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

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

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EDITORIAL

Hot topics in pancreatic cancer management

Damiano Caputo

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is a sneaky and lethal disease burdened by poor prognosis. PDAC is often detected too late to be successfully cured, and it has been estimated that it will be a leading cause of cancer-related deaths in the near future. During the last decade, multimodal treatments involving surgery, chemotherapy and radiotherapy have contributed to improving the prognosis of this disease; however, long-term results are still not satisfactory. Postoperative morbidity and mortality rates remain high, and systemic treatments are burdened by toxicity in both neoadjuvant and adjuvant settings. Advancements in technologies, targeted therapies, immunotherapy and PDAC microenvironment modulation strategies may represent useful potential weapons in the future. Nevertheless, in the fight against this dreadful disease, there is an urgent need for new, cheap and user-friendly tools for early detection. In this field, promising results have been found in nanotechnologies and "omics" analyses that search for new biomarkers to be used in primary and secondary prevention. However, there are many issues that need to be solved before considering these tools in daily clinical practice. This editorial reported the state of the art of pancreatic cancer management.

Key Words: Pancreatic cancer; Pancreatic ductal adenocarcinoma; Nanotechnology; Neoadjuvant therapy; Adjuvant therapy; Omics

Core Tip: The purpose of this editorial was to provide an up-to-date summary of pancreatic cancer management. The current state of multimodal therapies and the increasingly urgent need for development of tools for early diagnosis were summarized. The editorial also presented the high quality papers in the fields of basic, clinical, preventive and translational medicine that will help further investigations focused on this topic.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC), one of the biggest killers among solid tumors, is set to become the second leading cause of cancer-related deaths in the near future[1]. In recent years, a lot has been done in order to improve the prognosis of PDAC. However, multimodal treatments combining surgery, still considered the gold standard of care, with chemotherapy and radiotherapy in neoadjuvant or adjuvant settings have allowed only a little progress towards better outcomes. Therefore, according to Torphy *et al*[2], pancreatic cancer management still has a long way to go.

Because of the very aggressive biology of PDAC and its indolent behavior in the early stage, the battle against this dreadful disease will be fought on the fields of prevention and early detection and improving the molecular understanding of PDAC[2]. Nevertheless, the assessment of more effective systemic treatments and strategies to improve surgical outcomes will represent an important step forward in the management of pancreatic cancer. Furthermore, much is expected from developments in targeted therapies and modulation of tumor microenvironment to improve the efficacy of immunotherapies[3].

The purpose of this editorial was to provide an up-to-date summary on pancreatic cancer management. The current state of multimodal therapies and the increasingly urgent need for development of tools for early diagnosis were also summarized.

Early detection and advances in clinical diagnosis

Given that risk factors (*e.g.*, cigarette smoking, obesity, diabetes) and genetic predisposition contribute to the development of pancreatic cancer[4], it is clear that the control of the above-mentioned risk factors represents the first, although insufficient, step to prevent PDAC. PDAC is preceded by pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasm and mucinous cystic neoplasm, and follow-up guidelines of these conditions have been widely reported. On the other hand, subjects at higher risk for familial PDAC can be successfully screened by endoscopic ultrasound and magnetic resonance cholangiopancreatography[5]. One of the main issues to be solved is the identification of individuals who are at risk of the disease even in absence of positive familiar history[6].

Clearly, invasive and expensive diagnostic investigations cannot be applied indiscriminately on a large scale for asymptomatic adults[7]. On this basis, there is still an urgent need for tools for early diagnosis of pancreatic cancer that fulfill the criteria of reliability, reproducibility and cost control required by the World Health Organization[8].

Recent technological advances have led to the revision of the so called Affordable-Sensitive-Specific-User Friendly-Rapid-Equipment Free and Delivered criteria proposed in the early 2000s to the Real Time Connectivity-Ease of specimen collection-Affordable-Sensitive-Specific-User Friendly-Rapid-Equipment Free and Delivered criteria[9]. On this basis, it is clear that the development of new tools to be used for early detection of PDAC must consider the ease of collection of biological samples such as blood, saliva, urine, *etc.*

In this scenario, our group together with the researchers of the Department of Molecular Medicine of Sapienza University of Rome were among the first to exploit the potential of nanotechnologies to assist the early diagnosis of pancreatic cancer[10]. When nanoparticles interact with human fluids (*e.g.*, plasma), a shield of molecules, mostly proteins, cover them and form the so-called biomolecular corona or protein corona. Protein corona-based technologies proved their efficacy in distinguishing pancreatic cancer patients from controls with a high rate of sensitivity (up to 85%) and specificity (up to 100%)[11].

More recently, in an attempt to make nanoparticle-based diagnostic technology even more streamlined and reproducible, approaches based on the use of magnetic levitation of nanoparticles coated by personalized protein corona have been proposed. Magnetic levitation (MagLev) may overcome protein corona analysis limitations (*e.g.*, isolation of plasma proteins from nanoparticles), boosting reproducibility and clinical translation of these technologies[12].

In the attempt to search for new biomarkers to be used in the early detection of pancreatic cancer, other remarkable results have been provided by different "omics" technologies (*e.g.*, genomics,

epigenomics, non-coding RNA, metabolomics, liquid biopsy, *etc*). Studies in these fields identified many biomarkers that proved their utility alone or in panels with different combinations. Unfortunately, their application in daily clinical practice is still a long way off as large-scale validation studies are lacking, and these technologies require expensive and complex equipment[13].

As mutations in *KRAS*, *GNAS*, *CDKN2A*, *TP53* and *SMAD4* have been shown in different staged PDAC and precancerous lesions and due to "omics" analysis advancements, the opportunity of DNA-based molecular approaches for early PDAC detection is also gaining momentum. These approaches have the advantages of being based on the assessment of genetic mutations on easily obtainable samples (*e.g.*, blood, plasma)[14].

Treatment guidelines: Standards and challenges

Surgery: Surgical resection still represents the cornerstone of pancreatic cancer treatment. However, despite recent technological improvements and the increasing diffusion of the minimally invasive approaches, morbidity and mortality rates remain significant even in high-volume centers[15].

Neoadjuvant treatments: The growing number of studies supporting vascular resections, when indicated, together with the promising results obtained with neoadjuvant therapies have undoubtedly increased the rate of PDACs that are eligible for surgical treatment. Although vascular resection, mainly when arteries are involved, should be reserved in selected cases and performed in high-volume hospitals[16], neoadjuvant treatments are gaining consensus in both the scientific community and clinical practice.

In borderline resectable PDACs, higher rates of R0 resections and longer disease-free and overall survival rates have been reported when FOLFIRINOX-based neoadjuvant treatments are used[17]. Recently, a prospective multicenter phase 2 trial demonstrated promising results when gemcitabine plus nab-paclitaxel chemotherapy were administered before surgery[18]. Even though the data supporting the use of neoadjuvant therapies in resectable PDACs are more limited, this strategy is proposed in patients with "biological" borderline resectable tumors (*e.g.*, radiological resectable PDACs with elevated levels of Ca-199)[19].

In this field, a randomized phase 2 clinical trial showed the efficacy of perioperative regimens of gemcitabine plus nab-paclitaxel in terms of disease-free survival[20]. Nonetheless, for both resectable and borderline resectable PDACs, the Dutch Randomized Phase III PREOPANC Trial showed the efficacy of neoadjuvant treatments in terms of R0 resections and disease-free survival in the absence of significant improvement of overall survival rates[21]. The other side of the coin is that patients undergo significant surgical procedures for more advanced disease after chemotherapy and radiotherapy treatments contributing to high toxicity[22].

Reduction of complications, prevention and mitigation of the effects of postoperative pancreatic fistula, optimization of neoadjuvant therapies with careful selection of patients who will actually benefit from these treatments and identification of drugs and therapeutic regimens with a more favorable balance between efficacy and toxicity will represent a turning point in the management of pancreatic cancer[23,24].

Adjuvant treatments and metastatic disease: Adjuvant chemotherapy plays an important role in the treatment of pancreatic cancer. In 2013, results of the Conko-001 trial confirmed the usefulness of adjuvant chemotherapy in improving the disease-free survival rates of surgically removed PDAC[25].

Later, gemcitabine alone proved to offer the same oncological outcomes with lower toxicity when compared to 5-fluorouracil[26]. More recently, FOLFIRINOX-based regimens have led to significant improvement in overall survival, but because of their toxicity they can be administered to only very fit patients after surgery[27]. Based on the recent data reported by Choi *et al*[28], 5-fluoruracil regimens should be considered the optimal adjuvant treatment in patients with borderline resectable and locally advanced PDAC who already received neoadjuvant FOLFIRINOX. The PRODIGE 24/Canadian Cancer Trials Group PA6 just demonstrated that in resected PDACs, adjuvant FOLFIRINOX allows significantly longer survival when compared with gemcitabine[29].

Furthermore, there is increasing evidence in favor of the use of FOLFIRINOX for patients with unresectable metastatic disease[3]. On this basis, it is clear that advances have been made in the field of adjuvant therapy, but more investigations are needed. Improvement of oncological outcomes and significant reduction of toxicity are expected from targeted therapies and immunotherapy[30].

DISCUSSION

Torphy *et al*[2] has stated that much has been done but the way to win the battle against this cancer is still long. Early detection and novel therapeutic strategies represent the most urgent issues that need to be tackled. Hence, it is necessary to develop patient models and identify cheap, user-friendly and reproducible biomarkers that can be applied in daily clinical practice to assess the most effective treatment for each patient with PDAC.

Table 1 Most relevant topics in pancreatic ductal adenocarcinoma management with their current challenges and potential further perspectives

Topic	Challenges	Potential further perspectives
Prevention and early detection	Identification of high risk subjects	Nanotechnology
	Identification of novel biomarkers and signatures that satisfy the WHO REASSURED criteria	Omics technologies
Surgical treatment	Reduction of morbidity and mortality rates	Optimization of vascular resection in high skilled hospitals
Neoadjuvant treatments	Reduction of toxicity	Careful selection of fit patients
		Identification of therapeutic regimens with favorable balance between efficacy and toxicity
Adjuvant treatments	Improvement of oncological outcomes	Targeted therapies
	Significant reduction of toxicity	Immunotherapy
Biology and behavior	Lack of patient models of the tumor in order to improve translational medicine	Organoid *ex vivo* models

REASSURED: Real Time Connectivity-Ease of specimen collection-Affordable- Sensitive-Specific-User Friendly-Rapid-Equipment Free and Delivered; WHO: World Health Organization.

In this scenario, translational research is rapidly gaining ground; organoid *ex vivo* models of PDAC can be achieved from small biopsies and may represent a turning point for precision medicine approaches in cases of resectable, locally advanced and metastatic PDAC[31]. In other words, the time seems ripe to collect all the knowledge acquired in the preclinical field over the last few decades and to recommend models of PDAC in different stages that can be used to improve our diagnostic and therapeutic strategies[32].

CONCLUSION

In the very near future we will be increasingly called upon to fight the battle against PDAC. Improvements of surgical outcomes, careful selection of patients for neoadjuvant treatments and vascular resections and reduction of the toxicity of adjuvant therapies are unquestionably needed. However, in order to increase the odds of winning the battle against this lethal disease, the real gap to be filled is the assessment of cheap and easily reproducible strategies for the screening and early detection of PDAC. Indeed, the aim of this special issue was to collect quality studies in the fields of basic, clinical, preventive and translational medicine that will further help investigations focus on these topics (Table 1).

FOOTNOTES

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REVIEW

Minimum platelet count threshold before invasive procedures in cirrhosis: Evolution of the guidelines

Marco Biolato, Federica Vitale, Tiziano Galasso, Antonio Gasbarrini, Antonio Grieco

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Abstract

Cirrhotic patients with severe thrombocytopenia are at increased risk of bleeding during invasive procedures. The need for preprocedural prophylaxis aimed at reducing the risk of bleeding in cirrhotic patients with thrombocytopenia who undergo scheduled procedures is assessed *via* the platelet count; however, establishing a minimum threshold considered safe is challenging. A platelet count ≥ 50000/μL is a frequent target, but levels vary by provider, procedure, and specific patient. Over the years, this value has changed several times according to the different guidelines proposed in the literature. According to the latest guidelines, many procedures can be performed at any level of platelet count, which should not necessarily be checked before the procedure. In this review, we aim to investigate and describe how the guidelines have evolved in recent years in the evaluation of the minimum platelet count threshold required to perform different invasive procedures, according to their bleeding risk.

Key Words: Liver disease; Thrombocytopenia; Avatrombopag; Lusutrombopag; Transfusion

Core Tip: There are several reviews in the literature that deals with the management of thrombocytopenia in patients with cirrhosis undergoing scheduled invasive procedures. However, this review is one of the few to provide a comparison between the main guidelines concerning the platelet-count reference threshold to consider safely performing the various types of procedures.

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INTRODUCTION

Thrombocytopenia, defined as any decrease in platelet count below the normal limit (< 150000/μL), is a very common hematological alteration in advanced liver disease, with an incidence of 77% to 85% in patients with cirrhosis[1,2].

Thrombocytopenia is classified as moderate when the platelet count falls into the range of 50000-100000/μL and severe if the platelet count is < 50000/μL, with an observed prevalence of 13% and 1% of patients with chronic liver disease (CLD), respectively[3]. Thrombocytopenia is the most common peripheral blood alteration with respect to anemia and leukopenia in patients with cirrhosis[4].

The development of thrombocytopenia in patients with cirrhosis can be determined by two major mechanisms, platelet sequestration and increased clearance in the spleen due to congestive splenomegaly induced by portal hypertension, a phenomenon called "hypersplenism"[5,6], and decreased production of the growth factor thrombopoietin (TPO) in the liver that regulates megakaryocyte and platelet production, whose circulating levels are lower in cirrhotic patients with thrombocytopenia than in cirrhotic patients with normal platelet counts[7-10].

Other factors, including bone marrow suppression by chronic viral infections, antiviral treatments and anticancer agents, and the development of antiplatelet antibodies, can be involved in the etiopathogenesis of thrombocytopenia.

Thrombocytopenia, which can be considered a useful early prognostic marker in cirrhotic patients [11], is associated with increased bleeding risk, thereby narrowing the available treatment options and impacting the timing and outcome of invasive procedures in this population of patients[12,13].

Even though clinically significant spontaneous bleeding does not usually occur when the platelet count is > 10-20000/μL, cirrhotic patients with severe thrombocytopenia are at increased risk of bleeding, and invasive therapeutic procedures can often be challenging to perform because of the elevated hemorrhagic risk they present[14-16].

In the past, the management of thrombocytopenia in cirrhotic patients included platelet transfusion, splenic artery embolization, splenectomy, and transjugular intrahepatic portosystemic stent shunting. Preprocedural platelet transfusion was the most common approach. However, the efficacy of platelet transfusion to reduce bleeding risks in patients with thrombocytopenia and liver disease undergoing a scheduled procedure is variable and generally does not exceed an increase in platelet count by 5000-10000/μL with a half-life of 2-4 d. Adverse effects of platelet transfusion can be associated with potentially fatal complications, such as the development of febrile nonhemolytic reactions, the transmission of infectious agents, and transfusion-related acute lung injury. Moreover, after repeated administration of platelets, refractoriness due to human leukocyte antigen alloimmunization can occur [17-21]. Finally, it should be remembered that platelet transfusion is a limited health resource, the use of which is fundamental in other clinical contexts (for example, the management of post-trauma hemorrhage in patients with a low platelet count).

Small orally bioavailable TPO receptor agonists, namely, avatrombopag and lusutrombopag, act selectively on the human TPO receptor and activate signal transduction pathways, thereby promoting the proliferation and differentiation of bone marrow cells into megakaryocytes and increasing the platelet levels. These drugs represent a promising emerging therapeutic option for the treatment of thrombocytopenia to prevent hemorrhagic events and raise the platelet count before scheduled procedures[22-24].

The phase 3, randomized, placebo-controlled, ADAPT-1 and ADAPT-2 studies demonstrated that avatrombopag was superior to placebo in reducing the need for platelet transfusions or rescue procedures for bleeding in patients with thrombocytopenia and CLD undergoing a scheduled procedure[25]. In the phase 3, randomized, double-blind, placebo-controlled study, L-PLUS 2, lusutrombopag was demonstrated to be superior to placebo in avoiding preprocedural platelet transfusion and rescue therapy for bleeding (64.8% of patients in the lusutrombopag group *vs* 29.0% in the placebo group) and in achieving a durable platelet count response in patients with thrombocytopenia and CLD undergoing invasive procedures, with a safety profile similar to placebo[26].

Similarly, a systematic meta-analysis performed by Orme *et al*[27] showed the efficacy and safety of treatment with lusutrombopag in this patient population. More patients treated with lusutrombopag (compared to placebo) required no platelet transfusion and no rescue therapy for bleeding for at least 7 days post-procedure (RR 3.42; 95%CI: 1.86, 6.26; $P = 0.0001$). Moreover, they had a lower risk of any bleeding event (RR 0.55; 95%CI: 0.32, 0.95; $P = 0.03$) but similar thrombosis event rates (RR 0.79; 95%CI: 0.19, 3.24; $P = 0.74$).

The effects of lusutrombopag on post-invasive procedural bleeding in thrombocytopenic patients with CLD were also investigated in a study by Yoshida *et al*[28]. There was a lower incidence of bleeding events in the lusutrombopag group than in the platelet transfusion group (3.7% *vs* 8.2%, $P < 0.001$) and lower average medical costs, supporting the effectiveness of this drug as a prophylactic treatment for bleeding prevention.

The need for these preprocedural treatments aimed at reducing the risk of bleeding in cirrhotic patients with thrombocytopenia who undergo scheduled procedures is assessed *via* the platelet count compared with the reference threshold considered safe. Over the years, this value has changed several times according to the different guidelines proposed in the literature. In this review, we aim to investigate and describe how the guidelines have evolved in recent years in the evaluation of the minimum platelet count threshold required to perform different invasive procedures, according to their bleeding risk.

BLEEDING RISK OF DIFFERENT PROCEDURES AND MAIN GUIDELINES

Procedures are divided into three groups by the original Society of Interventional Radiology (SIR) consensus guidelines: (1) Low risk when they are expected to rarely have hemorrhagic complications or are occurring in areas where bleeding is easy to diagnose and control (paracentesis, thoracentesis, dental extraction, diagnostic endoscopy, variceal band ligation, uncomplicated polypectomy, cardiac catheterization, central line placement); (2) Moderate risk [lumbar puncture, percutaneous or transjugular liver biopsy, transjugular intrahepatic portosystemic shunt, percutaneous gastrostomy placement, biliary sphincterotomy, percutaneous biopsy of extrahepatic organ or lesions, trans-arterial or percutaneous hepatocellular carcinoma (HCC) therapies]; and (3) High risk when they are expected to have hemorrhagic complications, occurring in areas where bleeding will be difficult to diagnose or treat or in sites where even minor amounts of bleeding may have devastating consequences (brain or spinal surgery, cardiac, intra-abdominal and orthopedic surgery, intracranial pressure catheter insertion, large polypectomy with endoscopic mucosal or submucosal resection)[29-31].

According to SIR guidelines, for patients with minimal risk factors for bleeding, screening coagulation laboratory testing is not routinely recommended for procedures with low bleeding risk, but it may be considered for patients receiving warfarin or low molecular weight heparin or those with an inherently higher risk of bleeding. Platelet transfusion should be considered for low-bleeding-risk procedures that require arterial access when the platelet count is < 20000/μL and for high bleeding risk procedures if the platelet count is < 50000/μL, obtaining an appropriate preprocedural coagulation testing[31].

Thromboelastography (TEG) seems to be a more accurate tool for the evaluation of coagulation derangement than classical tests, such as the international normalized ratio (INR) and platelet count. The reaction time (r) and maximum amplitude (MA) of TEG are able to predict the need for blood transfusion in thrombocytopenic patients undergoing invasive procedures. In a recent controlled trial on 60 patients undergoing invasive procedures, significant savings of transfusion units (both fresh frozen plasma and platelets) were observed with the use of TEG parameters compared to INR and platelets with the same bleeding complication level[32]. Unfortunately, this study was criticized because of the transfusion thresholds employed in the control arm, which were considered too extensive and not consistent with what is routinely made in clinical practice. However, in the following years, other studies and randomized clinical trials will be able to confirm the role of TEG-based transfusion in guiding and restricting transfusion both in cirrhotic patients with acute variceal bleeding and in patients undergoing invasive procedures, such as percutaneous liver biopsy, transjugular intrahepatic portosystemic shunt, percutaneous acetic acid injection and transarterial chemoembolization, without compromising hemostasis or increasing the risk of bleeding[33-36].

The main recommendations for prophylactic platelet transfusion before invasive procedures reported in the British Committee for Standards in Hematology guidelines of 2016 are about central venous line placement (> 20000/μL), lumbar puncture (> 40000/μL), surgery or percutaneous liver biopsy (> 50000/μL), insertion or removal of epidural catheters (> 80000/μL) and neurosurgery or ophthalmic surgery (> 100000/μL).

No platelet transfusions are routinely recommended before bone marrow aspirate or biopsy, peripherally inserted central catheters, traction removal of tunneled central venous catheters (CVC), and cataract surgery[37].

A consideration of platelet transfusion before high-risk procedures or when active bleeding is encountered is recommended by current guidelines and expert opinions for patients with platelet

counts below 50000/mL[38]. A relationship between platelet levels < 75000/μL and procedure-related bleeding was demonstrated in one study among patients undergoing liver transplant evaluations[39], and platelet levels < 30000/μL were also an independent predictor of major bleeding among critically ill cirrhosis patients in the intensive care unit setting[40]. However, in another prospective study, there were no predictions of postprocedural bleeding in cirrhosis by baseline platelet levels[41].

According to the Italian Association for the Study of Liver Diseases and the Italian Society of Internal Medicine consensus conference of 2016, platelet counts ≥ 50000/μL are considered to ensure normal primary hemostasis, with a recommendation to perform platelet transfusion when counts are < 50000/μL that is supported only by biological plausibility[42].

An important statement about prophylactic platelet transfusions is reported by the National Institute for Health and Care Excellence guidelines of 2015 that suggest an increase in platelet count above 50000/μL in all the patients undergoing invasive procedures or surgery; a threshold of 50-75000/μL and > 100000/μL should be taken into consideration respectively for high risk of bleeding and surgery at critical sites[43].

The American Gastroenterology Association guidelines of 2019[44] and the American College of Gastroenterology guidelines of 2021[45] do not recommend coagulation assessment and prophylactic platelet transfusions before common procedures such as diagnostic and therapeutic paracentesis, thoracentesis, upper endoscopy to screen for and band esophageal varices, and diagnostic (but not therapeutic) colonoscopy, outside of significant renal dysfunction or sepsis, suggesting that higher platelet levels may be more appropriate for high-risk procedures such as the removal of large polyps and major surgery.

According to the International Society on Thrombosis and Hemostasis guidelines of 2019[46] and the American Association for the Study of Liver Diseases (AASLD) guidelines of 2020[47] there is not a strong recommendation to correct the platelet count prior to low- and high-risk procedures.

According to the American Gastroenterology Association guidelines of 2021[48], a specific value of platelets that identifies patients at an increased bleeding risk is not defined, suggesting against preprocedural testing. Similarly, the European Association for the Study of the Liver guidelines of 2022[49] does not recommend a laboratory evaluation of hemostasis to predict postprocedural bleeding in patients with cirrhosis undergoing invasive procedures, among cases with both low and high risk of bleeding, although such analysis may serve to provide a baseline status of the patient in case of bleeding events in high-risk procedures.

Liver biopsy

Liver biopsy is performed in some cases to clarify the etiology of CLD[50], but thrombocytopenia is often considered a relative contraindication to this procedure because of an elevated risk of bleeding, especially in patients with platelet counts ≤ 60000/μL[51,52].

The risk of bleeding in patients with CLD after a liver biopsy was first investigated in the Hepatitis C Antiviral Long-Term treatment against cirrhosis (HALT-C) trial, between 2000 and 2006, in a cohort of 2740 patients with advanced chronic hepatitis C[53] and platelets ≥ 50000/μL[51], evaluating the safety and efficacy of long-term, low-dose maintenance therapy with peginterferon alfa-2a and identifying a significant difference in bleeding risk according to the platelet count (0.2% with platelets ≥ 150000/μL, from 0.6% to 0.7% for platelets between 61-150000/μL and 5.3% for platelet ≤ 60000/μL).

Another study retrospectively reported a bleeding rate of 23% in patients with platelet counts < 60 000/μL compared with no episodes of bleeding with platelet counts above this range[54]. These results were similarly reported in another small retrospective study[55]. On the other hand, certain studies did not show any correlation between bleeding risk and coagulation tests[56].

In addition, an absolute platelet count threshold does not take into account platelet function; *in vitro* data proved that platelet-related thrombin production is shown to be adequate in cirrhotic patients with a platelet count of at least 56.000/mm^3 but *in vivo*, there is no evidence that this threshold can be considered a target for pre-procedure platelet count[57].

In 2009, the pivotal AASLD guidelines dedicated to liver biopsy recommended a platelet count of at least 50-60000/μL as the safety minimum threshold of platelets to perform a liver biopsy. In the case of a high risk of complications with percutaneous liver biopsy, a transjugular approach was suggested: in a series of 51 biopsies, a threshold count of 30000/μL was identified to be safe[58].

As shown by Potretzke *et al*[59], bleeding rates after subcapsular mass biopsy (0.86%) are not significantly different from those noted after non subcapsular (0.66%) or site biopsy (0.65%), suggesting that biopsy of subcapsular lesions should no longer be considered contraindicated.

In a different setting, evaluating the safety of percutaneous liver biopsy performed with a Klatskin needle, Takyar *et al*[60] identified platelets ≤ 100000/μL and aPTT > 35 as independent risk factors for post-biopsy bleeding and suggested a higher risk of major complications in certain acutely ill subjects and those with systemic illnesses, underlining the importance of considering risk/benefit balance of liver biopsy in these patients while alternative approaches are viable.

Among the invasive procedures performed in cirrhotic patients, liver biopsy is the one for which the most solid evidence is available. Despite this fact, the guidelines have evolved considerably in the following years. This evolution concerns both the minimum platelet threshold and the perception of the bleeding risk associated with the procedure. The evolution of the guidelines regarding the minimum

threshold for the platelet count before the percutaneous liver biopsy is shown in Table 1. According to the latest guidelines, liver biopsy is considered a low-risk procedure and can be performed at any platelet count level, which should not necessarily be checked before the procedure[30,31,42-49].

Endoscopy

Routine pre-endoscopy platelet assessment in patients with a high risk for thrombocytopenia is supported by current American Society for Gastrointestinal Endoscopy (ASGE) guidelines, but there is not a determined minimum platelet count necessary for safely performing endoscopic procedures[61].

A strict threshold for an upper endoscopy is not specified, so endoscopists act based on their preference. In 2012, ASGE guidelines suggested safe platelet levels ≥ 20000/μL for diagnostic upper endoscopy and a platelet count ≥ 50000/μL for endoscopic biopsies and variceal banding[62].

Similarly, no specific platelet guidelines exist for lower endoscopy and other endoscopic procedures. Even though they are categorized by the ASGE into high and low risk for bleeding, this risk cannot be applied specifically to patients with advanced liver disease, so the strategies are often individualized. Commonly, a platelet count ≥ 50000/μL is considered for higher-risk procedures, such as large polypectomy, endoscopic treatment of hemorrhage, endoscopic retrograde cholangiopancreatography with sphincterotomy, or endoscopic ultrasound with fine needle aspiration[63,64].

