghrelin and ghrelin receptor in human colorectal adenomas. We wanted to investigate the expression of ghrelin and ghrelin receptor in colorectal adenoma and in adenoma adjacent normal colorectal tissue. In our study we found that in adenomas ghrelin was in different intensity expressed in 98.8% of samples and ghrelin receptor in 98.9% respectively. In adjacent tissue ghrelin was in different intensity expressed in 79.3% of samples and ghrelin receptor in 94.6% respectively. Although ghrelin and ghrelin receptor are expressed in adenomas with low and high-grade dysplasia, in high-grade dysplasia there is a stronger expression of ghrelin, which could suggest that adenomas with high grade dysplasia produce locally more ghrelin. Waseem *et al*[10] in their study on 110 patients with colorectal carcinoma found that tumors cells as well as normal cells express ghrelin and ghrelin receptor, but the cells of well and moderately differentiated tumors produce more ghrelin in comparison with normal large intestine cells. The intensity of the immunohistochemical reaction for ghrelin was graded 0 to 4 and well differentiated tumors had a 1.92 ± 0.4 higher expression of ghrelin than normal cells, and moderately differentiated tumors had 2.25 ± 0.5 higher ghrelin expression than normal cells[10]. Interestingly, they also found that as the tumor cells lose its potential to differentiate, they also lose their ability to express ghrelin and ghrelin receptor (P < 0.05)[10]. Their results imply that ghrelin and ghrelin receptor could have a role in early tumor progression and that their importance is lost in poorly differentiated tumors. Ghrelin in an *in vitro* study acted proliferative on normal large intestine cells and tumor cells since it promoted the shift from G1 to S cell phase and influenced cell cycle progression (P < 0.05)[26]. This was mediated through activation of the adenylate cyclase independent epidermal growth factor receptor (EGFR) trans-activation and PI3K-Akt phosphorylation. Both these pathways converge to stimulate

Table 3 Spearman's rank correlation for immunohistocehmical expression of ghrelin and ghrelin receptor in adenoma and adjacent tissue with the grade of adenoma dysplasia

	ISI for ghrelin in adenoma	ISI for ghrelin in adjacent tissue	ISI for ghrelin receptor in adenoma	ISI for ghrelin receptor in adjacent tissue
Low grade dysplasia				
ISI for ghrelin in adenoma				
Rho	1.000	0.173	-0.108	-0.096
P value		0.235	0.459	0.511
n	49	49	49	49
ISI for ghrelin in adjacent tissue				
Rho	0.173	1.000	0.159	0.367
P value	0.235		0.276	0.009[a]
n	49	49	49	49
ISI for ghrelin receptor in adenoma				
Rho	-0.108	0.159	1.000	0.576
P value	0.459	0.276		< 0.001[b]
n	49	49	49	49
ISI for ghrelin receptor in adjacent tissue				
Rho	-0.096	0.367	0.576	1.000
P value	0.511	0.009	0.000	
n	49	49	49	49
High grade dysplasia				
ISI for ghrelin in adenoma				
Rho	1.000	0.347	0.519	0.077
P value		0.023[d]	< 0.001[c]	0.622
n	43	43	43	43
ISI for ghrelin in adjacent tissue				
Rho	0.347	1.000	0.230	0.409
P value	0.023[d]		0.138	0.007[e]
n	43	43	43	43
ISI for ghrelin receptor in adenoma				
Rho	0.519	0.230	1.000	0.467
P value	< 0.001[c]	0.138		0.002[f]
n	43	43	43	43
ISI for ghrelin receptor in adjacent tissue				
Rho	0.077	0.409	0.467	1.000
P value	0.622	0.007[e]	0.002[f]	
n	43	43	43	43

[a]*P* = 0.009 positive correlation between expression of ghrelin and ghrelin receptor in adjacent tissue for low grade dysplasia adenoma.
[b]*P* < 0.001 positive correlation between expression of ghrelin receptor in adenoma and adjacent tissue for low grade dysplasia adenoma.

[c]$P < 0.001$ positive correlation between expression of ghrelin and ghrelin receptor in adenoma for high grade dysplasia adenoma.
[d]$P = 0.023$ positive correlation between expression of ghrelin in adenoma and adjacent tissue for high grade dysplasia adenoma.
[e]$P = 0.007$ positive correlation between expression of ghrelin and ghrelin receptor in adjacent tissue for high grade dysplasia adenoma.
[f]$P = 0.002$ positive correlation between expression of ghrelin and ghrelin receptor in adjacent tissue for low grade dysplasia adenoma.
ISI: Immunohistochemical staining index; Rho: Spearman correlation coefficient.

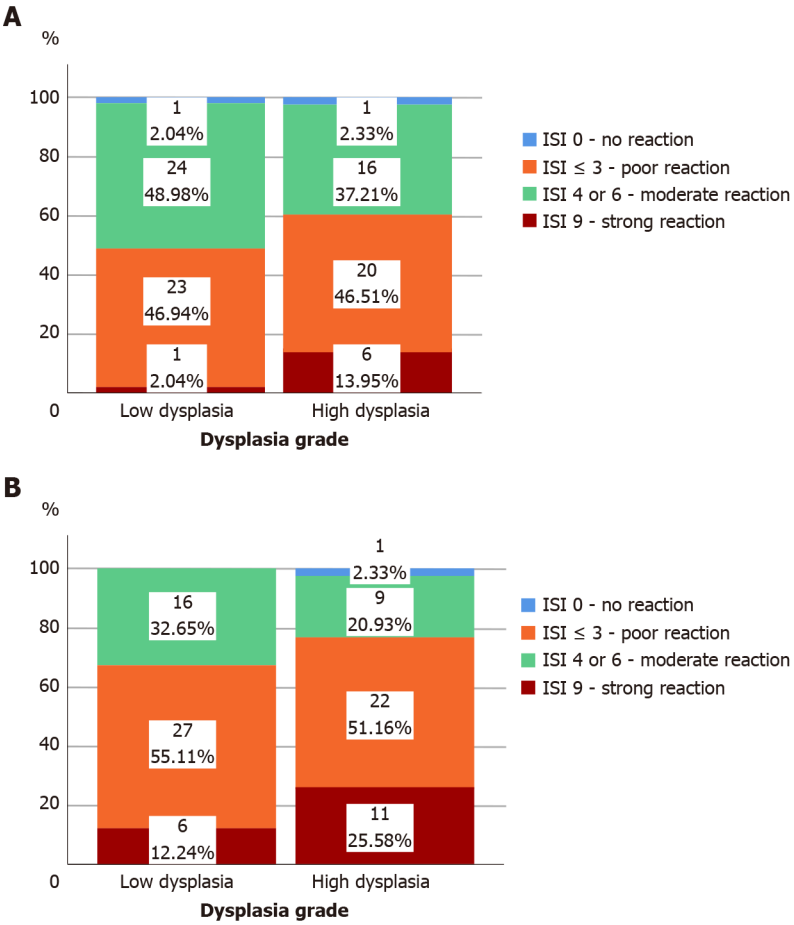

Figure 3 Immunohistochemical expression of ghrelin and ghrelin receptor in adenoma depending on the grade of adenoma dysplasia. A: Immunohistochemical staining index (ISI) of ghrelin in adenoma depending on grade of dysplasia in adenoma; B: ISI of ghrelin receptor in adenoma depending on grade of dysplasia in adenoma. ISI: Immunohistochemical staining index.

MAPK, ERK 1/2 signaling[26]. A genomic study on intra-tumor heterogeneity analyzing clonal origins and subclonal composition of adenomas and colorectal tumors detected several signaling pathways important in colorectal cancer evolution [27]. Accumulation of mutations in the PI3K-Akt pathway was found, among others, to be of vital importance[27]. A study assessing the expression of EGFR in normal colon tissue and colorectal adenoma tissue found that adenomas with high-grade dysplasia and tubule-villous features overexpress EGFR, while only 10 percent of adenomas with low-grade dysplasia expressed EGFR[28]. Another *in vitro* study found that ghrelin acts proliferative on colorectal carcinoma cells activating Ras, PI3K, Akt and mTOR signaling pathway[29]. Study on gastric adenocarcinoma and normal gastric cells found that gastric cells express ghrelin but adenocarcinoma cells lose its potential to express ghrelin[30]. Although we are moving away from the alimentary system, well differentiated breast tumors have a great potential for expression of ghrelin while less differentiated ones lose this ability[31]. In patients with serous ovarian tumors expression of ghrelin was increased in malignant compared to benign tumors[13].

We have not found a significant difference in ghrelin receptor expression between high and low-grade adenomas or adjacent normal colorectal tissue. Although our results point out that, based on ISI values, strong expression of ghrelin receptor was two times more frequent in adenomas with high grade dysplasia than in low grade dysplasia, it was not significant. A study by Liu *et al*[9], found that ghrelin and its

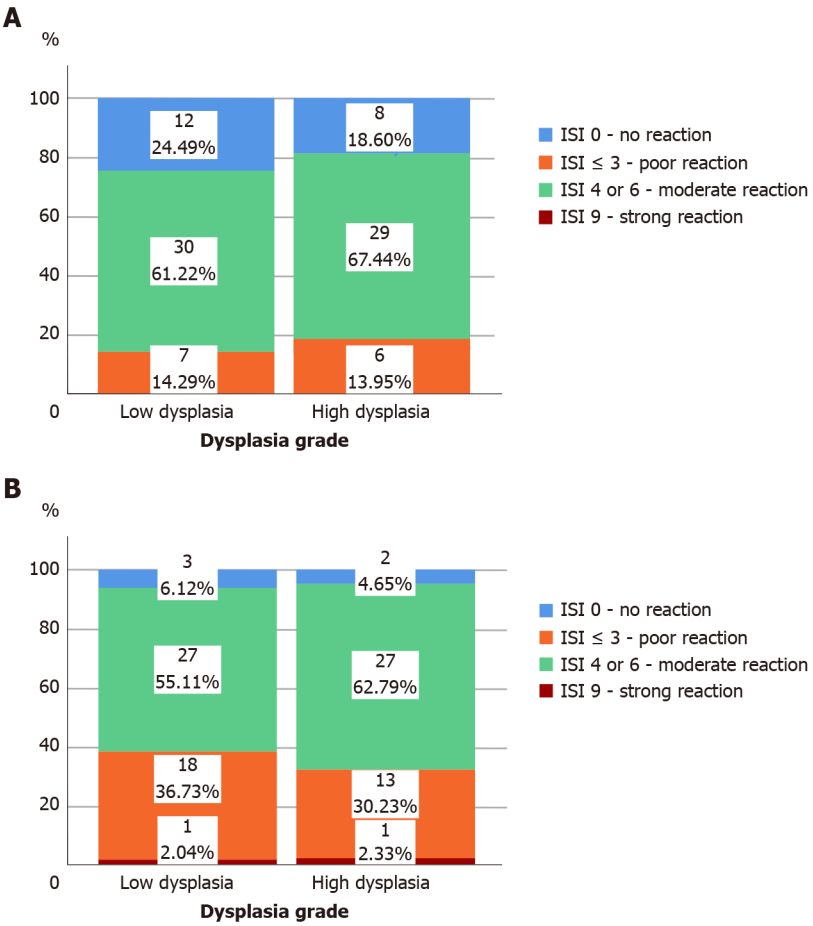

Figure 4 Immunohistochemical expression of ghrelin and ghrelin receptor in adjacent tissue depending on the grade of dysplasia in the corresponding adenoma. A: Immunohistochemical staining index (ISI) of ghrelin in adjacent tissue depending on grade of dysplasia in corresponding adenoma; B: ISI of ghrelin receptor in adjacent tissue depending on grade of dysplasia in corresponding adenoma. ISI: Immunohistochemical staining index.

receptor are markedly expressed in colorectal tumors and cell lines. They also report that after ghrelin receptor activation the probable mechanism of downstream regulation is through inhibiting phosphatase and tensin homolog, activating Akt and inhibiting p53[9]. In their mouse model, the expression of ghrelin receptor significantly correlated with colorectal cancer cell growth and tumor burden[9]. Similar results were reported in a mouse model of endometrial carcinoma[32]. Although our results don't concur with the previous studies we could hypothesize that the expression and importance of ghrelin receptor is more pronounced further down the dysplasia progression pathway. Ghrelin receptor role in colorectal adenoma dysplasia progression should be investigated in further studies.

Our results showed a positive correlation between immunohistochemical expression of ghrelin and ghrelin receptor in adjacent normal colorectal tissue independently of the fact whether the corresponding removed adenoma had high or low-grade dysplasia (P = 0.009 for low grade dysplasia, P = 0.023 for high grade dysplasia). We have to emphasize that in adjacent tissue samples we didn't find a great intensity of ghrelin expression, and in more than 75% of those samples ISI index was ≤ 3 which marked poor to none ghrelin expression. Our results didn't show a positive correlation between ghrelin and ghrelin receptor in adenomas with low-grade dysplasia (P < 0.05). Since similar studies concerning ghrelin and ghrelin receptor expression in adenoma with low and high-grade dysplasia as well as adjacent tissue are lacking we cannot compare our results with other studies, but are looking forward to future studies. The lack of our study is that the immunohistochemical staining used in our study did not differentiate the two types of ghrelin receptor (types GHS-R1a and GHS-R1b) in colorectal adenoma and adjacent tissue so this could be a subject for new studies. Although this was a relatively simple study our strongest point is that we are the first to address ghrelin and ghrelin receptor expression in colorectal adenomas since there has been no published data on this issue.

Our results point out to the conclusion that although ghrelin and ghrelin receptor are expressed in normal and adenoma tissue, in high-grade adenomas there is a higher expression of ghrelin due to its higher production, which promotes further proliferation.

CONCLUSION

Our study shows that ghrelin and ghrelin receptor are expressed in colorectal adenomas and adjacent tissue. We found that ghrelin expression was more pronounced in adenomas with high-grade dysplasia compared to those with low-grade dysplasia and that here is a positive correlation between ghrelin and ghrelin receptor expression in colorectal adenomas with high-grade dysplasia. Our results indicate the important role of ghrelin in dysplasia progression. Further studies on expression of specific ghrelin receptor types in colorectal adenomas are needed to ensure better understanding of the role of ghrelin receptors in promotion of cell proliferation and malignant transformation.

ARTICLE HIGHLIGHTS

Research background

Ghrelin is an adipokine that influences energy expenditure and appetite, modulates gastric motility, secretion of gastric acid, pancreatic endocrine function and has an important role in glucose metabolism, insulin resistance and metabolic syndrome. Metabolic syndrome is one of the known risk factors for colorectal carcinoma development, and both diseases have had a significant rise in prevalence. Colorectal adenomas are premalignant lesions that can with time progress to colorectal carcinoma, and have also been linked to metabolic syndrome. Ghrelin, as one of the links between metabolic syndrome and tumor progression, has been investigated in several tissues and tumors but current data are not sufficient for complete understanding of all ghrelin effects.

Research motivation

Researching the published data regarding influence of ghrelin and its receptor in colorectal carcinoma and colorectal adenoma progression, we realized that there is a need for further insight on the subject since data on this topic is lacking. Current guidelines on colorectal adenoma and carcinoma screening and postpolypectomy surveillance do not focus on the presence of metabolic syndrome or any of its components. Obtaining more insight into the link between metabolic syndrome and colorectal adenoma and carcinoma occurrence could possibly in future influence new guidelines.

Research objectives

We aimed to investigate the expression of ghrelin and ghrelin receptor in colorectal adenomas and adjacent colorectal tissue to give a new perspective on this problem.

Research methods

We conducted a prospective study (from June 2015 until May 2019) that included 92 patients who underwent polypectomy for colorectal adenomas in the Department of Gastroenterology and Hepatology, "Sestre milosrdnice" Clinical Hospital Center in Zagreb, Croatia. An additional sample of colon mucosa was collected in the proximity of the removed colorectal adenoma for further pathohistological analysis. Adenomas were graded according to the stage of dysplasia, and ghrelin and ghrelin receptor expression were determined immunohistochemically in both adenoma and adjacent colon tissue using the polyclonal antibody for ghrelin and ghrelin receptor.

Research results

High expression of ghrelin was 7 times more common in high-grade adenoma compared to low-grade adenomas (13.95% to 2.04%, $P = 0.048$), while the expression of ghrelin in adjacent colon tissue was low. We found no correlation between ghrelin receptor expression in adenoma and adjacent colon tissue and the grade of colorectal adenoma dysplasia. The most significant correlation was found between ghrelin and

ghrelin receptor expression in adenomas with high-grade dysplasia (rho = 0.519, $P < 0.001$).

Research conclusions

Our study is the first to show that ghrelin and ghrelin receptor are expressed in colorectal adenomas and adjacent tissue. We found that ghrelin expression was more pronounced in adenomas with high-grade dysplasia compared to those with low-grade dysplasia. The results of this study underline the importance of ghrelin in progression of dysplasia in colorectal adenoma but there is a need for further studies to determine the expression of different subtypes of ghrelin receptors in colorectal adenomas and exact ghrelin receptors role.

Research perspectives

Ghrelin and metabolic syndrome role in general need to be adequately investigated in colorectal adenoma progression since we are experiencing an epidemic of colorectal carcinoma intertwined with an epidemic of obesity. We believe that obtaining more insight into this problem could help us to better understand the dysplasia progression pathways, influence the surveillance programs and guidelines, and in that way ensure early recognition of patients in greater risk for colorectal carcinoma development.

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2021 December 27; 13(12): 1721-1735

DOI: 10.4240/wjgs.v13.i12.1721

ISSN 1948-9366 (online)

SYSTEMATIC REVIEWS

Right sided diverticulitis in western countries: A review

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Conflict-of-interest statement: All the authors declare that they have no competing interests.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: Italy

Specialty type: Surgery

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

Peer-review model: Single blind

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Abstract

BACKGROUND

Although the treatment guidelines for left sided diverticulitis are clear, the management of right colonic diverticulitis is not well established. This disease can no longer be ignored due to significant spread throughout Asia.

AIM

To analyse epidemiology, diagnosis and treatment of right-sided diverticulitis in western countries.

METHODS

MEDLINE and PubMed searches were performed using the key words "right-sided diverticulitis'', ''right colon diverticulitis'', ''caecal diverticulitis'', ''ascending colon diverticulitis'' and ''caecum diverticula'' in order to find relevant articles published until 2021.

RESULTS

A total of 18 studies with 422 patients were found. Correct diagnosis was made only in 32.2%, mostly intraoperatively or *via* CT scan. The main reason for misdiagnosis was a suspected acute appendicitis (56.8%). The treatment was a non-operative management (NOM) in 184 patients (43.6%) and surgical in 238 patients (56.4%), seven of which after NOM failure. Recurrence rate was low (5.45%), similar to eastern studies and inferior to left -sided diverticulitis. Recurrent patients were successfully conservatively retreated in most cases.

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

Received: March 30, 2021
Peer-review started: March 30, 2021
First decision: May 13, 2021
Revised: May 28, 2021
Accepted: November 30, 2021
Article in press: November 30, 2021
Published online: December 27, 2021

P-Reviewer: Preda SD, Sasaki Y
S-Editor: Ma YJ
L-Editor: Filipodia
P-Editor: Ma YJ

CONCLUSION
The management of right- sided diverticulitis is not well clarified in the western world and no selective guidelines have been considered even if principles are similar to those with left- sided diverticulitis. Wrong diagnosis is one of the most important problems and CT scan seems to be the best imaging modality. NOM offers a safe and effective treatment; surgery should be considered only in cases of complicated diverticulitis or if malignancy cannot be excluded. Further studies are needed to clarify the correct treatment.