Only the study by Soh *et al*[65] identified a correlation between postprocedural bleeding and platelet count (bleeding rate 27.5% with platelets ≤ 50000/μL *vs* 7.5%-relative risk 6), showing that Child-Pugh B or C cirrhosis (P = 0.011), a platelet count < 50000/μL (P < 0.001), 3 or more polyps (P = 0.017), endoscopic mucosal resection or submucosal dissection (P < 0.001), and polypectomy performed by trainees (P < 0.001) were independent risk factors for immediate post polypectomy bleeding.

Endoscopic band ligation of esophageal varices is a common procedure in cirrhotic patients. For patients undergoing this procedure, the risk of post banding ulcer bleeding has been variably reported, ranging from 2.8%[66] to 7.3%[67], but in both studies, the platelet count was not associated with bleeding risk. Other observational studies confirmed that platelet count is not a predictor of post ligation bleeding and six-week mortality in patients with rebleeding, but only lower fibrinogen levels have a significant correlation with them[68,69]. According to AASLD Practice Guidelines for the management of variceal bleeding, a recommendation about platelet transfusion in patients with variceal hemorrhage is not provided[70]. In contrast, other guidelines consider a platelet count of 50000/μL as a minimum threshold to perform the endoscopy procedure[71].

The guidelines for the minimum platelet count threshold before esophageal variceal band ligation are shown in Table 2. Additionally, in this case, the revision of the guidelines has gone toward the abolition of a minimum safety threshold of the platelet count to be obtained before the procedure. It should be noted that the perception of the risk of bleeding is very different between the various guidelines, depending on which of the few studies available were included in the bleeding risk calculation and what their relative weight was[30,42-49,61,70,71].

Even though transfusion of blood products in CLD has the apparent clinical benefits of correcting thrombocytopenia and deranging INR, many studies have shown its association with several risks, such as rising portal pressure and predisposition to a vicious cycle of rebleeding, extended hospital stays, and poorer outcomes[72-74].

Similarly, Biswas *et al*[75] investigated how platelet counts, platelet transfusions, and fresh frozen plasma transfusions affect the outcomes of acute variceal bleeding in cirrhosis patients in terms of bleeding control, rebleeding, and mortality. In a cohort of 913 patients stratified into three different groups according to platelet count (< 20000/μL, 20000/μL-50000/μL, > 50000/μL), thrombocytopenia did not affect rebleeding rates on days 5 and 42 (13%, 6.5%, and 4.7%, respectively, on day 5; and 21.7%, 17.3%, and 14.4%, respectively, on day 42) and mortality rates (13.0%, 23.2%, and 17.2%, respectively) that were similar between the three platelet groups. However, platelet transfusion increased rebleeding on day 5 (14.6% *vs* 4.5%; P = 0.039) and day 42 (32.6% *vs* 15.7%; P = 0.014) compared to patients who did not receive it, with a higher but nonsignificant effect on mortality (25.8% *vs* 23.6%)[75].

These studies support the view that a restrictive transfusion strategy is beneficial compared to a more liberal one and that the correction of coagulopathy is often a futile target in the management and control of acute variceal bleeding.

Paracentesis and thoracentesis

Data on patients with abnormal coagulation profiles (INR > 1.5 and/or platelet counts < 50000/μL) indicate that paracentesis[15,76,77] and thoracentesis[78-81] pose a very low risk for major bleeding.

Patients with advanced CLD usually need to undergo therapeutic large-volume paracentesis for the management of tense or recurrent ascites. It is an important routine diagnostic and therapeutic procedure used to evaluate the etiology of ascites and the presence of spontaneous bacterial peritonitis. Rarely, the procedure could be complicated by potential abdominal wall hematoma and hemoperitoneum after a puncture of abdominal wall collateral under high portal pressure[82].

However, the safety of this procedure in the setting of thrombocytopenia is demonstrated in real-world experiences, showing minimal bleeding complications (< 0.02%) in a platelet count range from 19000/μL to 341000/μL. In these two studies, risk factors for severe bleeding were only higher model for end-stage liver disease (MELD) scores and renal failure[83,84]. Rowley *et al*[85] confirmed that

Table 1 Threshold of platelet count before percutaneous liver biopsy: evolution of the guidelines

Society	Year	Bleeding risk	Platelet count threshold (/μL)	Ref.
National Institute for Health and Care Excellence	2015	Not classified	50000	National Clinical Guideline Centre (UK)[43]
British Committee for Standards in Haematology	2016	Not classified	50000	Estcourt *et al*[37]
Italian Association for the Study of Liver Diseases and the Italian Society of Internal Medicine	2016	Low	50000 "this recommendation is supported only by biological plausibility"	Under the auspices of the Italian Association for the Study of Liver Diseases (AISF) and the Italian Society of Internal Medicine (SIMI)[42]
International Coagulation in Liver Disease	2017	Intermediate	"Generally not recommended"	Intagliata *et al*[30]
American Gastroenterological Association	2019	Intermediate	50000	O'Leary *et al*[44]
Society of Interventional Radiology	2019	High	50000 (20000 for transjugular liver biopsy)	Patel *et al*[31]
American Association for the Study of Liver Diseases	2020	High	"Suggest individualized approaches"	Northup *et al*[47]
American College of Gastroenterology	2020	Not classified	Correction not recommended	Simonetto *et al*[45]
International Society on Thrombosis and Haemostasis	2021	High	Do not correct	Roberts *et al*[46]
American Gastroenterological Association	2021	High	"Suggests against the prepro-cedural testing"	O'Shea *et al*[48]
European Association for the Study of the Liver	2022	Low	"Cannot be generally indicated"	European Association for the Study of the Liver [49]

postprocedural hemorrhage is very rare (0.19%) when paracentesis is performed with real-time ultrasound guidance by radiologists, without correction of coagulation abnormalities with prophylactic blood product transfusion. In this setting, the incidence of hemorrhagic events is probably related to the patient's clinical condition rather than the platelet count since the presence of portal hypertension is associated with bleeding regardless of platelet count.

Other retrospective reviews on thoracentesis suggest similar results, reporting 17 bleeding-related complications after thoracentesis in 9320 patients (0.18%), all of which occurred in patients with platelet counts > 50000/μL[86].

Hence, no prophylactic blood product transfusions before paracentesis and thoracentesis are recommended by national and international consensus guidelines in the setting of thrombocytopenia and coagulopathy because of this very low risk of bleeding[85,87,88].

Central venous line

Insertion of a CVC for the management of gastrointestinal bleeding in the setting of intensive care treatment is commonly required in cirrhotic patients. Studies in the literature describe only a very low incidence of bleeding, such as mild oozing and hematomas controlled with local pressure, as a complication of this procedure in patients with thrombocytopenia, showing no association between platelet count and bleeding complications[89-91].

Only one study reported a high rate of non-severe bleeding (32%) in patients with platelet counts below 20000/μL[91]. Similarly, another study identified a platelet count of < 30000/μL as a cut-off for hematoma formation and ooze[92]. Stecker *et al*[93] observed a prolonged time of hemostasis in cirrhotic patients with tunneled cuffed CVC at the moment of removal but did not report a relevant relationship with the platelet count.

A 2015 Cochrane review highlighted that no randomized controlled trials about the platelet count minimum threshold to safely perform a CVC insertion were available[94], with an enormous variation of the reference recommended according to the different countries considered, from 50000/μL in the United Kingdom[95] to 30000/μL and 20000/μL respectively in Belgium[96] and the United States[97], and only 10000/μL in Germany.

Presently, non-randomized studies are available concerning the safety of invasive procedures in cirrhotic patients with thrombocytopenia without prophylactic platelet transfusions[98-100]. A guideline updated by the American Association of Blood Banks based on 8 observational studies asserts that a recommendation is given if the platelet count is < 20000/μL for patients undergoing elective CVC placement, and this is also supported by the American Society of Clinical Oncology, which states that "certain procedures, such as bone marrow aspirations and biopsies, and insertion or removal of CVCs, can be performed safely at counts > 20000/μL"[101].

Table 2 Threshold of platelet count before esophageal variceal band ligation: evolution of the guidelines

Society	Year	Bleeding risk	Platelet count threshold (/μL)	Ref.
American Society for Gastrointestinal Endoscopy	2014	Not classified	"Not recommended"	ASGE Standards of Practice Committee *et al* [61]
National Institute for Health and Care Excellence	2015	Not classified	50000	National Clinical Guideline Centre (UK)[43]
American Association for the Study of Liver Diseases	2016	Not classified	"Not provided a recommendation"	Garcia-Tsao *et al*[70]
Italian Association for the Study of Liver Diseases and the Italian Society of Internal Medicine	2016	Moderate	50000 "this recommendation is supported only by biological plausibility"	Under the auspices of the Italian Association for the Study of Liver Diseases (AISF) and the Italian Society of Internal Medicine (SIMI)[42]
Austrian Society of Gastroenterology and Hepatology and the Austrian Society of Interventional Radiology	2017	Not classified	50000	Reiberger *et al*[71]
International Coagulation in Liver Disease	2017	Low	"Generally not recommended"	Intagliata *et al*[30]
American Gastroenterological Association	2019	Low	"Prophylaxis not required, although the authors recognize that risk assessment will vary in the clinical context"	O'Leary *et al*[44]
American Association for the Study of Liver Diseases	2020	Low	"Suggest individualized approaches"	Northup *et al*[47]
American College of Gastroenterology	2020	Not classified	Correction not recommended	Simonetto *et al*[45]
International Society on Thrombosis and Haemostasis	2021	Low	Do not correct	Roberts *et al*[46]
American Gastroenterological Association	2021	Low	"Suggests against the preprocedural testing"	O'Shea *et al*[48]
European Association for the Study of the Liver	2022	High	"Generally not indicated"	European Association for the Study of the Liver[49]

Dental extractions

Dental extractions are frequently performed in cirrhotic patients to remove sources of systemic infection or before they are listed for liver transplantation (LT). Cocero *et al*[102] showed in their retrospective analysis of 1183 extractions in 318 patients that the bleeding rate was 0.4% in those with platelet count > 40000/μL and INR < 2.5 and that the rate increased with both platelet count < 40000/μL and INR > 2.5. In a study of 190 visits for the extraction of 333 teeth in cirrhotic patients with platelet counts 16-216000/μL, 12 patients (6%) had hemorrhagic complications that were controlled with local measures [103]. Similarly, in 23 patients with platelet counts > 30000/μL, postoperative bleeding was observed in only 2.9% (one patient) of procedures and was treated using only local hemostatic measures without the need for transfusion[104]. Overall, the data suggest that local hemostatic techniques or intranasal desmopressin can be employed instead of platelet transfusion, which is not necessary.

Lumbar puncture

Generally, platelet goals of 50000/μL are widely recommended for many procedures[101]. Devastating neurological consequences could potentially occur in cases of bleeding within the central nervous system. For this reason, procedures such as vertebral augmentation and procedures with a risk of epidural bleeding are usually classified as associated with high bleeding risk[105].

A platelet count of 50000/μL is recommended as the threshold for lumbar puncture by the American Association of Blood Banks[97]. Moreover, it is supported by the Canadian C17 guidelines committee [106], considering platelet transfusions for diagnostic lumbar puncture for newly diagnosed pediatric patients with leukemia when platelets are < 50000/μL and a threshold for transfusion of 20000/μL for pediatric patients in a stable condition requiring lumbar puncture.

However, Chung *et al*[107] recently conducted a study of oncology patients and compared the incidence of lumbar puncture-related complications for groups above and below the minimum platelet threshold (50000/μL). The results revealed that patients with platelet count less than 50000/μL did not have a higher incidence of clinically significant postlumbar puncture complications (P = 0.29). This evidence, although the study did not specifically involve patients with CLD, underlines the low-quality evidence of the minimum preprocedural platelet threshold of 50000/μL for transfusion, adding strength to the concept that further studies are necessary to clarify this assumption.

Neurological surgery and vascular procedures

For non-neurological surgery, a count of 50000/μL is considered acceptable, but higher platelet goals (closer to 100000/μL) are recommended in patients with neurosurgical needs[105,106,108]. Similarly, a correlation between a platelet count < 100000/μL and a higher incidence of post-angiographic hematoma in patients undergoing femoral arterial puncture for a diagnostic or therapeutic vascular procedure has been demonstrated[109].

Transarterial chemoembolization

There is very little evidence in the literature regarding transarterial chemoembolization. Several guidelines from 2017 to 2022 classified this type of procedure as posing intermediate or high risks of bleeding, but no recommended correction of the platelet count before the procedure was made[30,46,47,49].

The evolution of the guidelines regarding the minimum threshold of the platelet count before transarterial chemoembolization is shown in Table 3[30,43,46,47,49]. Additionally, in this case, the scarcity of evidence available in the literature is the basis of the evident inhomogeneity of the guidelines.

Regarding radiofrequency ablation, a correlation between a platelet count < 50000/μL and an increased risk of postprocedural bleeding (OR = 8.79) was found only by Park *et al*[110], but the study was biased by prophylactic platelet transfusion in patients with platelets < 50000/μL.

SIGNIFICANT LIMITATIONS AND FUTURE PERSPECTIVES

One of the limitations in this field is that currently in the literature, there are no studies with solid data relating to the risk of bleeding and the minimum platelet threshold considered safe for performing surgery either by laparotomy or laparoscopy.

Regarding urological surgery[111,112], cholecystectomy, and herniotomy[113-117], the available evidence is not enough to assess the association between platelet count and postprocedural bleeding risk because of the wide heterogeneity in the management of blood coagulation parameters in the preprocedural phases of surgical interventions.

Similarly, in LT, the risk and extent of bleeding are difficult to quantify, and in liver surgery, none of the studies available in the literature evaluate the association between platelet count and bleeding risk [118-123]. This is probably because moderate-to-severe thrombocytopenia is often considered a contraindication to liver surgery, and patients are treated with pre- or intraoperative platelet transfusions. Regarding this topic, Maithel *et al*[124] showed that even mild thrombocytopenia (platelet count < 150000/μL) was predictive of major postoperative complications and mortality after resection of HCC independent of functional scores.

Although Chai *et al*[125] reported successful combined coronary artery bypass grafting (CABG) and LT in a patient with a baseline platelet count of 50000/μL, the minimum threshold of platelets before CABG is > 50000/μL for the safe administration of heparin intraoperatively and dual antiplatelet therapy post-CABG. However, platelet transfusion during coronary artery bypass graft surgery was demonstrated by Spiess *et al*[126] to be associated with prolonged hospital stays, longer surgeries, more bleeding, reoperation for bleeding, more red blood cell transfusions, infections, vasopressor use, respiratory medication use, stroke, and death. In this scenario, a case report by Almalki *et al*[127] described the off-label, successful use of avatrombopag in a patient with a platelet count of 18000/μL and thromboembolic risks who was a candidate for combined coronary artery bypass grafting and LT, allowing him to proceed with 2 life-saving procedures.

Other areas that need further investigation include elderly patients, for whom there are currently no data collected in the literature, and the possible use of TEG to drive platelet transfusion before scheduled procedures. In this regard, more attention should be given to the inclusion criteria of patients and controls and the definition of a clear primary end-point (namely, procedural bleeding).

CONCLUSION

Thrombocytopenia is common in patients with advanced liver disease and can adversely affect treatments, limiting the ability to administer therapy and delaying planned surgical or diagnostic procedures because of an increased risk of bleeding. A platelet count ≥ 50000/μL is a frequent target in the literature, but levels vary by provider, procedure, and specific patient[3,128,129].

As we have presented in this review, the position of the guidelines has changed over the years, moving toward abolishing the concept of a minimum safety threshold of the platelet count to perform various procedures, with the need to individually evaluate each case according to a precision medicine strategy. However, this evolution has not been supported by new studies documenting the bleeding risk of the various invasive procedures in cirrhotic patients. In our opinion, that position reflects a methodological critique by the scientific community about TPO agonist trials. All trials on avatrombopag and

Table 3 Threshold of platelet count before trans-arterial chemoembolization: Evolution of the guidelines

Society	Year	Bleeding risk	Platelet count threshold (/μL)	Ref.
National Institute for Health and Care Excellence	2015	Not classified	50000	National Clinical Guideline Centre (UK)[43]
International Coagulation in Liver Disease	2017	Intermediate	"Generally not recommended"	Intagliata *et al*[30]
American Association for the Study of Liver Diseases	2020	High	"Suggest individualized approaches"	Northup *et al*[47]
International Society on Thrombosis and Haemostasis	2021	High	Do not correct	Roberts *et al*[46]
European Association for the Study of the Liver	2022	Low	"Cannot be generally indicated"	European Association for the Study of the Liver[49]

lusutrombopag were designed using the 50000/μL platelet threshold, choosing as the primary endpoint the number of platelet transfusions avoided and using a control arm in which all patients underwent platelet transfusions, assuming it was the standard of care. The criticisms were centered on the absence of a control arm without bleeding prophylaxis (which would have allowed a true estimate of the risk) and the decision not to choose bleeding as the primary endpoint.

To overcome this situation of open controversy between hepatologists and specialists of the various disciplines who practice invasive procedures on cirrhotic patients, more good quality evidence is needed to accurately define the bleeding risk of the various invasive procedures and their relationship with the platelet count, and studies of better methodological quality need to be carried out to support such decision-making.

FOOTNOTES

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REVIEW

Comprehensive multimodal management of borderline resectable pancreatic cancer: Current status and progress

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Abstract

Borderline resectable pancreatic cancer (BRPC) is a complex clinical entity with specific biological features. Criteria for resectability need to be assessed in combination with tumor anatomy and oncology. Neoadjuvant therapy (NAT) for BRPC patients is associated with additional survival benefits. Research is currently focused on exploring the optimal NAT regimen and more reliable ways of assessing response to NAT. More attention to management standards during NAT, including biliary drainage and nutritional support, is needed. Surgery remains the cornerstone of BRPC treatment and multidisciplinary teams can help to evaluate whether patients are suitable for surgery and provide individualized management during the perioperative period, including NAT responsiveness and the selection of surgical timing.

Key Words: Borderline resectable pancreatic cancer; Neoadjuvant therapy; Resectability; Surgery; Multimodality treatment; Multidisciplinary teams.

Core Tip: Borderline resectable pancreatic cancer (BRPC) is a type of pancreatic cancer with specific biological characteristics. To date, there is no unified comprehensive management for this disease. Thus, an evaluation of BRPC resection and neoadjuvant therapy (NAT) is needed. This review summarizes new resection methods and different NAT schemes, including treatment efficacy evaluation and management. This study also discusses the current progress of surgical treatment and the use of multidisciplinary teams to provide comprehensive multimodal management of BRPC treatment.

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INTRODUCTION

Pancreatic cancer (PC) has the poorest prognosis of all common cancers with a 5-year relative survival rate of only 11%. In the United States, the PC incidence rate ranked 10th among males and 8th among females in 2022[1]. Even with recent advances in treatment, survival has not improved significantly in the last 10 years[2]. The only potentially curative treatment for this disease is surgical resection, however, 80%–85% of patients are not candidates for resection due to nonspecific symptoms and a lack of early diagnostic methods[3].

It is critical to identify specific borderline resectable pancreatic cancer (BRPC) patients who could be eligible for radical surgery. This disease is currently classified into four types for clinical management: RPC, BRPC, and unresectable PC, including locally advanced pancreatic cancer (LAPC) and metastatic PC. BRPC is further divided into PC with arterial invasion and PC with superior mesenteric vein (SMV) /portal vein (PV) invasion only[4]. The indications for surgery have expanded over the past few decades with advances in surgical techniques and improved preoperative imaging precision. The term "borderline resectable" was first introduced by the MD Anderson Cancer Center group in 2006[5]. Although surgery is technically feasible because it is localized and does not metastasize, BRPC carries a high risk of positive margins due to vascular infiltration[6,7]. In other words, the microscopic/macroscopic residual (R1/R2) resection rate is high while the margin-negative resection (R0) rate is significantly associated with poor prognosis and early recurrence[8]. The preferred treatment for BRPC is neoadjuvant therapy (NAT) and re-assessment for possible curative resection. NAT has an early clinical benefit against PC but there is no consensus on the optimal regimen for patients with BRPC. In addition, patient responsiveness to NAT and the optimal protocol for biliary drainage and nutritional support requires further study. Over the past decade, there has been a lack of consensus about the optimal timing of surgery after NAT, the extent of lymph node dissection and arterial resection and reconstruction, and the need for intraoperative adjuvant therapy. Since BRPC patient management involves several medical fields, multidisciplinary teams (MDTs) are needed to assure the different treatment modalities are connected to maximize their benefit.

REAPPRAISAL OF RESECTABILITY CRITERIA

Historically, the resectability of PC has been dependent on the contiguous relationship between the celiac axis (CA), the superior mesenteric artery (SMA)/SMV, the PV, and the common hepatic artery (CHA). Improvements in surgical methods and post-surgical care have meant that tumor infiltration of the SMV/PV, SMA, HA, or CA is no longer a surgical contraindication. With the development of surgical techniques, especially increase in safety of vessel reconstruction, the range of resectability as defined by anatomy has expanded over the past 20 years[9-12]. The National Comprehensive Cancer Network (NCCN) guideline is the most widely used standard for the resectability of anatomy for BRPC patients because it distinguishes between pancreatic body/tail and pancreatic head/uncinate process tumors[13]. To assure uniformity and standardization in reporting and trial enrollment, this standard also eliminates the anatomically ambiguous terminology previously used to describe the interface between the tumor and nearby blood vessels (such as vascular "abutment," "encasement," "occlusion," and "impingement"), in favor of defining ≥ 180° as a detailed degree of the interface between the tumor and each vessel[14].

BRPC is shown to be a particularly aggressive disease that may not benefit from upfront surgery. Biological parameters are used to evaluate resectability[15]. Some patients have no peripheral vascular invasion and imaging results indicate that the lesions can be respected and preoperative carbohydrate antigen 19-9 (CA19-9) levels are significantly increased. Other patients have positron emission

tomography/computed tomography (PET/CT) results that indicate that the regional lymph nodes (LN) are suspicious and positive. Thus, a new international consensus on BRPC classification was suggested by the International Association of Pancreatology (IAP) in 2017[4].

IAP-BR-criteria added biological factors including CA19-9 ≥ 500 IU/mL and regional LN metastasis by biopsy or PET/CT into the BRPC definition based on anatomic criteria (BRPC type-a), defined as BRPC type-b. BRPC type-a with the addition of conditional factors such as Eastern Cooperative Oncology Group Performance Status (ECOG PS) 2 or more is defined as BRPC type-c. In a cohort of 369 patients with RPC, Kato *et al*[16] compared IAP-BR-criteria and NCCN-BR-criteria and found that IAP-BR-criteria were more effective at predicting prognosis.

In 2021, potential modifications to the current resectability classification based on IAP-BR-criteria, including additional candidate factors, were discussed at the Japanese Society of Hepato-Biliary-Pancreatic Surgery[17]. At this meeting, further candidate factors were proposed. PET/CT maximum standardized uptake values (SUV max) of the primary tumor were suggested for use as biological indicators to evaluate resectability and therapy response after NAT, while carcinoembryonic antigen, cancer antigen 125, or pancreatic cancer-associated antigen-2 were proposed for use as surrogate tumor markers in Lewis's antigen-negative patients. For conditional host-related factors, age, Charlson-Dayo comorbidity, and markers of the systemic inflammatory response such as the modified Glasgow Prognostic Score or the neutrophil/Lymphocyte ratio (NLR) were also suggested for evaluating the resectability. More interestingly, new prognostic "genomic" markers that include germline deoxyribonucleic acid (DNA) damage repair mutations such as *S100A2*, *S100A4*, *KRAS,* and therapeutic target markers, including microsatellite instability, *BRCA1*, *BRCA2*, and other homologous recombination deficiency gene mutations, were also considered to have application potential and to be of value for further research.

Several genomic, transcriptomic, morphological, proteomic, metabolomic, and immune subtyping methods for PC were reviewed by Huang *et al*[18], of which the immune and morphological subtypes are associated with prognosis. Wartenberg *et al*[19] used immunohistochemical staining of immune cells in the tumor microenvironment to classify PC into three types: Immune-escape, immune-rich, and immune-exhausted. The immune-rich subtype was associated with a better prognosis. N Kalimuthu *et al*[20] classified PC into gland-forming and non-gland forming subtypes by histopathology and reported that patients with < 40% non-gland forming subtypes had superior overall survival (OS). The other classification subtypes were primarily used to predict the feasibility of chemotherapy and the efficacy of immunotherapy or targeted therapies.

In summary, resectability aims to make resection "meaningful" and promote a more favorable prognosis rather than maintaining a single focus on the resection rate. The various subtyping approaches for PC should be integrated and simplified using multiomics. Current studies still rely solely on the anatomical definition of BRPC (Figure 1). Future research needs to consider BRPC biological factors and use standardized resectability evaluation criteria to ensure that findings are comparable across studies.

NAT FOR BRPC

To date, approximately 20% of PC patients are surgical candidates at the moment of diagnosis, 30% are BRPC or LAPC, and 50% have metastatic disease and are ineligible for surgery[3]. The architectural features of BRPC are such that even after extensive dissection of the nerve plexus along arteries, upfront surgery without NAT frequently results in a high R1 resection rate[6,7]. The current standard for BRPC treatment typically starts with preoperative chemotherapy or chemoradiotherapy, because NAT could degrade the stage and improve the R0 resection rate[21-25]. In addition to controlling local disease, the absence of tumor progression following NAT is a selection criterion for identifying tumors that are less biologically invasive or respond well to systemic therapy. Thus, this treatment can help to identify optimal surgical candidates. Moreover, because many postoperative patients cannot accept adjuvant therapy due to complications, NAT can help to reduce the incidence of pancreatic fistula and increase the completion rate of multimodality therapy. In summary, NAT is primarily used to select suitable surgery candidates and improve the tolerance of preoperative treatment[7,26,27].

Long-term results of the PREOPANC trial were published in 2022[27]. The findings revealed a significant difference in the OS of patients who received NAT (3 cycles of neoadjuvant gemcitabine + 2 cycles of radiotherapy with 36 Gy) and those who received upfront surgery. At a median follow-up of 59 mo, the neoadjuvant chemoradiotherapy group had a median survival time (MST) of 15.7 mo, while the upfront surgery group had an MST of 14.3 mo (HR, 0.73; 95%CI, 0.56–0.96; $P = 0.025$). Moreover, the 5-year OS rate for patients who underwent NAT or upfront surgery was 20.5% and 6.5%, respectively. The NAT group also had a higher R0 resection rate than the upfront surgery group (72% *vs* 43%, $P < 0.001$). Although single gemcitabine is no longer a standard treatment for PC patients, the PREOPANC trial showed that gemcitabine combined with NAT, surgery, and adjuvant chemotherapy was effective against BRPC. van Dam *et al*[28] conducted a meta-analysis and subgroup analysis of 5 randomized controlled trials (RCTs) in which BRPC was included and found that NAT was associated with higher

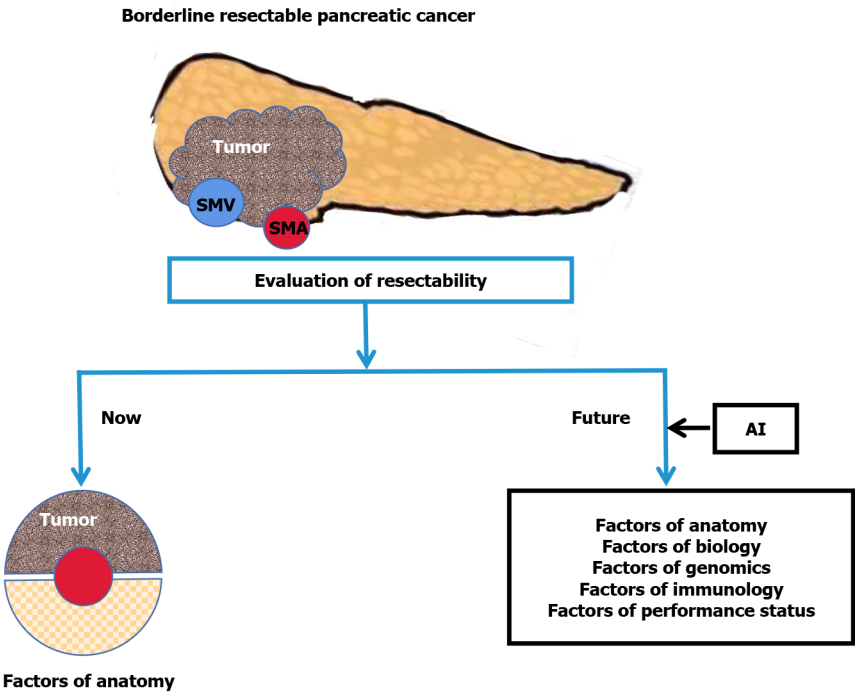

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Figure 1 Evaluation of resectability for borderline resectable pancreatic cancer. SMV: Superior mesenteric vein; SMA: Superior mesenteric artery; AI: Artificial intelligence.

OS of patients with BRPC (HR 0.61, 95%CI 0.44–0.85; P = 0.004; I^2 = 59%). Both neoadjuvant chemotherapy (NACT) (HR 0.54, 95%CI 0.34–0.87; P = 0.01; I^2 = 64%) and neoadjuvant chemoradiation (NACRT) resulted in a higher OS than upfront surgery (HR 0.74, 95%CI 0.58–0.95; P = 0.02; I^2 = 7%). Since NAT improves the R0 resection rate and OS, European Society of Medical Oncology (ESMO)[29] and NCCN guidelines[13] recommend NAT over upfront surgery for BRPC.

Neoadjuvant chemotherapy or neoadjuvant chemoradiation therapy?

Due to the lack of RCT data, there is no consensus on a preferred NAT regimen. However, NCCN guidelines[13] recommend fluorouracil-leucovorin-irinotecan-oxaliplatin/modified fluorouracil-leucovorin-irinotecan-oxaliplatin (FOLFIRINOX/mFOLFIRINOX) ± radiation or gemcitabine/nab-paclitaxel (GNP) ± radiation as the first-line regimens[13]. A SWOG-1505 preliminary analysis was reported more recently. This study evaluated mFOLFIRINOX and GNP in the NAT setting of RPC and found that the GNP arm was associated with a higher median disease-free survival (DFS) (14.2 *vs* 10.9 mo, P = 0.87) and a complete or moderate pathological response (42% *vs* 25%) than the mFOLFIRINOX arm. However, the resection rate, R0 resection rate, and 2-year OS did not differ between the groups [30]. Of note, there was no significant difference in the toxicity profile of the GNP and mFOLFIRINOX groups in this research. A phase II study conducted by Kondo *et al*[31] included 47 patients with BRPC-arterial contact who received six cycles of a neoadjuvant gemcitabine, nab-paclitaxel plus S-1 regimen. The R0 rate was 86%, and the 2-year OS rate and median OS time among 47 eligible patients were 70.1% and 41.0 mo, respectively. More RCTs are needed to compare these two first-line neoadjuvant chemotherapy regimens.

For PC patients with known *BRCA1/2* or *PALB2* mutations, NCCN guidelines recommend FOLFIRINOX/mFOLFIRINOX or GNP plus platinum complex treatment[13]. Similar to breast cancer, key proteins involved in homologous recombination during PC include *BRCA1* and *BRCA2*, and *PALB2* is a critical regulator of *BRCA2* function[32-34]. Prior studies have shown that platinum-based treatment increases the OS of patients with advanced PC who have germline mutations in *BRCA1*, *BRCA2*, or *PALB2*[35-37]. A retrospective study found that patients with these mutations had an overall response rate (ORR) of 58% while those in the control group had an ORR of 21% (P = 0.0022). In addition, the real-world progression-free survival was 10.1 mo for patients with these mutations and 6.9 mo for controls (HR 0.43; 95%CI 0.25–0.74; P = 0.0068)[38].

The role of radiation or chemoradiation during NAT for BRPC remains unclear[39]. NACRT uses radiotherapy to sterilize tumor boundaries that are in contact with vasculature and chemotherapy to treat any undiagnosed micro-metastatic disease. Intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT), three-dimensional conventional radiation therapy (3D-CRT), and intraoperative radiation therapy (IORT), have all been used for patients with BRPC[40]. Retrospective evidence suggests that NACRT may be associated with a higher proportion of margin-

negative resections than NACT[41].

Studies have further divided the current NACRT regimen into concurrent chemoradiotherapy with or without induction chemotherapy (Table 1). Until now, RCTs that directly compare NACRT and NACT are lacking in patients with BRPC. A021501 study enrolled 126 patients with BRPC, of whom 70 (55.6%) and 56 (44.4%) were randomized into an NACT arm and an NACRT arm, respectively. The NACT arm received eight doses of mFOLFIRINOX while the NACRT arm received eight doses of mFOLFIRINOX followed by a hypofractionated protocol that uses SBRT 33-40 Gy or image-guided radiotherapy (RT) with 25 Gy. After NAT, patients without disease progression underwent a pancreatectomy along with four additional doses of oxaliplatin-calcium-folinate-fluorouracil (FOLFOX6). Of the first 30 patients in each arm, the R0 rate was achieved in 10 (33%) and 17 (57%) patients in the NACRT and NACT arms, respectively, resulting in the closure of the NACRT arm and continuation of the NACT arm. The 18-mo OS rates were 66.7% and 47.3% in the NACT and NACRT arms, respectively, while the median OS of patients was 29.8 and 17.1 mo in the NACT and NACRT arms, respectively. These findings suggested that NACT alone was associated with a more favorable prognosis than NACRT among patients with BRPC[42].

ESPAC-5F is a four-arm, multicenter, phase II trial that evaluated different approaches to NAT among patients with BRPC. Ninety patients were randomly assigned to four arms: Upfront surgery, two cycles of gemcitabine + capecitabine followed by surgery, four cycles of FOLFIRINOX followed by surgery, and NACRT with 50.4 Gy over 28 fractions with concurrent capecitabine followed by surgery. There was no statistical difference in R0 rates between the arms (14%, 17%, 18%, and 37% for the upfront surgery, gemcitabine + capecitabine arm, FOLFIRINOX, and NACRT arms, respectively). There was a trend toward a higher R0 rate in the NACRT arm, but the intention-to-treatment (ITT) R0 rate was 19%, which was like the ITT R0 rates of the other three arms. It is worth noting that patients in the NAT arms had a higher 1-year OS than those in the upfront surgery arm (77% *vs* 42%, HR = 0.27; $P < 0.001$), but the NACRT arm did not confer a more prominent survival benefit than other arms[43]. Multiple single-institution retrospective studies have evaluated the efficacy of neoadjuvant SBRT for BRPC and LAPC, showing excellent R0 resection rates and promising OS[44-46]. These results contradict the A021501 study, potentially because the A021501 study had low rates of pancreatectomy (35%) and treatment completion (18%). It is worth mentioning that SBRT has a theoretical synergy with emerging immunotherapies, the effectiveness and safety of which have been confirmed by previous basic research and clinical studies[47,48].

In conclusion, the superiority of NACT and NACRT for BRPC remains unclear and there is still controversy about the most appropriate NAT regimen. Current research findings suggest that the clinical benefit of NAT over upfront surgery is tentatively certain. BRPC patients could actively participate in NACRT/SBRT/IMRT-related clinical trials but all radiotherapy procedures should be performed in a large experienced pancreatic center. A robust NAT study would ideally compare NACT with NACRT including 3D-CRT, IMRT, or SBRT.

Total NAT for BRPC

Most trials for BRPC have performed surgical resection between short-course NAT (SNT) and adjuvant therapy. As the biological behavior of PC has become better understood, some researchers have proposed a new modality called total NAT (TNT). TNT was designed to provide postoperative adjuvant therapy in a preoperative setting and includes concurrent chemoradiotherapy delivered before or after systemic chemotherapy[49]. The theoretical advantages of TNT over SNT include its ability to reduce the risk of delayed chemotherapy for postoperative patients and improve patient compliance and tolerance and ensure drug dose and intensity. A retrospective study found that TNT increased the surgical resection and R0 rates among BRPC and LAPC patients[50]. However, another study reported that while TNT improved the complete pathological remission rate, there was no statistical difference in the median OS between the two groups compared with the SNT mode[51]. In the SWOG-1505 trial, less than half of the patients completed systematic treatment, causing some doubt about whether TNT can help patients to receive the maximum amount of systemic therapy[30]. The use of the TNT mode for PC patients is still in its initial stages. The problems associated with TNT are the same as those of NAT, and this treatment modality still lacks a highly accurate and effective evaluation mechanism.

Response assessment of BRPC after NAT

While findings from RCTs of adjuvant chemotherapy given to patients receiving upfront surgery have suggested that the ideal time frame for perioperative systemic chemotherapy is 6 mo[52], there is no agreement on the length and cycle of NAT for BRPC patients. To make this decision, NAT endpoints will need to be defined to assess responsiveness and tumor re-staging during treatment. NAT patients are typically evaluated every 2 mo to measure treatment toxicity and assess objective clinical, radiologic, biochemical, or metabolic responses. However, there are few effective biomarkers or imaging techniques available to monitor treatment responses among patients with pancreatic neoplasms[51,53].

CA19-9 and CT are the only techniques widely used to assess objective response rates following NAT due to the absence of relevant high-quality study findings. However, there is a growing consensus that CT has important limitations including its inability to distinguish between the tumor and fibrosis or inflammation or to accurately determine tumor responsiveness to NAT[54,55]. Studies indicate that a

Table 1 Neoadjuvant chemoradiation for borderline resectable pancreatic cancer

Ref.	P	N	Induction chemotherapy	Concurrent chemotherapy	SNT/TNT	RT method	Total RT dose (Gy)	Resection rate (%)	R0 rate (%)	Median OS (mo)
Katz *et al* [147]	II	22	FOLFIRINOX	Cape	SNT	3D-CRT/IMRT	50.4	68	93	21.7
Nagakawa *et al*[148]	II	27	GEM	GEM+S-1	SNT	IMRT	50.4	70.3	94.7	22.4
Masui *et al* [149]	II	30	GEM	GEM	SNT	3D-CRT	39	50	83	13.8
						IMRT	42	67	83	32
Murphy *et al* [150]	II	48	FOLFIRINOX	Cape	TNT	Proton	25	67	97	37.7
						IMRT	58			
Tran *et al* [151]	II	25	FOLFIRINOX	GEM	SNT	IMRT	50	52	100	24.2
Versteijne *et al*[152]	III	54	GEM	GEM	SNT	3D-CRT	36	61	79	16
Takahashi *et al*[153]	II	41	NR	S-1	SNT	3D-CRT	50.4	85.4	74.3	30.8
Hayashi *et al* [154]	II	45	NR	S-1/GEM	SNT	3D-CRT	50.4	62.2	96.4	17.3
Sharp *et al* [155]	II	126	mFOLFIRINOX	NR	SNT	SBRT/HIGRT	33-40 / 25	35	25[1]	17.1
Ghaneh P *et al*[43]	III	88	NR	Cape	SNT	3D-CRT	50.4	NR	19[1]	NR

[1]Intention-to-treat (ITT).

P: Phase; N: Number of patients with borderline resectable pancreatic cancer; RT: Radiation therapy; 3D-CRT: Three-dimensional conformal radiotherapy; IMRT: Intensity modulated radiotherapy; HIGRT: Hypofractionated image-guided radiotherapy; OS: Overall survival; Cape: Capecitabine; GEM: Gemcitabine; FOLFIRINOX: Fluorouracil-leucovorin-irinotecan-oxaliplatin; mFOLFIRINOX: Modified FOLFIRINOX; SNT: Short-course neoadjuvant therapy; TNT: Total neoadjuvant therapy; SBRT: Stereotactic body radiotherapy; R0: Margin-negative resection; NR: Not report.

significant proportion of unresectable patients, assessed by CT using the Response Evaluation Criteria In Solid Tumors (RECIST) criteria following NAT, finally achieve an R0 resection[56,57].

Several radiologic approaches are being used to evaluate NAT responses including dual-energy CT (DECT), 18Ffluorodeoxyglucose-PET/CT (FDG-PET/CT), endoscopic ultrasound (EUS), and diffusion-weighted magnetic resonance imaging-MRI (DWI-MRI). Since variations in SUVs may represent the metabolic response of cancer to chemotherapy and FDG uptake is highly correlated with tumor load and viability, FDG-PET/CT is used to evaluate NAT efficacy toward a variety of solid malignancies[58-60]. The metabolic response observed by FDG-PET/CT offers a functional assessment of tumor responsiveness compared to RECIST criteria. Akita *et al*[58] demonstrated that maximal SUVs and tumor size were dramatically reduced following NACRT in BRPC and RPC patients. However, pancreatic tissues incorporate lots of stroma and a high infiltration of inflammatory cells such as macrophages and neutrophils and NAT can further promote both inflammatory cell infiltration and fibrosis. As a result, posttherapy SUV may not accurately reflect the pathological response. In addition, Akita *et al*[58] found that a favorable period for FDG-PET/CT assessment is 8 wk post-radiation. A histological inspection of the resected specimens at that time did not reveal inflammatory alterations in the peripancreatic tissues.

The differentiation of tumor composition can be discriminated by DECT which uses simultaneous scanning with special stages of electricity. DECT can precisely differentiate between PC and continual mass-forming chronic pancreatitis. Moreover, the iodine concentration for the duration of DECT can differentiate between pancreatic patients who successfully respond to chemotherapy and those who don't. This finding suggests that DECT may be used to identify fibrosis caused by NAT[61,62].

DWI-MRI can recognize tissue diffusivity characteristics and be used to perform quantitative and qualitative tumor evaluations. Cuneo *et al*[63] reported that tumor apparent diffusion coefficient (ADC) values of DWI-MRI were specifically linked to the amount of tumor cell destruction. Responders and non-responders had different pretreatment ADC values, suggesting that the ADC values of DWI-MRI prior to NAT can predict the histologic response of BRPC patients.

EUS is rarely used to evaluate NAT response in PCs. The influence of stroma is weak so the value of elastography for chemotherapy and radiation therapy remains unknown[64].

Radiomics is a quantitative image analysis technology that mines the in-depth features of images, allowing for the extraction of data on tumor intensity, shape, size, or volume from digital images. This technique is used as a biomarker for disease diagnosis, grading, prognosis evaluation, and responses to treatment and can both support personalized clinical decisions and improve individualized treatment options[65]. The role of radiomics to evaluate NAT responsiveness has been studied extensively in other solid tumors. Braman *et al*[66] found that a combined intertumoral and peritumoral radiomic feature identified by contrast-enhanced MRI can predict the complete response of breast cancer patients following NAT. Several studies have assessed the use of radiomics to aid PC prognosis and NAT responsiveness (Table 2). Ciaravino *et al* reported that 17 LAPC or BRPC patients reached the resectable stage after NAT, and CT texture analysis showed that there was a statistically significant difference between kurtosis before and after NAT (P = 0.0046)[67]. A prospective study by Borhani *et al*[68] included 39 patients with RPC or BRPC, all of whom had completed surgery after NAT. This study reported that the histologic response could be assessed by pretreatment mean positive pixel (MPP) at a fine- and medium-level filtration, pretreatment kurtosis at a medium-level filtration and changes in kurtosis, and higher MPP was related to favorable histologic response (OR 1.06; 95%CI, 1.002-1.12).

Currently, artificial intelligence (AI) technologies, including deep learning and machine learning, are also being developed to evaluate NAT efficacy in PC patients. One study divided 81 PC patients receiving NAT into a response group (333 images) and a non-response group (443 images). A model using only the deep learning (convolutional neural network) had an area under the curve (AUC) of 0.738, while a combined model incorporating CA19-9 and deep learning had an AUC of 0.785[69]. Not only does the discrimination and accuracy of this model need to be improved, but also small sample size, and heterogeneity caused by different NAT receptors, resectability, and CT slice thicknesses limited the generalizability of the study. New research has combined radiomics with AI. Delta radiomics is a quantitative approach used to assess the treatment-induced net change of radiomic features in a set of longitudinal images. This technique could theoretically be used for the early prediction of NAT treatment responsiveness. Nasief *et al*[70] analyzed 28 daily CT sets collected during routine CT-guided CRT along with pathological treatment response data from 90 patients with RPC or BRPC to obtain delta-radiomic features related to therapy response. The results showed that 13 delta-radiomic features passed the T-test and linear-mixed-effects models and changed significantly after 2-4 wk of treatment. The best-performing machine learning model for differentiating good *vs* poor responders was designed using the normalized-entropy-to-standard-deviation-difference, kurtosis, and coarseness. The AUC of this model was 0.94, but due to the limitation of sample size and the lack of biological interpretability of machine learning model, delta radiomics model distance to practical clinical application, additional studies are needed to validate the reproducibility of the model and to address the issues of model interpretability as well as visualization applications.

While CA19-9 is typically used to track the effectiveness of NAT among patients with BRPC, the predictive value of this marker remains limited. The relevance of a NAT-induced decrease in CA19-9 Levels has not been clearly defined, and the cut-off CA19-9 value for diagnosing NAT responders remains controversial. Prior studies have shown that a 20%–50% drop in CA19-9[71-74] or an absolute value of 72-400 (U/mL) CA19-9 after NAT[75-77] was associated with resectability or a favorable prognosis following resection. In addition, among patients who are Lewis's antigen expression negative or have abnormal bilirubin levels due to cholestasis, serum CA19-9 is inapplicable. Thus, more accurate and focused biomarkers are required to evaluate NAT responsiveness[78-80]. While circulating cell-free DNA, circulating tumor cells, exosomes, and ephrin typeA receptor 2 in tumor-derived extracellular vesicles all show good correlations with NAT responsiveness, larger sample RCTs are required to validate their roles[81-83]. For BRPC patients who received gemcitabine and S1 followed by radiotherapy, the augmentation of partial response rates after NAT was associated with positive expression of human equilibrative nucleoside transporter 1 and negative expression of thymidylate synthase[84]. Moreover, Glazer *et al*[85] demonstrated that the NLR is associated with the OS of BRPC patients who undergo surgical resection after NAT.

Non-invasive and accurate tumor restaging after NAT may be possible through AI approaches such as machine learning and deep learning, combined with different device-based radiomics and novel biomarkers. This will inform the choice of timing for post-NAT surgery among BRPC patients.

Nutritional support for BRPC patients during NAT

Malnutrition is a common problem among PC patients, two-thirds of whom are diagnosed with anorexia at the first visit[86]. NAT significantly alters the nutritional status of patients with esophageal and gastric cancer, which impacts postoperative recovery and surgery rates[87]. However, there is a lack of high-level evidence-based studies on the changes in nutritional status among BRPC patients during NAT as well as the optimal strategy for nutritional status assessment and support.

A retrospective study published in 2020 showed that the preoperative nutritional risk, an independent prognostic factor for OS (HR 5.24, P = 0.013), was significantly higher among patients receiving NAT (P = 0.026)[88]. Moreover, Kim *et al*[89] found that the average pre-NACT prognostic nutritional index (PNI) was higher than the post-NACT PNI, with a difference of 2.98. Moreover, if the

Table 2 Radiomics for treatment response in pancreatic cancer

Ref.	N	Imaging modality	Segmentation method	Feature extraction software	Extracted features	Statistically significant features	Extracted features type	% RQS (points)
Yue *et al*[156]	25	PET	Semi-automated	3D kernel-based approach	12	3	Second-order texture features	25% (9)
Chen *et al*[157]	20	CT	Manual	In-house developed software	8	4	First-order texture features	14% (5)
Ciaravino *et al*[67]	17	CECT	Manual	MaZda	5	1	First-order texture features	17% (6)
Kaissis *et al*[158]	55	MRI	Manual	Pyradiomics	1606	13	Shape features; First-order texture features; Second-order texture features; Filtered image features	36% (13)
Nasief *et al*[70]	90	CT	Manual	IBEX	1300	13	Shape features; First-order texture features; Second-order texture features; Customised features[1]	33% (12)
Borhani *et al*[68]	39	CECT	Manual	TexRAD	6	4	First-order texture features; Filtered image features	6% (2)

[1]Normalized entry to standard deviation features.

N: Sample size; Extracted features: Number of extracted features; Statistically significant features: Number of statistically significant features; CT: Computed tomography; CECT: Contrast-enhanced computed tomography; PET: Positron emission tomography; IBEX: Imaging biomarker explorer; RQS: Radiomics quality score; 3D: Three-dimensional; TexRAD: Texture radiology software; IBEX: Imaging biomarker explorer; NR: Not report.

change value of PNI, obtained by pre-NAT PNI minus post-NAT PNI, is lower than -1.94, it is a risk factor for the OS of PC patients following NAT. Thus, a nutritional evaluation of BRPC patients should be routinely performed, especially those who have received NAT.

In addition to scoring using conventional nutritional screening tools, CT-based body composition analysis is being increasingly used to evaluate the nutritional status of patients with PC. Several studies of body composition have shown that sarcopenia, defined by a reduction in the skeletal muscle index of the third lumbar spine, and an increase in the visceral fat area and subcutaneous fat area, are high-risk factors for postoperative pancreatic leakage and can affect the long-term prognosis of PC patients[90-94]. Sandini *et al*[95] found that patients with BRPC or LAPC who received NAT had a significant loss of adipose tissue. However, there was little reduction in lean body mass. This study also showed that NAT-induced increases in muscle mass were a reliable indicator of respectability.

At present, there is no unified standard management for the nutritional support of BRPC patients during NAT. An expert consensus from Spain in 2021[96] recommended that BRPC patients receiving NAT should receive a nutritional screening by Malnutrition Universal Screening Tool (MUST) before NAT, receive nutrition support with a MUST score ≥ 1, and be taking oral nutritional supplements. A position paper from the International Study Group on Pancreatic Surgery for nutritional support and therapy in pancreatic surgery[97] recommended that when one of the following criteria is met, nutritional support for patients with PC during NAT should be seriously considered: (1) Weight loss > 15%, (2) A BMI < 18.5 kg/m^2, (3) A subjective global assessment score C or nutritional risk score > 5, or (4) A serum albumin < 30 g/L (no evidence of liver or renal dysfunction).

Nutritional therapy during NAT for BRPC patients should be individualized to each patient's performance status. New nutritional screening tools should be designed to incorporate body composition analysis and corresponding cutoffs should be developed for clinical application.

Preoperative biliary drainage during NAT

Most pancreatic tumors are located in the head of the pancreas, which is prone to malignant biliary obstruction (MBO) and affects hepatic function, coagulation, and fibrinolysis. While it remains unknown whether early preoperative biliary drainage (PBD) or straightforward surgery is the better option[98-100], it is reasonable for BRPC patients to choose PBD. Since NAT is routinely required for patients with BRPC and the NAT period is generally 2-6 mo[101], PBD should be performed to ensure that chemotherapy can be safely completed without interruption from cholangitis or hepatic insufficiency while waiting for surgery[102].

There are two critical types of PBD: Percutaneous biliary drainage (PTBD) and endoscopic retrograde biliary drainage (ERBD), including endoscopic biliary stenting (EBS) and endoscopic naso-biliary drainage (ENBD)[103]. Before the introduction of ERBD, PTBD was the preferred type of biliary drainage. However, retrospective studies from Japan showed lower survival and higher rates of peritoneal recurrence among patients treated with PTBD than those receiving ERBD[104,105]. In addition, in a retrospective study of patients undergoing PTBD or ERBD, the PTBD group had significantly higher hepatic metastasis, more wound infections, and lower OS[100]. Sasahira *et al*[106] found that ENBD was associated with much less dysfunction than EBS in MBO. However, ENBD may not be suitable for long-term preoperative cure because of its impact on patient quality of life and disruptions in the enterohepatic circulation of bile salts[107].

Thus, EBS is repeatedly used when PBD is performed, and the used stents can be extensively divided into plastic stents (PS) and self-expandable metal stents (SEMS), including full-covered SEMS (FCSEMS), partially covered SEMS (PCSEMS) and uncovered SEMS (USEMS). Some studies have found that FCSEMS is more effective than PS for MBO among BRPC patients receiving NAT. Several RCTs have verified that the median patency of SEMS is 4–9 mo or more, which is notably longer than that of PS[108-111]. A recent RCT from Japan which included patients with BRPC who required PBD before GNP based NAT, illustrated that the rate of stent dysfunction was drastically lower in the FCSEMS arm than in the PS arm (18.2% *vs* 72.8%, $P = 0.015$), and showed that FCSEMS and PS had a similar safety profile and medical costs[112]. A retrospective study of 749 patients with MBO found that covered SEMS (CSEMS) and USEMS had similar rates of clinical success in bile-duct obstruction treatment and patency duration. However, the USEMS arm was associated with less tumor growth than the CSEMS arm (76% *vs* 9%, $P < 0.001$)[113]. While no studies have directly compared PCSEMS and FCSEMS, a decision on the choice of biliary stents for BRPC patients receiving NAT would ideally be made following a joint evaluation by a surgeon and a pathologist.

EUS-guided biliary drainage (EUS-BD) has emerged as a positive approach for biliary drainage when ERCP is unsuccessful and can reduce the likelihood of pancreatitis, injury to the pancreatic tissue, and irritation. However, due to the risk of potential bile leakage and the high demand at the endoscopist level, more studies are needed to compare the efficacy and safety of EUS-BD with other methods for preoperative biliary drainage[114].

While study findings remain insufficient, available data suggest that SEMS is more suitable in PBD for patients with BRPC during NAT. However, the choice of PS is most suitable when the window period for preoperative therapy is short. More high-quality studies are required to demonstrate the most appropriate method for PBD during NAT.

UPDATE ON INTRAOPERATIVE STRATEGIES FOR BRPC

Lymph node dissection and vascular reconstruction

Lymph node recurrence is an important part of the postoperative recurrence of PC[115]. There remains some controversy about the scope of surgical lymph node dissection, and most researchers believe that expanding regional lymph node dissection cannot improve patient prognosis. However, a few studies indicate that there is value in expanding dissection[116,117]. Lymph nodes in the arterial and portal regions are the main sites for the local recurrence of PC[118]. A series of meta-analyses showed no significant increase in the median survival time and 1-, 3-, and 5-year survival rates of patients receiving extended lymphadenectomy in pancreaticoduodenectomy (EPD) versus standard lymphadenectomy in pancreaticoduodenectomy (SPD) and an increased risk of complications[119,120]. The standard lymph node dissection ranges are 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a, and 17b for pancreatic head cancer. For cancers of the pancreatic body and tail, dissection of stations 10, 11, and 18 is standard and dissection of station 9 is only recommended for patients with cancer of the pancreatic body[121]. No definitive studies have illustrated the benefit of expanded lymph node dissection for BRPC patients. The concept of Heidelberg triangle surgery was proposed by the University of Heidelberg in Germany[122]. In addition to conventional lymph node dissection, all lymph nodes, vessels, and nerve tissue in the Heidelberg triangle can be dissected.

One study found that about one in five patients who received pancreatoduodenectomy (PD), distal pancreatectomy (DP), or DP with abdominal axis resection (DP-CAR) for pancreatic tumors had lymph node recurrence. Of these, peri-pancreatic head (peri-Ph), para-aortic, and SMA lymph node recurrences were the most common, accounting for 12%, 11%, and 10%, respectively[123]. The precise type of lymph node dissection should be chosen according to the tumor's location and other characteristics.