Key Words: Right-sided diverticulitis; Cecal diverticulitis; Right colonic diverticulitis; Western countries; Emergency surgery; Diverticulitis

Core Tip: This paper underlined the importance to collect more data on right-sided diverticulitis to understand if it is a more common condition than we thought, and if we really need more selective guidelines or we can simply apply the principles already proposed for left-sided diverticulitis.

Citation: Epifani AG, Cassini D, Cirocchi R, Accardo C, Di Candido F, Ardu M, Baldazzi G. Right sided diverticulitis in western countries: A review. *World J Gastrointest Surg* 2021; 13(12): 1721-1735
URL: https://www.wjgnet.com/1948-9366/full/v13/i12/1721.htm
DOI: https://dx.doi.org/10.4240/wjgs.v13.i12.1721

INTRODUCTION

Historically, diverticula in western countries are mostly located in sigmoid colon while right-sided diverticulosis (RSD) is rare. Conversely, colonic diverticula are mostly located on the right colon in eastern patients in contrast to those in Europe and the United States[1,2]. Recently several studies show an important spread of RSD in the world over Asia[3-5].

Regarding the diverticula of the right colon, we differentiate the diverticula of the cecum (solitary or multiple) and the ascending colon. In 1912, Potier[6] first described a case of cecum diverticulum. While the first case of diverticulitis in the ascending colon was described by Telling *et al*[7] in 1916, in this review we analyzed both subtypes.

The etiology and the real prevalence of this difference is still unclear. All studies about management of acute right-sided colonic diverticulitis (ARCD) are related to the Asian population and no specific guidelines are still available. The aim of the present study was to review epidemiology, diagnosis and treatment of ARCD to better analyze this disease in Western populations.

MATERIALS AND METHODS

Literature search

An extensive search for literature was carried out using MEDLINE (PubMed) and Cochrane Database of Collected Reviews for potentially relevant studies between January 1, 1990, and January 1, 2021.

The terms used for the search were: ''right-sided diverticulitis'', ''right colon diverticulitis'', ''caecal diverticulitis'', ''ascending colon diverticulitis'' and ''caecum diverticula''.

Exclusion criteria were studies based on the Asian population, left-sided diverticulitis, undefined laterality or both left-sided and right-sided diverticulitis, irrelevant publications, age < 18 years. Articles not written in English or full text not available as well as case reports and case series (< 5 patients), review articles and letters to the editor were excluded.

Right-sided laterality was defined as diverticulitis involving the cecum or the ascending colon until hepatic flexure.

"Correct diagnosis" was defined as radiologically confirmed diagnosis of diverticulitis, before any medical or surgical treatment.

"Presumptive diagnosis" was defined as diagnosis of diverticulitis deemed likely despite the absence of radiological confirmation, before any medical or surgical treatment.

"Diagnostic accuracy" was defined as the rate of correct diagnosis over the total number of patients analyzed.

"Non-operative management" was defined as any treatment not requiring surgery (*e.g.*, bowel rest, antibiotics with or without percutaneous drainage).

Two reviewers (Epifani AG, Accardo C) will independently have screened titles and abstracts, evaluating the full text of potentially eligible studies. Any doubt or disagreements has been resolved by a third reviewer (Cassini D).

We included studies from Turkey because geopolitically it is also a European country and from Israel because most people are Caucasian with similar lifestyles to western countries and finally from Qatar because of their westernized diet and lifestyle.

We excluded the review by Schlussel *et al*[8] because their study included patients from the NIS database which is based on the international statistical classification of diseases and related health problems (ICD) coding method. By selecting the cases in this way it has not been possible to argue many of their results and we have not been able to do an adequate data extraction. Furthermore, lacking a specific code for coding ARCD, the low accuracy of this research method was also highlighted in another study in which the authors who had initially screened ARCD with ICD codes, found a high percentage of misdiagnosed cases (74%) when they subsequently analyzed every medical chart[9].

Statistical analysis

We analyzed data regarding study design, number of patients, demographic characteristics (age, sex), location of diverticula, diagnostic evaluation methods, misdiagnosis and modified Hinchey classification[10]. We also analysed data regarding the treatment distinguished between non-operative management (NOM) (every treatment not requiring surgery, *e.g.*, bowel rest, antibiotic, percutaneous drainage) and surgery (reporting every procedure and relative approach). We therefore analysed short-term and long-term outcomes: length of stay, complications, reintervention, need for ostomy, death, recurrence (rate and type of treatment) and median follow-up. Data were analyzed with descriptive statistics.

Primary outcome was the analysis of short-term and long-term outcomes, especially regarding recurrence rate. The secondary outcome was the evaluation of diagnosis methods and percentage of misdiagnosis.

Quality of studies were evaluated by a methodological index for non-randomized studies (MINORS) score[11]. MINORS is a valid tool to easily assess the quality of non-randomized surgical studies both comparative or not (with a maximum score of 24 and 16, respectively). Of the 18 included studies, 16 had a retrospective cohort design and 2 had a retrospective cross-sectional design.

RESULTS

With our research we initially found 1375 articles. After removing 55 duplicates, we screened titles and abstracts excluding 1188 other articles. We therefore evaluated 130 full-text reviews and obtained 18 eligible studies. The entire process of screening is shown in Figure 1[9,12-28].

We analysed 18 studies, for a total of 422 patients. A summary of results is shown in Table 1, Table 2, Table 3, and Table 4[9,12-28] and in Figure 2. There were 212 females (50.2%) and 190 males (45%), however in 20 patients (4.7%) sex was not recorded. Mean patient age was 50.9 years (range: 30-65).

The diagnosis was correctly achieved or presumed in 136 cases (32.2%), *via* CT scan in 96 cases (70.6%), by sonography in 17 cases (12.5%), and rarely by barium enema (4 cases, 2.9%), radiography or colonoscopy (one case each, accounting for 0.2%).

A correct diagnosis was achieved only intraoperatively in 98 cases (23%), while a misdiagnosis occurred in 162 cases (38.4%), 92 of which were suspected acute appendicitis.

Table 1 Study characteristics

Ref.	Year	Country	Numbers of patients	Minors	Follow-up (Mo)	Age	Male	Unc[1] or Hinchey I/II	Hinchey III/IV	LOS[2] (d)	Total recurrence (rate)
Lane *et al*[12]	1999	United States	49	7		32	30			12.7	4 (8.16%)
Violi *et al*[13]	2000	Italy	20	5							0
Junge *et al*[14]	2003	Germany	7	7	42	56	1				
Papaziogas *et al*[15]	2005	Greece	8	10	174	54.2	6			22	1
Hildebrand *et al*[16]	2007	Germany	16	16		60.9	4			11	
Radhi *et al*[17]	2011	Canada	15	7		65	6				
Issa *et al*[18]	2012	Israel	15	12	32	52	10	15			1 (6%)
Kalcan *et al*[19]	2015	Turkey	6	8	6	34	4			4.5	
Hot *et al*[20]	2015	Turkey	10	11	60	38.9	5			5	
Cristaudo *et al*[21]	2015	Australia	13	11	12	44	8			4	0
Koshy *et al*[22]	2016	Qatar	10	11	18	30.4	9				0
Monari *et al*[23]	2017	Italy	18	11	29	50	10				0
Yardimci *et al*[24]	2017	Turkey	12	12	5.5	45	6	12			0
Al-Temimi *et al*[9]	2018	United States	33	17		56	13	20	9	7.6	
Courtot *et al*[25]	2019	France	93	12	33	54	58	30	4		7
Destek *et al*[26]	2019	Turkey	22	11	24	50.9	13	22			4
Kaya *et al*[27]	2020	Turkey	11	12	52		7			4.6	1
Zuckerman *et al*[28]	2020	United States	64	13	74.4	51.2	27	60	4	5	5
Tot	29 yr	10	422		32	50.9	190 (45.2%)	179	20	5	23 (5.45%)

[1]Uncomplicated.
[2]Length of stay.
MINORS: Methodological index for non-randomized studies.

Diverticula were caecal in 142 cases (33.6%), located in the right colon in 41 cases (12%), mixed in 3 cases and also 54 patients (12.8%) had left-sided diverticulosis (LSD). The exact location of right-sided diverticula (whether cecal or ascending) was not reported in 242 cases (57.3%). When reported, Hinchey classification was the most used scale (42%). They have reported 159 Hinchey I/II or uncomplicated diverticulitis, 17 Hinchey III and 3 Hinchey IV cases. Misdiagnosis occurred in 131 out of 219 patients (59.8%).

The treatment was NOM in 184 patients (median 43.6%) and surgery in 238 patients (56.4%), seven of which after NOM failure (2.94%). Surgical approach was open in 122 cases (51.2%) and laparoscopic in 70 patients (with a conversion rate of 28.6%).

Regarding surgical procedures: diverticulectomy in 30 patients; primary resection and anastomoses (PRA) in 182 patients (76.4%): when specified we found 31 ileocecal resections and 151 right hemicolectomies. In 33 cases an appendectomy was performed and 17 cases were associated with diverticulectomy.

Regarding post-operative complications, 45 adverse events were recorded (even if the surgical ones are not always differentiated) (10.7%), five diverting stoma were created (1.18%) and six reoperations were needed (2.5% of surgically treated patients). No deaths were reported. The mean length of hospital stay was 5 d (range: 4–22 d),

Table 2 Diagnosis

Ref.	Year	Country	Numbers of patients	Diagnosis pre-op[1]	Ultrasound	CT	Barium enema	Other	Diagn intra-op[2]	Misdiagnosis (appendicitis)	Cecum (solitary)	Right	PAN-Div[3]
Lane *et al*[12]	1999	United States	49	3		2	1		41	46 (nr)	49 (37)	0	
Violi *et al*[13]	2000	Italy	20	5	3	3	3			11			
Junge *et al*[14]	2003	Germany	7	2		2			7	5 (4)	7 (6)		
Papaziogas *et al*[15]	2005	Greece	8	0						7 (7)	8 (nr)		2
Hildebrand *et al*[16]	2007	Germany	16	7						9 (5)			
Radhi *et al*[17]	2011	Canada	15										
Issa *et al*[18]	2012	Israel	15	15		15					3	9	3
Kalcan *et al*[19]	2015	Turkey	6	0					4	6	6		
Hot *et al*[20]	2015	Turkey	10	1					10	9 (9)	10 (10)		
Cristaudo *et al*[21]	2015	Australia	13	10	1	9			3	3 (3)	13		
Koshy *et al*[22]	2016	Qatar	10	1		1			9	9 (9)			
Monari *et al*[23]	2017	Italy	18	9	1	6	1	1 XR 1 colon	9	9	11	7	
Yardimci *et al*[24]	2017	Turkey	12	12	10	2							
Al-Temimi *et al*[9]	2018	United States	33	13						20 (11)			
Courtot *et al*[25]	2019	France	93							6 (6)			49
Destek *et al*[26]	2019	Turkey	22							2 (2)	9	13	
Kaya *et al*[27]	2020	Turkey	11	8	2	6				5 (5)	6		
Zuckerman *et al*[28]	2020	United States	64	50		50			11	15 (10)	33	22	
Tot	29 yr	10	422	136 32.2%	17 12.5%	96 70.6%	4 2.9%	2 1.9%	98 (23.2%)	162 (92) 38.39%	155 (97) 36.7%	51 12%	54 12.8%

[1]Pre-operatively diagnosis.
[2]Intra-operatively diagnosis.
[3]Pan-diverticulosis (diverticulosis in all colonic segments).

CT: Computed tomography.

Table 3 Treatment and outcome

Ref.	Year	Country	Numbers of patients	NOM	Surgery	Surgery after NOM	Complications	Re-intervention	Death	Recurr[1] after NOM	Recurr[1] after Surg[2]	Recurr[1] treatment
Lane *et al*[12]	1999	United States	49	0	49		7	4	0		4	4 Surg[2]
Violi *et al*[13]	2000	Italy	20	0	20						0	
Junge *et al*[14]	2003	Germany	7	0	7							
Papaziogas *et al*[15]	2005	Greece	8	0	8						1	1 NOM
Hildebrand *et al*[16]	2007	Germany	16		16		0					
Radhi *et al* [17]	2011	Canada	15		15							
Issa *et al*[18]	2012	Israel	15	15						1		1 NOM
Kalcan *et al*[19]	2015	Turkey	6		6							
Hot *et al*[20]	2015	Turkey	10		10		0	0	0		0	
Cristaudo *et al*[21]	2015	Australia	13	10	3					0	0	
Koshy *et al*[22]	2016	Qatar	10	1	9		2			0		
Monari *et al*[23]	2017	Italy	18		18		3	0	0		0	
Yardimci *et al*[24]	2017	Turkey	12	12					0	0		
Al-Temimi *et al*[9]	2018	United States	33	4	33		10					
Courtot *et al*[25]	2019	France	93	68	25	6	19	1	0	6	1	5 NOM; 2 Surg
Destek *et al*[26]	2019	Turkey	22	19	3	0	0	0	0	4	0	4 NOM
Kaya *et al*[27]	2020	Turkey	11	6	5		2			1		1 NOM
Zuckerman *et al*[28]	2020	United States	64	49	15	1	2			5	0	4 NOM; 1 Surg
Tot	29 yr	10	422	184 (43.6%)	238 (56.4%)	7 (2.9%)	45 (10.6%)	6 (2.5%)	0	17 (6%)	6 (2.5%)	16 NOM; 7 Surg

[1]Recurrence.
[2]Surgery.
NOM: Non operative management.

Table 4 Surgical procedures

Ref.	Year	Country	Numbers of patients	DIV	AP	DIV + AP	ICR	Right colectomy	Ostomy	Open	VLS	Converted (rate)
Lane *et al*[12]	1999	United States	49	7	3			39	1	49		
Violi *et al*[13]	2000	Italy	20	6				14				
Junge *et al*[14]	2003	Germany	7				6	1	0			
Papaziogas *et al*[15]	2005	Greece	8	6		0	2		0	8		
Hildebrand *et al*[16]	2007	Germany	16				3	16	0	15		
Radhi *et a* [17]	2011	Canada	15					15			15	1 (6%)
Issa *et al*[18]	2012	Israel	15									
Kalcan *et al*[19]	2015	Turkey	6			5		1		4	2	2 (100%)
Hot *et al*[20]	2015	Turkey	10	1		9			0	10		
Cristaudo *et al*[21]	2015	Australia	13		2			1			3	1 (33.3%)
Koshy *et al*[22]	2016	Qatar	10		5		4				9	4 (44.4%)
Monari *et al*[23]	2017	Italy	18	5			4	9	0	4	14	5 (35.7%)
Yardimci *et al*[24]	2017	Turkey	12									
Al-Temimi *et al*[9]	2018	United States	33	4				29	2	23	10	2 (20%)
Courtot *et al*[25]	2019	France	93	1	2		6	16	2	9	16	5 (31%)
Destek *et al*[26]	2019	Turkey	22		2			1	0			
Kaya *et al*[27]	2020	Turkey	11		2	2		1				
Zuckerman *et al*[28]	2020	United States	64				6	8				
Tot	29 yr	10	422	30 12.6%	16 6.7%	17 7.1%	31 13%	151 63.4%	5 2.1%	122 63.5%	70 36.5%	20 28.6%

DIV: Diverticulectomy; AP: Appendectomy; ICR: Ileocecal resection; VLS: Videolaparoscopy.

and the median follow-up was 32.5 mo (range: 5–174 mo).

Recurrence occurred in 23 cases (5.45%), sixteen of which after NOM (3.8% of total, 5.98% of NOM cases), six after surgery (1.4% total, 2.5% of surgery cases) and in one case was not reported if recurrence occurred after NOM or surgery failure (treated with antibiotic). In the other cases, treatment after NOM was NOM again in 13 cases, while three patients underwent surgery; as well as two patients after surgery were treated *via* NOM and four patients underwent surgery again.

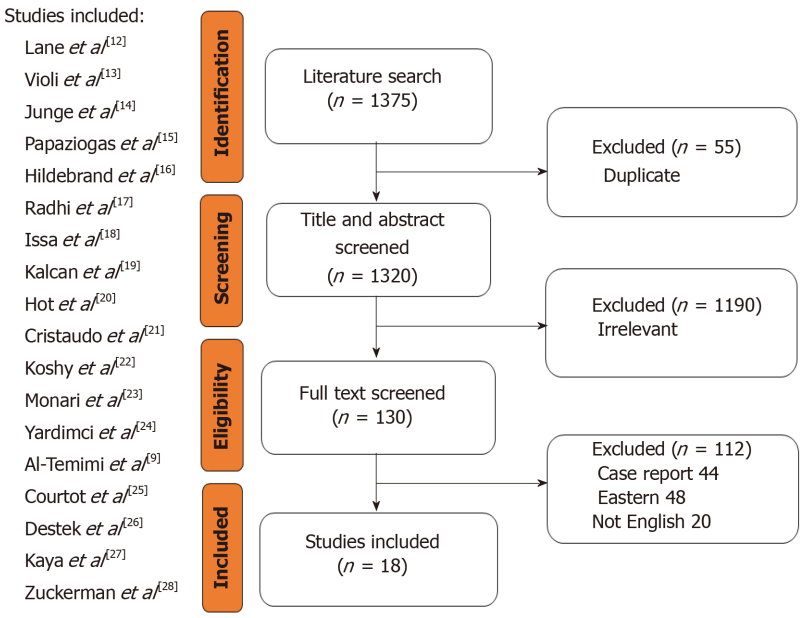

Figure 1 Process of studies screening.

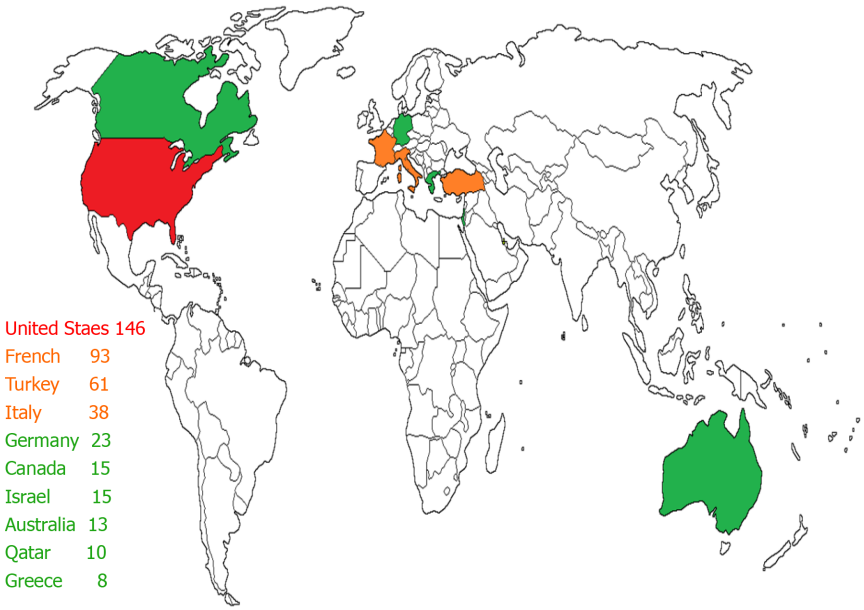

Figure 2 World map of included studies: number of patients in each country.