BRPC is often associated with the invasion of important vessels such as the celiac trunk and common hepatic artery, resulting in low clinical resection rates. Studies illustrate that combined external pancreatic atherectomy in patients with tumor invasion of SMA, CA, and HA is often associated with more postoperative complications and higher mortality rates and has no impact on survival. Thus, reconstructive pancreatic resection with arterial invasion is not recommended for this patient population[124,125]. However, some recent studies have questioned these results, suggesting that in highly specialized pancreatic centers, even atherectomy can be performed safely and promote long-term

outcomes similar to standard surgery for radical cure[126,127]. Distal pancreatectomy with abdominal axis resection DP-CAR or modified Appleby resection improves the safety of BRPC combined with atherectomy. Since this technique allows en block resection of the celiac axis and the common hepatic artery, arterial reconstruction is not required. However, the feasibility and effectiveness of this procedure remain to be evaluated in future clinical studies.

Many studies have focused on how to increase the rate of radical resection and thus improve survival among patients with BRPC. The depth of arterial tumor invasion has a greater impact on radical resection than the circumferential size of the tumor invasion[128]. Arterial wall invasion in PC is often confined to the arterial epithelium and rarely breaks through the outer elastic layer of dense connective tissue. Some studies have proposed the concept of "arterial sheath debridement," using the loose tissue between the arterial epithelium and the outer elastic layer as the anatomical plane to debride the peri-arterial nerve fiber connective tissue, to obtain radical resection while avoiding severe complications associated with arterial resection[129]. However, the current understanding of treatment for junctional resectable patients and the common use of preoperative radiotherapy have shown an increase in peri-arterial tissue inflammation and fibrosis. This has made it difficult to free the affected artery and completely debride peri-arterial tissue invaded by the tumor during surgery.

Most PC patients have SMV-portal vein axis involvement. However, radical surgery combined with vein resection and reconstruction is shown to be safe and feasible with a good prognosis in several studies[130,131]. Dua *et al*[132] propose various vascular anastomoses such as longitudinal vascular suture, transverse vascular suture, end-to-end vascular anastomosis, vessel wall patch repair, and autograft or artificial vascular reconstruction. The most appropriate approach is chosen based on the circumference and length of the invading vessels. There is no consensus about the best mechanism for revascularization, but direct suturing, patch repair, and autograft are preferred because of the increased risk of thrombosis associated with artificial implants.

SURGERY COMBINED WITH INTRAOPERATIVE RADIOTHERAPY

Patients who undergo pancreatic tumor resection are prone to local recurrence and distant metastasis after surgery. Local control of the tumor is essential to prolonging survival and improving quality of life. Previous studies have shown that neoadjuvant chemotherapy, radiotherapy, and extracorporeal irradiation therapy can improve local and regional control and survival. However, external-beam radiotherapy is limited in its clinical application by the challenge of delivering sufficient doses of radiation. In contrast, IORT has the unique advantage of delivering the maximum dose of ionizing radiation precisely to the tumor, tumor bed, surrounding lymph node area, superior mesenteric margin, portal vein, and areas at high risk for recurrence, while surgically removing radiation-sensitive organs such as the small intestine from the radiation field to minimize damage to surrounding normal tissue. In addition, the surgeon and radiation therapist can coordinate intraoperatively under direct vision to determine the exact location and extent of the irradiated target area to avoid missing risk areas. Simultaneous completion of surgery and radiotherapy can significantly shorten the treatment course of patients. IORT patients have a median survival time of 19.1 mo, a 2-year survival rate of 42.1%, and a 2-year local control rate of 83.7% after resection, which are all higher than patients in the control group. In addition, the pain relief rate after IORT is 94.9%[133]. Harrison *et al*[134] found that after FOLFIRINOX-based NAT, survival rates at 12, 24, 48 and 60 mo were 99%, 79%, 47%, and 28%, respectively, for all forms of resection plus IORT (10 Gy). For patients who only received IORT (20 Gy), the survival rates at 12, 24, 48, and 60 mo were 98%, 49%, 13%, and 9%, respectively. The overall complication rate of IORT was 26.7%, including gastroparesis, gastrointestinal bleeding, pancreatic leakage, and celiac leakage. Clinical and experimental studies have shown that IORT at 10–20 Gy is still well tolerated by organs, even in patients with combined revascularisation[135]. These findings suggest that patients with postoperative pathology showing residual tumors visible to the naked eye at the margins or positive margins on frozen pathology, or patients with moderate or severe pain and ineffective pain relief, can improve their prognosis and quality of survival following combined IORT.

Radioactive Particle Implantation

^{125}I particle implantation directly implants particles into tumor tissues to achieve precise treatment of tumor. Gamma rays released by these particles reach tumor cells with reduced decay and a high effective dose, causing tumor tissues to receive more radiation and undergo higher levels of necrosis. The gamma-ray irradiation distance is short so most of the energy can be absorbed by tumor tissues, minimizing the damage to surrounding normal tissues. In addition, toxic side effects, including radiation-induced inflammation, seed displacement, pancreatic fistula, bleeding, and gastrointestinal obstruction are minimal[136]. A refined and standardized treatment approach with reasonable preoperative planning of the particle number and distribution and accurate prediction of energy distribution will improve treatment efficacy and reduce the incidence of acute adverse effects. By maximizing the radiation dose to the tumor and reducing radiation damage to the surrounding normal tissues, local invasion of the tumor is significantly inhibited and patient OS is increased. However, there is still a lack

of corresponding research to support whether BRPC patients will benefit from this treatment.

Intraoperative cryoablation therapy and intraoperative combined cryoablation and hyperthermia

Intraoperative cryoablation therapy is a tumor treatment technique based on the idea that physical action kills cells. Lesion tissue is repeatedly frozen and thawed, tumor cells appear to be dehydrated and burst, and the microstructure inside the broken tumor cells can activate the immune system to control tumor progression. In addition, platelets in the blood vessels around the tumor accumulate and form thrombi to destroy the blood supply to the tumor, thus indirectly killing the tumor cells. Compared with other solid tumors, PC cryoablation treatment is more difficult because the anatomical location of the pancreas is deeper and the path selection is smaller, making it a challenge to cover a satisfactory treatment area. Some studies have also shown that intraoperative combined cryoablation and hyperthermia can complement the advantages of cold and heat ablation. Compared with cryoablation alone, combined cold and heat ablation is associated with improved surgical efficiency, tumor control, and complication rates[137,138].

Irreversible electroporation

Irreversible electroporation (IRE), also known as NanoKnife, is a new non-thermal physical ablation technique. By applying short and high pulse voltages between two electrodes made of unique materials, the original membrane potential of the cell is altered, creating irreversible nanoscale pores in the lipid bilayer of the membrane and causing disruption of cellular homeostasis that leads to cell death.

This ablation method only causes cell death in a specific area while preserving the integrity of the tissue scaffold and the fibrous structure of the cells. In contrast, the adjacent tissues, including blood vessels and surrounding normal tissues are not damaged, avoiding the "heat sink effect" in the ablation area and facilitating tissue repair. IRE is used to achieve local ablation by disrupting cellular homeostasis and destroying or controlling tumor growth. This technique is more selective to tissues and cells than other modalities and can protect the surrounding blood vessels, bile ducts, and other important tissues, and cause the physiological death of cells in the ablation area to avoid excessive tissue necrosis and increase the body's immune burden. The addition of IRE to conventional therapy promotes significantly longer patient survival than that of historic controls[139]. Papoulas *et al*[140] showed that intraoperative IRE and PD can be used successfully in appropriate BRPC patients to achieve clear microdissection margins, minimizing the risk of local recurrence and improving outcomes.

MULTIDISCIPLINARY BRPC PATIENT TEAMS

MDTs have become a popular way to guarantee the best care for cancer patients and reliably improve the diagnosis and treatment of PC[141-143]. Unfortunately, there is a lack of data on the role and criteria of MDTs in PC. Syed *et al*[144] found that the multidisciplinary pancreas conference led to a significantly higher rate of adjuvant chemotherapy initiation than has been previously reported. Hansen *et al*[145] analyzed 7,015 patients with diagnosed or suspected pancreatic and duodenal tumors who received MDTs and compared the results from similar patients seen at the same hospital before the implementation of MDTs. In this study, patients with advanced stages of disease who received MDTs had a higher rate of surgery, including vascular reconstruction, and there was no increase in morbidity and mortality. Neither study identified long-term survival benefits of MDTs for PC patients.

As discussed previously, there is no broad consensus on the standard of care for BRPC, so the core task of MDTs is diagnosis and assessment for resectability and treatment, including the selection of a surgical scheme and NAT regimen and the evaluation of NAT responsiveness[146]. The MDT mode established around BRPC should: (1) Build on the outpatient department of MDTs and involve experts from different clinical specialties and subspecialties, including but not limited to pancreatic surgery, gastroenterology, radiology, medical oncology, pathology, nutriology, therapeutic radiology, and anesthesiology, (2) Ensure that specialist nurses in the clinic serve as the hub for various experts, (3) Ensure stability and communication between team core members, (4) Require that medical records are quantitatively evaluated and a long-term follow-up system is established, and (5) Ensure that MDT time, personnel, location, and equipment are fixed (Figure 2). MDTs can formulate a regular review plan for patients, dynamically evaluate treatment effects and adverse events, adjust the treatment plan as needed, and terminate treatment if necessary. The MDT can also carry out multidisciplinary research, including clinical trials.

A 2019 study found that MDTs from different centers varied substantially in resectability rates for non-metastatic PC[146]. The researchers suggested that for patients with PC, uniform MDT patterns and criteria require further exploration. Large sample-sized and multicenter studies are required. In addition, it is necessary to reduce the heterogeneity that results from differences in the equipment used across centers.

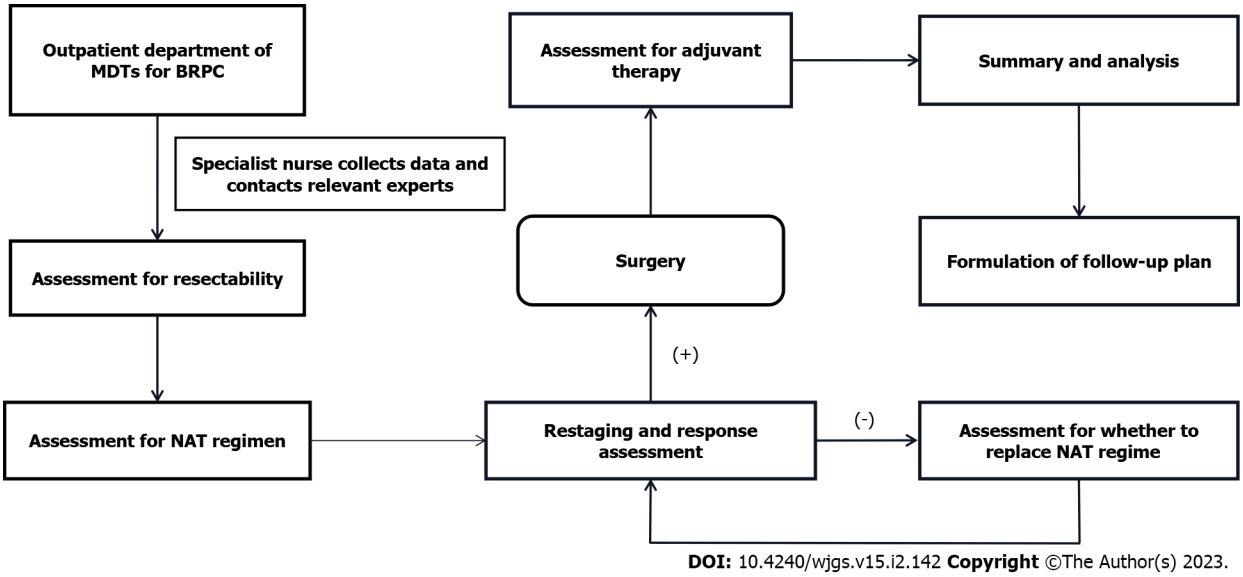

Figure 2 Multidisciplinary teams process for Borderline resectable pancreatic cancer. BRPC: Borderline resectable pancreatic cancer; NAT: neoadjuvant therapy; (+): No progression or downstaging of disease and no serious adverse effects; (-): Poor response to treatment, disease progression or occurrence of serious adverse effects; MDTs: Multidisciplinary teams.

CONCLUSION

BRPC management has entered the era of multimodality therapy with a single surgical treatment. In the past 20 years, more studies have identified that surgical treatment for PC is insufficient. Even extensive surgery is a local treatment, while cancer, especially PC, is a systemic disease. Thus, appropriate management for BRPC should not only focus on improving surgical rates but also assess how to maximize the survival benefit of radical surgery through the rational selection of patients along with individualized neoadjuvant regimens and surgical modalities.

This review provides a comprehensive discussion of current multimodality treatment regimens for patients with BRPC, including the assessment of resectability, the overall management of NAT, advances in surgical modalities, and preliminary exploration of MDTs. Several clinical trials are exploring optimal NAT regimens, which confer a long-term survival benefit for BRPC patients, the results of these trials can be followed in the future. Using precision medicine, the assessment of resectability at the molecular and genetic levels becomes possible, suggesting that molecular targeted therapy or immunotherapy could be a breakthrough for BRPC treatment. The combination of AI and multiomics, including genomic, transcriptomic, and radiomics emerges as a promising tool that could be used to develop personalized management for patients with BRPC. However, large clinical trials are required to establish more clearly defined protocols.

Radical resection is currently the cornerstone of PC treatment, and intraoperative adjuvant therapy regimens continue to evolve. The first step to maximize the benefits of surgery is to accurately select "suitable surgical candidates". MDTs need to focus on the full personalized management of patients with BRPC, using radiology combined with tumor biology and general status to assess and evaluate resectability and multimodality treatment options.

FOOTNOTES

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Impact of endoscopic ultrasound-guided radiofrequency ablation in managing pancreatic malignancy

Cosmas Rinaldi Adithya Lesmana

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Abstract

Pancreatic malignancy is still the most lethal gastrointestinal malignancy. It has a very poor prognosis with low survival rate. Surgery is still the main treatment option for pancreatic malignancy. Most patients already have locally advanced and even late stage disease due to non-specific abdominal symptoms. Even though some cases are still suitable for surgical treatment, due to its aggressiveness adjuvant chemotherapy is becoming the standard treatment for controlling the disease. Radiofrequency ablation (RFA) is a thermal therapy that has been used as one of the standard treatments for liver malignancy. It can also be performed intraoperatively. There are several reports on percutaneous RFA treatment for pancreatic malignancy using transabdominal ultrasound and guided by computed tomography scan. However, due to its anatomical location and the risk of high radiation exposure, these methods seem to be very limited. Endoscopic ultrasound (EUS) has been widely used for pancreatic abnormality evaluation due to its ability to detect more accurately, especially small pancreatic lesions, compared to other imaging modalities. By the EUS approach, it is easier to achieve good visualization of tumor ablation and necrosis as the echoendoscope position is closer to the tumor area. Based on studies and a recent meta-analysis, EUS-guided RFA is a promising treatment approach for most pancreatic malignancy cases, but most studies only collected data from a small sample size. Larger studies are needed before clinical recommendations can be made.

Key Words: Endoscopic ultrasound; Radio frequency ablation; Percutaneous; Surgery;

Pancreatic malignancy

Core Tip: Pancreatic cancer is still the most lethal gastrointestinal malignancy. Most patients are diagnosed at the late stage of the disease. Surgery is still the definitive treatment for managing pancreatic cancer. However, skill, experience, and expertise are required of the surgeon due to its high risk of complications. Recently, endoscopic ultrasound has been used for managing pancreatic cancer. Studies have shown its practicability, efficacy, and benefit in combination with standard chemotherapy. It would need larger studies before it can be recommended as standard management in clinical practice.

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INTRODUCTION

Pancreatic malignancy is still the most lethal gastrointestinal malignancy, and it is ranked seventh for mortality. It has a very poor prognosis with a low survival rate[1]. There are many risk factors that might contribute to pancreatic cancer development, such as genetics, obesity, diabetes mellitus, smoking, chronic pancreatitis, fatty pancreas, and heavy alcohol consumption[2]. It has been classified into two categories, *i.e.*, exocrine cancer, which is dominated by pancreatic adenocarcinoma, and endocrine cancer, also known as pancreatic neuroendocrine tumor (pNET). In the clinical stage, it is classified into type IA and IB (considered as resectable disease with a maximum 4 cm diameter), type II (locally advanced with diameter > 4 cm with possible lymph nodes involvement), type III (unresectable with vascular involvement), and type IV (metastatic cancer)[3].

Pancreatoduodenectomy (Whipple) operation is still the best option to prolong survival. However, most cases already come in at the late stage, and overall mortality remains low. Endoscopic ultrasound (EUS) is an innovation dedicated to managing pancreatobiliary disorders[4]. In the history of developing the EUS procedure, a diagnostic comparison study by Palazzo *et al*[5] showed that EUS had higher accuracy to detect small pancreatic lesions when compared to computed tomography (CT) scan or ultrasonography. Based on the pioneering study by Vilmann *et al*[6] in which the EUS-guided pancreas biopsy technique used a catheter with aspiration needle, therapeutic EUS has been recently developed not only for biliary drainage procedure but also for managing pancreatic malignancy through direct tumor ablation therapy or radiofrequency ablation (RFA) in a multidisciplinary context and evaluation[4,7].

The RFA procedure is an electrocautery-based technique that results in tissue necrosis. It has been used widely for managing unresectable primary as well as secondary liver cancer, where it has been previously reported by Nießen *et al*[8]. The local recurrence was primarily dependent on tumor size. Another RFA innovation study has been reported by Gervais *et al*[9] for managing renal cell carcinoma up to 5 cm in size with overall median survival of 9.9 mo. No recurrent disease in patients with technically successful treatment, no metastasis during treatment course, and no dialysis was needed in post ablation patients.

SURGICAL TREATMENT IN PANCREATIC MALIGNANCY

Surgery is still the main treatment option for pancreatic malignancy. However, due to its aggressiveness, neo-adjuvant chemotherapy is becoming the standard treatment for controlling the disease. Most patients are diagnosed at an advanced stage of cancer. In surgical treatment, tumor size and margin, vascular involvement, and lymph nodes are important parameters for the patient's outcome [10]. A questionnaire-based retrospective study was conducted for pancreatic cancer with 6-year follow-up on patient outcomes, and it showed that the 30-d mortality rate was 5.3% with median survival of only 16.3 mo. Three out of twenty patients who had 5-year survival with positive histology results had recurrent disease in the 6-year follow-up. Some of these patients already showed locally advanced disease as there was evidence of positive margin. The median survival was lower in patients with positive margin compared to patients with negative margin (13.9 mo *vs* 20.6 mo)[11].

Another study looking at patient survival after pancreatic head resection for ductal adenocarcinoma observed an overall mortality rate of 4.10% and 3-year and 5-year survival rates of only 31.50% and 11.86%, respectively. In this study, 81.50% of patients already had obstructive jaundice condition. The pathology results of tumor differentiation revealed that 52.40% of patients were already at G2 intermediate differentiation, 42.00% of patients at G3 poor differentiation (42.00%), and 2.60% of patients at G4 differentiation[12].

A recent systematic review on quality of life in patients who underwent pancreatoduodenectomy showed that there was a decrease in physical functioning 3 mo after operation. Mental health issues were the only parameter shown to be stable 3 mo after operation. Several parameters, such as fatigue, postoperative pain, dyspnea, insomnia, loss of appetite, and bowel movement problems, were reported as negative influences after the operation, even though most parameters were resolved within 3 to 6 mo. This might become an important issue since most patients are offered for chemotherapy after the operation[13].

RFA TREATMENT AND ITS ROLE IN PANCREATIC MALIGNANCY

There are different ablation methods following temperature increase or impedance and probes (surgical or endoscopic using catheters or needles), such as chemical ablation and thermal ablation (cryoablation and hyperthermic ablation). RFA is one of the thermal therapies that has been used as one of the standard treatments for liver malignancy[14]. A prospective study by Curley *et al*[15], which was looking at the role of RFA treatment for primary as well as metastatic liver malignancies, showed that this procedure was effective and safe for tumor destruction with low tumor recurrence rate and no mortality related to the procedure.

An experimental study by Date *et al*[16] on pig pancreas with surrounding organ and vessels were ablated using temperature changing evaluation showed that temperature is the most important parameter to achieve complete ablation. With localized ablation therapy, there was no damage at the duodenal site or the other parts of the pancreas. Another innovative study by Hadjicostas *et al*[17] reported their experience in performing intraoperative RFA concomitantly with surgery for locally advanced and unresectable pancreatic cancer patients. RFA seemed to be a promising treatment as it could control the tumor growth.

A case series by Varshney *et al*[18] on RFA treatment guided by CT scan during the operation for unresectable pancreatic cancer showed that tumor necrosis could be achieved without any mortality events related to the procedure. The percutaneous RFA approach using abdominal ultrasound has also been reported by D'Onofrio *et al*[19] in patients with locally advanced pancreatic adenocarcinoma, where a 93% technical success rate was reported without any complications. The survival rate was recorded to be longer than 6 mo. However, there are limitations for the percutaneous RFA treatment approach. RFA treatment using transabdominal ultrasound is sometimes difficult due to overlying abdominal gas, and there is a risk of radiation exposure when using a CT scan-guided approach. On the other hand, Karim *et al*[20] reported several technical complications after the Whipple procedure, such as wound infection in 23.5% of patients and pancreatic leak in 21.4% of patients. Other complications noted in this study were lung complications (17.3%) and intra-abdominal collection (12.2%).

INNOVATION ON EUS-GUIDED RFA IN PANCREATIC MALIGNANCY

EUS has been widely used for pancreatic abnormality evaluation due to its ability to detect lesions more accurately, especially small pancreatic lesions, compared to other imaging modalities[21]. One pioneer animal experimental study by Goldberg *et al*[22] showed that EUS-guided RFA (EUSRA) can be successfully performed with a good necrosis coagulation target area. Recently, a needle dedicated for EUSRA was developed (Figure 1), where it showed a 100% technical success rate in animal models. There are four types of EUS-guided radiofrequency dedicated needles or probes, namely the 19 G fine needle aspiration (Radionics, Inc., Burlington, MA, United States), the Habib catheter (EMcision Ltd., London, United Kingdom), the Hybrid cryothermy probe (Hybrid-Therma; ERBE, Tubingen, Germany), and the EUSRA needle (STARmed, Koyang, Korea). The only bipolar probe is Hybrid cryothermy. Both the Hybrid cryothermy probe and EUSRA needle have internal cooling system. The cooling system uses a water-based cooled needle (cool-tip system). This system uses the electrical current from a generator with a monopolar electrode because bipolar pancreatic probes under endoscopic control do not exist. The electrode types are single internally cooled electrodes, cluster internal cooled electrode systems, and variations (StarBurst from RITA and LeVeen from Boston Scientific). All RFA needles or probe are connected to the generators to deliver a thermal effect to the lesion[23].

By using the EUS approach, it is easier to achieve good visualization of the tumor ablation and necrosis as the echoendoscope position is closer to the tumor area (Figure 2). Several case series have been reported to have a high technical success rate (73%-100%). However, several adverse events (AE) have also been noted, such as abdominal pain, bleeding, hyperamylasemia, obstructive jaundice,

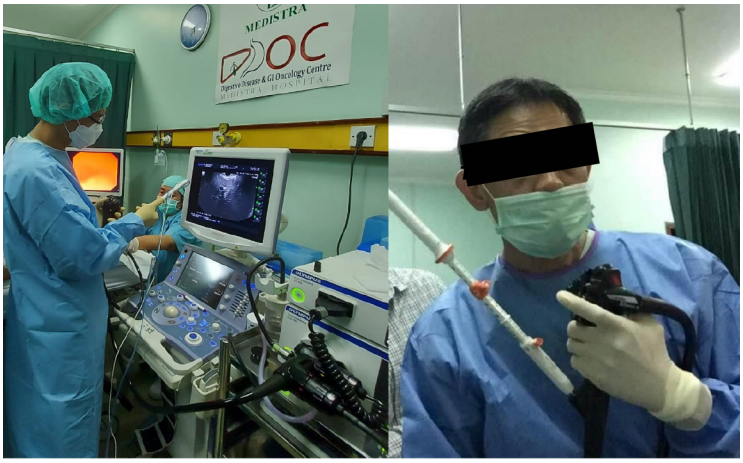

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Figure 1 Endoscopic ultrasound-guided radiofrequency ablation procedure using dedicated radiofrequency ablation needle. Medistra Hospital, Jakarta.

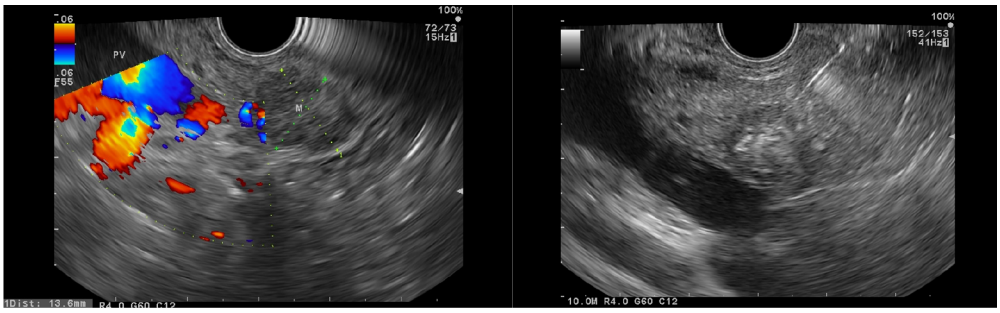

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Figure 2 Endoscopic ultrasound images of a patient with a pancreatic neuroendocrine tumor who underwent endoscopic ultrasound-guided radiofrequency ablation. Endoscopy unit database, Medistra Hospital, Jakarta.

duodenal stricture, pancreatitis, pancreatic duct stenosis, and bacteremia[24,25]. In 2016, Lakhtakia *et al*[26] reported their experience using the EUSRA procedure in 3 patients with insulinoma. After a 12-mo follow-up, patients were still asymptomatic with a normoglycemic condition. A multi-center pilot study was conducted on the use of EUSRA in pancreatic cystic neoplasms and pNETs, where EUSRA was completed in all cases, and no major complications were observed after the procedure. There was complete resolution in 2 patients as well as cyst reduction in 3 patients after a 3-6-mo follow-up. Patients with pNETs showed a good response as tumor necrosis was recorded[27].

A pilot study by Rossi *et al*[28] on the feasibility, efficacy, and safety of EUSRA for secreting pNET patients showed that serum hormone levels reverted to normal within 24 h, and the symptoms regressed. After a 34-mo follow-up, no mortality was recorded, and tumor shrinkage and disappearance were noted after 24 mo. A case series by de Nucci *et al*[29] on patients with pNETs showed that complete ablation can be achieved within one session with a short period of hospitalization. Another prospective study by Song *et al*[30] using the EUSRA treatment approach for unresectable pancreatic cancer showed that the procedure was performed successfully in 6 cases, and systemic chemotherapy was completed on the same day in 3 patients. In this study, there were no major AEs even though 2 patients experienced mild abdominal pain.

Recently, a meta-analysis on EUSRA efficacy in pancreatic tumor management was performed with 13 studies included in the analysis. Based on this meta-analysis, the technical success rate was 100%, and the overall clinical success rate was 91.8%. Abdominal pain was the most common AE observed (9.82%), whereas perforation and infection were found in 1 patient, and pancreatitis was noted in 2 patients. This analysis concluded that EUSRA is a promising treatment strategy. However, most studies only collected a small sample size[31].

A recent longitudinal cohort study by Thosani *et al*[32] in 10 patients with pancreatic adenocarcinoma, where one to four RFA sessions per patient were performed, revealed that CA 19-9 levels decreased after 12 treatment sessions. Tumor size reduction of more than 50% was recorded in 3 patients. The median survival was 20.5 mo, whereas median survival of 13.4 mo was recorded after RFA treatment. All patients also underwent systemic chemotherapy. No significant complications were

recorded in this study. A recent clinical case series study by Rossi *et al*[33] in elderly patients with pancreatic insulinoma showed that the EUSRA procedure was a safe procedure for elderly patients at high surgical risk. In this study, no major complications occurred during the procedure.

CONCLUSION

EUSRA is a promising treatment approach for pancreatic malignancy. However, further larger studies are needed, especially in pancreatic adenocarcinoma. The role of EUSRA in combination with systemic chemotherapy might become a new approach for managing unresectable pancreatic cancer. It may also become a promising combination strategy for tumor downstaging where it can be followed by surgery for possible tumor elimination or cure.

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FOOTNOTES

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MINIREVIEWS

Current management of concomitant cholelithiasis and common bile duct stones

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Abstract

The management policy of concomitant cholelithiasis and choledocholithiasis is based on a one- or two-stage procedure. It basically includes either laparoscopic cholecystectomy (LC) with laparoscopic common bile duct (CBD) exploration (LCBDE) in the same operation or LC with preoperative, postoperative and even intraoperative endoscopic retrograde cholangiopancreatography-endoscopic sphincterotomy (ERCP-ES) for stone clearance. The most frequently used worldwide option is preoperative ERCP-ES and stone removal followed by LC, preferably on the next day. In cases where preoperative ERCP-ES is not feasible, the proposed alternative of intraoperative rendezvous ERCP-ES simultaneously with LC has been advocated. The intraoperative extraction of CBD stones is superior to postoperative rendezvous ERCP-ES. However, there is no consensus on the superiority of laparoendoscopic rendezvous. This is equivalent to a traditional two-stage procedure. Endoscopic papillary large balloon dilation reduces recurrence. LCBDE and intraoperative ERCP have similar good outcomes. The risk of recurrence after ERCP-ES is greater than that after LCBDE. Laparoscopic ultrasonography may delineate the anatomy and detect CBD stones. The majority of surgeons prefer the transcductal instead of the transcystic approach for CBDE with or without T-tube drainage, but the transcystic approach must be used where possible. LCBDE is a safe and effective choice when performed by an experienced surgeon. However, the requirement of specific equipment and advanced training are drawbacks. The percutaneous approach is an alternative when ERCP fails. Surgical or endoscopic reintervention for retained stones may be needed. For asymptomatic CBD stones, ERCP clearance is the first-choice method. Both one-stage and two-stage management are acceptable and can ensure improved quality of life.

Key Words: Biliary diseases; Cholelithiasis; Choledocholithiasis; Gallstones; Endoscopic

management; Laparoscopic management

Core Tip: One- or two-stage management of concurrent cholelithiasis and choledocholithiasis is safe and acceptable and does not show significant differences. Current diagnostic tools and interventional techniques can offer the optimal outcome, especially in difficult cases or recurrent stones. The relevant training and gained expertise play an essential role in performing the kind of available and acceptable method of minimally invasive treatment.

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INTRODUCTION

Cholelithiasis is a common disease affecting up to 20% of the adult population in Western countries but is usually asymptomatic. Common bile duct (CBD) stones are secondary in the vast majority of cases coexisting with cholelithiasis (10%-15%) originating from the gallbladder through the cystic duct. Its incidence increases with advancing age. Primary or native stones are relatively rare[1-5]. One-stage or two-stage management continues to be controversial, but both provide equivalent outcomes[4,6].

Patients with symptomatic cholelithiasis have a 10% possibility of concomitant CBD stones without causing symptoms. A study from the United States found that laparoscopic cholecystectomy (LC) accompanied by routine intraoperative cholangiography, in cases of symptomatic cholelithiasis with asymptomatic choledocholithiasis, was better than preoperative magnetic resonance cholangiopancreatography (MRCP) in terms of effectiveness and cost analysis[7]. However, the latter is the preferred method in clinical practice in symptomatic cases with transient obstructive jaundice or elevated liver function tests and previous episodes of acute pancreatitis[8]. A debate still exists about the routine or selective use of intraoperative cholangiography[9], but it seems more reasonable in the era of MRCP availability based on well-defined indications[10].

A recent study demonstrated advantages of intraoperative cholangiography compared to preoperative endoscopic retrograde cholangiopancreatography (ERCP)[11]. A recent meta-analysis showed that prophylactic cholecystectomy after ERCP- endoscopic sphincterotomy (ERCP-ES) CBD stone clearance was better than the wait-and-see policy. It was associated with fewer complications (acute cholecystitis, acute cholangitis, acute pancreatitis and biliary colic)[12]. However, it should be particularly considered in extremely elderly patients with limited life expectancy or unfit frail patients. A recent controversy has emerged about the role of routine prophylactic cholecystectomy after ERCP, postulating that it must be re-evaluated given the low risk of the above complications[13].

A previous nationwide study from the United States found a conversion rate from laparoscopic to open cholecystectomy of between 5%-10%; major conversion factors were recognized as acute cholecystitis, choledocholithiasis, male sex and obesity[14]. However, since then, much progress has been made in the laparoscopic management of choledocholithiasis.

The most widely used approach for concomitant gallbladder and CBD stones is ERCP-ES then LC followed by simultaneous LC and CBD exploration and intraoperative ERCP-ES and LC[6,15-17]. A recent survey among surgeons from the United Kingdom showed that for suspected choledocholithiasis, MRCP was the preferred first choice by the vast majority (80.0%), and intraoperative imaging was preferred by the remaining minority (14.4%). Intraoperative cholangiography (83.0%) prevailed over intraoperative ultrasound (17.0%). ERCP-ES followed by LC (two-stage procedure, 62.1%) prevailed over LC and laparoscopic common bile duct exploration (LCBDE) (one-stage procedure, 33.4%). For LCBDE, the preferred route was through the CBD (62.5%) using T-tube drainage selectively. The requirement of specific equipment and advanced training are drawbacks for LCBDE[8]. LCBDE and intraoperative ERCP have similar good outcomes[18].

A previous similar scoring system was proposed[19], but the guidelines of the American Society for Gastrointestinal Endoscopy and the Society of American Gastrointestinal and Endoscopic Surgeons for the management of suspected choledocholithiasis have defined several graded predictors. They include the following: (1) Very strong (CBD stone on ultrasound, bilirubin > 4 mg/dL); (2) Strong (CBD > 6 mm, bilirubin 1.8-4 mg/dL); and (3) Moderate (abnormal liver function tests other than bilirubin, age > 55 years, previous acute biliary pancreatitis)[20]. For suspected choledocholithiasis in acute cholecystitis, a model consisting of three preoperative predictive factors (increased serum glutamic pyruvic transa-

minase or alanine aminotransferase more than threefold, elevated alkaline phosphatase and CBD diameter more than 6 mm) was defined. When 0-1 factors exist, the possibility of CBD stone absence will be 98.6%, but when all three factors exist, the risk of CBD stones will be 77.8%[21].

The recurrence after successful CBD stone clearance reaches up to 8.4% within a median time of 2.5 years, and it is more often found after ERCP-ES than after LCBDE[18,22]. This is particularly related to some morphological subtypes (S and polyline type) of CBD[23], and regular follow-up is necessary in cases with risk factors[24].

In this mini review, we evaluated the current management options of concomitant gallbladder and CBD stones, highlighting the updated knowledge by selection and focus of the most relevant articles from PubMed. The current options of minimally invasive treatment of cholelithiasis and choledocholithiasis are summarized in Figure 1.

MANAGEMENT

One-stage procedure

Rendezvous technique: This technique is a well-established method for the management of CBD stones that combines ERCP-ES stone clearance and LC in the same operation with the patient under general anesthesia[1,6,25]. It is feasible, safe and effective not only in elective but also in emergency cases, as shown in a recent study including 61 cases and 120 cases, respectively[26]. In addition, the method has applications in pediatric patients with excellent results[27]. A recent comparative study found that this intraoperative application of ERCP-ES was superior to its postoperative application regarding the better success rate and the decrease in postoperative acute pancreatitis, hospitalization and financial cost[28].

The Swedish National Registry for Gallstone Disease and ERCP included 1770 cases of rendezvous ERCP-ES, either intraoperative (n = 1205) or postoperative (n = 565). Comparison between the two groups found a higher rate of retained stones (5.5% *vs* 0.6%) and overall complications in the postoperative group (19.7% *vs* 14.0%). The main complications included post-ERCP acute pancreatitis (6.4% *vs* 3.2%) and postoperative infections (4.4% *vs* 2.3%). These differences were statistically significant (P < 0.005)[29]. Therefore, the postoperative rendezvous ERCP-ES has been limited but is still an acceptable alternative method when relevant equipment is unavailable[25].

A recent systematic review and meta-analysis including 1061 patients (542 with intraoperative rendezvous and 519 with two-stage preoperative ERCP and subsequent LC) found that no differences existed regarding stone clearance and postoperative bleeding, cholangitis or bile leak and conversion rate. However, the intraoperative rendezvous group had a longer operative time but less postoperative pancreatitis, morbidity and hospitalization[30]. A recent retrospective study from Italy demonstrated that laparoscopic rendezvous shortened the endoscopic time and may be a reasonable alternative to intraoperative ERCP[31].

Balloon sphincteroplasty by a transcystic wire balloon catheter to dilate the sphincter of Oddi and saline flushing may facilitate stone passage in 75% of cases[32]. Intervention *vs* surveillance to clear CBD stones during LC is better and has been recommended[33].

LC and LCBDE: This approach has all the benefits of a minimally invasive operation and ensures the resolution of concomitant gallbladder and CBD stones in a single session, as does traditional open CBD exploration[34], thus avoiding any complications of preoperative ERCP-ES (pancreatitis, cholangitis, bleeding, duodenal perforation)[35,36]. However, it requires specific equipment and advanced training that encourage the vast majority of surgeons to prefer the two-stage procedure by preoperative ERCP-ES[5]. Subsequently, the one-stage LC and LCBDE is a safe and cost-effective choice but only where expertise and equipment are available[37].

Severe ischemic heart disease, American Society of Anesthesiologists III or IV score is not a contraindication for LC and LCBDE. However, its safe performance requires both surgical and anesthesiological experience, continuous intraoperative monitoring and low-pressure pneumoperitoneum of 10-12 mmHg. After the latter's abolition, the patient's condition will be better because of the minimal invasiveness application[38].

A recent study from the United Kingdom including 311 cases of LCBDE [the majority (66%) were emergency procedures] showed laparoscopic ultrasound as the main diagnostic tool (73%). The completion rate was 94%. The route through choledochotomy was 56%, and transcystic was 44%. Bile leak occurred in 4.2% of patients, retained stones after 3 mo were present in 3.9% of patients, and the mortality rate was 0.66%[39]. Laparoscopic ultrasound instead of intraoperative cholangiography is a reasonable alternative performed during LC because it may delineate the anatomy and detect CBD stones[40].

Another recent retrospective multicenter study including 3950 cases of LCBDE showed a prevalence of the transcystic approach (63.1%), with a failure rate of 4% and a morbidity rate of 13.6%. However, most importantly, a survey defined a high rate (82.4%) of poor or very poor current training[41]. For primary CBD stones without cholelithiasis, LCBDE preserving the gallbladder has been recently reported[42]. A recent study from Scotland including 1318 LC and LCBDE among 5739 total LC

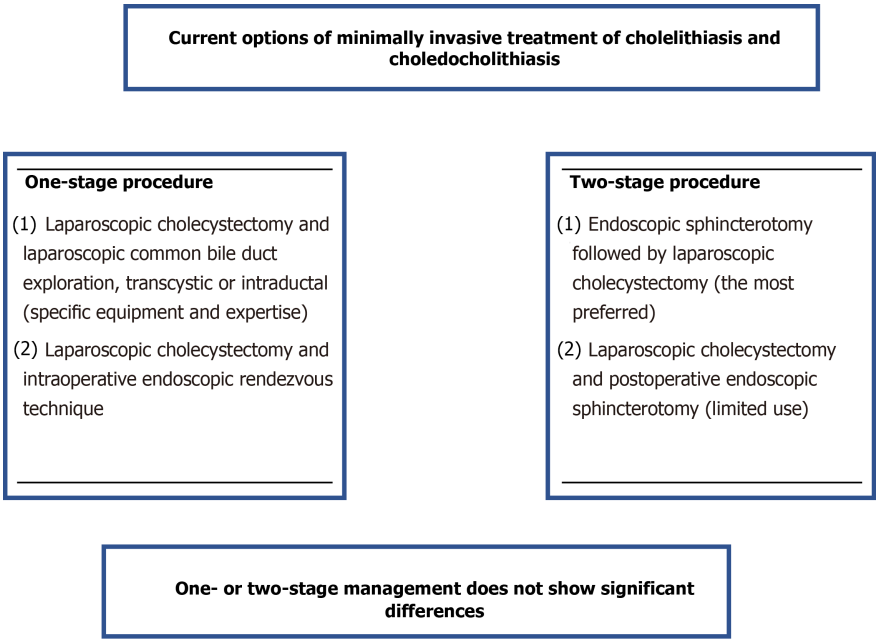

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Figure 1 Current options of minimally invasive treatment of cholelithiasis and choledocholithiasis.

performed (23%) showed a rate of intraoperative cholangiography of 98%, the transcystic approach rate of 66%, a conversion rate of 2.1%, retained stones in 2.1% of patients, a morbidity rate of 18.7% and a mortality rate of 0.2%[37].

A recent systematic review and meta-analysis found that LC and LCBDE after previous ERCP-ES failed CBD clearance had acceptable results and constituted a reliable alternative choice after endoscopic failure[43]. A recent retrospective study from the United Kingdom found that the transcystic or transductal approach for LCBDE had similar results regarding stone clearance, conversion to open surgery and mortality, but morbidity and complications were higher in the transductal route[44]. For LCBDE, an impacted stone may have a more difficult extraction, and multiple CBD stones are associated with a higher complication risk[45].

Primary closure of the CBD without T-tube placement after LCBDE has been proposed as a safe and feasible choice even in patients ≥ 70-years-old[46] and in cases of acute cholangitis[47]. In patients > 75-years-old, one-stage LC and CBDE were found to be better than two-stage ERCP-ES and LC. However, for multiple stones, a choledochoduodenal anastomosis may be an acceptable choice[48]. Choledochoscopic CBD exploration at the time of LC *vs* ERCP has been proposed with a stone clearance success rate of 84% and a risk of recurrence of 2%[49].

Two-stage procedure

ERCP-ES and subsequent LC, the most preferred method worldwide[4,17,50], is a safe management process even in patients with cardiovascular disease[51]. A randomized controlled study showed that routine nasobiliary tubes after endoscopic CBD stone clearance can facilitate subsequent LC by the ability of the intraoperative cholangiography and ensure the anatomical integrity of the CBD[52].

In the United States, 10%-15% of ERCP CBD stone-clearance cases are difficult or complex[53]. In difficult CBD stones, step-by-step management is indicated. ES and large balloon dilation is the initial approach. Mechanical lithotripsy or preferably cholangioscopy-assisted lithotripsy are alternative options, but the latter may be used as the initial step[54,55]. Additionally, fully covered metal stents are safe and may be useful when they remain for more than 1 mo, especially in males and stone sizes less than 2 cm[56].

A national survey from South Korea on the management of difficult CBD stones (above 15-20 mm in size) showed the following findings: (1) In the vast majority (74.4%), a large balloon dilation after ES was the followed method or alone in cases of bleeding predisposition; (2) Double wire use in periampullary diverticulum and cannulation difficulty; and (3) Percutaneous transhepatic cholangioscopy or cap-fitted endoscopy in cases of previous gastrectomy[57].

A recent large study from China found differences between two expertise centers in choledocholithiasis characteristics and ERCP stone clearance with emphasis on the presence of periampullary diverticulum. After ERCP, the complications and residual stones did not differ between patients with or without a periampullary diverticulum, but the diameter of the CBD was wider in those with it than those without it[58].

A recent randomized controlled trial from China showed that CBD stone recurrence and re-recurrence after ERCP were reduced efficiently by endoscopic papillary large balloon dilation at a median follow-up of 56 mo[59]. A recent study determined predictive factors of ERCP-ES failure for stone clearance by multivariate analysis. They included previous biliary exploration, advanced age, intrahepatic stones, elevated serum total bilirubin, stones in the cystic duct or Mirizzi syndrome, CBD dilatation and the need for suprapapillary opening[60]. After ERCP-ES failure, LCBDE is feasible and safe[61].

In selected cases of cholelithiasis and choledocholithiasis, endoscopic ultrasound-guided gallbladder drainage combined with ERCP-ES is a reasonable modern approach that can manage the disease by endoscopic means[62]. When ERCP-ES is not possible for various reasons, a reliable alternative is the percutaneous management of CBD stones that is feasible and safe[3]. Reinterventions in stone recurrence, mainly ERCP or surgical (laparoscopic or open), may be needed[63].

For asymptomatic CBD stones, ERCP-ES is the first choice of recommended management despite the higher complication rate, especially of acute pancreatitis, than that of symptomatic cases. However, it is not yet clear by evidence-based data that this approach is justifiable[50]. The opposite point of view postulates by assessing the natural history that while early endoscopic removal of silent stones does not absolutely prevent further biliary complications, it has the risk of post-ERCP severe pancreatitis (5.2%). Therefore, wait-and-see management has been considered as the best choice for asymptomatic CBD stones[64].

In patients with acute cholecystitis and CBD stones, early management either by preoperative ERCP-ES followed by LC or LC and LCBDE is acceptable for both, with similar results[65]. In cases of severe acute biliary pancreatitis, CBD stenting by preventing stone passage reduces the risk of recurrence from the recommended delayed cholecystectomy[66]. The assessment of quality of life showed similar satisfaction of improvement between preoperative ERCP-ES followed by LC or LC and LCBDE[67].

The experience of general surgery residents on CBD exploration has decreased due to the application of ERCP-ES. This training deficiency should be managed effectively[68].

CONCLUSION

Much progress has been made in the current management of concomitant gallbladder and CBD stones in recent years. Preoperative ERCP-ES followed by LC is the most commonly used method in clinical practice. LCBDE is a safe and effective choice when it is performed by an experienced surgeon and the required equipment with all facilities is available. The rendezvous technique ensures a single intervention combining ERCP-ES and LC. Both one-stage and two-stage management have equivalent results. In difficult or recurrent cases, advanced endoscopic, radiologic and minimally invasive techniques are in use but require expertise. The surgeon must choose the most appropriate intervention for accurate diagnosis and the best management based on his or her own experience, the preoperative assessment and intraoperative findings.

FOOTNOTES

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MINIREVIEWS

Surveillance strategies following curative resection and non-operative approach of rectal cancer: How and how long? Review of current recommendations

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Abstract

Different follow-up strategies are available for patients with rectal cancer following curative treatment. A combination of biochemical testing and imaging investigation, associated with physical examination are commonly used. However, there is currently no consensus about the types of tests to perform, the timing of the testing, and even the need for follow-up at all has been questioned. The aim of this study was to review the evidence of the impact of different follow-up tests and programs in patients with non-metastatic disease after definitive treatment of the primary. A literature review was performed of studies published on MEDLINE, EMBASE, the Cochrane Library and Web of Science up to November 2022. Current published guidelines from the most authoritative specialty societies were also reviewed. According to the follow-up strategies available, the office visit is not efficient but represents the only way to maintain direct contact with the patient and is recommended by all authoritative specialty societies. In colorectal cancer surveillance, carcinoembryonic antigen represents the only established tumor marker. Abdominal and chest computed tomography scan is recommended considering that the liver and lungs are the most common sites of recurrence. Since local relapse in rectal cancer is higher than in colon cancer, endoscopic surveillance is mandatory. Different follow-up regimens have been published but randomized comparisons and meta-analyses do not allow to determine whether intensive or less intensive follow-up had any significant influence on survival and recurrence detection rate. The available data do not allow the drawing of final conclusions on the ideal surveillance methods and the

frequency with which they should be applied. It is very useful and urgent for clinicians to identify a cost-effective strategy that allows early identification of recurrence with a special focus for high-risk patients and patients undergoing a "watch and wait" approach.

Key Words: Rectal cancer; Follow-up; Surveillance; Recurrence; Carcinoembryonic antigen; Computed tomography

Core Tip: Follow-up programs following rectal cancer curative treatment are widely accepted as an integrated part of the therapeutic pathway, but there is still no consensus regarding which test should be performed, the time schedule, the frequency and the duration of surveillance. The impact on survival has also been questioned with recurrence detection not necessarily associated with curative surgery. The aim of this review was to provide an overview of recommendations on this topic with supporting evidence.

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INTRODUCTION

Currently, the treatment of rectal cancer is based on a multimodal approach that involves not only the surgeon but other specialists such as gastroenterologists, radiotherapists, and oncologists. Due to the wide range of circumstances in the initial stage and responsivity to neoadjuvant treatments, many therapeutic pathways are available that may lead to different follow-up plans and open the door to the debate. There is currently no consensus about the types of tests to perform, the timing of the testing, and even the need for follow-up at all has been questioned. Only patients treated radically for the primary tumor with non-metastatic disease are eligible for post-operative follow-up. Although at the time of diagnosis, approximately 70% of patients affected by colorectal cancer will be treated surgically with curative intent[1], recurrence occurs in about 30% to 50% of patients undergoing curative treatments, including both local relapse and distant metastasis[2]. Therefore, surveillance programs following radical rectal cancer resection are an integral part of the therapeutic pathway. The most common sites of distant metastasis are the liver followed by the lungs; however, rectal cancer is correlated more often to local failure than colon cancer, carrying a significantly higher risk of local recurrence. Specifically, anastomotic recurrence is recorded in 5% to 15% of patients[3], although it should be noted that the recurrence more frequently grows extraluminally, generally in the pre-sacral area and less often in the anastomosis site[4]. The rate of distant metastasis in colon and rectal cancer is similar instead[5]. Treatment with curative intent of recurrence is feasible, and this increases prognosis and overall survival. Given the great risk of relapse, to improve prognosis of patients with disease recurrence, follow-up regimens should detect cancer recurrence early. The key point is to find the best surveillance programs that allow the early detection of recurrent cancer when it is still responsive to curative treatment. Follow-up programs have strategic importance only in this setting. Finally, we should consider two more aspects related to surveillance programs. Follow-up has an important psychological impact indeed: on the one hand it may provide comfort, reassuring the cancer survivor that there is no evidence of recurrence; on the other hand, it may induce negative effects such as stress and anxiety due to the intensive testing the patient is forced to go through. Finally, follow-up tests are costly and bring the inevitable risk of false positives, leading to pointless procedures and potential complications. In light of the clear benefits and potential risks of follow-up programs, it is urgent to establish a cost-effective strategy to guarantee early recognition of disease relapse and reduce potential shortcomings, narrowing surveillance to the highest-risk patients.

The aim of this study was to review the evidence of the impact of different follow-up tests and programs in patients with non-metastatic disease following surgery of the primary tumor. Current published guidelines from the most authoritative specialty societies were also reviewed and presented.

RISK ASSESSMENT

Recurrence could be local or distant and numerous risk factors have been related to cancer relapse including tumor stage, grading, circumferential margin, location, obstruction, perforation, type and adequacy of resection, lympho-vascular invasion, blood transfusions, anastomotic leak, patient constitution and sex, and last but not least, the surgeon's know-how and expertise leading to the saying "colorectal surgeons do it better"[6-9]. Nonetheless, the critical factor related to the risk of recurrence is the original histopathological cancer stage with an increased risk associated with advanced primary American Joint Committee on Cancer (AJCC) staging. Therefore, the follow-up strategy involves patients affected by early-stage disease, focusing especially on those belonging to stage II and III according to AJCC regarded as the highest risk patients. Patients affected by stage 0 neoplasia (carcinoma in situ without extension into the submucosa), patients operated with no curative intent and patients with major comorbidities that even in case of recurrence would be excluded from any active treatment, should not be followed-up. Finally, both locoregional and distant recurrences occur in most cases within 3 years of surgery, highlighting the importance of intensive early testing and suggesting a limited impact of longer follow-up[10].

FOLLOW-UP TESTS

Taking into account the different types of metastases, more than one surveillance test is usually performed to evaluate the different possible sites of recurrence. A combination of biochemical tests and imaging investigations are associated with physical examination to identify locoregional and distant metastases at an early stage. The most used tools to perform a complete surveillance include medical history and physical examinations, serial measurement of carcinoembryonic antigen (CEA), liver function tests, endoscopy, liver imaging and chest imaging and possibly, positron emission tomography (PET) scanning.

MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Anamnesis and clinical examination are the first approach for any patient with rectal cancer history and are recommended by all scientific societies as an integral part of surveillance programs[4,11-15]. However, the value and role of the office visit are not still clear. The lack of specific symptoms makes diagnosis complicated and often delayed, and only 1.7% to 7% of patients with symptoms caused by recurrence have resectable disease[16-18]. Furthermore, about one-quarter of patients, even though within an intensive surveillance program, delay reporting symptoms until their next clinic visit[19]. The digital rectal examination (DRE) has progressively lost importance for the early detection of local recurrence and nowadays office evaluation remains key only for maintaining direct contact with patients, better planning surveillance tests and coordinating with different figures to avoid useless diagnostic procedures and pointless anxiety[15].

CEA

CEA is the most used tumor marker and hematic test in colorectal cancer follow-up. Its role has been extensively evaluated and it has been used in colorectal cancer for more than 40 years. CEA has not as much specificity and sensibility as a screening test, but is often the first indicator of relapse even in the case of cancers without CEA elevation prior to surgery[20]. CEA level is reported as being elevated in up to 75% of patients with colorectal cancer recurrence[21]. The reported sensitivity of CEA varies respectively from 44% to 89%, while specificity ranges from 42% to 98%[22-32]. The sensitivity and specificity of CEA for detecting recurrence depends on the cut-off value considered: a CEA cutoff of 10 μg/L is associated with sensitivity of 68% and specificity of 97%, while a cutoff of 2.5 μg/L has a sensitivity of 82% and a specificity of 80%[33]. Thus, a lower threshold level has resulted in increased sensitivity but reduced specificity. It has been reported that only 22.9% (range between 7.5% and 33%) of recurrences, identified by CEA elevation, are resectable at the time of diagnosis[10]. Recently, the follow-up after colorectal surgery (FACS) trial randomly assigned 1202 patients to four different types of follow-up. The authors report that CEA screening alone detected 6.7% of resectable metastases, compared with 8% in the computed tomography (CT) alone group and 6.6% in the group with association of CEA and CT. Thus, the rates of surgical treatment of recurrences were similar in the CEA alone group and CT alone group, without advantages in combination of CEA and CT[34]. CEA remains the most cost-effective method of identification of recurrence, although the curative rate of surgery in this scenario remains low. It should be noted that the possibility of false-positive CEA rising is real. The false-positive rate for CEA can be as high as 16%, especially in smokers[28]. For this reason, it is a

common opinion to wait for a second CEA level to confirm an elevation trend and in the case of rising CEA on sequential measurements it is suggested to embark on more specific diagnostic tools. This attitude was recently confirmed by the CEA watch trial from the Netherlands that compared usual follow-up care with an intensified follow-up schedule performed with CEA measurements every 2 months and imaging in the case of two CEA rises. Intensive CEA surveillance protocol resulted in higher recurrence detection and more recurrence suitable for curative treatment. The time of detection of recurrent disease was shorter as well[35]. Rising CEA should be managed by investigating the possible recurrence site and even the employment of a PET or PET/CT is justified if the localization of the relapse is not clear[14,36]. Finally, CEA represents the only established tumor marker in colorectal cancer follow-up programs and is strongly recommended by all major scientific societies[4,11-15].