DISCUSSION

Background

Diverticula presents as herniations of the bowel wall, mostly located in areas of structural weakness, such as the site of vessel penetrance. The bowel in diverticular disease patients appears shortened and shows thickened circular and longitudinal muscle layers due to elastosis. Patients with diverticular disease showed also irregular muscle bundle orientation, reduced myosin (MYH11) heavy chain gene expression, enhanced collagen crosslinking, which all contribute to the risk for bowel wall herniation[29-31].

Other relevant factors involved in the development of diverticular are abnormal bowel motility (due to altered enteric nervous system), gut microbiome, low fiber intake and western lifestyle[5-8].

Historically, RSD have been considered congenital and true (made of all layers) as opposed to LSD considered to be mostly acquired and false (made of mucosa and

muscularis mucosa)[1,32,33]. Instead, according to further studies was found that most [34,35] or even all[36,37] of the cases of RSD were actually false, both solitary and multiple. This demonstrates that the underlying pathophysiology has not yet been fully clarified and that the etiology of diverticular disease on the right-side and left-side is probably more similar than we think.

The incidence of diverticular disease has been increasing in both Europe and the United States[3]. Although acute right-sided colonic diverticulitis (ARCD) is still considered a rare disease in the western world, the real incidence is not that rare[38] ranging from 5% to 20%[3,5,28,39].

Historically, a century ago it was seen in early studies that the prevalence of RSD was higher than expected (2%-5%)[40,41]. As early as 1961, Miangolarra[42] firstly describes the diverticulitis of the right colon as "an important surgical problem".

Nevertheless, the evidence of ARCD is almost exclusively based on single-center or case reports. In fact, we found only 5 studies reporting more than 20 patients, demonstrating that it is not a widespread reality and that it is often managed according to individual surgeons[9,12,25,26,28].

In patients affected by ARCD we found that the median age was 50.9 years and was higher in patients with the Hinchey stage II than Hinchey I (45.7 *vs* 63, 57 years)[26]. Also, in comparison studies, we found an earlier onset than LSD (53 *vs* 64 years)[16,23,28].

Diagnosis

Patients affected by ARCD typically presented at the emergency department with fever, pain in the right iliac fossa and often signs of peritoneal irritation. Blood tests show leukocytosis and increased C-reactive protein[12-15,18,19,24-27]. Similar symptoms and young age are confounding factors and they can be wrongly identified with the diagnosis of acute appendicitis in most of the cases described[14,15,17,22].

Recently Zuckerman *et al*[28] reported that 67% of patients underwent an operation for a misdiagnosis of appendicitis. This illustrates the importance of accurate diagnostic criteria to avoid unnecessary appendectomy or even a right hemicolectomy.

In fact, the diagnostic accuracy we calculate in all the studies is a poor 32.2%, when the reported misdiagnosis rate is 38.39% (162 cases), where 56.79% of the time (92 cases) diagnosis is clearly mistaken for acute appendicitis.

Effective diagnosis is therefore the main achilles heel of ARCD. In some studies, nuanced differences emerge in the clinical presentation that could help us in the differential diagnosis such as the longer duration of symptoms[26], the presence of diarrhea in the weeks preceding the pain[21] and the absence of nausea and vomiting[20,23]. Making the correct diagnosis can be very difficult relying only on the clinical evaluation especially if we consider that the Alvarado score shows a poor negative predicting value in distinguishing acute appendicitis from ARCD[23].

The awareness of this condition and the use of the correct imaging can help us to increase the rate of correct diagnosis. So, in the Kalcan study there was a 100% misdiagnosis rate because no physician did radiological investigations[19].

According to Wilson *et al*[43], it is possible to make an ultrasound diagnosis of diverticulitis when there are two of the following features: thickening of the wall (≥ 4 mm), diverticula with signs of inflammation, inflammatory modifications in the pericolic fat, pericolic or intramural inflammatory mass and intramural fistulas.

We know that in expert hands sonography may allow a correct diagnosis of ARCD, directly or suspected by indirect sign[15]. We also know that has a limited utility in obese patients and is user dependent[24,32,44]; and especially in emergency cases, diagnosis of ARCD can be even more difficult without more advanced and objective imaging exams such as CT scan[19]. Therefore, the ultrasound should not be the only imaging technique in a case of suspected diverticulitis and magnetic resonance imaging (MRI) might be useful when CT is contraindicated[45,46]. Nevertheless, MRI is not always available in the emergency setting and rarely used[47]. In particular, in patients presenting with right lower abdominal pain, thin-section helical CT scan may identify or exclude other clinical conditions[48].

For both sonography and CT there are very specific diagnostic criteria for ARCD such as colonic wall thickening and edema, pericolic fat infiltration or abscess and extraluminal air around the colon[24].

In our review only 12.5% of cases were diagnosed *via* sonography compared to 70.6% of correct CT-driven diagnosis; while other methods of diagnosis have rarely been effective.

The importance of tomography is clear in the article by Cristaudo *et al*[21] in which CT scan was necessary to detect the pathology in 90% of cases. Also, in the study of Kaya *et al*[27] in which CT scan recognized aggressive liver cancer domains (ALCDs)

where the sonography failed. Moreover, the CT scan shows the exact extent of the degree of inflammation in order to be able to accurately plan any surgical intervention [16].

Certainly, the diffusion and accessibility of this imaging technique improved the diagnostic accuracy, as can be seen from the increase in the diagnosis rate in two periods, before and after 2007, in Zuckerman's study[28].

Finally, when surgical exploration may be the only way to obtain an effective diagnosis and allow the most adequate treatment then the minimally invasive approach may be the most suitable way to do it[23].

Treatment

For the first time, in the latest WSES 2020 update for the management of acute colonic diverticulitis in the emergency setting, ARCD is defined as a distinct clinical entity and the principles of diagnosis and treatment are suggested to be similar to those in ALCD. However, patients with RCD require surgery less often than patients with ALCD, but their management is not well defined, and no unique guidelines have been proposed until now[49].

The correct diagnosis is very important because it allows a conservative management to successfully treat uncomplicated ARCD (uARCD)[21,24,25].

But historically the treatment of ARCD has been mostly surgical and it has always remained at the discretion of the surgeon since the first reported surgical treatment of acute right-side diverticulitis was made by an American surgeon in 1954[50].

As for surgical treatment, there are multiple options for complicated forms such as conservative (appendectomy), limited (diverticulectomy), or extensive (ileocecal resection or right hemicolectomy[12,32,51].

Mostly the indication for surgery was secondary to a wrong diagnosis, leading to the aggressive choice of surgical procedures based on the intraoperative findings[16,23,25]. Lane *et al*[12] for example advocated diverticulectomy in cases of a solitary diverticulum, and immediate right hemicolectomy in the case of cecal phlegmon or multiple diverticula.

Over the years, the interventions have been less and more reasoned. If the inflamed area was limited, then a narrow diverticulum resection has been proposed as a safe and effective technique[20,23]. And this attitude was confirmed after a 14-year follow-up study, with a unique case of recurrence 8 years after the reported episode[15].

Furthermore, removing the appendix was also useful for two reasons. First, there was a "contiguous appendicitis" secondary to diverticular inflammation[15,25] and second because the removal of the appendix would have allowed a simpler diagnosis in case of a new episode of pain in the right iliac fossa[19,22,27].

As much as 40% of ARCD patients underwent right hemicolectomy after finding a mass mimicking colon cancer[32]. It is also true that in some cases the histological analysis on the surgical specimen found the presence of adenocarcinoma of the cecum associated with multiple diverticula[17]. According to Radhi *et al*[17], single diverticula are more present in young patients and tend to be symptomatic, while multiple diverticula are incidental findings or associated with carcinoma in older patients.

Intraoperative findings of suspected tumors or complicated patients with significant extent of diverticulitis remained therefore the only reasons for extensive surgery[15,16,19,20] and could potentially avoid a formation of diverting stoma[9].

Analyzing our research, we found a very low number of stoma (1.18%) and reoperations needed (2.5%). Furthermore, our results agree with the recent studies which shows that need for ostomy was significantly less frequent in the ARCD group than ALCD (6.3% *vs* 62.5%) probably also due to the more favorable anatomical location of right colon (being retroperitoneal may limit the spread of inflammation in contrast to sigmoid colon) with ileocolic anastomosis burdened by a lower risk of leak compared to the colorectal ones[52].

Although the use of laparoscopy was often secondary to a wrong diagnosis of acute appendicitis[9], since the first laparoscopic diverticulectomy was performed in 1994 [53], a more careful selection of patients allowed in experienced hands to perform even colonic resection with primary anastomosis with minimally invasive approach[16,23].

Conversion was mainly due to the detection of small bowel dilatation or difficult clinical picture such as free fluid or big abscess when laparoscopic approach was initially chosen to perform appendectomy instead[23].

Finally, Hildebrand *et al*[16] stated that there was no big difference in the treatment of right-sided diverticulitis compared to left-sided diverticulitis. We confirm his conclusion, and we report in Figure 3 a synthesis of the therapeutic options highlighted in the therapeutic diagnostic algorithm inspired by the study of Kaya *et al*

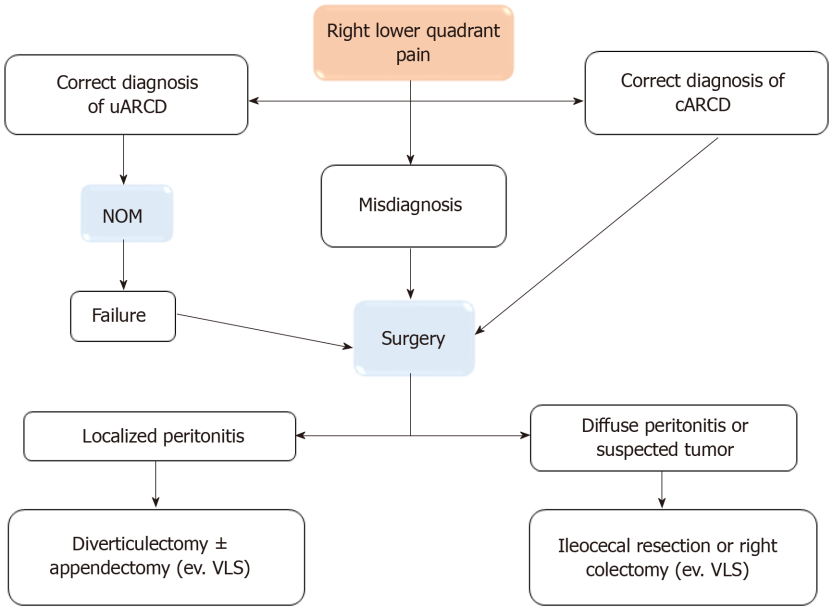

Figure 3 Diagnostic-therapeutic algorithm. uARCD: Uncomplicated acute right-sided colonic diverticulitis; NOM: Non-operative management; cARCD: Complicated acute right-sided colonic diverticulitis; VLS: Videolaparoscopy.

[27].

Outcomes

In our review we found a low recurrence rate (5.45%). Cristaudo *et al*[21] and Yardımcı *et al*[24] had no recurrence at all after NOM management, demonstrating the benign course of the disease. Other studies had a low range of recurrence (6%-21%). In fact, in the 23 cases of recurrence reported, 16 of which were successfully treated conservatively again[15,18,25-28]; seven cases of recurrence underwent surgery[12] and only two cases occurred after a previous NOM[25,28].

Eastern studies also show similar recurrence rate (1%-20.5%) after conservative management both for uncomplicated and recurrent RCD[54-56].

Zuckerman *et al*[28] also show a lower recurrence rate after ARCD compared with ALCD (4.1% *vs* 32.8%).

Furthermore, according to the analysis of Imaeda *et al*[1], there are fewer complicated RCDs than liver cancer domains (LCDs). In fact, the complication rate was also low (10.66%), with only 1.66% of major complications according to Clavien Dindo (CD) classifications (six reported CD 3 complications and only one CD4)[12,22,23,25].

A very important aspect was demonstrated by Courtot *et al*[25]as the recurrence rate was low and similar for both complicated and uncomplicated ARCD (6.8% and 8.8%, respectively) demonstrating the benign course of this condition.

Furthermore, in the Zuckerman *et al*[28] study it is shown that 5% of patients with an initial diagnosis of RCD subsequently developed colon cancer. And being a higher rate than average-risk[57], an endoscopic screening program for these patients could be scheduled.

Confront vs east

Although the incidence of RSD is much higher in Asian countries, we have not found specific guidelines. Nonetheless, several authors have published studies showing their management for this condition.

For example, in two important studies the authors show that most cases of ARCD are uncomplicated (78.5% and 92.8%) and that they are successfully treated conservatively (reaching as much as 98% of cases)[58,59]. NOM is also effective in 41.7% of complicated ARCD (cARCD), reserving surgery only in the remaining cases and making it possible to convert an urgent intervention into an elective one.

In support of the efficacy of conservative treatment, two recent meta-analysis show similar results. In particular, they show a low recurrence rate after uncomplicated ARCD (10.9% and 12%). The first study[60] focused on the fact that only 4.4% of recurrences were complicated and there was only a 1.7% of re-recurrence rate. While the second[61] showed that only a small percentage of patients underwent surgery after recurrence (9.9% as urgent cases, 5.4% as elective cases). Both authors conclude

that NOM is safe and feasible for Hinchey 1b-2 stages, similarly to the management of uncomplicated left-sided diverticulitis, while surgery should only be performed in selected cases.

The effectiveness of the NOM is even the background from which the authors started to design a prospective randomised controlled trial (RCT). Kim *et al*[62] compared the conservative treatment of uARCD with or without antibiotic obtaining similar results regarding to treatment failure rates (4.7% *vs* 1.6%), length of hospital stay and recurrence rate (7.8% *vs* 9.8%). Moreover, the group without antibiotics was burdened by a lower cost.

In the only recent study that defends the surgical approach, Luu *et al*[63] stated that laparoscopic diverticulectomy could be offered to selected patients (younger patients, who live in remote areas or with higher risks of recurrence). The author points out that, compared to conservative management, minimally invasive approach has similar outcomes in terms of complications (12.2% *vs* 8.6%) and treatment failure (13.5% *vs* 9.9%) and with a lower recurrence rate (0% *vs* 16.6%).

In this regard, there is some confusion on the main predictors of recurrence. In another study, multiple diverticula were found to be the main reason[64]. But this result seems to be disproved in the aforementioned RCT of Luu *et al*[63] in which fever and markers for inflammation were predictive, instead[62]. Other predictors were young age and longer duration of symptoms before hospital admission[65].

CONCLUSION

The management of ARCD remains a great challenge for surgeons. Although recent updates of WSES guidelines suggest that all the statements for ALCD may also apply to ARCD, several topics need to be investigated. Lack of diagnosis is the most important problem and CT scan seems to be the best imaging modality. NOM remains the preferred treatment in uncomplicated cases, whereas surgery should be considered in unstable patients or complicated disease. Laparoscopic approach should be offered whenever it is feasible. Further studies are needed in order to understand epidemiology, diagnosis and optimal management of this rare condition.

This review underlines the importance to collect more data, especially in western countries, to understand if it's a condition more common than we thought, and if we really need more selective guidelines or we can simply apply the principles already proposed for left side diverticulitis.

ARTICLE HIGHLIGHTS

Research background

Right sided diverticulitis is very frequent in Asian countries, while in western countries it has always been considered very rare. On the other hand, in recent studies, the condition has been shown to be increasing in recent years.

Research motivation

Despite this rapid spread, there are no clear guidelines on the management of RSD. Until now, their management has been based on knowledge gained from left sided diverticulitis.

Research objectives

The authors therefore wanted to analyze the studies in the literature to have a broader and deeper point of view to understand what could be the correct management.

Research methods

The authors analyzed the articles from western countries starting from 1990 in which the management and the subsequent outcome of right sided diverticulitis were shown.

Research results

The authors found that most cases of right colonic diverticulitis are treated effectively with non-operative management, reserving surgical treatment especially for complicated cases. Recurrences have a low rate and are also successfully treated conservatively.

Research conclusions

Right sided diverticulitis has a similar management in both western and Asian countries.

Research perspectives

Further studies will serve to identify more precisely which cases should be reserved for surgical treatment.

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2021 December 27; 13(12): 1736-1753

DOI: 10.4240/wjgs.v13.i12.1736

ISSN 1948-9366 (online)

SYSTEMATIC REVIEWS

Platelet rich plasma effectiveness in bowel anastomoses: A systematic review

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Author contributions: Geropoulos G, Psarras K and Giannis D equally contributed to this study; Geropoulos G, Giannis D and Psarras K designed the research; Papaioanou M, Martzivanou EC and Kakos CD performed the research; Geropoulos G, Giannis D, Psarras K and Papaioanou M wrote the paper; Martzivanou EC, Pavlidis ET and Symeonidis N analyzed the data; Koliakos G and Pavlidis TE supervised the paper; all authors read and approved the final manuscript.

Conflict-of-interest statement: The authors declared no potential conflicts of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript

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Abstract

BACKGROUND

Anastomotic leak constitutes a major problem in abdominal surgery. Technical insufficiency, topical or systemic factors contribute to disrupted healing of the performed bowel anastomosis and result in anastomosis leakage, with detrimental effects on patient postoperative outcomes. Despite the investigation of several factors and the invention of protective materials, the ideal agent to prevent anastomotic leaks is yet to be determined.

AIM

To study the effect of platelet rich plasma (PRP) on the healing of bowel anastomoses.

METHODS

A systematic literature search was performed in PubMed, EMBASE, and Scopus

was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: United States

Specialty type: Gastroenterology and hepatology

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

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

Received: April 19, 2021
Peer-review started: April 19, 2021
First decision: July 27, 2021
Revised: August 11, 2021
Accepted: November 18, 2021
Article in press: November 18, 2021
Published online: December 27, 2021

P-Reviewer: Yasukawa K
S-Editor: Gao CC
L-Editor: A
P-Editor: Gao CC

databases to identify studies investigating the effect of PRP application on bowel anastomosis.

RESULTS
Eighteen studies were eligible with a total population of 712 animals including rats (14 studies), rabbits (2 studies) and pigs (2 studies). No postoperative complications were reported following PRP application. Fourteen out of 18 studies reported a statistically significant higher anastomosis bursting pressure in PRP groups compared to control either in healthy animals or animal models with underlying condition or intervention, such as intraperitoneal chemotherapy or peritonitis. Similar results were reported by ten studies in terms of tissue hydroxyproline levels. One study reported significant increase in collagen deposition in PRP groups. PRP application resulted in significantly decreased inflammatory cell infiltration in the presence of peritonitis or intraperitoneal chemotherapy (6 studies).

CONCLUSION
The application of PRP is associated with improved bowel anastomosis outcomes, especially in animal models having an underlying condition affecting the normal healing process. PRP application seems to augment the normal healing process under these circumstances. However, further studies are needed to investigate the potential role of PRP on bowel anastomosis healing, especially in clinical settings.