LIVER IMAGING

The most used imaging means of studying liver parenchyma are ultrasonography (US) and CT. US is operator dependent and has lower sensitivity than CT scans, but both may detect liver recurrence early. However, the real benefit of early recurrence detection in terms of curative resection is still controversial. Mäkelä *et al*[37] reported only 6 of 22 (27%) liver metastases identified by either ultrasound (4 cases) or CT scan (2 cases), prior to elevation of CEA. This was not associated with any resection. Schoemaker *et al*[38] demonstrated a significant identification rate of asymptomatic liver metastasis by CT scan, but these figures were not associated with increased hepatic resection rates (3 resections in the intensive surveillance group and 4 in the standard arm). The tests used in the standard arm (CEA and liver function tests) allowed identification of resectable liver recurrences with CT scans not adding any substantial advantages. More recently, the results of the FACS trial were similar: liver metastases were detected both by scheduled CEA only or scheduled CT only. No advantages were reported in combining CEA and CT. CEA is evidently more cost-effective, even though CT is crucial for confirming and localizing the recurrence[34]. Only in the randomized controlled trial (RCT) from Rodríguez-Moranta *et al*[39] either abdominal CT or US were able to detect 10 (28.5%) distant metastases, 4 of which were resectable (40%). Indeed, there is an overlap between liver imaging and CEA, suggesting that isolated liver imagines in routine follow-up programs are not so useful. Nevertheless, liver imaging is recommended almost annually by all specialty societies[4,11-15].

CHEST IMAGING

Rectal cancer, more than colon cancer, frequently recurs in the lung given its particular venous drainage to the caval system, with an incidence of isolated lung metastasis of 2-10% of cases[40,41]. Unfortunately, as reported by a multicenter retrospective study, only 38% of those patients are eligible for curative metastasectomy and undergo surgical resection[42]. Mitry *et al*[43] reported even worse figures: only 4% of patients with synchronous pulmonary metastases and 14% of patients with metachronous pulmonary metastases are curatively resected. Lung recurrences may be detected by conventional chest radiography (CXR) or CT scan. The role of CXR has been evaluated, especially in the case of colon cancer follow-up, suggesting that it is not a valuable method for detecting resectable disease. Considering trials including both colon and rectal cancers, CXR was able to identify lung resectable recurrence in 1.8% to 12% of patients, which did not substantially modify survival[37,38,44]. Similarly, Rodríguez-Moranta *et al*[39] more recently reported that CXR was the first method indicating lung tumor recurrence in 3 patients (9%) in the intensive strategy group. However, only two recurrences were resectable (11%), and just one (25%) considering recurrence related to rectal cancer. These figures look similar to those published previously but highlight how the performance of CXR as a diagnostic tool is better if we consider only the patients affected by rectal cancer. However, even though CXR is not costly, a very low number of patients can benefit from scheduled CXR, and its role remains marginal in surveillance programs. Chest CT scan appears to be the only reliable method for investigating the lungs and it is suggested by all the specialty societies, at the expense of CXR[4,11-15].

ENDOSCOPY

The role of colonoscopy and rectosigmoidoscopy after curative resection is crucial and is a very important tool for identifying anastomotic recurrence and metachronous colorectal cancers. In rectal cancer, especially in patients who did not receive any neoadjuvant treatment, about 3% to 50% of cases show a locoregional recurrence, including anastomotic recurrences, that is more frequent than in colon cancers[45]. Patients affected by rectal cancer have a lifetime risk of developing a metachronous tumor in the residual viscera that ranges from 1.1% to 6.3%[20], while the risk of developing a metachronous adenoma is up to 56%[46]. Taking into account the reported figures of metachronous lesions, the role of

colonoscopy is undisputed despite the invasiveness and the risk of possible complications, such as bleeding or perforation. Two studies[38,47] reported complications related to colonoscopy surveillance in only seven cases (three perforations and four hemorrhages out of 2112 colonoscopies: 0.4%). Eight RCTs included colonoscopy and proctoscopy as a part of intensive surveillance programs, compared either with less frequent or even no endoluminal testing[16,37-39,44,47-49]. These trials, except those reported by Rodríguez-Moranta *et al*[39] and Wang *et al*[47], suggest only a marginal benefit from colonoscopy. Instead, Rodríguez-Moranta *et al*[39] and Wang *et al*[47] reported a significant identification of local relapses that can be treated with salvage surgery, leading to significantly longer survival in patients undergoing intensive colonoscopic surveillance. However, the bad results of six RCTs[16,37,38,44,48,49] adopting intensive colonoscopy programs were probably due to the short median observation period reported by each study, which was less than 5 years. The reality is that patients treated for colon and rectal cancers have a life-long and cumulative risk of developing bowel cancer again and therefore the recommendation to perform a colonoscopy over a longer period is warranted and may prove more beneficial. The major scientific societies suggest colonoscopy as a follow-up modality for removing early adenomatous polyps and detecting metachronous cancer[4,11,13,14]. The American Society of Colon and Rectal Surgeon (ASCRS)[4], The Association of Coloproctology of Great Britain and Ireland (ACPGBI)[11], The American Society of Clinical Oncology (ASCO)[13] and The National Comprehensive Cancer Network (NCCN)[14], actually suggest colonoscopy at 1 year, and subsequently according to findings. Furthermore, the ASCRS[4], ASCO[13], and NCCN[14] recommend surveillance rectosigmoidoscopy even more frequently (every 3 to 6 months for 5 years) in the presence of local recurrence risk factors and consider transanal local excision and absence of neoadjuvant radiation a risk factor *per se*. However, colonoscopy is not able to detect extra-luminal recurrent disease, which is more frequent than intraluminal recurrence in the case of rectal cancer. More often a positive circumferential margin at the time of original resection results in an extra-parietal recurrence, usually in the pre-sacral site. Endorectal ultrasound (ERUS) may overcome this limit, giving an accurate imaging of surrounding pelvic tissues. The role of ERUS for the diagnosis of local recurrence after local excision and radical surgery for rectal cancer was evaluated by de Anda *et al*[50]. The authors reported that asymptomatic local recurrences are identified by ERUS in 30% of cases and these recurrences were actually missed by digital examination or proctoscopic examination. However, only 44% of cases were amenable to salvage surgery and the impact of earlier diagnosis was not significant in terms of patient survival. Larger, multi-institutional RCTs are needed to confirm the real role and effectiveness of ERUS. Considering the lack of clear data, the ASCR and NCCN recommend surveillance endoscopy "with or without" ERUS, or alternatively magnetic resonance imaging (MRI) in surveillance programs[4,14].

PET SCANNING

PET with the use of radio-labeled glucose analogue ^{18}F-fluorodeoxyglucose (FDG) and PET associated with a CT scan (FDG PET/CT) are metabolic imaging that highlight lesions with higher glucose metabolism. Malignant lesions have higher glucose metabolism and thus a higher uptake of FDG. The use of PET/CT in colorectal cancer follow-up is currently controversial. A review and meta-analysis[51] evaluating the performance of FDG-PET or PET/CT to detect recurrences of colorectal cancer in patients with raised CEA, identifies 11 studies with a total of 510 patients. In the case of an increase in CEA, one hundred and six patients (106/510: 20.8%) had a true-negative FDG-PET/ or PET/CT. Thus, both imaging modalities ruled out 20% of false positive elevations of CEA. Moreover, the diagnostic accuracy of these techniques was 88.6% and allows a differentiation of an inflammatory process from a recurrence. PET and PET/CT had a sensitivity of 90.3% and 94.1% and a specificity of 80% and 77.2% respectively. Similarly, both modalities had good accuracy (89.03% and 92.38% respectively). Supplementary analysis showed that PET and PET/CT gave a significantly higher diagnostic performance than CT scans. Sanli *et al*[52] reported that colorectal cancer relapse was accurately detected also in the case of normal CEA rates. The NCCN[14] suggests PET/CT scans in the case of an increasing CEA, even with negative CT scans. Recently, a novel hybrid technique was introduced in the oncological field matching PET and MRI in one examination: FDG-PET/MRI. Hybrid PET/MRI combines metabolic imaging of PET with excellent soft tissue morphology of MRI[53]. The accuracy of FDG-PET/MRI is apparently superior to MRI alone in restaging after neoadjuvant chemoradiation (naCRT). The study from Crimì *et al*[54] showed that in patients with locally advanced rectal cancer undergoing restaging following preoperative chemoradiotherapy, FDG-PET/MRI was more accurate and sensitive than MRI alone both for residual cancer and regional lymph nodes (respectively ypT accuracy 92% *vs* 89%; ypN accuracy 92% *vs* 86%). Two recent studies investigated the role of FDG-PET/MRI in pelvic recurrence of rectal cancer[55,56]. The first paper from Plodeck *et al*[55] was a retrospective, single reader study, assessing the performance of FDG-PET/MRI without any comparison to MRI alone: sensitivity, specificity and accuracy were 94%. The same group published a retrospective evaluation of diagnostic performance of PET/MRI compared to MRI alone in the diagnosis of pelvic recurrence of rectal cancer: sensitivity and accuracy of PET/MRI were respectively 94% and 93% compared to 88% sensitivity and 85% accuracy of MRI in detecting recurrence. Both imaging modalities are accurate in this setting even though PET/MRI

increases confidence in diagnosis or exclusion of local recurrence and reduces the number of equivocal cases[56]. We can conclude that both PET and PET/CT provide useful information about sites of recurrence, especially extra-hepatic lesions, and possible metachronous tumors contributing substantially to patient management. Patients with a suspected recurrence, based on clinical findings or rising CEA, might benefit from a PET/CT as a first line imaging modality, since a negative CT scan does not definitively exclude a recurrence and will be followed by a PET/CT anyhow. PET/MRI is a promising imaging modality combining functional imaging and soft tissue contrast leading to more accurate evaluation of pelvic recurrence. Unfortunately, no prospective studies have evaluated the role of PET imaging in any colorectal cancer surveillance program. Indeed, the main limits of PET, PET/CT and PET/MRI are its limited availability and high cost: these drawbacks limit its use in follow-up programs and make PET imaging not realistic as a routine diagnostic method.

INTENSIVE *VS* LESS INTENSIVE FOLLOW-UP

Different follow-up regimens have been studied in RCTs and non-randomized studies, meta-analysis and systematic review, that aimed to elucidate the impact of different surveillance programs and schedule in terms of survival, recurrence detection rate and the ability to offer salvage surgery in the case of recurrence. Intensive, less intensive or even no surveillance has been proposed and the influence on cancer related outcomes has been analyzed. We identified 17 RCTs[16,34-39,44,47-49,57-63] and 8 meta-analyses[19,64-70], evaluating different follow-up strategies during surveillance programs after curative colorectal cancer surgery. Results of RCTs and meta-analyses are summarized respectively in Tables 1 and 2. Three trials[58,60,61] comparing different settings of monitoring did not show any differences in terms of recurrence detection rates and time to detection between a hospital/specialist setting and a general practice setting. Medical safety was uncompromised even if the follow-up was performed by a trained nurse. Eight trials did not show any significant differences in survival between intensive and less intensive surveillance[16,34,37,38,44,49,62,63]. The trial by Ohlsson *et al*[44] did not show any survival improvement even comparing intense follow-up with no follow-up. On the other hand, in six trials, intensive follow-up was associated with an improved overall survival, instead[35,39,47,48,57,59]. Six meta-analyses showed that, in patients with colorectal cancer followed after curative resection, an intensive follow-up program improves overall survival, detection of asymptomatic relapses and reoperation with curative intent[19,64-68]. On the other hand, there are two more recent meta-analyses that were not able to demonstrate any significant benefit from an intensification of surveillance programs[69,70]. It should be noted that the recent COLOFOL trial[63] is not included in any published meta-analyses. This trial randomized 2509 patients with stage II or III colorectal cancer to either low frequency follow-up regimens (CEA and chest/abdomen CT scan at 12 and 26 months) or high frequency follow-up regimens (CEA and CT scan at 6-12-18-24-36 months) with patients undergoing the same kind of tests. No significant advantage of the high frequency follow-up testing, both in 5-year overall mortality and colorectal cancer-specific mortality was recorded[63]. Furthermore, Renehan *et al*[64] in their meta-analysis showed that intensive surveillance leads to a 10% decrease in 5-year mortality, however only in 2% of cases salvage surgery was possible. The authors suggested that intensive follow-up programs can ameliorate psychosocial support and well-being, alter dietary and lifestyle factors and finally improve treatment of coincidental diseases leading to survival benefits. However, Baca *et al*[10] suggested that meta-analytic techniques could not be appropriate to evaluate results because of the inadequacy of sample sizes and the high heterogeneity in surveillance programs considered in the different RCTs. Finally, it has been suggested that a structured follow-up should be performed only in patients who can benefit from further treatments[15].

COST OF FOLLOW-UP

The pressure of rising health care costs has forced clinicians to review surveillance protocols to make them more effective and cheaper, trying to save unnecessary tests. Economic analysis of eleven different 5-year postoperative follow-up programs based on Medicare-allowed charges showed a wide range of costs: from $910 to $26717. Despite these significant disparities, no clear benefits were found in higher cost strategies in terms of quality of life and survival rate[71]. In the same year, Kievit *et al*[72] presented the results of a cost-effectiveness analysis comparing the results of three different policies comparing no follow-up, selective follow-up and intensive follow-up. In most cases, follow-up will only increase costs significantly without an increase in life expectancy and the author concluded that colorectal cancer follow-up is not "evidence-based medicine." A Markov model was used to simulate follow-up over a 7-year period in patients who had undergone curative resection of colorectal cancer[73]. The influence of follow-up on the quality-adjusted life expectancy of patients who had Duke's stage A and B colorectal cancer was marginal, while it ameliorated the survival in Duke's stage C patients. Graham *et al*[17] analyzed the cost of the single diagnostic method per resectable recurrence: CEA was the most cost-effective method, costing $5696 per recurrence, while CXR and colonoscopy cost $10078 and $45810 per

Table 1 Randomized controlled trials: Different surveillance strategies following curative colorectal cancer resection

Ref.	Surveillance strategy	No. of patients randomized	Significant benefit
Ohlsson *et al*[44], 1995	Total	107	No
	None (FOBT)	54	
	Intensive follow-up: examinations, FOBT, CEA, endoscopy, CXR, CT	53	
Mäkelä *et al*[37], 1995	Total	106	No
	Standard	54	
	More intensive examinations, FOBT, CEA, colonoscopy, CXR, liver US, CT	52	
Kjeldsen *et al*[16], 1997	Total	597	No
	Standard	307	
	More intensive examinations, blood tests, FOBT, CXR, colonoscopy	290	
Schoemaker *et al*[38], 1998	Total	325	No
	Standard: examinations, blood test, CEA, FOBT	158	
	Intensive: standard plus CXR, CT, colonoscopy	167	
Pietra *et al*[57], 1998	Total	207	Yes (increased curative reoperation; increased survival)
	Standard	103	
	More intensive examinations, CEA, colonoscopy, CXR, liver US, CT	104	
Secco *et al*[48], 2002	Total	358 (21 drop out)	Yes (increased curative reoperation; increased survival)
	Minimal: examinations yearly and on demand	145	
	Risk-adapted	192	
	-Low risk: less frequent examinations, CEA, rectosigmoidoscopy, CXR, US	84	
	-High risk: more frequent examinations, CEA, rectosigmoidoscopy, CXR, US	108	
Wattchow *et al*[58], 2006	Different settings no different tests	203 (46 lost fu)	No
	General Practitioner	81	
	Surgeon visit	76	
Rodríguez-Moranta *et al*[39], 2006	Total	259	Yes (increased curative reoperation, increased survival only for stage II colon tumor and rectal tumor)
	Standard: examinations, blood tests and CEA. Colonoscopy only if history of HNPCC and synchronous neoplasm	127	
	Intensive: standard plus annual colonoscopy, CXR, US and CT	132	
Sobhani *et al*[59], 2008	Total	130	Yes (increased curative reoperation; number of patients too small to evaluate survival)
	Standard: examinations, CEA, CXR, US and CT	65	
	Intensive: standard plus ^{18}FDG-PET	65	
Wang *et al*[47], 2009	Total	326	Yes (increased curative reoperation; no increased survival)
	Standard: examinations, CEA, colonoscopy, CXR, liver US and CT	161	
	Intensive: standard plus more frequent colonoscopy	165	
Strand *et al*[60], 2011	Different settings no different tests	110	No
	Nurse	54	
	Surgeon visit	56	

Augestad *et al*[61], 2013	Different settings no different tests	110	No
	General Practitioner	55	
	Surgeon visit	55	
Primrose *et al*[34] (FACS), 2014	Total	1202	No
	Minimal follow-up: no scheduled follow-up except a single CT scan at 12-18 mo	301	
	CEA follow-up: CEA every 3 mo for 2 yr, then every 6 mo for 3 yr, with a single CT scan at 12-18 mo	300	
	CT follow-up: CT scan every 6 mo for 2 yr, then annually for 3 yr	299	
	CEA and CT follow-up: combined CEA and CT imaging as above	302	
Treasure *et al*[62] (the CEA Second-Look trial), 2014	Total	Tot 216	No
	Standard: CEA monitoring with no further action even in case of CEA rising	108	
	Aggressive: CEA monitoring followed by second-look operation and possible resection in case of CEA rising	108	
Verberne *et al*[35] (CEAwatch)[1], 2015	Total	3223	Yes (increased curative reoperation; no increased survival)
	Standard: CEA every 3 mo, examinations, liver US and CXR every 6 mo	1182	
	Intensive: CEA every 2 mo, examinations and CT annually. If CEA rise, repeat CEA after 1 mo. If two consecutive CEA rise, CT scan	316	
	Standard and Intensive: patients participated both in the standard protocol and in the intensive protocol	1725	
Rosati *et al*[49] (GILDA), 2016	Total	1228	No
	Standard: examinations, CEA, colonoscopy, CXR, liver imaging (US or CT scan)	613	
	Intensive: standard plus CA19-9, blood test, more frequent colonoscopy, CXR and liver imaging (US or CT), CT abdomen-pelvis	615	
Wille-Jørgensen *et al*[63] (COLOFOL), 2018	Total	2509	No
	Standard: CEA, CT chest, abdomen and pelvis at 12 and 36 mo	1256	
	Intensive: CEA, CT chest, abdomen and pelvis every 6 mo for 2 yr, then at 36 mo	1253	

[1]During the study period, hospitals changed from a standard follow-up schedule to the intensive follow-up schedule every 3 months. CEA: Carcinoembryonic antigen; CT: Computed tomography; CXR: Conventional chest radiography; FOBT: Fecal occult blood test; HNPCC: Hereditary non-polyposis colorectal cancer; mo: months; US: Ultrasonography; yr: years.

recurrence respectively. A risk adjusted follow-up policy, considering that older age and favorable cancer stage decrease cost-effectiveness, should focus solely on high-risk patients for the first 2-3 years using the most cost-effective test to increase benefits. On the other hand, a prospective, multicenter, RCT comparing a simple surveillance program including just clinical evaluation and CEA with an intensive strategy with abdominal-pelvic CT, CXR, and colonoscopy, found that, even though the overall cost of an intensive surveillance program was higher (€300315 *vs* €188630), the intensive follow-up was more cost-effective when resectability of recurrent disease was considered. In fact, the cost per resectable recurrence was €16684 in the intensive surveillance group, compared with €18863 in the simple follow-up strategy[39]. Therefore, justification of a surveillance strategy should be fundamentally based on evidence of clinical value allowing identification of recurrence at the point where a cure is still possible. Finally, the study from Augestad *et al*[61] demonstrated that a general practitioner's organized follow-up was cost-effective compared with surgeon's organized follow-up (£8233 *vs* £9889). Delegating follow-up can be effective but also safe with no harm for patients, but probably a precise algorithm of surveillance programs is the only way to help clinicians in charge for surveillance.

Table 2 Meta-analyses of follow-up studies with different surveillance strategies

Ref.	Studies included and number of patients	Benefit on survival
Bruinvels *et al*[19], 1993	7 nonrandomized	Yes
	3283 patients	
Rosen *et al*[67], 1998	2 RCTs, 3 nonrandomized	Yes
	2005 patients	
Renehan *et al*[64], 2002	5 RCTs	Yes
	1342 patients	
Figueredo *et al*[68], 2003	6 RCTs	Yes
	1679 patients	
Tjandra *et al*[65], 2007	8 RCTs	Yes
	2923 patients	
Pita-Fernández *et al*[66], 2015	11 RCTs	Yes
	4055 patients	
Mokhles *et al*[69], 2016	11 RCTs	No
	4515 patients	
Jeffery *et al*[70], 2016	15 RCTs	No
	5403 patients	

RCT: Randomized controlled trial.

CURRENT GUIDELINES AND RECOMMENDATIONS

Published guidelines from the most authoritative specialty societies indicate different protocols including medical history and physical examination, CEA levels, abdominal-pelvic and chest imaging and endoscopy. Follow-up recommendations from ASCO[13], ASCRS[4], European Society of Medical Oncology (ESMO)[12], ACPGBI[11], NCCN[14] and European Society of Coloproctology (ESCP)[15] are summarized in Table 3. In 2013, ASCO[13] endorsed the Cancer Care Ontario guidelines on follow-up care and added some statements[74]. The guidelines are primarily for patients with stage II and III disease, while stage I patients and patients resected for metastatic disease should be monitored according to the discretion of the health care provider. The suggested surveillance program considers, in the first 2-4 years, more intensive testing since 80% of recurrences occur in the first 2-2.5 years from surgery[13]. NCCN[14] and ESMO[12] guidelines actually suggest semi-annual to annual abdomen and chest CT scans for 5 years considering that up to 10% of recurrences occur after 3 years[75]. The ASCRS guidelines[4] are very similar to the previous recommendations but support the advantage of follow-up in terms of survival in patients with stage I disease. The ASCRS[4] and NCCN[14] recommend a more intensive approach for patients treated by transanal excision, while ASCO[13] suggests the same intensive approach for patients not having received radiotherapy. In NCCN guidelines[14], surveillance programs are a little more frequent than other programs. The ESMO[12] and ACPGBI[11] recommendations suggest slightly less intensive testing with a minimum of two CT scans of the chest, abdomen and pelvis associated with regular serum CEA tests in the first 3 years. The ESCP[15] recommendations are actually an overview of national and international clinical practice guidelines. Interestingly, colonoscopy and endoscopic inspection of anastomosis are recommended but the optimum time schedule and duration of surveillance are not specified since the analyzed guidelines were not all concordant[15]. A different issue is represented by the significant variation in adhesion and compliance both of members of scientific societies and patients with the recommended follow-up tests. A postal survey was mailed to active members of ASCRS in 2000 assessing the methods and frequency of follow-up. The most used tests were colonoscopy and CEA but there was wide variation in the frequency of follow-up and the diagnostic modalities employed. More interestingly, only 50% of surgeons followed the recommended guidelines of the ASCRS to whom they belonged[76]. It is clear that specialty society's recommendations differ and health care providers may find it difficult to choose the ones which are most appropriate. This may explain the low percentage of surgeons adhering to the recommended guidelines. It appears more sensible to adopt the follow-up scheme according to available manpower and local facilities.

Table 3 Summary of current surveillance guidelines from specialty societies

Guideline	MH & PE	CEA	Abdomen imaging	Chest imaging	Colonoscopy
ASCO[13]	Every 3-6 mo for 5 yr	Every 3-6 mo for 5 yr	CT of abdomen and pelvis annually for 3 yr, for high-risk patients every 6-12 mo for 3 years and then annually for 2 yr	CT of chest annually for 3 yr, for high-risk patients every 6-12 mo for 3 yr	Colonoscopy at 1 yr, subsequently according findings and every 5 yr if normal. Rectosigmoidoscopy every 6 mo for 5 yr in rectal cancer not irradiated
ASCR[4]	Every 3-6 mo for 2 yr, then every 6 mo for 3 yr	Every 3-6 mo for 2 yr, then every 6 mo for 3 yr	CT of abdomen and pelvis 2 times in 5 yr, for high-risk patients annually for 5 yr	CT of chest 2 times in 5 yr, for high-risk patients annually for 5 yr	Colonoscopy at 1 yr, subsequently according findings and every 5 yr if normal. Rectosigmoidoscopy (+/- ERUS) every 6-12 mo for 3 to 5 yr for patients treated with TME; every 6 mo in patients treated with local excision
ESMO[12]	Every 6 mo for 2 yr	Every 6 mo for 3 yr	CT of abdomen and pelvis 2 times within 3 yr	CT of chest 2 times within 3 yr	Colonoscopy every 5 yr up to age 75
ACPGI [11]	No recommendation for frequency	Every 6 mo for 3 yr	CT of abdomen and pelvis 2 times within 3 yr	CT of chest 2 times within 3 yr	Colonoscopy at 1 yr subsequently according findings and every 5 yr if normal
NCCN[14]	Every 3-6 mo for 2 yr, then every 6 mo for 3 yr for stage II or greater	Every 3-6 mo for 2 yr, then every 6 mo for 3 yr for stage II or greater	CT of abdomen and pelvis every 3-6 mo for 2 yr, then every 6-12 mo for 3 yr	CT of chest every 3-6 mo for 2 yr, then every 6-12 mo for 3 yr	Colonoscopy at 1 yr, repeat in 3 yr then every 5 yr, Proctoscopy (with ERUS or MRI) every 3-6 mo for 2 yr, then every 6 mo for 3 yr for patients treated with transanal excision
ESCP[15]	No recommendation for frequency. Until 5 yr after surgery with a more frequent regimen in the first 2 yr to 3 yr	Every 3–6 mo for 2–3 yr, then every 6-12 mo until 5 yr after surgery	CT abdomen alternating with US for at least 5 yr with a more frequent regimen in the first 2-3 yr	CT of chest alternating with CXR every 3-12 mo for at least 5 yr after surgery	No recommendation for colonoscopy and proctoscopy

ACPGI: The association of Coloproctology of Great Britain and Ireland; ASCO: American Society of Oncology; ASCRS: American Society of Colon Rectal Surgeon; CEA: Carcinoembryonic antigen; CT: Computed tomography; CXR: Conventional chest radiography; ERUS: Endorectal ultrasound; ESMO: European Society for Medical Oncology; ESCP: European Society of Coloproctology; mo: months; MH & PE: Medical history and physical examination; MRI: Magnetic resonance imaging; NCCN: National Comprehensive Cancer Network; TME: Total mesorectal excision; US: Ultrasonography; yr: years.

FOLLOW-UP FOLLOWING A COMPLETE RESPONSE AFTER CHEMORADIATION

Locally invasive rectal cancer is currently managed by neoadjuvant combined modality therapy (chemoradiation or even radiation alone regimens) followed by total mesorectal excision. The benefit of neoadjuvant therapy is not only the long-term local disease control, but also tumor regression. naCRT induces tumor regression (downsizing) and eventually lymph node sterilization (downstaging). After naCRT, up to 25% of patients have complete pathological tumor regression with no residual viable tumor cells at the time of surgery[77-80]. These patients have the so called "pathologic complete response (pCR)". A pCR is defined as an absence of viable tumor on histologic examination of the resection specimen and is reported as ypT0N0[81]. In a systematic review, the finding of pCR was associated with local recurrence rate and distant metastasis respectively of 0.7% and 8.7%. The 5-year overall survival rate was 90.2%, the disease-free survival (DFS) rate 87%[82]. These surprising results in patients with pCR have changed the role of standard surgery, especially considering morbidity and mortality associated with rectal surgery. Habr-Gama *et al*[83] from Brazil firstly proposed a non-operative approach for patients with significant or complete tumor regression. This alternative approach is also described as "organ-sparing treatment", "rectal preservation" or the "watch and wait" strategy. Patients with apparent clinical complete response (cCR) after naCRT are ideal candidates for conservative strategy. cCR is usually described as absence of tumor according to clinical, radiological and endoscopic investigations; however, the description cannot be as clear as pCR. Although the definition of cCR remains an active question and there is no uniform consensus, the absence of any palpable tumor at DRE and no visible lesion (flat scar, whitening of the mucosa or teleangiectasia) at endoscopy are widely accepted as main criteria to define cCR. The clinical criteria are normally complemented by the absence of residual tumor and metastatic lymph nodes on MRI[84].The landmark paper based on this approach was firstly published in 2004 and since that time the San Paolo group has regularly updated their work[83,85]. Over 18 years, 67 (39%) patients were considered to have cCR after being reassessed following completion of radiotherapy at least 8 weeks later. At a mean follow-up of more than 5 years, overall survival reached 96% and DFS was 72% in nonoperative patients. Local recurrence (only endoluminal) and distant metastasis were observed in 11% and 10% respectively. All local recurrences were responsive to salvage therapy: 4 patients underwent radical surgery, 3 local excision and 1 additional endorectal brachytherapy[85]. Similar results have been reported by different authors in

smaller studies[86,87], but these surprising results have not been repeated by other studies with an 80% relapse rate following cCRs within 10 months of observation[88,89]. The data from the International Watch and Wait Database, including more than one-thousand patients managed by watch and wait strategy, showed a local regrowth rate of 25% and 8% distant metastasis at 3 years[90]. More recently, a total neoadjuvant therapy (TNT) has also been adopted with application of both radiation and full systemic chemotherapy before surgery leading to even better results in terms of tumor response[91]. In the prospective, randomized phase II trial from Garcia-Aguilar *et al*[91] the 3-year DFS was 76% and organ preservation was achievable in up to 53% of patients treated with TNT. Considering all these figures, the watch and wait strategy sounds promising and appealing since it avoids the significant morbidity related to surgery. Patients with a complete clinical response may achieve similar overall survival and local cancer control of patients undergoing standard surgery. The main challenge to a non-operative approach of locally advanced rectal cancer is the identification of patients with a true complete tumor regression since there is a real risk of leaving occult residual disease within the rectum or perirectal nodes. Thus, patients reported to have a cCR may bear microscopical disease with a high risk of early recurrence. These considerations are crucial for determining what kind of surveillance protocols should be adopted especially in this particular subset of patients. Again, the Brazil group[92] suggests a strict follow-up program including DRE, rigid proctoscopy with biopsy of suspicious lesions and CEA levels every 1-2 months for the first year, every 6 months in the second year and yearly thereafter. Chest X-ray and abdominal CT scans are recommended at 6 months and 12 months and yearly thereafter. The recently published RESARCH study[84] also adopts a strict follow-up strategy in patients who undergo a rectal sparing approach following neoadjuvant therapy: physical examination including digital rectal exploration, CEA levels and proctoscopy every 3 months for 2 years and subsequently every 6 months for 3 years. Chest and abdomen CT scans are recommended annually, while MRI of the pelvis is performed every 6 months for 2 years and yearly thereafter. Colonoscopy is performed at 1 year and 4 years following surgery[84]. Even though it is not suggested by the Habr-Gama *et al*[92] and the RESARCH study[84], FDG-PET and PET-CT may play an important role for surveying non-operative patients, considering that these imaging modalities are the most accurate and may help to distinguish fibrosis from viable tumor cells. Recently it has been suggested that FDG-PET/MRI may improve accuracy in restaging patients deemed to have a cCR. FDG-PET/MRI evaluating residual disease at restaging following TNT had an accuracy of 100% compared to 71% of MRI alone, adding value in restaging and surveillance programs of patients enrolled in non-operative management[93]. Finally, patients elected for this novel approach must be committed to an intensive follow-up regimen until the natural history of the non-operative approach is definitively clarified. The watch and wait strategy can only be offered to patients who will be compliant with frequent clinical and radiological evaluation. However, the key point of this novel approach remains to identify a true pCR without a resection and through targeted follow-up. Achieving the equivalence between cCR and pCR represents the crossroads to avoid either useless major resections or the risk of early local recurrence or, more correctly, tumor persistence.

CONCLUSION

Follow-up programs after rectal cancer resection are intuitively beneficial and appealing even though there is no clear evidence of benefits in terms of earlier detection of recurrence, surgical resections with curative intent and improved overall survival. The literature does not agree with the type of ideal surveillance methods and the timeframe with which they should be applied. Moreover, the cost-effectiveness of various surveillance strategies, the quality-of-life implications and the role of different surveillance techniques have not yet been clearly evaluated. In this difficult age for healthcare economies, the optimization of resources and therefore also of surveillance programs is necessary. The improvement of recurrence risk stratification, the identification of the patient population that will truly benefit from follow-up and avoid unnecessary examination in low-risk patients should be the main goal in designing a value-based follow-up strategy. The main purpose of a surveillance program must be early identification of a recurrence when curative interventions are still possible.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Causes of epigastric pain and vomiting after laparoscopic-assisted radical right hemicolectomy - superior mesenteric artery syndrome

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Abstract

BACKGROUND

Superior mesenteric artery syndrome (SMAS) is a rare condition causing functional obstruction of the third portion of the duodenum. Postoperative SMAS following laparoscopic-assisted radical right hemicolectomy is even less prevalent and can often be unrecognized by radiologists and clinicians.

AIM

To analyze the clinical features, risk factors, and prevention of SMAS after laparoscopic-assisted radical right hemicolectomy.

METHODS

We retrospectively analyzed clinical data of 256 patients undergoing laparoscopic-assisted radical right hemicolectomy in the Affiliated Hospital of Southwest Medical University from January 2019 to May 2022. The occurrence of SMAS and its countermeasures were evaluated. Among the 256 patients, SMAS was confirmed in six patients (2.3%) by postoperative clinical presentation and imaging features. All six patients were examined by enhanced computed tomography (CT) before and after surgery. Patients who developed SMAS after surgery were used as the experimental group. A simple random sampling method was used to select 20 patients who underwent surgery at the same time but did not develop SMAS and received preoperative abdominal enhanced CT as the control group. The angle and distance between the superior mesenteric artery and abdominal aorta were measured before and after surgery in the experimental group and before surgery in the control group. The preoperative body mass index (BMI) of the experimental group and the control group was calculated. The type of lymphadenectomy and surgical approach in the experimental and control groups were recorded. The differences in angle and distance were compared preoperatively and postoperatively in the experimental group compared. The differences in angle, distance, BMI, type of lymphadenectomy and surgical

approach between the experimental and control groups were compared, and the diagnostic efficacy of the significant parameters was assessed using receiver operating characteristic curves.

RESULTS

In the experimental group, the aortomesenteric angle and distance after surgery were significantly decreased than those before surgery ($P < 0.05$). The aortomesenteric angle, distance and BMI were significantly higher in the control group than in the experimental ($P < 0.05$). There was no significant difference in the type of lymphadenectomy and surgical approach between the two groups ($P > 0.05$).

CONCLUSION

The small preoperative aortomesenteric angle and distance and low BMI may be important factors for the complication. Over-cleaning of lymph fatty tissues may also be associated with this complication.

Key Words: Right hemicolectomy; Superior mesenteric artery syndrome; X-ray computed tomography

Core Tip: This study retrospectively analyzed 256 patients undergoing laparoscopic-assisted radical right hemicolectomy, and six patients developed superior mesenteric artery syndrome (SMAS). The preoperative and postoperative aortomesenteric angle and distance were compared in the six patients, and 20 patients without postoperative SMAS were randomly selected for comparative analysis with 6 patients developed SMAS. The results and literature review suggest possible reasons and preventative measures for SMAS after right hemicolectomy.

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INTRODUCTION

A series of symptoms may occur after right hemicolectomy. They include nausea, bilious vomiting, epigastric pain, and postprandial abdominal fullness and distension. A total of 256 cases of laparoscopic-assisted radical right hemicolectomy was performed between January 2019 and May 2022 at the Affiliated Hospital of Southwestern Medical University, with six cases of postoperative complications of persistent upper gastrointestinal obstruction and a final diagnosis of superior mesenteric artery syndrome (SMAS). Several factors have been identified that have an impact on the occurrence of SMAS. The most common is significant weight loss, which leads to loss of retroperitoneal fat. These predisposing factors include wasting diseases (burns, cancer, and endocrine disorders), severe injuries (head or spinal trauma, and application of a body cast), dietary disorders (anorexia nervosa and malabsorptive diseases), and postoperative states (treatment for scoliosis, and abdominal surgery)[1]. Postoperative SMAS following intra-abdominal procedures is extremely rare. In this paper, we analyze cases and review the relevant literature to discuss the possible causes and preventative measures of SMAS after right hemicolectomy.

MATERIALS AND METHODS

Patients

Among the 256 patients in this group who underwent laparoscopic-assisted radical right hemicolectomy, including 130 men and 126 women, aged 19–84 years (median 61.8 ± 13.8 years), postoperative SMAS occurred in six patients (2.3%), including four men and two women, aged 29–64 years (median 50.3 ± 13.0 years).

Clinical manifestations

Patients developed upper gastrointestinal obstruction symptoms after 5–10 d postoperatively. In patients with postoperative gastric tube drainage, the drainage continuously exceeded 500–800 mL/d. The patients experienced epigastric distention, eructation, and vomiting after meals or removal of the gastric tube. The vomiting volume was large, similar to pyloric obstruction. The vomit contained bile, partially excluding pyloric obstruction and gastric emptying disorder. Two cases displayed an associated 10%–18% weight loss and electrolyte disturbances. The prominent feature of this group of cases was that the obstructive symptoms were position-related. The symptoms decreased or disappeared when patients were in the left lateral or prone position.

Imaging

All six patients underwent abdominal contrast-enhanced computed tomography (CT) before surgery. After surgery, three of the patients were simultaneously examined by abdominal contrast-enhanced CT and an upper gastrointestinal series. The other three patients received abdominal contrast-enhanced CT only. Figure 1A–1E shows the image of a patient with postoperative SMAS.

Management

Based on the clinical and radiological findings, a diagnosis of SMAS was suspected. All six cases were initially treated conservatively with gastric tube placement, fasting, and increased rehydration. These patients were gradually introduced to enteral feeding. In one case, endoscopic nasojejunal tube feeding was performed. Two cases did not improve with conservative treatment and were treated with duodenojejunostomy or gastrojejunostomy. Electrolyte abnormalities were carefully treated. All six patients showed weight gain and symptom resolution, corroborating our diagnosis.

Statistical analysis

Of the six patients, five had ascending colon cancer and one had ascending colon lymphoma. All six patients were examined by CT before and after surgery. The median age of patients with postoperative SMAS was 50.3 ± 13.0 years, including 130 men and 126 women, and the median age of all patients in the same period was 61.8 ± 13.8 years, including four men and two women.

There was little difference in sex and age between patients with postoperative SMAS and all surgical patients in the same period. It seemed that sex and age were not risk factors for SMAS. Patients who developed SMAS after surgery were used as the experimental group. A simple random sampling method was used to select a control group of 10 male and 10 female patients who underwent surgery at the same time but did not develop SMAS and received preoperative abdominal enhanced CT. Arterial phase images of both groups were reconstructed by sagittal multiplanar reformation. The angle and distance between the superior mesenteric artery (SMA) and abdominal aorta (AA) were measured before and after surgery in the experimental group and before surgery in the control group. The preoperative body mass index (BMI) of the experimental and control groups was calculated. The type of lymphadenectomy and surgical approach in the experimental group and the control group were recorded. Types of lymphadenectomy include D3 lymphadenectomy and D2 lymphadenectomy. There were three surgical approaches , the lateral approach , intermediate and caudal approach. SPSS 23.0 software was used for statistical analyses of the above risk factors. The Kolmogorov–Smirnov method was used to test whether the measurement data conformed to the normal distribution. The data conforming to the normal distribution was expressed as mean ± standard deviation. The t test was used to compare the differences in angle and distance preoperatively and postoperatively in the experimental group. The differences in angle, distance and BMI between the experimental and control groups were compared by independent sample t test, and the differences in type of lymphadenectomy and surgical approach between the two groups were compared by χ^2 test. Receiver operating characteristic curves were used to analyze the optimal diagnostic threshold and diagnostic efficiency of statistically significant parameters. The difference was statistically significant at $P < 0.05$.

RESULTS

In the experimental group of six cases, the angle between the SMA and AA was 18°–29° (mean 23.50° ± 4.23°) in the preoperative period and 10°–18° (mean 14.67° ± 3.08°) in the postoperative period. The distance between the SMA and the AA was 7–11 mm (mean 9.33 ± 1.37 mm) in the preoperative period and 3–8 mm (mean 5.17 ± 1.72 mm) in the postoperative period. Preoperative BMI ranged from 16.8 to 25.1 kg/m^2 (mean 18.82 ± 3.13 kg/m^2). Five patients received D3 lymphadenectomy and one D2 lymphadenectomy. There were three surgical approaches: Lateral in two cases, intermediate in one, and caudal approach in three. In the control group, the angle between the SMA and AA of the 20 patients ranged from 19° to 49° (mean 36.35° ± 8.13°). The distance between SMA and AA ranged from 7 to 25 mm (mean 14.45 ± 4.44 mm). BMI ranged from 18.7 to 27.2 kg/m^2 (mean 22.85 ± 2.33 kg/m^2). Fifteen patients received D3 lymphadenectomy and five D2 lymphadenectomy. There were three surgical

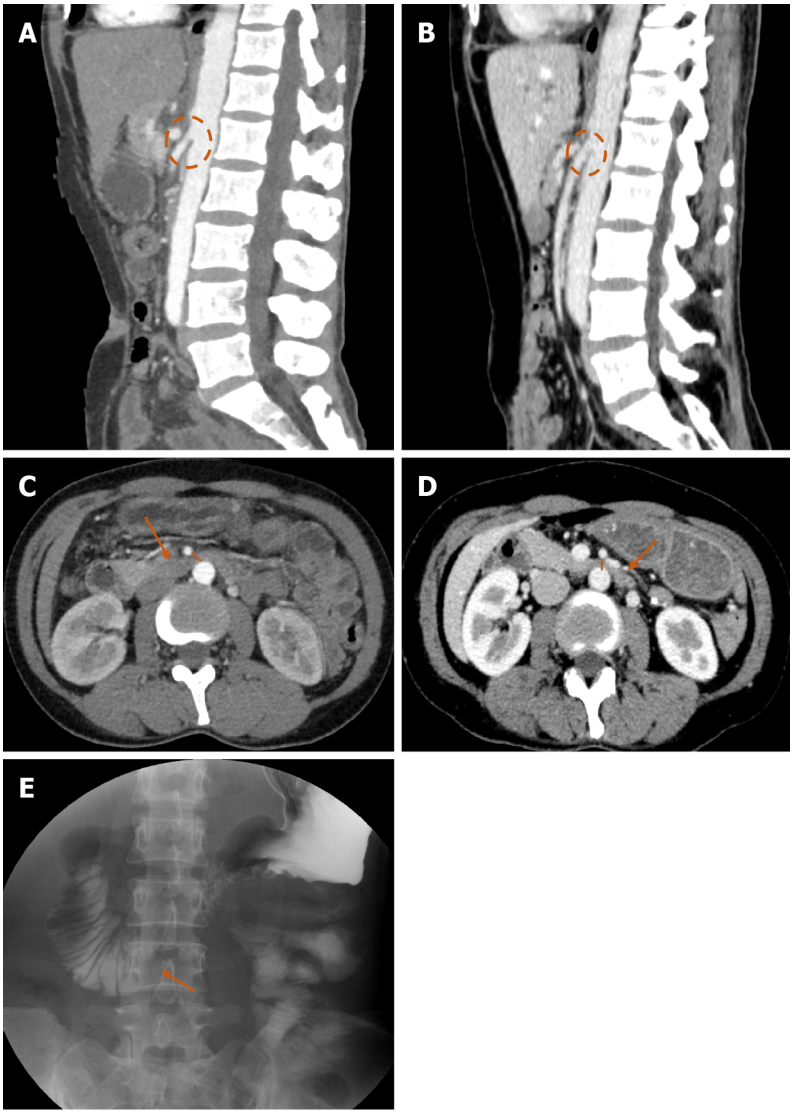

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Figure 1 Imaging of a patient with postoperative superior mesenteric artery syndrome. A: Abdominal enhanced computed tomography (CT) in the preoperative period showing the angle between the superior mesenteric artery (SMA) and abdominal aorta (AA) was 19°; B: Abdominal enhanced CT in the postoperative period showing the altered anatomical position of the SMA and the aortomesenteric angle was 10°; C: Abdominal enhanced CT in the preoperative period showing the distance between the SMA and AA in the third portion (large arrow) of the duodenum was 7 mm (short thin line); D: Abdominal enhanced CT in the postoperative period showing the reduced aortmesenteric distance in the third portion (large arrow) was 4 mm (short thin line); E: Representative image from upper gastrointestinal series showing abrupt cutoff of oral contrast in the third portion of the duodenum (arrow) and slight dilation of the proximal duodenum, suggestive of superior mesenteric artery syndrome.

approaches: Lateral in five cases, intermediate in eight, and caudal approach in seven. In the experimental group, the angle and distance after surgery were significantly decreased than those before surgery ($P < 0.05$) (Table 1). The angle, distance and BMI were significantly higher in the control group than in the experimental ($P < 0.05$) (Table 2). There was no significant difference in the type of lymphadenectomy and surgical approach between the two groups ($P > 0.05$). The area under receiver operating characteristic curve for aortomesenteric angle, distance and BMI was 0.913, 0.888, 0.867, and cutoff of the aortomesenteric angle, distance and BMI to identify the control and experimental groups was 29.50°, 11.50 mm, 18.45 kg/m^2 respectively (Table 3).

DISCUSSION

SMAS is a rare medical condition that describes the clinical symptoms resulting from vascular compression of the third part of the duodenum in the angle between the SMA and AA. This syndrome is also known as aortomesenteric artery compression, arteriomesenteric duodenal compression, Wilkie's syndrome, and cast syndrome. The incidence of SMAS reported in previous studies has ranged from 0.13%–0.78%[2]. The symptoms of SMAS can be vague, chronic, and significantly overlap with more

Table 1 Comparison of preoperative and postoperative angle and distance in the experimental groups

	Preoperative	Postoperative	*t*	*P* value
Angle (°)	23.50 ± 4.23	14.67 ± 3.08	12.562	0.000
Distance (mm)	9.33 ± 1.37	5.17 ± 1.72	6.934	0.001

Table 2 Comparison of risk factors between the two groups

Risk factor		Experimental group (*n* = 6)	Control group (*n* = 20)	t/χ^2	*P* value
Angle (°)		23.50 ± 4.23	36.35 ± 8.13	3.686[b]	0.001
Distance (mm)		9.33 ± 1.37	14.45 ± 4.44	4.491[b]	0.000
BMI (kg/m^2)		18.82 ± 3.13	22.85 ± 2.33	3.436[b]	0.002
Type of lymphadenectomy				0.000[a]	1.000
	D3	5	15		
	D2	1	5		
Surgical approach				1.219[a]	0.544
	Lateral approach group	2	5		
	Intermediategroup	1	8		
	Caudal approach group	3	7		

[a]χ^2 test.
[b]*t* test.
BMI: Body mass index.

Table 3 Receiver operating characteristic results

Risk factor	AUC	SE	*P* value	95%CI	Cut off	Sensitivity	Specificity
Angle	0.913	0.056	0.003	0.803–1.000	29.50°	0.800	1.000
Distance	0.888	0.065	0.005	0.760–1.000	11.50 mm	0.750	1.000
BMI	0.867	0.123	0.007	0.625–1.000	18.45 kg/m^2	1.000	0.833

AUC: Area under curve; SE: Standard error; BMI: Body mass index.

common gastrointestinal disorders, such as gastritis, peptic ulcer disease, irritable bowel syndrome, and gastroparesis[3]. Chief complaints of patients with SMAS include early satiety, postprandial pain or discomfort, nausea and bilious emesis that often develop after a meal, bloating, eructation, and reflux. The latter is classically relieved by lying in the left lateral decubitus position or follows an episode of emesis[4-6]. Death in SMAS is due to aspiration pneumonia, acute gastric rupture, severe electrolyte imbalance, hypokalemia, and cardiovascular collapse[7]. The normal anatomical aortomesenteric angle and aortomesenteric distance is 25°–60° and 10–28 mm, respectively. An aortomesenteric angle of 22°–25° and distance of 8 mm correlates with symptoms of SMAS[3,8]. The diagnosis of SMAS must be based on clinical symptomatology correlated with radiographic information[9]. Once diagnosed, SMAS can be safely treated conservatively, including by nasogastric decompression and correction of electrolytes and intravenous hydration, followed by enteral nutrition through a nasojejunal tube or parenteral nutrition if necessary. Operative management is indicated only when conservative management fails[10]. The multiple surgical approaches include lysis of the ligament of Treitz, gastrostomy tube placement, or proximal bypass of the common channel to the distal stomach or duodenum (i.e., duodenojejunostomy and/or gastrojejunostomy)[11]. Once the third portion of the duodenum is bypassed, the symptoms resolve quickly.

Postoperative SMAS following intra-abdominal procedures is extremely rare, but has previously been reported following colectomy[12], proctoright hemicolectomy[13], retroperitoneal sarcoma resection[14] and Roux-en-Y gastric bypass[15]. Corrective spinal surgery for scoliosis, which requires relative lengthening of the spine and results in the narrowing of the aortomesenteric angle, is the most frequently cited cause of postoperative SMAS with an estimated incidence of 1%–4.7%[16].

Many previous studies have described the common causes for the occurrence of SMAS, but further research will be needed to investigate the etiopathogenesis of SMAS after right hemicolectomy. In this study, we discussed the cases of SMAS occurring after right hemicolectomy and reviewed the relevant literature to suggest five possible reasons and preventative measures.

First, the unifying theme for most cases of postoperative SMAS is a sudden major rearrangement of intra-abdominal anatomy[14]. The postoperative CT in this group showed that the position of intestinal structures in the abdominal cavity was changed. The right hemicolectomy disrupted the suspension of the transverse colon from the hepatic region of the colon, resulting in prolapse of the anastomosed colonic segment and excessive pulling of the colonic mesenteric root, resulting in the compression of the duodenal root. The six patients had no clinical manifestation of SMAS before the surgery. Postoperative visceral prolapse and further depletion of mesenteric fat resulted in reduction of the aortomesenteric angle and distance significantly. Six patients with postoperative SMAS were selected as the study subjects. The control group comprised 20 patients who had undergone surgery at the same time but who did not have postoperative SMAS. All patients underwent abdominal contrast-enhanced CT before surgery. The statistical results showed that the aortomesenteric angle and distance were smaller in the experimental group than in the control group. Thus, the pre-existing small preoperative aortomesenteric angle and distance were anatomical factors leading to SMAS. Further reductions in angle and distance after right hemicolectomy led to the development of SMAS symptoms.

Second, careful analysis of the surgical data of all patients revealed over-cleaning of lymph fatty tissues in the six patients. Five patients who underwent D3 clearance and the other who underwent D2 clearance also had a partially dissected naked surface of the SMA. Over-cleaning of lymph fatty tissues may have contributed to the postoperative SMAS in this group of patients. However, the type of lymphadenectomy in the experimental and control groups did not differ significantly, which may be due to the small sample size, leading to the lack of strict statistical significance of the conclusions. More evidence needs to be accumulated and observed in more cases.

Third, during right hemicolectomy, the electric knife dissociated the second and third part of the duodenum, resulting in injury of the duodenal intestinal plexus. This may affect peristalsis and tone of the duodenum, inducing the development of SMAS[17].

Fourth, intestinal peptides influence gastric function. Reduced sources of intestinal peptides after right hemicolectomy may inhibit the movement of the duodenum and affect its digestion and absorption, inducing the development of SMAS. Finally, local mesenteric traction of tissue near the SMA due to confined abdominal exudate and peritoneal adhesions after right hemicolectomy may be a contributing factor to SMAS.

Patients with an angle between the SMA and AA < 29.50°, distance < 11.50 mm, and especially those with BMI < 18.45 kg/m^2 are at greater risk of developing SMAS after right hemicolectomy. To reduce the incidence, early nutrition should be enhanced to reduce visceral fat consumption. Intraoperative preservation of some peritoneal structures to enhance the support of mesenteric vessels as much as possible is prudent. Other important aspects are: To reduce SMAS to prevent postoperative adhesions by standardizing surgery; to ensure that the anastomosis is tension-free and has good blood flow; correctly placing the drainage tube; accelerating healing of the anastomosis; reducing the occurrence of peri-anastomotic infection; and avoiding adhesions that can form a mass that pulls the superior mesenteric vessels. Reduction of the number of intraoperative electrocautery procedures can reduce damage to the intestinal wall plexus. Finally, the use of pro-gastrointestinal drugs postoperatively can increase propulsive gastrointestinal motility.

CONCLUSION

SMAS is an uncommon phenomenon. Postoperative SMAS following right hemicolectomy is rarer. We reported six cases of SMAS after laparoscopic-assisted radical right hemicolectomy and reviewed the literature to analyze potential risk factors or determining factors for the occurrence of SMAS. Some suggestions were put forward to reduce the occurrence of SMAS. Future studies should explore whether the occurrence of obstruction can be reduced in patients prone to SMAS after right hemicolectomy by improving reconstruction of the anastomotic colonic segment to reduce its pull on the superior mesenteric vessels or by prophylactic release of the ligament of Treitz.

ARTICLE HIGHLIGHTS

Research background

Superior mesenteric artery syndrome after laparoscopic-assisted radical right hemicolectomy is a rare complication and can often be unrecognized by radiologists and clinicians.

Research motivation

Help people understand postoperative superior mesenteric artery syndrome.

Research objectives

Potential risk factors for the development of superior mesenteric artery syndrome were analyzed through case discussions and review of the literature.

Research methods

The preoperative and postoperative aortomesenteric angle and distance were compared in the experimental group of 6 patients, and 20 patients without postoperative SMAS in the 256 patients were randomly selected for comparative analysis with 6 patients developed SMAS.

Research results

In the experimental group, the aortomesenteric angle and distance after surgery were significantly decreased than those before surgery. The aortomesenteric angle, distance and BMI were significantly higher in the control group than in the experimental. There was no significant difference in the type of lymphadenectomy and surgical approach between the two groups.

Research conclusions

The small preoperative aortomesenteric angle and distance and low BMI may be important factors for the complication. Over-cleaning of lymph fatty tissues may also be associated with this complication.

Research perspectives

Future studies should explore whether the occurrence of obstruction can be reduced in patients prone to SMAS after right hemicolectomy by improving reconstruction of the anastomotic colonic segment to reduce its pull on the superior mesenteric vessels or by prophylactic release of the ligament of Treitz.

FOOTNOTES

Author contributions: Xie J, Bai J, Zheng T, Shu J, and Liu ML designed and performed the research; Xie J analyzed the data and wrote the manuscript.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of Affiliated Hospital of Southwest Medical University (Approval No. KY2022233).

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 report no relevant conflicts of interest for this article.

Data sharing statement: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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ORIGINAL ARTICLE

Retrospective Study

Analysis of the impact of ERAS-based respiratory function training on older patients' ability to prevent pulmonary complications after abdominal surgery

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Abstract

BACKGROUND

In China, as the population grows older, the number of elderly people who have died from respiratory problems has increased.

AIM

To investigate whether enhanced recovery after surgery (ERAS)-based respiratory function training may help older patients who had abdominal surgery suffer fewer pulmonary problems, shorter hospital stays, and improved lung function.