Key Words: Platelet rich plasma; Colonic anastomosis; Small bowel anastomosis; Large bowel anastomosis; Bowel anastomosis; Surgery

Core Tip: The positive effect of platelet rich plasma (PRP) in bowel anastomoses has been shown by several studies. The application of PRP in bowel anastomoses in the presence of impaired wound healing conditions like ischemia, infection or chemotherapy significantly improved anastomosis burst pressure and tissue hydroxyproline, two of the most common used parameters to test anastomosis integrity. The current literature supports the effectiveness of PRP in animal models. Further studies are needed in order to determine the potential role of PRP in clinical practice.

Citation: Geropoulos G, Psarras K, Giannis D, Martzivanou EC, Papaioannou M, Kakos CD, Pavlidis ET, Symeonidis N, Koliakos G, Pavlidis TE. Platelet rich plasma effectiveness in bowel anastomoses: A systematic review. *World J Gastrointest Surg* 2021; 13(12): 1736-1753
URL: https://www.wjgnet.com/1948-9366/full/v13/i12/1736.htm
DOI: https://dx.doi.org/10.4240/wjgs.v13.i12.1736

INTRODUCTION

Bowel anastomosis related complications are frequently encountered in patients undergoing major abdominal surgery involving bowel excision. Anastomotic leak seems to be the most common complication and its rate is approximately 10% in operations involving bowel anastomosis[1-4]. However, in the presence of an underlying condition, such as malignancy or intraperitoneal hyperthermic chemotherapy, an anastomotic leak may occur in up to 25% of the cases[5-7]. Multiple factors have been previously investigated and have been proven to affect the integrity of bowel anastomosis. Advanced age, sepsis, hypoalbuminemia, low hematocrit, immunosuppression, diabetes mellitus, and reduced blood supply are systemic factors that may negatively affect anastomotic healing[8,9]. In addition, topical factors, including suturing technique, anastomotic tension, bowel infection, fecal contamination and peritonitis, could also result in delayed healing and increase the rate of anastomotic leak[10].

Several topical mechanical and pharmaceutic agent applied to bowel anastomosis have been reported in the literature, demonstrating variable effects in the healing process of anastomoses. The vast majority of these agents have been tested in experimental animal (mainly rat) models. However, very few agents were applied to the clinical practice[9].

Platelet rich plasma (PRP) is widely used in maxillofacial reconstructive surgery, orthopedic surgery, plastic surgery, and diabetic skin ulcers with highly acceptable effects in terms of improved wound healing and tissue regeneration[11-13]. PRP is easily extracted from a small amount of peripheral blood and its production roughly requires a two-step centrifugation or even a one-step centrifugation technique[14]. The effects of PRP are mainly attributed to its endogenous concentration of growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), hepatocyte growth factor, and insulin-like growth factor (IGF)[15]. Furthermore, inflammatory biomolecules like interleukin (IL)-1β, IL-6 and IL-4 have been also reported in the PRP biochemical analysis[16].

The synergic effect of these factors modulates and/or augments angiogenesis, cell mitosis and extracellular matrix remodeling, which are processes involved in normal wound healing[17-19].

The aim of this study is to systematically review the current literature on the effects of PRP application on bowel anastomosis.

MATERIALS AND METHODS

Search strategy

This systematic review was performed according to the PRISMA guidance[20] after approval of the study protocol by all authors. A comprehensive literature search (last search date as of October 1, 2020) was performed by two researchers (Kakos CD and Martzivanou EC) in PubMed (Medline), EMBASE, and Scopus. The search term included several combinations of "platelet rich plasma", "PRP", "colon" and "anastomosis" keywords (Supplementary Table 1). A manual search was also performed using the snowball methodology to identify any relevant studies in the list of references of the included articles[21].

Study selection process

Our systematic review included retrospective animal studies that investigated the effect of PRP on bowel anastomosis. There was no restriction regarding the animal models that were used and these included healthy animals as well as animals with peritonitis or undergoing intraperitoneal chemotherapy. Studies were excluded based on the following criteria: (1) Non-available full texts; (2) Non-peer reviewed publications, including theses, conference papers, and book chapters; (3) Non-original studies, such as systematic reviews and narrative reviews; (4) Studies with non-extractable data; and (5) Studies with overlapping or duplicated data.

Data extraction

A data extraction template was created and modified based on an initial pilot testing. Three investigators (Kakos CD, Martzivanou EC and Geropoulos G) independently identified and extracted the variables of interest. Extracted variables included study details (author, year, country, study type), animal type, underlying animal condition, study subgroups, origin of PRP, preparation method of PRP, dose of PRP, PRP application technique, type of anastomosis, interval between PRP application and animal sacrifice, postoperative complications, postoperative outcomes (bursting pressure, hydroxyproline levels, adhesions) and histopathology results (inflammatory cell infiltration, necrosis, angiogenesis, edema, collagen deposition, fibrosis, fibroblast count, anastomotic epithelialization, granulation). Any discrepancies between the results of extraction were discussed and resolved, while a fourth investigator (Giannis D) was consulted if needed.

Quality assessment

The risk of bias of included studies was evaluated with the Systematic Review Centre for Laboratory animal Experimentation risk of bias tool (SYRCLE's RoB tool)[22]. The quality assessment tool is based on the Cochrane Risk Of Bias tool, but it is adjusted to estimate the risk of bias in animal/preclinical studies. Each question is answered as

"yes" (low risk of bias), "no" (high risk of bias), or "unknown" (unknown/unclear risk of bias). Two authors (Martzivanou EC and Geropoulos G) independently assessed the 10 components of the SYRCLE's RoB tool. Any conflicts were resolved by discussion with a third investigator (Giannis D).

RESULTS

Literature search, included studies and selection process

Among the 3858 studies that were identified, 2407 were screened after removal of duplicates, through the use of Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia) and manual screening of titles and abstracts[23]. According to the predefined inclusion and exclusion criteria, 26 studies were selected for full text screening. Eventually, eight studies were excluded (four studies not describing the effect of PRP on bowel anastomosis, one duplicate study published in two different journals[24,25], one comment paper, one conference paper and one letter to the editor without extractable data. After manual literature search in the references of the eligible studies, which did not provide any additional eligible studies, 18 studies were finally included in this systematic review (Figure 1). Two out of the 18 included studies investigated the effect of platelet rich fibrin (PRF), which is similar to PRP in terms of high platelet concentration. However, PRF is rich in fibrin, which is thought to trap platelets and ease the application around the anastomotic surface[16,26] (Table 1).

Surgical procedure

The majority of the studies (12 studies) investigated the effect of PRP on colonic anastomosis, while six studies investigated the effect on small bowel anastomosis[16,18,19,25,27]. End-to-end anastomosis was performed to restore the bowel continuity in all included studies. Concurrent bowel resection was reported in three studies[16,28,29]. Suturing method was continuous in four studies[16,17,28,29] or simple interrupted in six studies[18,19,30-33]. Circular stapler was used in one study[26].

PRP origin, pharmacokinetics and method of application

The origin of PRP was homologous or autologous. Autologous PRP was used in three rat studies[9,10,34], two rabbit studies[25,27] and three pig studies[19,26,28]. Daglioglu *et al*[9] and Özçay *et al*[16], in the autologous PRP group, extracted 2.5 mL and 1 mL from each rat, respectively, while Yol *et al*[10] did not report the amount of blood taken from each rat. In the pig and rabbit groups, a total of 60-100 mL and 8-10 was taken, respectively. All ten studies that investigated the effect of homologous PRP were conducted on rats[17,18,29-36] and the number of rat donors ranged from five to twelve rats, while the amount of blood drawn from each donor ranged between 5-10 mL. A two-step centrifugation technique was applied in 16 studies investigating PRP. Dauser *et al*[26] utilized a specific kit for the preparation of PRF, while Özçay *et al*[16] used an one step centrifugation technique to extract PRF.

Direct application of PRP on bowel anastomosis was mentioned in 13 studies[9,10,16,18,26,29-36], merging of the bowel edges with PRP enriched material in three studies[19,25,28], PRP injection adjacent to anastomosis in one study[25], and anastomosis performed with PRP coated sutures in two studies[17,27]. Lastly, two studies investigated PRP pharmacokinetics[18,27]. PDGF subunit A release to the media from PRP coated sutures was stable and showed no significant changes at 1, 2, 24 and 48 h post application. Similarly, the release of TGF-β1 was increased significantly in the first hour, but thereafter the release was stable without any major changes[27]. PDGF-BB and TGF-β1 showed statistically significant higher concentration in the high concentration PRP *vs* low concentration PRP and platelet poor plasma groups[18].

Postoperative outcomes and complications

In total, eight deaths were reported and included one death in the PRP group[9] and seven deaths in the comparison groups. No postoperative complications related to PRP were reported among the included studies.

Common anastomosis related parameters measured among the included studies are the anastomotic bursting pressure, tissue hydroxyproline, collagen deposition and inflammatory cell infiltration. These results are summarized in Table 2. The comparison and the associated statistical significance of PRP, control and other agents

Table 1 Basic characteristics of the included studies

Ref.	Country	Animal model (race)	Sample size (*n*)	Number of groups (*n*)	Animal per group (*n*)	Day at animal sacrification	Underlying animal condition that PRP was tested	PRP amount in anastomosis (and factors mixed with PRP)	Control	Primary comparison
Daglioglu *et al* [9], 2018	Turkey	Rat (Winstar-Albino)	36	3	12	Day 7	Normal	0.5 mL PRP	Simple end-end colon anastomosis	PRP *vs* fibrin glue
Ocak *et al*[34], 2019	Turkey	Rat (Winstar-Albino)	35	3	10	Day 7	Hyperthermic intraperitoneal chemotherapy (HIPEC)	200 μL PRP (200 μL thrombin and 100 μL calcium solution)	Hyperthermic saline after anastomosis	PRP *vs* non PRP application in rats having HIPEC with cisplatin
Yol *et al*[10], 2008	Turkey	Rat (Sprague Danwley)	30	3	10	Day 7	Normal	1 mL PRP (0.1 mL thrombin and 1 mL calcium solution)	Simple end-end colon anastomosis	PRP *vs* bioglue
Buk *et al*[35], 2020	Turkey	Rat (Winstar-Albino)	35	3	10	Day 7	HIPEC	1 mL PRP (1 mL thrombin and 0.5 mL calcium solution)	Hyperthermic saline after anastomosis	PRP *vs* non PRP application in rats having HIPEC with oxaliplatin
Dzhumabekov *et al*[25], 2019	Kazakhstan	Rabbit (Chinchillas)	81	3	27	Day 7	Normal	0.2 mL/m^2 PRP	Normal saline injected in the muscular layer of end-end small bowel anastomosis	PRP injection in bowel muscular layers *vs* soaking of bowel edges in PRP before anastomosis
Aydin *et al*[17], 2020	Turkey	Rat (Sprague Dawley)	24	3	8	Day 7	Normal	0.7 μL PRP absorbed by sutures	Simple end-end colon anastomosis	Higher *vs* lower platelet concentration PRP-impregnated vicryl sutures
Dauser *et al*[26], 2020	Austria	Pig	16	4	4	Day 0, 4, 10 and 30	Normal	PRF spray	Each group had one animal as a control: A simple anastomosis was performed with a circular stapler	PRF *vs* no PRF application tested in several postoperative days
Giusto *et al*[28], 2017	Italy	Pig (Landace X Large White)	8	2	4	Day 8	Normal	1 mL PRP (50 μL calcium solution)	2 out of 6 anastomoses performed in each animal used as a control anastomosis [no PRP or platelet rich in growth factors (PRGF) applied]	PRP *vs* PRGF
Zhou *et al*[29], 2014	China	Rat (Sprague Dawley)	30	3	10	Day 7	Open abdomen. A polypropylene mesh used for abdomen closing in the open abdomen group	1 mL PRP	Simple end-end colon anastomosis	PRP *vs* non PRP application in a background of open abdomen
Göksu *et al*[30], 2020	Turkey	Rat (Wistar Albino)	24	3	8	Day 7	HIPEC	PRP alone (dose not mentioned)	Hyperthermic saline after anastomosis	PRP *vs* non PRP application in rats having HIPEC with 5-fluorouracil (5-FU)
Özçay *et al*[16], 2018	Turkey	Rat (Sprague Dawley)	40	4	10	Day 7	Mesenteric ischemia/reperfusion injury (IR injury)	PRF membrane applied around the anastomosis	Simple end-end colon anastomosis	PRF *vs* non PRF application following IR injury
Fresno *et al*[19],	Spain	Pig (White)	35	7	3 or 10	Day 1, 2, 3, 4	Normal	1 mL PRP (50 μL	1 out of 2 anastomoses performed	PRP effect on several

2010						and 7		calcium solution)	in each animal used as a control anastomosis (no PRP or PRGF applied)	postoperative days
Daradka *et al* [27], 2019	Jordan	Rabbit (mixed-breed)	30	3	10	Day 3 and 10	Normal	Sutures submerged in 1 ml PRP solution	Simple end-end ileal anastomosis	PRP *vs* sodium citrate coated sutures
Yalı *et al*[36], 2020	Turkey	Rat (Wistar-Albino)	56	4	12	Day 5	Peritonitis	1 mL PRP (1 mL calcium solution)	Simple end-end colon anastomosis	PRP in normal abdomen *vs* peritonitis
Pehlivanli *et al* [33], 2019	Turkey	Rat (Wistar Albino)	55	5	10	Day 10	Mesenteric ischemia	1 mL PRP	Simple end-end colon anastomosis	PRP *vs* Zeolite *vs* thymoquinone
Sozutek *et al* [31], 2016	Turkey	Rat (Wistar Albino)	50	4	10	Day 7	Peritonitis	1 mL PRP (1 mL thrombin and 50 µL calcium solution)	Simple end-end colon anastomosis	PRP in normal abdomen *vs* peritonitis
Yamaguchi *et al* [18], 2012	Japan	Rat (Sprague-Dawley)	77	4	12	Day 5	Normal	180 µL PRP (180 units of bovine thrombin and 30 µL of calcium solution).	Simple end-end colon anastomosis	Platelet poor plasma *vs* low *vs* high platelet rich plasma
Gorur *et al*[32], 2020	Turkey	Rat (Wistar Albino)	50	4	10	Day 7	Intraperitoneal administration of 5-FU	1 mL PRP (1 mL thrombin and 50 µL of calcium solution)	Simple end-end colon anastomosis	PRP *vs* non PRP application in rats having intraperitoneal administration of 5-FU

PRP: Platelet rich plasma.

are presented with the related *P* value. Other reported outcomes are descripted subsequently.

Macroscopic findings

Intrabdominal adhesions were assessed in five studies[16,25-28]. Soaking of the bowel edges in PRP resulted in increased formation of intrabdominal adhesions compared to the injection of PRP along the anastomosis line and compared to the control group [25]. Compared to the platelet rich in growth factors (PRGF) and control groups, the use of PRP resulted in a non-significantly increased formation of intrabdominal adhesions[28]. In another technique, suture soaking in PRP material was associated with significantly lower adhesion scores in the anastomotic sites in a rabbit animal model[27]. Dauser *et al*[26], reported that the application of PRF was not associated with significant changes in adhesion formation, compared to the control group. In contrast, Özçay *et al*[16] reported that the application of PRF resulted in significantly decreased formation of intra-abdominal adhesions in the ischemia/reperfusion injury animal model compared to the non PRF groups[16].

Circulating inflammatory markers and immunohistology changes

Daglioglu *et al*[9], reported no statistically significant changes in proinflammatory

Table 2 Anastomotic burst pressure, tissue hydroxyproline, collage deposition and inflammatory cell infiltration

Ref.	Anastomotic burst pressure (mm/hg)				Tissue hydroxyproline (μg/mg)				Collagen deposition	Inflammatory cells deposition
	PRP	Control	Other agent	*P* value	PRP	Control	Other agent	*P* value		
Daglioglu *et al* [9], 2018	146 ± 44.55 mm/hg	119 ± 35.65 mm/hg	149.1 ± 72.29 mm/hg (Fibrin glue)	*vs* Control (0.026); *vs* Fibrin glue (0.896)	120.1 ± 51.5 μg/mg	96.2 ± 29.22 μg/mg	118.71 ± 42.18 μg/mg	*vs* Control (0.023); *vs* Fibrin glue (0,745)	No significant difference between groups	No significant difference between groups
Ocak *et al*[34], 2019	146 ± 21.85 mm/hg	180 ± 9.14 mm/hg	115.8 ± 18.19 mm/hg (HIPEC with cisplatin group)	*vs* Control (< 0.001); *vs* HIPEC with cisplatin (0.01)	256.59 ± 84.03 ng/mg	314.69 ± 47.56 ng/mg	148.02 ± 26.57 ng/mg (HIPEC with cisplatin)	*vs* Control (0.335); *vs* Hyperthermic saline group (< 0.001)	-	Inflammatory cell infiltration is significant decreased with PRP application in HIPEC and cisplatin model
Yol *et al*[10], 2008	270 ± 29.8 mm/hg	195 ± 15.3 mm/hg	214 ± 16.46 mm/hg (bioglue)	*vs* Control (< 0.001); *vs* Bioglue (< 0.001)	18.2 ± 4.95 μg/mg	10.96 ± 5.94 μg/mg	11.08 ± 5.08 μg/mg	*vs* Control (0.016); *vs* Bioglue (0.026)	Rich collagen production was observed in the PRP group. No comparison between groups	Less inflammatory cell infiltration in the PRP group
Buk *et al*[35], 2020	125.7 ± 15.64 mm/hg	180 ± 9.14 mm/hg	94.90 ± 9.9 mm/hg (HIPEC with oxiliplatin)	*vs* Control (< 0.001); *vs* HIPEC with oxiliplatin group (< 0.001[1])	280.92 ± 45.85 ng/mg	314.69 ± 75.57 ng/mg	92 ± 26.97 ng/mg (HIPEC with oxiliplatin)	*vs* Control (< 0.001); *vs* HIPEC with oxiliplatin) (< 0.001[1])	-	Inflammatory cell infiltration is significant decreased with PRP application in oxiplatin model
Dzhumabekov *et al*[25], 2019	1.76 ± 0.28 (PRP soakinggroup)[1]	1.54 ± 0.23[1]	1.81 ± 0.17[1] (PRP injecting group)	*vs* Control (0.05); *vs* PRP injecting group (0.69)	-	-	-	-	No significant differences between groups	Inflammatory cell infiltration significantly lower in the PRP soaking or injection group
Aydin *et al*[17], 2020	121 ± 57 mm/hg	124 ± 61 mm/hg	180 ± 49 mm/hg (low concentration PRP)	*vs* Control (> 0.05); *vs* low concentration PRP (< 0.001[1])	0.39 ± 0.10 μg/mg	0.25 ± 0.17 μg/mg	0.56 ± 0.37 μg/mg (low concentration PRP)	*vs* Control (< 0.001); *vs* low concentration PRP (< 0.05[1])	-	No significant difference between groups
Dauser *et al* [26], 2020	Median = 210 mm/hg (day 10)	Median = 60 mm/hg (day 10)	-	The study reports no statistically significant changes between groups due to small sample size	-	-	-	-	Matrix treated animals showed less immature collagen deposition (type III) compared to the control group (day 10). However no significant differences were observed	No significant changes in the M2 or non-M2 macrophage density in the mucosal, mural and serosal layers. No significant changes in inflammatory cell infiltration
Giusto *et al* [28], 2017	117.5 mm/hg (range: 80-190)	154 mm/hg (range: 50-180)	165 mm/hg (range: 100-190) (PRGF); And 175 mm/hg (range: 160-190) (intact bowel)	*vs* Control or PRGF (> 0.05); *vs* Intact bowel (0.0007[1])	-	-	-	-	No significant difference between groups	No significant difference between groups
Zhou *et al*[29], 2014	177 ± 6.95 mm/hg	184.8 ± 6.6 mm/hg	158 ± 5.08 mm/hg (open abdomen group without PRP application)	*vs* Control (0.398); *vs* non-PRP application in open abdomen (0.041)	399.7 ± 9.46 μg/mg	403.6 ± 8.55 μg/mg	353.5 ± 6.75 μg/mg (open abdomen group without PRP application)	*vs* Control (0.74); *vs* non-PRP application in open abdomen (0.001)	Significantly higher in the PRP and control group	No significant differences between groups

Göksu *et al*[30], 2020	143 ± 17.35 mm/hg	150 ± 20.49 mm/hg	119.38 ± 17.65 mm/hg (5-FU HIPEC without PRP application)	*vs* Control (0.718); *vs* non-PRP 5-FU HIPEC (0.047)	253.64 ± 5.35 µg/mg	259.6 ± 7.95 µg/mg	244.04 ± 7.28 µg/mg (5-FU HIPEC without PRP application)	*vs* Control (0.224); *vs* non-PRP 5-FU HIPEC (0.03)	-	Decreased lymphocytes in the PRP compared to the other groups. No statistically significant changes in neutrophil infiltration
Özçay *et al*[16], 2018	198.1 ± 36.5 mm/hg	205.1 ± 41.1 mm/hg	106.1 ± 33.9 mm/hg (IR injury without PRF)	*vs* Control (> 0.05); *vs* non PRF in IR injury (< 0.01)	-	-	-	-	Moderate to severe collagen deposition in all groups but no significant changes between groups	Moderate to severe cellular infiltration but no significant changes between groups
Fresno *et al* [19], 2010	1.34 ± 0.07 kgf [1] (day 3); 1.14 ± 0.11 kgf [1](day 7)	1.21 ± 0.08 kgf [1](day 3); 1.08 ± 0.08 kgf [1] (day 7)	1.8 ± 0.08 kgf [1](normal tissue)	*vs* Normal tissue (< 0.05); *vs* Control day 3 or 7 (> 0.05)	-	-	-	-	No significant difference between groups	-
Daradka *et al* [27], 2019	60.2 ± 5.5 mm/hg	54.5 ± 7.5 mm/hg	55.6 ± 10.2 mm/hg (sodium citrate coated sutures)	*vs* Control (0.211)	0.76 ± 0.1 µg/mg	0.47 ± 0.13 µg/mg	0.52 ± 0.07 µg/mg (sodium citrate- coated sutures)	*vs* Control (< 0.05) on day 10; *vs* Control (> 0.05) on day 3	Statistically significant higher collagen deposition compared to uncoated suture groups on day 10	Statistically significant less inflammatory infiltration compared to PRP uncoated suture groups
Yalı *et al*[36], 2020	129.66 ± 26.6 mmH20	143.25 ± 37.47 mmH20	154.9 ± 27.64 mmH20 (colon anastomosis in peritonitis) and 173.5 ± 29.49 mmH20 (colon anastomosis and PRP application in peritonitis)	*vs* Control (> 0.05); *vs* Colon anastomosis and PRP application in peritonitis (< 0.05)	-	-	-	-	Statistically significant higher collage storage values in PRP treated group compared to control and peritonitis model	Statistically significant differences between groups in terms of inflammatory reaction
Pehlivanli *et al* [33], 2019	225 (range: 180-250)[2]	200 (range: 90-230)[2]	235 (range: 220-250)[2] thymoquinone; 132.5 (range: 85-150)[2] Zeolite	*vs* Control (> 0.05); *vs* Zeolite (< 0.05); *vs* Thymoquinone (> 0.05)	613.22 (range: 158.55-801.82)[2]	371.27 (range: 164.51-785.45)[2]	473.03 (range: 215.33-963.43)[2] thymoquinone; 459.15 (range: 182.44-738.21)[2] Zeolite	*vs* Control (> 0.05); *vs* Zeolite (> 0.05); *vs* Thymoquinone (> 0.05)	-	No significant difference in terms of inflammation at the anastomotic line in between groups
Sozutek *et al* [31], 2016	209 ± 14.4 mm/hg	179.5 ± 10.3 mm/hg	129.3 ± 14.2 mm/hg (colon anastomosis in peritonitis); 167.5 ± 7.5 mm/hg (colon anastomosis and PRP application in peritonitis)	*vs* Control (0.01); *vs* Colon anastomosis in peritonitis (0.01); *vs* Colon anastomosis and PRP application in peritonitis (0.01)	17.4± 1.21 µg/mg	10.8± 0.67 µg/mg	8.98 ± 1.04 µg/mg (colon anastomosis in peritonitis); 10.6 ± 0.52 µg/mg (colon anastomosis and PRP application in peritonitis)	*vs* Control (0.023); *vs* Colon anastomosis in peritonitis (0.01); *vs* Colon anastomosis and PRP application in peritonitis (0.012)	Application of PRP in peritonitis group did no increase collagen deposition significantly	Macrophages significantly increased in PRP *vs* control group and lymphocytes were significantly decreased in PRP + peritonitis compared to peritonitis group
Yamaguchi *et al* [18], 2012	148 ± 25 mm/hg (H-PRP)	171 ± 20 mm/hg	174 ± 23 mm/hg (PPP); 189 ± 17 mm/hg (L-PRP)	*vs* Control (< 0.05); *vs* L-PRP (< 0.05); *vs* PPP (< 0.05)	407 ± 143 µg/mg	515 ± 130 µg/mg	495 ± 123 µg/mg (PPP); 629 ± 120 µg/mg (L-PRP)	*vs* Control (< 0.05); *vs* L-PRP (< 0.05); *vs* PPP (< 0.05)	In L-PRP more collagen deposition in the serosa layer compared to other groups. H-PRP showed the lesser collagen deposition compared to other groups	-
Gorur *et al*[32],	246.7± 25.1	232.6± 19.5	127.5± 17.7 mm/hg	*vs* Control (> 0.05); *vs*	1939.5 ±	2994.6 ±	591 ± 84.4 µg/mg (colon	*vs* Control (0.212); *vs*	Increased but no	No significant differences

2020	mm/hg	mm/hg	(colon anastomosis and 5-FU intraperitoneal); 202.9 ± 28.8 mm/hg (colon anastomosis + PRP and 5-FU intraperitoneal)	Colon anastomosis and 5-FU intraperitoneal (< 0.05); Colon anastomosis + PRP *vs* non PRP and 5-FU intraperitoneal (< 0.05)	586 μg/mg	2132.4 μg/mg	anastomosis and 5-FU intraperitoneal); 1171 ± 301.7 μg/mg (colon anastomosis + PRP and 5-FU intraperitoneal)	Colon anastomosis and 5-FU intraperitoneal (< 0.05); Colon anastomosis + PRP *vs* non PRP and 5-FU intraperitoneal (< 0.05)	statistically significant collagen deposition in colon anastomosis + PRP *vs* non PRP on a background of intraperitoneal 5-FU administration	between groups

[1]Breaking strength: Minimal force required for anastomosis rupture.

[2]Anastomotic bursting pressure and tissue hydroxyproline units not reported.

5-FU: 5-Fluorouracil; HIPEC: Hyperthermic intraperitoneal chemotherapy; IR injury: Ischemia/reperfusion injury; PRF: Platelet rich fibrin; PRGF: Platelet rich in growth factors; PRP: Platelet rich plasma.

cytokines IL-6, IL-10 and procalcitonin levels between the PRP and control groups. Higher circulating tumor necrosis factor-α and IL-1b levels in the PRP compared to the control group were observed by Pehlivanli *et al*[33].

Table 2 summarizes the collagen deposition and inflammatory cell infiltration in the PRP treated groups compared to the control or other agents that were also tested. Table 3 describes the results of the Verhofstad histopathology scale that was recorded by some of the included studies. The Verhofstad histopathology scale is used to analyze wound healing by assessing on a 0-3 scale the necrosis, polymorphonuclear leukocytes, macrophages, edema, mucosal epithelium and submucosal-muscular layer healing[37].

Dauser *et al*[26] reported no significant difference in the PRF compared to the control group in terms of foreign body reactivity, mucosal regeneration and inflammatory cell infiltrates. Anastomotic thickness, mean mucin percentage, and microvascular density (at day 30 postoperatively) were also non-significantly increased in the PRF treated anastomosis. The application of PRF was associated with bacterial colonization and infiltration of neutrophils at day 4 in all animals. Both Özçay *et al*[16] and Dauser *et al*[26] did not observe residual PRF material on day 10 and day 30 postoperatively. In contrast, PRP material was visualized in the anastomosis microscopic examination as an eosinophilic material[19]. Epithelialization, cellular infiltration, fibroblast proliferation, and neovascularization did not present a significant increase in the PRF group in the ischemia/reperfusion injury animal model [16]. Staining for the endothelium specific Factor VIII did not present significant changes in the PRP compared to control groups[19].

On postoperative days 1, 2, 3, and 7, Dzhumabekov *et al*[25] studied the fiber-crypt index, intraepithelial lymphocyte count, epithelial-stromal coefficient and mitosis count (mitosis observed outside lymphoid follicles). Higher mitosis rate in the mucosal crypt area was observed in the PRP injection group compared to PRP soaking and control groups on postoperative days 3 and 7. Epithelial-stromal coefficient decreased in the control group. Intraepithelial lymphocyte infiltration did not present any significant difference between groups[25].

Table 3 Verhofstad histopathology scale

Groups	Necrosis	Neutrophil	Lymphocyte	Macrophages	Oedema	Mucosal epithelium	Submucosal layer	Bridging	Total
Ocak *et al*[34]									
Control	2.3 ± 0.82	2.5 ± 0.52	2.5 ± 0.52	2.5 ± 0.52	2.9 ± 0.31	2.6 ± 0.966	0.8 ± 0.63	-	-
PRP	2.6 ± 0.69	2.8 ± 0.42[a]	2.7 ± 0.48[a]	2.7 ± 0.48[a]	2.9 ± 0.31	2.6 ± 0.516	1.4 ± 0.69	-	-
Fibrin glue	2 ± 0.66	2.1 ± 0.31[a]	2.1 ± 0.31[a]	2.1 ± 0.31[a]	2 ± 0.47	2.6 ± 0.516	1.3 ± 0.67	-	-
Buk *et al*[35]									
Control	2.3 ± 0.82	1.9 ± 0.56[a]	1.8 ± 0.42[a]	2 ± 0.47	2.1 ± 0.56[a]	2.6 ± 0.966	0.8 ± 0.63[a]	-	-
Oxaliplatin	2.5 ± 0.52	2.9 ± 0.52[a]	2.4 ± 0.51[a]	2.5 ± 0.52	2.8 ± 0.42[a]	2.6 ± 0.516	2 ± 0.94[a]	-	-
Oxaliplatin + PRP	2.7 ± 0.58	2 ± 0.47[a]	1.8 ± 0.42[a]	2.3 ± 0.67	2.1 ± 0.56[a]	2.5 ± 0.54	1.6 ± 0.96[a]	-	-
Aydin *et al*[17]									
Control	1 ± 1	2 ± 1	-	2 ± 0	2 ± 1	3 ± 1	3 ± 0	-	-
L-PRP	0 ± 2	2 ± 1	-	2 ± 0	1 ± 0[a]	2.5 ± 1[a]	3 ± 2	-	-
H-PRP	1.5 ± 2	2 ± 2	-	2 ± 1	0 ± 0[a]	1 ± 2[a]	3 ± 0	-	-
Göksu *et al*[30]									
Control	2.38 ± 0.51	2.38 ± 0.518	2.38 ± 0.51[a]	-	2.75 ± 0.46[a]	2.63 ± 0.51	1.75 ± 0.46	-	-
5-FU	2.63 ± 0.51	2.50 ± 0.463	2.63 ± 0.51[a]	-	2.75 ± 0.46[a]	2.50 ± 0.53	1.25 ± 0.46	-	-
5-FU + PRP	2.13 ± 0.35	2.13 ± 0.518	2 ± 1[a]	-	2 ± 0.53[a]	2.63 ± 0.51	1.25 ± 0.46	-	-
Sozutek *et al*[31]									
Control	0.3 ± 0.48	1.3 ± 0.94	1 ± 0.47	1 ± 0[a]	0.4 ± 0.51	0.3 ± 0.48	-	0.6 ± 0.51	4.9 ± 1.28
Control + PRP	0.2 ± 0.42	0.7 ± 0.67	1 ± 0.47	1.6 ± 0.51[a]	0.3 ± 0.48	0.4 ± 0.48	-	0.2 ± 0.42	4.3 ± 1.33
Septic	1.1 ± 0.64	1.5 ± 0.53	1.6 ± 0.51[a]	1.1 ± 0.83	1.2 ± 0.71[a]	1 ± 0.53	-	1.2 ± 0.71	9.8 ± 1.12[a]
Septic + PRP	0.7± 0.48	1.2 ± 0.42	1.3 ± 0.48[a]	1.5 ± 0.52	0.4 ± 0.51[a]	0.5 ± 0.51	-	0.8 ± 0.42	6.1 ± 1.37[a]
Gorur *et al*[32]									
Control	0.3 ± 0.67[a]	1.3 ± 0.9	1 ± 0.47	1 ± 0	1.1 ± 0.31[a]	0.3 ± 0.57[a]	-	1.2 ± 0.78[a]	-
5-FU	1 ± 1.05[a]	1.5 ± 0.53	1.4 ± 0.32	1.1 ± 0.83	2 ± 0.73[a]	1.1 ± 0.42[a]	-	1.5 ± 0.52[a]	-
Control + PRP	0[a]	0.7 ± 0.67	1 ± 0.67	1.8 ± 0.31	1 ± 0.47[a]	0.3 ± 0.57[a]	-	0.9 ± 0.87[a]	-
5-FU + PRP	0.1 ± 0.3	1.2 ± 0.42	1.5 ± 0.58	1.6 ± 0.53	1.7 ± 0.48	0.6 ± 0.57	-	1.1 ± 0.31	-

[a]$P < 0.05$, represents a statistically significant difference between values.
5-FU: 5-Fluorouracil; PRP: Platelet rich plasma.

Aydin *et al*[17] reported that PRP coated sutures with either high or low platelet concentration resulted in significantly decreased formation of granulation tissue compared to the control group[17]. In contrast, Fresno *et al*[19] reported that on postoperative day 7 the PRP treated anastomosis developed increased, but not significantly different, mature granulation tissue and fibrosis. Yalı *et al*[36] findings were significant for higher vascularization, fibroblast organization and epithelial formation in the PRP treated peritonitis model. Pehlivanli *et al*[33] compared several agents and concluded that PRP application was associated with better re-epithelialization scores compared to Zeolite application and control groups.

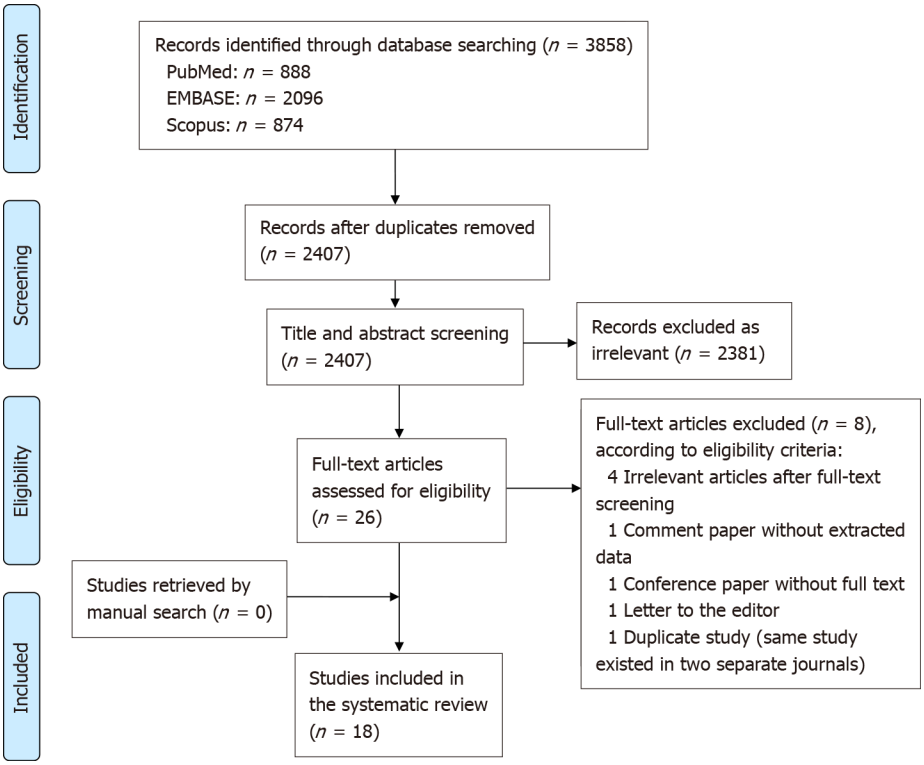

Figure 1 PRISMA flow diagram of the study selection process.

Giusto *et al*[28] reported no statistically significant changes in neovascularization and fibroblast proliferation. Mucosa epithelialization was significantly increased in the PRGF group. Yol *et al*[10] found that the fibroblast count was significantly increased in the PRP group compared to the control group, but the results were comparable between the PRP and the bioglue groups. In addition, Daglioglu *et al*[9] showed that fibroblast density and neovascularization were not significantly different between the fibrin glue or PRP application and control groups. Buk *et al*[35] reported that submucosal bridging was significantly increased in the control and PRP/oxaliplatin groups compared to the oxaliplatin group alone. Lastly, Zhou *et al*[29], utilizing an open abdomen animal model, reported that fibroblast ingrowth was significantly higher in the PRP group compared to the control and open abdomen group. The vascular ingrowth of the PRP was significantly increased compared to the open abdomen, but was comparable to the control group[29].

Study quality and risk of bias

Regarding selection bias, 17 of the 18 included studies (94%) did not report whether the allocation sequence was adequately applied and concealed. Only one study reported the use of a random number generator. Concerning the baseline characteristics, 10 of the 18 studies (56%) described comparable groups at the baseline.

Regarding performance bias, one study reported that the researchers were blinded, while other studies did not report data regarding the housing parameters or researcher's blinding. Therefore, the risk of bias is considered unclear.

Regarding detection bias and specifically the animals' selection method for the assessment of outcomes, all studies were scored as having unclear risk of bias due to missing relevant information. However, outcome assessment methods were similar between the groups in all studies and the risk of bias regarding the blinding of the outcome assessors is characterized as low.

Regarding attrition bias, 5 of the 18 included studies (28%) did not describe the handling method for incomplete data (unclear bias). Two studies were scored as high risk of bias, including one study where the authors excluded unequal number of animals that died in different groups and another study where the authors did not provide sufficient information about the death of two animals in one of the groups.

Regarding reporting bias, in 17 of the 18 studies (94%) adequately described the outcomes and the reporting bias risk was low. In one study, the tissue hydroxyproline levels were not reported, despite being included as an expected outcome in the materials and method section (high risk).

Regarding other sources of bias, in one study a preparation kit was used and one of the co-authors had a relevant conflict of interest with the manufacturer. Two studies (11%) did not provide information regarding any funding that may have affected their work.

Regarding the approval from an ethical committee, all included studies reported approval from their local ethical committee. The quality assessment results are summarized in Supplementary Table 2.

DISCUSSION

The application of PRP in bowel anastomosis is associated with improved outcomes in terms of anastomoses bursting pressure and tissue hydroxyproline, which are the two most common parameters used for the evaluation of anastomosis integrity[17].

Anastomotic bursting pressure is an indirect indicator of anastomosis healing. It reflects the balance between collagen synthesis and degradation[18,38]. Although 50% (9/18) of the included studies reported no statistically significant changes in the anastomosis bursting pressure in PRP-treated compared to control groups, five studies reported that the application of PRP in the presence of an underlying medical or surgical condition, improved the anastomosis bursting pressure. Furthermore, the application of PRP in the open abdomen, ischemic /reperfusion injury, peritonitis, intraperitoneal 5-fluorouracil (5-FU) infusion, and hyperthermic intraperitoneal chemotherapy with 5-FU animal models was associated with statistically significant improved anastomosis bursting pressure[16,29,30,32,36]. Among, the other four studies, Dauser *et al*[26] investigated the application of PRF, which presents some component differences compared to PRP. Giusto *et al*[28] reported significantly lower bursting pressure in the PRP compared to the control group, although the application of PRGF significantly increased the anastomotic bursting pressure compared to PRP or control group. Lastly, Daradka *et al*[27] used PRP coated sutures and Pehlivanli *et al*[33] studied the application of several topical factors in the anastomosis. Both studies report no significant changes in anastomotic bursting pressure in PRP compared to control groups.

Hydroxyproline level is a widely accepted marker of tissue collagen synthesis, including the anastomotic area[39]. Increased collagen synthesis and collagen maturation are thought to be induced by hydroxyproline molecules[10]. Low levels of tissue hydroxyproline exert a negative impact in wound healing[40,41]. According to the included studies, tissue hydroxyproline is measured on or close to the 7th postoperative day. Despite not being reported by six studies, tissue hydroxyproline levels were consistent with the anastomotic bursting pressure in all except three studies. In two studies the anastomotic bursting pressure was significantly increased in the PRP-treated group while anastomotic tissue hydroxyproline levels did not show any significant changes[17,34]. Gorur *et al*[32] reported that PRP application was associated with increased tissue hydroxyproline levels in the intraperitoneal 5-FU infusion animal model.

Similarly, anastomotic wound inflammatory cellular infiltration in control compared to PRP groups did not show any statistically significant changes among the included studies. However, it was reported that in the presence of an underlying detrimental condition like intraperitoneal chemotherapy or infection, PRP application significantly decreased the inflammatory cellular infiltration in bowel anastomosis[30-32,34-36]. Theoretically, enhanced anastomosis strength associated with PRP application could partially be attributed to decreased inflammatory cell-mediated collagen degradation[42].

The intestinal wound healing process can be roughly divided into three phases: inflammation, proliferation, and maturation. Following a surgical intervention, platelets are among the first cells that reach the traumatized tissue area, while their main functions include the formation of a protective clot and the release of growth factors[43]. The role of growth factors in wound healing has been extensively investigated in previous studies. PDGF secretion was shown to improve epithelialization, secretion of several other tissue growth factors, and tissue regeneration[44]. Synthesis and deposition of several extracellular matrix factors as well as increased *in vitro* keratinocyte motility have been associated with FGF[45]. VEGF family proteins play a significant role in early angiogenesis. In vitro studies have demonstrated that the VEGF family proteins facilitate the angiogenic properties of stem cells and improve the wound healing process[46,47]. IGF acts as a mitogenic growth factor for fibroblasts [48]. PRP, which is a carrier of growth factors, is expected to improve the anastomosis

wound healing and reduce the incidence of postoperative anastomosis-related complications (Figure 2).

The first week following a bowel anastomosis seems to be the critical period for the development of anastomosis leaks. Most of the anastomosis leakages are reported 5-10 d postoperatively, when the strength of anastomosis is considered to be at its lowest level[49]. A possible explanation involves the collagen remodeling during wound healing process. Experimental studies have shown that collagen degradation starts on the third postoperative day and peaks on the seventh day following surgical trauma. Permanent collagen deposition in the anastomotic area is believed to take place a few days postoperatively. In view of initial collagen degradation during wound healing over the first few days, the anastomosis integrity is mainly supported by fibrin deposition and anastomotic technique (suturing method)[9,29,35,50,51]. Based on these experimental studies, all included studies investigated the effects of PRP application around postoperative day 7, when the anastomotic strength is considered to be at its lowest level.

Anastomotic leak is associated with increased morbidity and mortality rate[10,52]. Dysregulation of circulating platelets, the main component of PRP, has been associated with anastomotic leak. Both thrombocytosis and thrombocytopenia have been described as factors associated with anastomotic leak. However, these results should be interpreted with caution as the dysregulation of circulating platelets could be attributed to malnutrition (thrombocytopenia) or sepsis (thrombocytosis), which are well established risk factors associated with anastomotic leak[53,54]. Patients developing anastomotic leaks tend to have prolonged intensive care unit and hospital stay and significantly increased medical care costs[29]. Intra-abdominal infections, fistulas between adjacent organs, and poor abdominal wound healing are some of the long-term complications of anastomotic leak that may result in significant consequences on patient's quality of life[55].

The optimal method and/or agent to prevent these detrimental complications has not been identified yet. The prevention of bowel anastomosis leak involves the modification of risk factors that predispose to impaired wound healing. To this end, immunomodulators, hormones, growth factors, antibiotics and proteinase inhibitors have been previously applied topically or administered systematically and have been associated with improved bowel anastomotic healing[56]. The underlying mechanisms ,that promote enhanced anastomosis integrity, include increased blood supply, reduced inflammatory cell infiltration, and rapid collagen deposition[56]. Despite the presence of numerous studies on agents that could promote wound healing, the ideal agent is yet to be determined. PRP contains a variety of growth factors, immunomodulators, as well as other constituents that promote tissue healing and is a promising candidate in terms of clinical applications.

Preparation of PRP is a simple process with very low cost compared to other materials used for anastomosis reinforcement[57]. Currently, most studies report that a sample of 5-20 mL of peripheral blood is required to extract 2-5 mL of PRP. The amount of peripheral blood required for PRP preparation depends on the technique or commercial kit that are used during the isolation process[14,58]. Furthermore, its autologous nature increases biocompatibility[9,32]. However, some technical issues and concerns were raised among the included studies. The majority of the growth factors are presynthesized within the platelets and are secreted within one hour after platelet activation. As a result PRP associated growth factors are released immediately after PRP application to the anastomotic area[19,59]. Interestingly, platelets could also synthesize and secrete growth factors during their lifespan in the area of bowel anastomosis for up to 7 d. This growth factor release is supplemental to the initial growth factor secretion taking place immediately after PRP application[10,19,60]. Nevertheless, the platelet concentration of PRP applied to the anastomotic area may also affect the healing outcomes. To that extend, Aydin *et al*[17] showed that low platelet concentration results in superior outcomes in terms of anastomotic bursting pressure and collagen concentration at the anastomotic site compared to high platelet concentration PRP.

Our study has several strengths, including the total number of included studies, the large number of animal models, as well the variety of conditions that the PRP was tested on. However, we have to recognize that our findings are not free of limitations and should be interpreted cautiously. Animal models, studies heterogeneity and small samples are among the major limitations of our study. Only two studies investigated the effects of PRP on pigs, which have intestines that are structurally closer to human bowel. As a result, the clinical application and generalizability of our findings in large animal models are questionable. Furthermore, high heterogeneity was observed in the histopathological scales used for the assessment of anastomotic cellular infiltration.

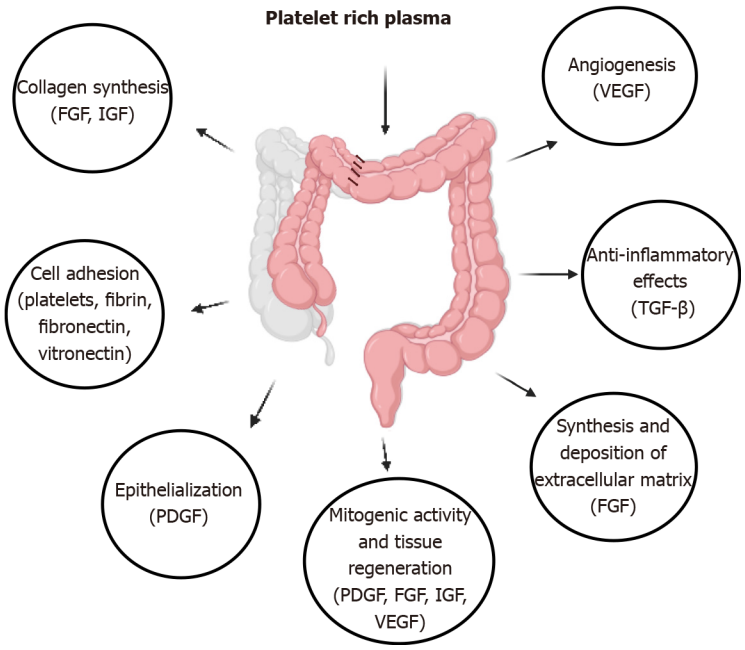

Figure 2 Platelet rich plasma effect on the healing process of bowel anastomosis (created with BioRender.com). FGF: Fibroblast growth factor; IGF: Insulin-like growth factor; PDGF: Platelet-derived growth factor; TGF-β: Transforming growth factor-β; VEGF: Vascular endothelial growth factor.

Although pathologists were reported to be blinded regarding the origin of the samples, the lack of a uniform scale, such as the Verhofstad scale, pose difficulties in terms of results interpretation and measurement bias.

CONCLUSION

The application of PRP in bowel anastomosis is a feasible approach and it seems to improve the integrity of bowel anastomosis. PRP application compared to control groups did not show any significant changes in the majority of the included studies. However, in the presence of an underlying condition that impairs intestinal wound healing, including peritonitis or chemotherapy, the application of PRP could potentially improve the healing process. Its preparation does not require significant expertise and can be easily extracted from patient's own blood. Taking into consideration its cost effectiveness, PRP could be considered in the clinical practice for bowel anastomosis reinforcement material. Apparently, further research is needed to confirm the safety and effectiveness of PRP on human bowel anastomoses.

ARTICLE HIGHLIGHTS

Research background

Several applications of platelet rich plasma (PRP) have been reported in the literature. Some examples include maxillofacial, orthopedic and plastic surgery where PRP is considered to improve the wound healing process. PRP is easily extracted from patient's blood and includes a variety of growth factor that is thought to improve the wound healing process.

Research motivation

Preclinical studies shows that the PRP has a positive impact in the healing process of bowel anastomosis.

Research objectives

The aim of this study is to define the role of PRP in general surgery, especially in procedures involving bowel anastomosis. Therefore, a systematic review of the literature was performed.

Research methods

A systematic literature search was performed in PubMed, EMBASE, and Scopus databases. Animal studies that investigated the effect of PRP on bowel anastomosis were included in our analysis.

Research results

Among the 2407 studies screened, 18 animal studies were finally included in our analysis. An end-to-end bowel anastomosis was performed in all included studies. PRP origin was autologous in 8 studies and homologous in 10 studies. In 13 out of 18 studies PRP was applied topically to the bowel anastomosis. No postoperative complications attributed to PRP application were reported. Common anastomosis related parameters measured among the included studies were the anastomotic bursting pressure, tissue hydroxyproline, collagen deposition and inflammatory cell infiltration. The individual study results in the aforementioned parameters are presented in tables.

Research conclusions

The application of PRP in bowel anastomosis is feasible and seems to be free of any major complications. PRP application compared to control groups did not show any significant changes in the majority of the included studies. However, in the presence of an underlying condition that impairs intestinal wound healing, including peritonitis or chemotherapy, the application of PRP could potentially improve the healing process.

Research perspectives

Although the results of this study support the use of PRP in bowel anastomosis, further research is needed to confirm the safety and effectiveness of PRP on human bowel anastomoses.

ACKNOWLEDGEMENTS

This review is part of a PhD thesis research project, taking place at the Graduate School of Medicine, Aristotle University, Thessaloniki, Greece.

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2021 December 27; 13(12): 1754-1769

DOI: 10.4240/wjgs.v13.i12.1754

ISSN 1948-9366 (online)

SYSTEMATIC REVIEWS

Current and future role of three-dimensional modelling technology in rectal cancer surgery: A systematic review

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Author contributions: Przedlacka A designed the research; Przedlacka A and Fletcher J performed the data search and screening; Przedlacka A, Pellino G and Kontovounisios C analysed the data; Przedlacka A drafted the manuscript; Pellino G, Kontovounisios C, Bello F and Tekkis PP revised the manuscript; All authors approved the final manuscript.

Conflict-of-interest statement: All the authors declare that they have no competing interests.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: Italy

Specialty type: Surgery

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

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Abstract

BACKGROUND

Three-dimensional (3D) modelling technology translates the patient-specific anatomical information derived from two-dimensional radiological images into virtual or physical 3D models, which more closely resemble the complex environment encountered during surgery. It has been successfully applied to surgical planning and navigation, as well as surgical training and patient education in several surgical specialties, but its uptake lags behind in colorectal surgery. Rectal cancer surgery poses specific challenges due to the complex anatomy of the pelvis, which is difficult to comprehend and visualise.

AIM

To review the current and emerging applications of the 3D models, both virtual and physical, in rectal cancer surgery.

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

Received: April 28, 2021
Peer-review started: April 28, 2021
First decision: June 17, 2021
Revised: June 9, 2021
Accepted: November 15, 2021
Article in press: November 15, 2021
Published online: December 27, 2021

P-Reviewer: Lee T
S-Editor: Liu M
L-Editor: A
P-Editor: Liu M

METHODS
Medline/PubMed, Embase and Scopus databases were searched using the keywords "rectal surgery", "colorectal surgery", "three-dimensional", "3D", "modelling", "3D printing", "surgical planning", "surgical navigation", "surgical education", "patient education" to identify the eligible full-text studies published in English between 2001 and 2020. Reference list from each article was manually reviewed to identify additional relevant papers. The conference abstracts, animal and cadaveric studies and studies describing 3D pelvimetry or radiotherapy planning were excluded. Data were extracted from the retrieved manuscripts and summarised in a descriptive way. The manuscript was prepared and revised in accordance with PRISMA 2009 checklist.

RESULTS
Sixteen studies, including 9 feasibility studies, were included in the systematic review. The studies were classified into four categories: feasibility of the use of 3D modelling technology in rectal cancer surgery, preoperative planning and intraoperative navigation, surgical education and surgical device design. Thirteen studies used virtual models, one 3D printed model and 2 both types of models. The construction of virtual and physical models depicting the normal pelvic anatomy and rectal cancer, was shown to be feasible. Within the clinical context, 3D models were used to identify vascular anomalies, for surgical planning and navigation in lateral pelvic wall lymph node dissection and in management of recurrent rectal cancer. Both physical and virtual 3D models were found to be valuable in surgical education, with a preference for 3D printed models. The main limitations of the current technology identified in the studies were related to the restrictions of the segmentation process and the lack of 3D printing materials that could mimic the soft and deformable tissues.

CONCLUSION
3D modelling technology has potential to be utilised in multiple aspects of rectal cancer surgery, however, it is still at the experimental stage of application in this setting.

Key Words: Rectal cancer; Three-dimensional modelling; Three-dimensional printing; Image-guided surgery; Surgical navigation; Surgical education

Core Tip: Three-dimensional (3D) modelling technology has revolutionized preoperative planning, intraoperative navigation, and surgical training in several surgical specialties. Rectal cancer surgery poses significant challenges due to the complex anatomy of the pelvis. While there is marked interest in the application of 3D modelling in this field, it appears to be still in its relative infancy. Future research and technological developments will enable clinical application of the virtual and physical 3D models to enhance surgical vision before and during rectal cancer surgery.

Citation: Przedlacka A, Pellino G, Fletcher J, Bello F, Tekkis PP, Kontovounisios C. Current and future role of three-dimensional modelling technology in rectal cancer surgery: A systematic review. *World J Gastrointest Surg* 2021; 13(12): 1754-1769
URL: https://www.wjgnet.com/1948-9366/full/v13/i12/1754.htm
DOI: https://dx.doi.org/10.4240/wjgs.v13.i12.1754

INTRODUCTION

Colorectal cancer is the second leading cause of cancer deaths worldwide[1]. Cancer of the rectum accounts for approximately 30% of all colorectal malignancies. Rectal cancer surgery has undergone revolutionary changes within the last three decades. The standard application of the total mesorectal excision (TME), the use of

combination of chemo- and radiotherapy and the advent of minimally invasive approaches have all contributed to the improvement of patients' surgical and oncological outcomes[2,3]. However, rectal cancer surgery still poses significant technical challenges due to the complex anatomy of the pelvis, which contains crucial digestive, urinary and gynaecological organs, surrounded by the intimately interlinked minute pelvic nerves and vessels, all together enclosed within a rigid and often narrow space.

Obtaining the correct diagnosis and formulating a comprehensive management plan requires an effective multidisciplinary communication between the radiologists, surgeons and oncologists, which heavily relies on the radiological investigations. Magnetic resonance imaging (MRI) has become the gold standard in rectal cancer assessment[4]; however, it can be very difficult to comprehend for a non-expert eye. The use of three-dimensional (3D) models, both virtual and 3D printed, presents the information obtained from the two-dimensional radiological images in a way that resembles the complex 3D pelvic space encountered intraoperatively.

3D models have been found beneficial to all aspects of surgical care, from the recognition of patient's individual anatomy and creation of precise surgical roadmap, through surgical education to patient interaction[5,6].

Within the colorectal surgery, 3D imaging is used in computed tomography (CT) colonography where it provides the "fly-through" views of the colon, and in 3D reconstruction of CT angiography, which has already become a routine part of preoperative planning for cancer segmental colectomies in many institutions[7,8]. While the use of these two modalities has been thoroughly reported, the use of 3D modelling technology in rectal cancer surgery has not been reviewed. The two most recent systematic reviews of the applications of 3D printing in colorectal surgery identified only one paper addressing its use in rectal surgery, however these systematic reviews did not address the use of 3D virtual models[9,10].

This systematic review aims to provide a comprehensive picture of the current role of the 3D modelling technology in rectal cancer surgery and to identify the future directions of exploration of its application.

MATERIALS AND METHODS

Literature search

Electronic databases, PubMed/MEDLINE, Embase and Scopus, were searched to identify studies describing the use of 3D models, both virtual and physical, in rectal cancer surgery between 2000 and 2020. Keywords in the search strategy included: "3D", "three-dimensional", "model", "colorectal", "rectum", "surgery", "planning"', "navigation", "simulation", "surgical education", "patient education". The reference section of each paper was further screened for other relevant papers.

Inclusion criteria

All full-text studies published in English, which described 3D virtual or physical models used in any aspect of rectal cancer surgery were considered eligible for inclusion, regardless of study type.

Exclusion criteria

Duplicate articles, review papers and conference abstracts were excluded. Studies in which 3D models were derived from animals or cadavers, as well as studies of pelvic volumetry and radiotherapy planning were excluded.

Screening and data extraction

Title and abstract screening were performed independently by two reviewers (Przedlacka A and Fletcher J). The cases where consensus was not achieved, were resolved by Kontovounisios C and Pellino G. Full-text review and data extraction were performed independently by two reviewers (Przedlacka A and Kontovounisios C). The manuscript was drafted by Przedlacka A and revised by all authors.

The following information was extracted from each study: Author, year of publication, country where study was conducted, patient demographics, indication for 3D modelling, type of model (virtual or physical), methodology of image segmentation, time and cost of 3D modelling and 3D printing, study outcomes and limitations. The manuscript was prepared and revised according to the PRISMA 2009 Checklist[11].

RESULTS

Study characteristics

The details of the study screening are presented in Figure 1. Sixteen studies were found to be eligible for inclusion in the present systematic review. There were 8 studies from Asia, 7 from Europe and one from the United States. The studies were published between 2006 and 2020, with 14 out of 16 published since 2017. There was one single-centre open-label randomised controlled trial, 4 retrospective studies, 9 feasibility or pilot studies and 2 case reports. The characteristics of the studies and their participants are shown in Table 1. The application of 3D modelling in each study is presented in Table 2.

The use of virtual 3D models was reported in 13 studies, 3D printed models in one and both types of models in two studies. Models were derived from CT scans in 8 studies, from MRI scans in five studies, while the combination of both modalities was used in two studies. Further characteristics of the methodology of 3D modelling and 3D printing described in studies are presented in Table 3.

For the purpose of the descriptive presentation of the results of the present systematic review, the studies were divided into four categories: (1) Feasibility of application of 3D modelling technology in rectal cancer surgery; (2) Surgical planning and navigation; (3) Surgical education; and (4) Surgical device design.

Feasibility of application of 3D modelling technology in rectal cancer surgery

Feasibility of construction of 3D models of normal pelvic anatomy: Kontovounisios *et al*[12] constructed 10 models of healthy volunteers (5 males and 5 females) to demonstrate the feasibility of creation of virtual models of normal pelvic anatomy. MRI images were manually segmented in ITK-SNAP and further post-processing was applied in MeshLab. The particular focus was placed on the central pelvic compartment, which contains the rectum, intra/extra-luminal fat and the mesorectum, and is relevant to the TME resection. The authors noted that the methodology could be applied to create models of rectal cancer, which could be utilised for surgical planning and patient consultation.

Hamabe and Ito[13] explored the feasibility of creation of a 3D printed model of pelvic anatomy relevant to rectal cancer surgery and specifically to lateral pelvic lymph node (LPN) dissection. The CT images of a healthy male volunteer and a female with rectal cancer were manually segmented to create 3D replicas of patients' anatomy, including pelvic bones, pelvic floor muscles, internal and external iliac vessels with their branches, nerves and urogenital organs. The central compartment with the mesorectum and the rectum were not included in the models. The full-sized models were 3D printed with ultraviolet-cured resin. They could be cleaved in a sagittal plane to allow for the inspection of the deep parts.

Feasibility of construction of 3D models of rectal cancer: Sahnan *et al*[14] presented the feasibility of construction of two 3D virtual models for surgical planning of transanal TME (TaTME). These were created through manual segmentation of standard axial T2-weighted Spectral Attenuated Inversion Recovery sequences performed by a specialist consultant gastrointestinal radiologist. In the first case of a male patient with low rectal cancer, the model provided insight into the location at which the tumour penetrated the rectal wall and demonstrated the close relation but clearance of the tumour from the prostate and the urinary system. In the second case of a male with ulcerative colitis who was scheduled for combined single incision laparoscopy and TaTME completion proctectomy and ileoanal pouch, it provided an understanding of the anatomical landmarks and the insight into the relation between the internal sphincter and rectum, as well as between the prostate and urethra.

Przedlacka *et al*[15] reported constructing thirty 3D virtual models derived from the MRI T2 weighted sequences of patients with rectal cancer. The authors showed the feasibility of manual segmentation of the rectal wall layers to present the difference in the 3D appearance of T1 and T3 tumours. The authors also presented a model demonstrating infiltration of the prostatic gland in a T4 tumour. The models of early rectal cancer which comprise the central compartment only can be utilised for the assessment of suitability for the local excision of rectal cancer, while models of advanced tumours which display the central compartment in the context of the entire pelvic anatomy can be applied for preoperative planning of the beyond-TME surgery.

Garcia-Granero *et al*[16] presented the feasibility of application of a mathematical 3D-based model of image processing and reconstruction (3D-IPR) method to generate virtual 3D models of pelvis and to assess the invasion of the prostate by the rectal cancer. Two cases demonstrate the use and the diagnostic reliability of 3D-IPR models

Table 1 Characteristics of the studies and participants

Ref.	Country	Study type	Number of participants	Age (yr)	Gender (male/female)
Kontovounisios *et al*[10], 2019	United Kingdom	Feasibility	10	No data	5/5
Hamabe *et al*[11], 2017	Japan	Feasibility	2	No data	1/1
Sahnan *et al*[12], 2018	United Kingdom	Feasibility	2	No data	2/0
Przedlacka *et al*[13], 2020	United Kingdom	Feasibility	30	No data	No data
Garcia-Granero *et al*[14], 2020	Spain/Italy	Feasibility	2	No data	2/0
Garcia-Granero *et al*[15], 2020	Spain/Italy	Feasibility	2	No data	1/1
Sueda *et al*[16], 2019	Japan	Case report	1	83	0/1
Chen *et al*[17], 2020	China	Case report	1	68	1/0
Kim *et al*[18], 2020	South Korea	Prospective observational	10	Median 60; range (40-80)	8/2
Hojo *et al*[19], 2020	Japan	Retrospective Qualitative	30	No data	No data
Horie *et al*[20], 2018	Japan	Retrospective	10	Median 62; range (43-77)	8/2
Hojo *et al*[21], 2020	Japan	Retrospective	11Rectal cancer: 5	Median 67; range (56-79)	6/5
Nijkamp *et al*[22], 2018	The Netherlands	Feasibility	33Rectal cancer: 8	No data	No data
Hassinger *et al*[23], 2020	United States	Pilot study	10	No data	No data
Hojo *et al*[24], 2019	Japan	Single-centre randomised controlled	102		No data
Brannigan *et al*[25], 2006	Belgium	Feasibility	6	Mean 66.5; range (54-81)	3/3

based on preoperative pelvic MRI and correlated with pathology as reference standard. A 60-year-old male with locally advanced primary rectal cancer was found to have infiltration of levator ani muscle and prostate with an uncertain urethral invasion on the MRI scan. Contrary to that, the 3D-IPR model showed infiltration of the puborectalis muscle, but neither prostate nor urethra was invaded. Patient underwent abdominoperineal excision with TME and partial *en bloc* prostatectomy with neoadjuvant chemoradiotherapy. Pathology showed R0 resection with no residual tumour cells in the prostate gland.

The second case illustrates a patient with ulcerative colitis and locally advanced primary rectal cancer infiltrating the puborectalis muscle and the prostate, treated with neoadjuvant chemoradiotherapy. The post-treatment MRI showed low tumour regression with persistent infiltration of the puborectalis muscle and the prostate gland. The 3D-IPR reconstruction based of the post-treatment MRI showed infiltration of the puborectalis muscle bilaterally and the prostate. Patient underwent total pelvic exenteration. The histopathology report confirmed a mucinous adenocarcinoma infiltrating the puborectalis muscle and the prostate with R0 resection.

In a separate study[17], the feasibility and diagnostic reliability of the same mathematical approach with 3D-IPR model based on pelvic MRI was evaluated in the assessment of the circumferential resection margin in two patients with locally advanced primary and recurrent rectal cancer. In the first case, the MRI reported locally advanced rectal cancer infiltrating the posterior vaginal wall and the internal sphincter with dubious external sphincter infiltration. 3D-IPR confirmed infiltration of these structures but indicated clearance of the external sphincter. Patient underwent neoadjuvant chemoradiotherapy followed by inter-sphincteric anterior resection of the rectum extended into posterior vaginal wall. Pathology showed presence of fibrosis and acellular mucin pools in the posterior vaginal wall and internal sphincter and confirmed that the R0 resection was achieved. In the second case of a patient who had

Table 2 Application of the three-dimensional modelling technology

Ref.	Pathology	Surgical procedure	Application	Main findings
Kontovounisios *et al*[10]	Normal pelvis	NA	NA	Feasibility of construction of virtual 3D models of pelvis
Hamabe *et al*[11]	Normal pelvisRectal cancer	NA	NA	Feasibility of construction of 3D printed models of pelvis and rectal cancer
Sahnan *et al*[12]	Low rectal cancerUlcerative colitis	TaTME	NA	Feasibility of application of 3D models in surgical planning of TaTME
Przedlacka *et al*[13]	Rectal cancer T1-T4	NA	Preoperative planning	Feasibility of construction of virtual 3D models of T stages of rectal cancer
Garcia-Granero *et al*[14]	Locally advanced rectal cancer	TME with en block prostatectomyTotal pelvic exenteration	Preoperative planning	Feasibility of application of a mathematical method to generate 3D models and assess prostate invasion in men with rectal cancer
Garcia-Granero *et al*[15]	Locally advanced primary and recurrent rectal cancer	Beyond TME	Preoperative planning	Feasibility of application of a mathematical method to generate 3D models and assess CRM status
Sueda *et al*[16]	Upper rectal cancer	Laparoscopic anterior resection	Preoperative planning	Identification of Retzius venous short circuit prior to laparoscopic anterior resection
Chen *et al*[17]	Rectal cancer (T3N2Mx)	Laparoscopic-assisted radical resection of rectum	Preoperative planning	Preoperative recognition of situs inversus
Kim *et al*[18]	Rectal cancer with metastatic LPNs	TME with LPLND	Preoperative planning and navigation	Index LPNs among ICG-bearing lymph nodes can be identified intraoperatively by matching 3D models
Hojo *et al*[19]	Rectal cancer with metastatic LPNs	LPLND	Preoperative planning and navigation	3D -printed models are useful for surgical planning of LPLND, especially in cases with LPN metastases
Horie *et al*[20]	Advanced low rectal cancer	TME, tumour-specific mesorectal resection or total proctocolectomy with LPLND	Preoperative planning	3D reconstruction revealed vascular anatomy variations in 40%
Hojo *et al*[21]	Infra-renal recurrence of colorectal cancer	Curative resection beyond TME	Preoperative planning and navigation	Usefulness of 3D models in surgical planning and navigation for resection of infra-renal recurrence of colorectal cancer, including rectal cancer
Nijkamp *et al*[22]	Locally advanced primary and recurrent rectal cancer	Resection of tumour	Intraoperative navigation	Feasibility of integration of 3D model into the novel EM- based navigation system
Hassinger *et al*[23]	Normal pelvic anatomy	NA	Surgical education	VAPS teaches clinically relevant anatomy and is preferred to traditional methods. More detailed model is required
Hojo *et al*[24]	Lower rectal cancer	Relevant to LPLND	Surgical education	3D virtual and printed models are useful for teaching LPLND
Brannigan *et al*[25]	Middle and lower rectal cancer	Laparoscopic resection of rectal cancer	Surgical device design	The optimal angulation of a stapling device for transverse rectal transection is between 62° and 68°

TaTME: Transanal total mesorectal excision; TME: Total mesorectal excision; CRM: Circumferential resection margin; LPN: Lateral pelvic sidewall lymph nodes; LPLND: Lateral pelvic lymph node dissection; VAPS: Virtual pelvic anatomy simulator.

previously undergone anterior resection for rectal cancer, MRI images showed pelvic sidewall recurrence infiltrating the levator ani muscle and the left obturator muscle without bone infiltration. 3D-IPR also indicated the invasion of the levator ani and the left obturator muscles but additionally, it suggested the infiltration of the left seminal vesicle and the left ischial spine. Patient underwent abdominoperineal excision extending to the pelvic periosteal lamina. Pathology showed R1 resection with the invasion of the left seminal vesicle, levator ani, obturator muscle and positive CRM at the bone surface as indicated by the 3D-IPR[14].

Application of 3D modelling technology in preoperative planning and intraoperative navigation in rectal cancer surgery

Preoperative recognition of vascular anatomy: Sueda *et al*[18] reported the usefulness of the 3D reconstruction of the CT images in pre-operative planning in an 83-year-old

Table 3 Details of the three-dimensional model creation process

Study	3D model	Radiological modality	Segmentation	Segmentation performed by	Segmentation time	3D Printing time	3D printing material
Kontovounisios *et al*[10]	Virtual	MRI	Manual	No data	No data	NA	NA
Hamabe *et al*[11]	Printed	CT	Manual	Colorectal Surgeon and Technician	40 h	M – 37 h 30 min; F – 34 h 20 min	Ultraviolet-curated resin
Sahnan *et al*[12]	Virtual	MRI	Manual	Consultant gastrointestinal radiologist	Segmentation: 15 minSmoothing: 10 min	NA	NA
Przedlacka *et al* [13]	Virtual	MRI	Manual	No data	No data	NA	NA
Garcia-Granero *et al*[14]	Virtual	MRI	3D-IPR	No data	No data	NA	NA
Garcia-Granero *et al*[15]	Virtual	MRI	3D-IPR	No data	No data	NA	NA
Sueda *et al*[16]	Virtual	CT	No data	No data	No data	NA	NA
Chen *et al*[17]	Virtual	CT/MRI	No data	No data	No data	NA	NA
Kim *et al*[18]	Virtual	CT	No data	No data	No data	NA	NA
Hojo *et al*[19]	Virtual/printed	CT	Manual	Colorectal surgeon	No data	40 h (decreased with experience)	No data
Horie *et al*[20]	Virtual	CT	No data	No data	No data	NA	NA
Hojo *et al*[21]	Virtual	No data	No data	No data	No data	No data	NA
Nijkamp *et al*[22]	Virtual	CT	Automatic (bones); Semi-automatic (arteries); Manual (other structures)	No data	1-3 h		NA
Hassinger *et al* [23]	Virtual	CT/MRI	No data	No data	No data		NA
Hojo *et al*[24]	Virtual/Printed	CT	No data	Colorectal Surgeon and Radiologist	No data	22 h	
Brannigan *et al* [25]	Virtual	CT	Semi-automatic	No data	No data	NA	NA

MRI: Magnetic resonance imaging; CT: Computed tomography; 3D-IPR: Three-dimensional image processing and reconstruction.

Japanese woman with upper rectal cancer and an unexpected finding of a rare venous malformation - the Retzius venous short circuit between the inferior mesenteric vein and the inferior vena cava. During laparoscopic anterior resection, the Retzius vein and the inferior mesenteric vein were ligated without bleeding, and the mesorectal excision was successfully completed.

Chen *et al*[19] described the application of preoperative recognition of anatomy which enhanced surgical planning in a 68-year-old Chinese woman with rectal cancer (T3N2Mx) and situs inversus. Preoperative identification of the congenital anomaly through the use of 3D virtual reconstruction of patient's radiological images (CT and MRI) with Mimics system (Materialise) allowed for the safe completion of laparoscopic-assisted radical resection of rectal cancer with distal ileostomy.

LPN dissection: Kim *et al*[20] described the use of 3D reconstruction of preoperative CT images for surgical planning and intraoperative navigation during LPN dissection (LPLND). Thirteen patients scheduled to undergo TME with LPLND for rectal cancer were prospectively enrolled in the study. 3D images were constructed through volume rendering and depicted bones and essential structures in the pelvic sidewall, such as the obturator nerve and muscles, arteries and index LPNs, defined as metastatic LPNs identified on pre-treatment MRI. During surgery, LPNs were removed under the guidance of real-time fluorescence imaging with indocyanine green (ICG). The

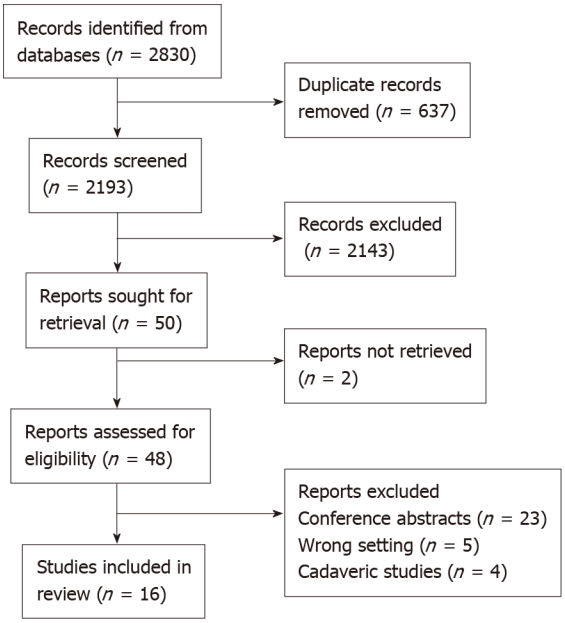

Figure 1 PRISMA flowchart.

surgeon verified the position of the index nodes with 3D reconstruction images displayed on the computer or the console monitor in the case of robotic surgery. All index LPNs among ICG-bearing lymph nodes were clearly identified intraoperatively by matching the corresponding 3D reconstructions.

Hojo *et al*[21] evaluated the subjective utility of 3D pelvic images and 3D physical models for surgical planning and navigation in LPLND. 3D images were constructed preoperatively from the enhanced CT scan images in 22 patients planned for LPLND for rectal cancer (5 open, 12 Laparoscopic, 5 robotic procedures). The models were printed with white polylactic acid. LPN metastasis was confirmed in 19 sides in 17 patients. Thirty surgeons with experience of laparoscopic colorectal surgery evaluated the subjective usefulness of 3D virtual and printed models by answering a three-item questionnaire using the 5-point Likert scale. The mean score for the subjective usefulness of a 3D model for understanding anatomy was 4.68 (range 3-5) and it was statistically significantly higher in cases with LPN metastases than in those without. Sixty percent of surgeons indicated 3D model, and 27% 3D image as the best modality for preoperative simulation. Eighty-seven percent indicated 3D model, and 13% 3D image as the best modality for intraoperative navigation. 3D models were found to be more helpful for comprehension of 3D spatial anatomy than the virtual models (4.83 and 4.36, respectively, $P < 0.001$). The ease of use of 3D models and 3D images was scored 4.60 and 4.20, respectively ($P = 0.015$).

Horie *et al*[22] reported the application of 3D virtual images in surgical planning and preoperative simulation for laparoscopic LPLND. 3D images were created from CT images and depicted the tumour, branches of the internal mesenteric artery, the iliac artery and vein, ureters, urinary bladder, enlarged lymph nodes, iliopsoas muscle and bones. The records of 10 consecutive patients with advanced low rectal cancer (below peritoneal reflection) who underwent TME, tumour-specific mesorectal resection or total proctocolectomy with LPLND after preoperative 3D simulation were retrospectively reviewed. In four cases (40%) 3D reconstruction revealed variations in vascular anatomy (confirmed intraoperatively), such as duplicate inferior vesical arteries or the obturator artery with a common origin with the internal iliac artery. Authors concluded that 3D preoperative reconstruction can be useful for the safe performance of laparoscopic LPLND.

Recurrent rectal cancer: Hojo *et al*[23] reported the utility of the 3D virtual and 3D printed models in surgical planning and navigation for the resection of intra-abdominal infra-renal recurrence of colorectal cancer. Amongst eleven patients included in the study, rectum was the site of primary cancer in five, out of which four underwent open and one laparoscopic surgery. 3D virtual images were created preoperatively for nine patients and 3D printed models for two patients. In all patients with rectal cancer virtual models used for intraoperative navigation. R0 resection was

achieved in 8 cases. The clinical applicability of this technology was presented in a case of a 65-year-old male with recurrent rectal cancer invading the external iliac artery and vein following low anterior resection. R0 resection of the recurrent tumour together with artificial replacement of both external iliac artery and vein was achieved after the multidisciplinary approach to surgical planning based on 3D virtual model.

Integration of 3D modelling and stereotactic navigation: Nijkamp *et al*[24] explored the integration of two novel technologies to enhance pelvic cancer surgery. A virtual 3D model of pelvis, including pelvic bones, arteries, veins, and ureters, derived from an enhanced CT scan was integrated into a novel electromagnetic (EM) surgical navigation system for pelvic cancer resections. The 3D model serving as a surgical roadmap was registered to an intraoperative CT scan performed with C-arm cone-beam CT during surgery. The navigation system achieved accuracy of 5 mm and required an additional operating time of 20 min. Thirty-three patients with at least one rigid tumour target were included in the study. Amongst these, seven had a locally advanced primary rectal cancer and one a recurrent rectal cancer with a deposit between external and internal iliac artery. Thirteen surgeons assessed the usability of the tracking system of which 12 completed the questionnaire. The fusion of two novel technologies was found to be feasible. The System Usability Scale score ranged between 57.5 and 95.0 (mean 74), indicating high probability of acceptance.

Surgical education

Normal pelvic anatomy: Hassinger *et al*[25] presented a pilot study of the usability and perceived effectiveness of a virtual pelvic anatomy simulator (VAPS) – an interactive virtual 3D model created through the segmentation of MR and CT images of a male patient. The interactive 3D model can be manipulated in space, and radiological images were displayed alongside the model. Pelvic structures are labelled with clinically relevant descriptions. All participants (5 medical students and 5 surgical residents) agreed that VAPS teaches clinically relevant anatomy and 90% preferred this type of education to traditional methods. Participants felt that the addition of surgically relevant anatomical details such as Denonvillier's and Weldeyer's fascia would be beneficial.

LPLND: Hojo *et al*[26] conducted a single-centre, open-label, randomised, controlled trial to compare the effectiveness and usefulness of a 3D printed pelvic model as an educational tool for LPLND. Four 3D printed models, previously used for surgical planning of LPLND in patients with rectal cancer and which displayed pelvic bones, ureter, external iliac artery and its branches, obturator nerve and pelvic sidewall muscles, were utilised. The objective utility of 3D models was evaluated with a short and long test. The short test included 10 questions related to pelvic anatomy knowledge. In the long test, participants were asked to name the anatomical structures in the textbook, in virtual 3D images, in 3D printed model and within the intraoperative scene. The subjective utility was assessed through a questionnaire.

A total of 102 participants (34 medical students, 34 residents and 34 junior colorectal surgeons without LPLND experience) were randomly assigned to two groups: the 3D model group and the textbook group. In the first education round, participants studied pelvic anatomy from the 3D model (3D model group) or from the textbook (textbook group). The groups then switched the educational methods. The participants' knowledge was assessed after each education round. Before education, there was no significant difference in knowledge between the two groups. After education, the short and long test scores of the 3D model group were significantly higher than those of the textbook group for students (short test; $P = 0.05$, long test; p-0.03), residents (short test; $P = 0.05$, long test; $P = 0.002$), and surgeons (short test; $P = 0.009$, long test; $P < 0.001$). The questionnaire showed the positive feedback rate to exceed 60%. The rate of positive feedback was lower amongst students than residents and surgeons.

Surgical device design

Brannigan *et al*[27] applied 3D modelling technology to evaluate the interaction of a standard stapling device with the rectum while dividing it during the TME procedure. Pelvic 3D models were created though semi-automatic segmentation of CT images of six patients planned to undergo elective laparoscopic resection for cancer of the middle and lower third of the rectum. Additionally, a 3D virtual model of a 45º roticulating surgical stapler was created, which allowed for preoperative assessment of the position of the cartridge head in relation to the rectum a simulation tool. The main finding was that with the use of such a stapler, it is physically impossible to achieve

perpendicular transection of the rectum. It was shown that to achieve a perpendicular position of the stapler with the mesorectal plane, the stapling device would have to enter the abdomen through right pelvic bone. The standard roticulator with angulation 45° must align with the rectum at an angle of at least 12°. The optimal angulation of the roticulating stapler for transverse rectal stapling would be between 62° and 68°.

DISCUSSION

This systematic review provides an overview of the current applications and the future directions for exploration of the 3D modelling technology in rectal cancer surgery. A small number of eligible studies identified in a thorough literature search and a relatively high proportion of the feasibility or pilot studies indicate that 3D modelling is still in its infancy within the realm of rectal cancer surgery.

TME, which can be performed *via* open, laparoscopic or robotic approach, has long been established as the gold standard surgical approach to the curative resection of rectal cancer[28,29]. The 3D models, displayed as virtual images[12,25] or physical models[11] can be used to appreciate the spatial pelvic relationships relevant to the TME surgery.

TaTME is a relatively new surgical technique, which was introduced to overcome the inherent limitations of the abdominal approach, such as poor exposure of the TME plane and difficult instrument manipulation in a deep pelvic space[30]. Sahnan *et al* [14] present the feasibility of construction of a virtual model which can enhance surgical planning and the general comprehension of the TaTME planes. As opposed to the traditional two-dimensional radiological image, a 3D model can be rotated to present the anatomy from the same angle as encountered during surgery. The opacity of the individual components of the model can also be manipulated as required.

MRI is accepted as the gold standard for assessment of rectal cancer[31,32]. The most important prognostic factor from the MR image is the distance of the tumour to the CRM[31]. CRM involvement is associated with an increased risk of local cancer recurrence[33]. Threatened CRM can be reliably assessed on preoperative MRI[34]. However, MRI has been reported to overestimate the CRM involvement in low and anterior tumours[35]. Garcia-Granero *et al*[16] present a promising novel diagnostic approach to the assessment of the CRM involvement and prostatic infiltration in locally advanced rectal cancer with the mathematic 3D-IPR model which was shown in this feasibility study to have good correlation with the pathology findings.

The same model was demonstrated to be useful in the assessment of infiltration of other surrounding structures in locally advanced primary and recurrent rectal cancer in which case the feasibility of achieving an R0 resection is of paramount significance [17]. In the case presented by the authors 3D-IPR correctly predicted the local infiltration of the ischial bone, which if used for surgical planning, would have allowed for the correct determination of the extent of resection required to achieve R0. The 3D-IPR method may have potential to identify the extent of tumour infiltration more accurately than the MRI images it was derived from but further studies are required to evaluate this.

The management of early rectal cancer presents its own challenges. Almost one-third of screening-detected rectal cancers are confined to the bowel wall without nodal spread[36]. Currently, there is wide variation in management of early rectal cancer but majority proportion of patients are treated with major surgery[37]. However, the minimally invasive approaches, such as transanal excision or transanal minimally invasive surgery are gaining increasing acceptance. High resolution MRI allows for clear depiction of the fine details of the rectal wall and it is possible to distinguish mucosa from the submucosa and the muscularis propria[38]. Przedlacka *et al*[15] demonstrate the feasibility of segmentation of the rectal wall to illustrate the depth of tumour invasion three-dimensionally. This presents the future direction of the exploration of the role of 3D models as a tool for the assessment of the indication and the extent of local minimally invasive resection.

A separate group of studies describe the role of 3D reconstructions of CT images commonly applied to the assessment of aberrant vascular anatomy or vascular pathologies which if unrecognised, pose a risk of intraoperative bleeding. The 3D virtual[39] and printed[40] models of vascular anatomy relevant to the complete mesocolic excision, particularly when performed with D3 Lymph node dissection, have been shown to be accurate[41] and to improve surgical outcomes, such as operative time, intraoperative blood loss or lymph node harvest[8,42].

In the context on rectal cancer, CT-based 3D images are particularly applicable to the LPLND. Metastasis to the internal iliac and obturator lymph nodes occur in approximately 15% of patients with low rectal cancer[43]. The optimal management of metastatic LPNs is still a subject to a debate with significant differences between the management in Eastern (particularly Japan) and Western countries[44]. Eastern countries tend to adapt a more radical surgical approach with prophylactic LPLND, while Western countries favour the use of neoadjuvant chemoradiotherapy. TME with LPLND is associated with prolonged operative time and potential morbidity, including blood loss and autonomic nerve dysfunction[45]. 3D models can be utilised to assess patient individual vascular anatomy and to locate the metastatic lymph nodes.

Hojo *et al*[21] demonstrated the subjective usefulness of the 3D models for preoperative planning and intraoperative navigation for LPLND, especially in cases with clinically metastatic LPNs. While large metastatic LPNs are easy to locate intraoperatively, the metastatic LPNs which have reduced in size due to CRT can be more difficult to identify. The use of 3D models derived from the initial staging CT scans obtained prior to the CRT can facilitate locating these nodes. The 3D printed model was perceived superior in this context to the virtual model. The value of 3D printed anatomical models in transferring complex anatomical knowledge has been previously shown by Marconi *et al*[46].

Novel technologies complement each other in providing a sophisticated environment which enhances surgical vision. Nijkamp *et al*[24] showed that it was feasible and beneficial to implement virtual 3D models into the stereotactic navigation with a novel EM-tracking system. A similarly promising feasibility for the application of a 3D model in stereotactic navigation for right hemicolectomy was reported by Volonté *et al*[47]. Optical stereotactic navigation has been previously explored in laparoscopic and robotic locally advanced rectal cancer surgery by Atallah *et al*[48,49] but in these cases it did not include the use of a 3D reconstructed model. As shown by Brannigan *et al*[27], 3D modelling technology can also be utilised to guide the development of surgical devices.

Technological advances have revolutionised surgical training as well. It has been shown that computer-based training can enhance acquisition of anatomical and pathological knowledge and that students value highly this approach[49-51]. Due to the low availability, high cost and ethical issues associated with the use of cadavers, traditional cadaver-based training is now largely replaced with simulation or even virtual reality modules[52]. However, as shown by Pellino *et al*[53] 3D models can equally enhance even the cadaveric simulation. In a patient with a rare retrorectal tumour, a 3D virtual model derived from patient's radiological images was used for cadaveric simulation of the planned complex procedure with abdominal and perineal approach.

The main factors that contribute to the slow uptake of the 3D modelling technology in rectal cancer surgery are related to the methodology of 3D image generation. 3D models are generated through the segmentation of a two-dimensional radiological image, which can be described as dividing an image into multiple labelled areas representing organs or tissues. Image segmentation relies on the principle that different tissues are characterised by specific range of pixel intensities. It can be performed manually, where each pixel of each slice of the radiological image is labelled manually, semi-automatically or fully automatically, where algorithms that recognise pixel distribution according to a pre-specified threshold are used.

3D modelling has an established role in surgical planning in maxillofacial, orthopaedic and liver surgery[5,6]. Organs, such as bones and muscles, with large contrast between pixel intensities between different tissues on radiological images, lend themselves well to the automatic or semi-automatic segmentation. Radiological MR images of the pelvis require manual segmentation due to close proximity of pixels with similar intensity representing separate organs. This can be extremely labour- and time-consuming. Hamabe and Ito[13] reported time of construction of virtual model of up to 40 h, however, it did significantly decrease with experience.

The ability to reconstruct minute pelvic structures is crucial for the clinical application of 3D modelling[24]. One of the complications of the TME surgery is the autonomic nerve injury leading to impaired urinary and sexual function. This is due to the difficult visualisation of the pelvic plexus, neurovascular bundles and pudendal nerves[54]. It has been shown in the cadaveric and living human studies that it is possible to create 3D representations of the autonomic pelvic nerves, which are at risk of injury during pelvic surgery, from the MRI scans of the cadavers or healthy volunteers, respectively[55,56]. None of the models in the studies reviewed presented pelvic anatomy in such detail.

The potential barrier in the way of clinical application of the 3D printed models in rectal cancer surgery is related to the lack of appropriate material that could replicate the elasticity and plasticity of the bowel wall or fat tissue. Hamabe and Ito[13] noted that technological developments are required before the models suitable for surgical simulation can be fabricated. While cost of 3D printing has been previously cited as another potential barrier, it was not identified as a possible limitation in the present review.

While the feasibility, clinical applicability in selected cases and subjective usefulness of the 3D models in rectal cancer surgery were reported in the studies, their accuracy and the true therapeutic impact of their use in preoperative planning and intraoperative navigation on surgical and oncological outcomes will require further investigation in well-designed randomised controlled studies.

This systematic review has limitations. Firstly, only studies published in English language were included. The level of evidence is low due to the intrinsic studies' quality. Similarly, owing to the large proportion of feasibility studies, the lack of patients' demographic information in other studies and heterogenous outcomes reported, no meaningful statistical analysis could be performed.

The future directions of development of the 3D modelling technology in rectal cancer concluded from this review should focus on three main areas – improvement of the 3D modelling technology, validation of the technology and assessment of the benefits and limitations of its application in surgical practice. Firstly, the automation or semi-automation of the segmentation of the two-dimensional radiological image should be sought to reduce the time and workload required for the construction of the 3D model. This can be achieved through the application of the artificial intelligence and machine learning algorithms.

Secondly, the fidelity of 3D models of rectal cancer and pelvis ought to be assessed through well-designed blinded studies validating the prediction of rectal cancer staging provided by the 3D model against the histological assessment of the surgical specimen. Similarly, the accuracy of the patient-specific pelvic anatomical information needs to be validated against the intra-operative findings.

Thirdly, the future randomised controlled studies are required to establish the impact of the application of 3D models on the surgical and oncological outcomes, compared to the established practice of the use of traditional two-dimensional radiological studies in the process of surgical planning. Well-designed multi-centre, randomised trials are required to assess whether there is a statistically significant difference in outcomes, such as surgical time, blood loss, complication rate, R0 resection, CRM, cancer recurrence rate or cancer-free survival, when the use of 3D models and 2D radiological images in operative planning are compared.

The current systematic review identified the need for the future exploration of the application of the 3D models in surgical training. The two examples identified in this review[25,26] indicate a level of interest in this area and show a perceived and objective improvement in anatomical knowledge with the use of 3D models in normal pelvic anatomy and anatomy specifically relevant to LPLND. However, further well-designed randomised controlled studies are needed to establish the impact of the use of the 3D models on the acquisition of pelvic and rectal anatomy understanding, as well as practical surgical skills relevant to the performance of surgical tasks during the rectal cancer surgery, such as TME procedure or minimally invasive rectal cancer approaches.

Lastly, the systematic review revealed the lack of application of 3D modelling technology in patient interaction. The future exploration of this technology needs to also focus on this aspect of the rectal cancer surgical care. It will be necessary to explore the possibility and the impact of the use of 3D models in the process of patient consultation, discussion of the treatment options and obtaining an informed consent.

The future exploration of the 3D modelling technology in rectal cancer surgery should also address the question whether the 3D printed models present any additional benefits compared to the 3D virtual models. This will be relevant to all the fields of application of this technology – surgical planning and operative rehearsal, as well as in the acquisition of the anatomical knowledge or surgical skills, and in patient interaction. In parallel, the technological improvements in the 3D printing materials are required for the construction of clinically relevant 3D printed models and are expected to allow for the creation of physical models, which can more accurately resemble human tissues.

CONCLUSION

The systematic review provides a complete, practical and comprehensive review of the current role of 3D modelling in rectal cancer surgery. It identifies the main areas of interest in this novel approach to patient-tailored image-guided surgery for rectal cancer, and it demonstrates its limitations and directions for the future development and research.

There is an increasing interest in the application of 3D modelling technology in surgical planning and navigation, as well as education, within the realm of rectal cancer surgery. The sixteen studies identified in the review were largely represented by the feasibility or pilot studies, suggesting the relative infancy of the application of this technology in rectal cancer surgery and the need for further research to evaluate its benefits and limitations in clinical practice.

3D modelling can be applied to construct the 3D models, both virtual and physical, of normal pelvic and rectal anatomy, as well as different stages of rectal cancer, including those invading other pelvic structures. 3D models can be applied in surgical planning and navigation in TME, TaTME, beyond-TME surgery or LPLND. They have been showed to improve perceived and objective anatomical knowledge relevant to rectal cancer surgery. However, thus far, 3D models of rectal cancer have not been employed in the patient education or interaction.

Further developments in the 3D modelling methodology and technological developments in 3D printing, as well as future well-designed randomised controlled trials, are necessary for the 3D modelling technology to become clinically applicable in rectal cancer surgery.

ARTICLE HIGHLIGHTS

Research background

Three-dimensional (3D) modelling technology has been gaining an increasing interest in various surgical subspecialities and aspects of surgical care, such as operative planning and navigation, surgical education and patient interaction. However, the uptake of this novel technology lags behind in rectal cancer surgery.

Research motivation

The motivation of the current systematic review is to evaluate the role of 3D modelling technology in rectal cancer surgery and to provide the future directions for its development.

Research objectives

The systemic review aims to provide a comprehensive and up-to-date review of the current applications of 3D modelling technology in rectal cancer surgery and to identify its benefits and limitations.

Research methods

Electronic databases, PubMed/MEDLINE, Embase and Scopus, were searched to identify studies addressing the application of 3D models, both virtual and physical, in rectal cancer surgery between 2000 and 2020. All full-text studies were considered eligible. Animal and cadaveric studies, as well as studies of pelvic volumetry and radiotherapy planning were excluded.

Research results

Sixteen studies were found to be eligible for inclusion in the current systematic review, amongst which there was one single-centre open-label randomised controlled trial, 4 retrospective studies, 9 feasibility or pilot studies and 2 case reports. Thirteen studies described the use of virtual 3D models, one study evaluated 3D printed models and both types of models were described in two studies. The applications of 3D modelling technology in rectal cancer surgery could be divided into four categories: (1) Feasibility of application of 3D modelling technology in rectal cancer surgery; (2) Durgical planning and navigation; (3) Surgical education; and (4) Surgical device design.

Research conclusions

The 3D modelling technology is in its relative infancy in the field of rectal cancer surgery. While the creation of virtual and physical 3D models of rectal cancer and pelvic anatomy has been shown to be feasible, future developments in segmentation technique and 3D printing materials are needed to make it clinically relevant.

Research perspectives

Further well-designed randomised controlled studies are required to assess the fidelity of virtual and physical 3D models of rectal cancer and pelvic anatomy, and to evaluate the influence of their use on surgical and oncological outcomes in rectal cancer surgery.

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