METHODS

The data of 231 elderly individuals having abdominal surgery was retrospectively analyzed. Based on whether ERAS-based respiratory function training was provided, patients were divided into ERAS group (n = 112) and control group (n = 119). Deep vein thrombosis (DVT), pulmonary embolism (PE), and respiratory tract infection (RTI) were the primary outcome variables. Secondary outcome variables included the Borg score Scale, FEV1/FVC and postoperative hospital stay.

RESULTS

The percentage of 18.75% of ERAS group participants and 34.45% of control group participants, respectively, had respiratory infections (P = 0.007). None of the individuals experienced PE or DVT. The ERAS group's median postoperative hospital stay was 9.5 d (3-21 d) whereas the control groups was 11 d (4-18 d) (P = 0.028). The Borg score decreased on the 4th d following surgery in the ERAS group compared to the 2nd d prior (P = 0.003). The incidence of RTIs was greater in the

control group than in the ERAS group among patients who spent more than 2 d in the hospital before surgery (P = 0.029).

CONCLUSION

ERAS-based respiratory function training may reduce the risk of pulmonary complications in older individuals undergoing abdominal surgery.

Key Words: Pulmonary complications; Respiratory function training; Enhanced recovery after surgery; Abdominal surgery

Core Tip: One of the major factors contributing to morbidity and mortality during the perioperative period were postoperative pulmonary complications after abdominal surgery. Clinical judgment and improved outcomes required rapid identification of high-risk individuals and intervention. We compared the pulmonary complications between the two groups using the predefined observation indicators after retrospectively analyzing the postoperative data of 231 older patients divided into two groups based on various preoperative respiratory function training methods. As compared to traditional respiratory function training techniques, enhanced recovery after surgery-based respiratory function training may reduce the probability of pulmonary complications in older patients who have undergone abdominal surgery.

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INTRODUCTION

The age of hospitalized patients is increasing as the rate of the aging population in our nation accelerates. Elderly people have sluggish physical reactions and a variety of basic illnesses, such as a high prevalence of chronic bronchitis, hypertension, coronary heart disease, diabetes, and cerebral infarction. According to statistics, pulmonary complications accounted for 89% of fatalities in adults over 65 who had more than one underlying condition[1]. When referring to pulmonary complications with post-operative clinical manifestations in elderly patients, such as atelectasis, pneumonia, bronchitis, respiratory insufficiency, and others, it was important to note that these complications could have a negative impact on the course of the disease[2]. The incidence of pulmonary complications following abdominal surgery in the elderly ranged from 15% to 75%, which was significantly higher than the incidence of cardiovascular complications[3]. These complications had a significant impact on postoperative recovery and were one of the major causes of perioperative death in elderly patients.

In addition to using traditional treatment approaches like anti-inflammatory medication and oxygen inhalation, elderly patients must also engage in pulmonary breathing exercises in order to decrease the incidence of postoperative pulmonary complications and improve their lung function during the perioperative period. Effective breathing exercises could assist to restore lung function as quickly as feasible and lower the risk of postoperative pulmonary infection[4]. The goal of respiratory function training is to increase the respiratory muscles' ability to maintain tension and endurance throughout the exercise, decrease the amount of oxygen used for that exercise, and increase the efficiency as a result. Therefore, perioperative respiratory muscle training to enhance lung function can successfully enhance patients' capacities for spontaneous breathing, expectoration, and cough, hence lowering the risk of problems and postoperative pulmonary infection[5]. This was a crucial topic that touched doctors, patients, and their families on a common level. It was also a strategy to facilitate the rapid recovery of surgical patients.

Enhanced recovery after surgery (ERAS) has abandoned many conventional perioperative therapies and the nursing model by adopting a variety of efficient methods to prevent surgical trauma produced by stress, related complications and helping postoperative patients to recover faster[6,7]. This study investigated the effect of ERAS-based respiratory function training on pulmonary complications in elderly patients undergoing abdominal surgery during the perioperative period in order to evaluate the practical application value of the training.

MATERIALS AND METHODS

Baseline characteristics

Two hundred and thirty-one elder patients over 65 who underwent abdominal surgery at Shanghai Fourth People's Hospital between April 2019 and September 2021 were the subject of a retrospective data collection. Inclusion criteria: Patients who agreed to participate in the study, those who are able to talk well and are aware, those who have undergone abdominal surgery, and those who are older than 65. Exclusion criteria: Mental illness and cognitive decline, the presence of serious lung conditions before surgery, such as pulmonary infection and moderate to large pleural effusions, amalgamated thoracotomy, and the need for mechanical ventilation before surgery. The study received informed consent from the participants, and our hospital's institutional ethics committee approved it (No. 2022108-001).

Age, sex, smoking, operation type, pulmonary function, arterial blood gas analysis, oxygen saturation, duration of surgery, and data from chest X-rays, computed tomography (CT) scans, and ultrasounds were collected as baseline information. Effective expectoration means that the patient could cough up phlegm easily; ineffective expectoration is sticky expectoration or an erroneous expectoration technique that makes it difficult for the patient to expectorate and requires the guidance and aid of medical staff. Hypoxemia was the lowest subnormal arterial blood oxygen pressure level. The following pulmonary complications could occur: Pleural effusion, atelectasis, pulmonary infection, and respiratory failure, depending on imaging results and a doctor's clinical judgment. The anticipated endpoint events included postoperative patient deaths, postoperative discharges, and hospital stays longer than 30 d.

Main outcome measures included new or altered chest X-ray abnormalities indicative of infection as well as respiratory tract infection (RTI), which was defined as the occurrence of at least two of the following: (1) Patients receiving medications for respiratory infections; (2) white blood cells (WBC) > 12000/mL; (3) cough and expectoration; and (4) postoperative unexplained tympanic temperature > 38.0 °C (not for other infections). Any clinical or radiographic evidence of deep vein thrombosis (DVT) or pulmonary embolism (PE), such as spiral CT or ultrasound, was also included in the primary outcome measures. Secondary outcomes were subjective respiratory Borg scores from the 2nd d through the 4th d after surgery[8]. Length of postoperative hospital stay was also highlighted as a secondary outcome. We also looked at whether longer preoperative hospital stays in the case and control groups was associated with a greater incidence of respiratory infections.

Construction of a study investigator group

The group of 11 persons included a project leader who was in charge of developing a training program to enhance respiratory function and 10 team members who were responsible for carrying out the study.

Concept of ERAS-based respiratory function training

All patients in the case group had ERAS-based respiratory function training. The specific implementation strategy was described in Figure 1.

Before admission, patients should stop smoking for more than 2 wk before they arrive at the hospital, be protected from colds, and instructed to walk quickly on level ground for 30 min every morning and afternoon.

After admission, the responsible nurse would demonstrate and explain ERAS to patients, distribute ERAS brochures to help patients understand the concept, and explain the need for the steps involved in implementing ERAS. The nurse also evaluated the respiratory function associated with admission, made arrangements for patients to undergo testing for blood gas analysis, lung function, chest X-rays, or chest CTs. Together, doctors and nurses evaluated the patients designed surgical and respiratory training plans, and experienced nurses chose the most efficient respiratory training methods based on patient evaluation. The teach-back approach to health education was used to assess the patient's competence to do breathing training correctly and independently.

Before surgery, the patient's mastery of the respiratory function training approach was reconfirmed by the doctor and nurse.

After surgery, 1-2 L/min low-flow oxygen inhalation, dynamic oxygen saturation (SpO2) monitoring, and SpO2 94 percent maintenance were done; implemented a program for an early activity and took a semi-decubitus position (above 30 degrees) of rest; active activity steadily increases, moving from in bed to out of bed to bedside activities; program for preventative multimodal analgesia was put in place.

Before discharge, active maintenance of respiratory function training; the chest CT, arterial blood gas analysis, pulmonary function, *etc.* were examined based on the patient's condition; dynamic evaluation of pulmonary complications.

Respiratory function training methods

Respiratory function training includes lip constriction breathing, abdominal breathing, effective coughing with wound protection, balloon blowing exercises, card education, and other techniques[9-12]. The ERAS group received the ERAS-based concept of respiratory function training in addition to

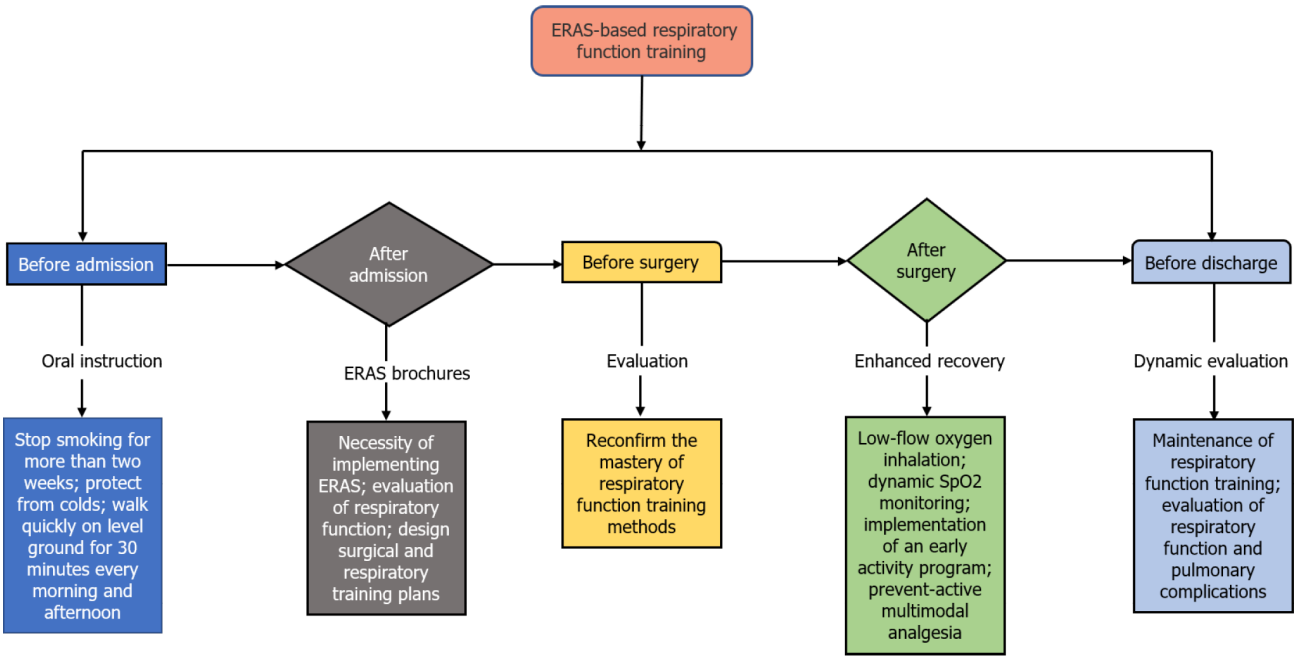

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Figure 1 Specific implementation strategy of enhanced recovery after surgery-based respiratory function training. ERAS: Enhanced recovery after surgery; SpO2: Oxygen saturation.

the conventional respiratory function training technique, whereas the control group received the abovementioned traditional respiratory function training approach.

Statistical analysis

The statistical analysis of counting and measuring data was carried out using SPSS 23.0 statistical software (IBM, 2015, United States). Each variable's normality was checked using the Kolmogorov-Smirnov and Shapiro-Wilk tests, and further tests were run as necessary. The age distribution of the two groups was compared using the unpaired Student's *t* test. Mann-Whitney *U* test was used to compare the type of surgery. The ratio of male to female, smoking status, and usage of epidural analgesia were all compared between the two groups using the chi-square test. In order to compare key outcomes between the case and control groups, the Chi-square test was also applied. The primary result was compared between the ERAS group and the control group, both of which had spent more than 2 d in the hospital prior to surgery, using the Fischer precision test. Mann-Whitney *U* test was used to compare the length of postoperative hospital stay between the two groups (secondary outcome). On the 2nd and 4th d following surgery, the Wilcoxon rank-sum test was used to compare the Borg score. Statistics were considered significant for *P* values under 0.05.

RESULTS

Data on 231 older patients over 65 who underwent abdominal surgery at Shanghai Fourth People's Hospital were collected from April 2019 to September 2021. There were no statistically or clinically significant differences between ERAS group and control group in terms of demographics, smoking status, American Society of Anesthesiologists (ASA) classification, types of operation, epidural analgesia, and other parameters (Table 1).

In 231 patients, laparoscopic cholecystectomy and laparoscopic appendectomy accounted for approximately 43.3 percent of the cases; however, there was no obvious difference in surgery types between the ERAS group and the control group. The details of the procedure were displayed in Table 2.

The ERAS group's patients all participated in the ERAS-based respiratory function training, and from the second to the 4th postoperative day, Borg scale scores and vital signs were collected. Each patient in the ERAS group received standardized respiratory function training based on ERAS, and there were no negative events during or after the training. After surgery, patients' vital signs were steady during the 2nd to 4th d (Table 3).

The total incidence of RTI in this research was 26.84 percent. RTIs were present in 41 (34.45%) of the 119 patients in the control group and 21 (18.75%) of the 112 patients in the ERAS group. According to the findings, there was 15.7% difference between the two groups' rates of RTIs. Respiratory function

Table 1 Demographic and surgical characteristics of the 231 patients

Variable	ERAS group	Control group	*P* value
Age in yr	72.06 ± 4.72	72.40 ± 4.89	0.59
Sex as male:female	61:51	55:64	0.21
Smoking as yes:no	45:67	53:66	0.50
ASA grade			0.22
I	39 (34.82%)	50 (42.02%)	
II	40 (35.71%)	30 (25.21%)	
III	33 (29.47%)	39 (32.77%)	
IV	0 (0%)	0 (0%)	
Classification of surgical complexity			0.96
1	0 (0%)	0 (0%)	
2	11 (9.82%)	13 (10.92%)	
3	72 (64.29%)	76 (63.87%)	
4	29 (25.89%)	30 (25.21%)	
5	0 (0%)	0 (0%)	
Epidural analgesia	62	52	0.08

ASA: American Society of Anesthesiologists; ERAS: Enhanced recovery after surgery.

Table 2 Details of the 231 patients' surgeries

Surgery	ERAS group	Control group	*P* value
Hepatobiliary and pancreatic surgery: hepatectomy, bile duct exploration, pancreaticoduodenal surgery, *etc.*	28 (25.0%)	26 (21.85%)	0.72
Cholecystectomy: laparoscopic or open	31 (27.68%)	27 (22.69%)	
Gastric and esophageal surgery	9 (8.03%)	12 (10.09%)	
Colorectal surgery	11 (9.82%)	10 (8.40%)	
Small intestine: small bowel resection	2 (1.79%)	1 (0.84%)	
Others: hernia repair, splenectomy, appendix, *etc.*	31 (27.68%)	43 (36.13%)	

ERAS: Enhanced recovery after surgery.

training was more successful in the ERAS group, and the frequency of RTIs was low. This difference was statistically significant (P = 0.007; Table 4) and had a 95% confidence interval of 0.239 to 0.805. DVT or PE were not present in any individuals in either group.

The average of Borg scores in the ERAS group showed a decline on the 4th postoperative day as compared to the 2nd postoperative day (P = 0.003, Wilcoxon rank-sum test); the average declined considerably by 1.36. The median postoperative hospital stay in the ERAS group was 9.5 d (with a range of 3-21 d), whereas it was 11 d in the control group (with a range of 4-18 d). Since the variables in the ERAS group and the control group did not follow a normal distribution, the Kolmogorov-Smirnov test was employed to compare the length of the postoperative hospital stay between the two groups. With a mean difference of 1.35 d between the two groups' postoperative hospital stays, the ERAS group was in the hospital for shorter time than the control group. The 95 percent confidence interval for the postoperative hospital stay for both groups was 9.84-10.98. Therefore, ERAS-based respiratory function training significantly reduced the postoperative hospital stay for older patients after abdominal surgery (Mann-Whitney U test, P = 0.028).

The probability of RTI was higher in the control group (24/65, 36.9%) than in the ERAS group (11/59, 18.6%) for patients who had spent more than 2 d in the hospital before surgery (P = 0.029, Fischer's test; Table 4). Therefore, the incidence of RTIs among patients in the two groups with preoperative hospitalization days longer than 2 d was 28.23 percent, with a range of 17.1 to 89.5 percent. Postoperative lung function tests revealed that the control group's lungs functioned worse than those of the ERAS group (P

Table 3 Walking test parameters for 231 patients at 2 d, 3 d, and 4 d after surgery

Parameter	Baseline value	ERAS group			Control group		
		2 d	3 d	4 d	2 d	3 d	4 d
Borg score median	2	2	2	2	3	2	2
Heart rate median/min	86	88.5	81	78	84	81	79
Respiratory frequency median/min	18	19	16	17	18	17	17
SaO2 median %	95	96	97	92	96	97	92

ERAS: Enhanced recovery after surgery.

Table 4 Comparison of main outcomes between enhanced recovery after surgery group and control group

Parameter	ERAS group	Control group	*P* value
Main outcome			
Respiratory tract infection	21 (18.75%)	41 (34.45%)	0.007
New/changed X-ray findings	48 (42.86%)	64 (53.78%)	0.114
White blood cell more than 12	39 (34.82%)	56 (47.06%)	0.063
Temperature more than 38 degree centigrade	37 (33.04%)	54 (45.38%)	0.060
Positive sputum bacteria	19 (16.96%)	31 (26.05%)	0.111
Antibiotic therapy	22 (19.64%)	40 (33.61%)	0.018
Secondary results			
Preoperative hospitalization time more than 2 d	59 (52.68%)	65 (54.62%)	
Preoperative hospitalization time more than 2 d in patients with respiratory tract infection	11 (9.82%)	24 (20.17%)	0.029
The postoperative length of stay in d	9.5 (3-21)	11 (4-18)	0.028
FEV1/FVC more than 70%	86 (76.79%)	74 (62.18%)	0.022

ERAS: Enhanced recovery after surgery; FEV1: Forced expiratory volume in 1s; FVC: Forced vital capacity.

= 0.022, Chi-square test). Epidural analgesic usage or smoking habits did not significantly differ between the two groups.

DISCUSSION

Significantly longer hospital stays and higher medical expenses were linked to an increase in pulmonary problems, postoperative morbidity, and death[13,14]. The literature has documented that pulmonary complications in individuals after abdominal surgery could raise hospital expenditures by US $31000 (US $2000 per person/year) for an 11-d stay. In all, the increase in the typical hospital stay that could be directly linked to postoperative complications was around 8 d[15]. In the ERAS group, we discovered that ERAS-based respiratory function training decreased the frequency of postoperative pulmonary problems in half. In comparison to the regular respiratory function training group, the ERAS group's postoperative hospital stay was often shorter. The median reduction in postoperative hospital stays in the population might range from 9.84 d to 10.98 d (mean 10.41 d). Based on the concept of ERAS, patients with a longer preoperative hospital stay (case group and control group), *i.e.* more than 2 d, had a significantly reduced mean risk of respiratory infection if they completed respiratory function training. ERAS-based respiratory function training helped this population's rates of respiratory infection reduce by 17.1% to 89.5% (28.2 percent on average).

According to the Borg dyspnea scale, postoperative respiratory function was also improved in the ERAS group. Patients in the ERAS group did not experience any negative side effects from respiratory exercise. Postoperative respiratory function decline was involved in the etiology of respiratory problems. These included the reduction in lung mechanics brought on by pain and the suppression of diaphragm function brought on by neuro-reflexes. Various humoral cascade systems, the metabolism of

arachidonic acid, cytokines, and endothelial adhesion factors might also be involved. Additionally, standard postoperative treatment, which entailed spending hours each day laying on your back, might impair lung mechanics and oxygenation. There isn't a single, standard method for enhancing postoperative lung function and avoiding pulmonary complications as of yet[16-18]. In order to enhance patients' postoperative pulmonary function, we thus created a respiratory function training approach based on the concept of respiratory function training.

Comparisons with patients undergoing abdominal surgery should be done with caution since perioperative training plans in individuals receiving thoracic surgery have been proven to enhance respiratory function. In patients undergoing lung cancer resection, preoperative intervention based on moderate-to-high-intensity aerobic exercise improved lung function and reduced postoperative morbidity, whereas postoperative intervention alone did not appear to reduce respiratory complications or length of hospital stay, according to a systematic review of perioperative physiotherapy in these patients[19]. A randomized controlled trial conducted on lung cancer patients in 2014 found that high strength and endurance and strength training (60 min each time, three times a week, for 20 wk) was well tolerated and significantly improved peak oxygen uptake, muscle strength, total muscle mass, functional health, and quality of life in the intervention group 5 wk to 7 wk after surgery[20]. ERAS-based respiratory function training used in this study lasted longer than the traditional respiratory function training, had clear benefits, and might have had a significant impact on lowering postoperative respiratory complications and postoperative hospital stays.

The comprehensive study by Sullivan *et al*[21] found no proof that utilizing incentive spirometry might decrease pulmonary complications following upper abdominal surgery. Preoperative rehabilitation treatment and respiratory muscle training significantly decreased postoperative pulmonary problems and the length of hospital stay, according to another comprehensive evaluation of seven randomized controlled studies[22]. Due to improved lung function, ERAS-based respiratory function training could lower the incidence of postoperative respiratory illness. This was consistent with a recently published article that suggested aerobic exercise and induced spirometry might help reduce pulmonary complications following laparoscopic cholecystectomy[23]. The cause for the shorter hospital stay was unknown, although it most likely stems from a number of reasons. Long preoperative hospital stays were a well-known risk factor, and ERAS-based respiratory function training was expected to improve physiological function and shorten preoperative hospital stay.

The elderly's increased pulmonary parenchyma fiber connective tissue causes their lung compliance, ventilation reserve, and air exchange intensity and volume to decline. Furthermore, having difficulty coughing and expectorating caused a reduction in lung and breathing capacity. Surgery, trauma, and other stresses could increase the risk that pulmonary infection, atelectasis, and other problems would develop in patients with chronic obstructive pulmonary disease who were surgical patients. The diaphragm rising during abdominal surgery, the stimulation of the intercostal nerves, and the traumatic stimulation brought on by the close proximity of the surgical site to the thoracic cavity all resulted in decreased lung compliance and decreased thoracic volume, which temporarily impaired respiratory function by causing hypoventilation and restricted ventilation dysfunction[24,25]. However, these problems of abdominal surgery were plainly solved by ERAS-based respiratory function training, which also greatly minimized the probability of postoperative pulmonary complications.

The research did have certain limitations. There was a chance of bias because there wasn't a prospective, randomized research on patients. Since this study was retrospective, information about compliance was also difficult to get. To reduce this bias, the findings in Table 1 that there were no appreciable variations in the two groups' demographic traits, surgical complexity, smoking status, use of epidural analgesia, and surgical techniques. Meanwhile, analgesics and antimicrobial prophylaxis were administered to all ERAS groups and control groups in accordance with the accepted protocol of medical best practices. To determine whether ERAS-based respiratory function training was superior to conventional respiratory function training in reducing postoperative pulmonary complications, additional large-scale randomized controlled, multi-center studies and physiological tests were required.

CONCLUSION

An efficient respiratory function training approach that could reduce postoperative pulmonary problems in elderly patients who had abdominal surgery was the ERAS-based respiratory function training.

ARTICLE HIGHLIGHTS

Research background

Five to ten percent of surgical patients and nine to forty percent of abdominal surgery patients

experienced postoperative pulmonary problems. Following abdominal surgery, postoperative pulmonary complications have been associated with a higher morbidity and fatality rates.

Research motivation

To determine if enhanced recovery after surgery (ERAS)-based respiratory function training was effective at preventing pulmonary complications in elderly patients after abdominal surgery.

Research objectives

Using ERAS-based respiratory function training to decrease pulmonary diseases in elderly patients after abdominal surgery.

Research methods

Retrospective analysis was performed on the clinical information of 231 elderly individuals having abdominal surgery. According to whether patients utilized ERAS-based respiratory function training following surgery, patients were divided into ERAS group (n = 112) and control group (n = 119). The two groups' postoperative pulmonary complications were analyzed.

Research results

The respiratory infection rate was only 18.75% following the use of ERAS-based respiratory function training which was significantly lower than that of traditional respiratory function training. The length of hospital stay was significantly shortened after using ERAS-based respiratory function training, and the rate of respiratory tract infection in patients who were hospitalized for more than 2 d before surgery was significantly decreased.

Research conclusions

An efficient preoperative respiratory function training approach that could minimize postoperative pulmonary complications in patients having abdominal surgery was ERAS-based respiratory function training.

Research perspectives

Elderly patients were more likely to experience postoperative pulmonary complications. Effective respiratory function training during the perioperative period could dramatically shorten hospital stays and mortality rates.

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FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Prognostic value of preoperative immune-nutritional scoring systems in remnant gastric cancer patients undergoing surgery

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Abstract

BACKGROUND

Remnant gastric cancer (GC) is defined as GC that occurs five years or more after gastrectomy. Systematically evaluating the preoperative immune and nutritional status of patients and analyzing its prognostic impact on postoperative remnant gastric cancer (RGC) patients are crucial. A simple scoring system that combines multiple immune or nutritional indicators to identify nutritional or immune status before surgery is necessary.

AIM

To evaluate the value of preoperative immune-nutritional scoring systems in predicting the prognosis of patients with RGC.

METHODS

The clinical data of 54 patients with RGC were collected and analyzed retrospectively. Prognostic nutritional index (PNI), controlled nutritional status (CONUT), and Naples prognostic score (NPS) were calculated by preoperative blood indicators, including absolute lymphocyte count, lymphocyte to monocyte ratio, neutrophil to lymphocyte ratio, serum albumin, and serum total cholesterol. Patients with RGC were divided into groups according to the immune-nutritional risk. The relationship between the three preoperative immune-nutritional scores and clinical characteristics was analyzed. Cox regression and Kaplan–Meier analysis was performed to analyze the difference in overall survival (OS) rate between various immune-nutritional score groups.

RESULTS

The median age of this cohort was 70.5 years (ranging from 39 to 87 years). No significant correlation was found between most pathological features and immune-nutritional status (P > 0.05). Patients with a PNI score < 45, CONUT score or NPS score ≥ 3 were considered to be at high immune-nutritional risk. The areas under the receiver operating characteristic curves of PNI, CONUT, and NPS systems for predicting postoperative survival were 0.611 [95% confidence interval (CI): 0.460–0.763; P = 0.161], 0.635 (95%CI: 0.485–0.784; P = 0.090), and 0.707 (95%CI: 0.566–0.848; P = 0.009), respectively. Cox regression analysis showed that the three immune-nutritional scoring systems were significantly correlated with OS (PNI: P = 0.002; CONUT: P = 0.039; NPS: P < 0.001). Survival analysis revealed a significant difference in OS between different immune-nutritional groups (PNI: 75 mo *vs* 42 mo, P = 0.001; CONUT: 69 mo *vs* 48 mo, P = 0.033; NPS: 77 mo *vs* 40 mo, P < 0.001).

CONCLUSION

These preoperative immune-nutritional scores are reliable multidimensional prognostic scoring systems for predicting the prognosis of patients with RGC, in which the NPS system has relatively effective predictive performance.

Key Words: Remnant gastric cancer; Immune-nutritional score; Prognostic nutritional index; Controlled nutritional status; Naples prognostic score

Core Tip: Three preoperative immune-nutritional scores of patients with remnant gastric cancer (RGC) were calculated, including prognostic nutritional index (PNI), controlled nutritional status (CONUT), and Naples prognostic score (NPS). Patients were divided into groups according to the immune-nutritional risk. The three immune-nutritional scoring systems were significantly correlated with overall survival (OS) (PNI: P = 0.002; CONUT: P = 0.039; NPS: P < 0.001). Survival analysis revealed a significant difference in OS between different immune-nutritional groups (PNI: 75 mo *vs* 42 mo, P = 0.001; CONUT: 69 mo *vs* 48 mo, P = 0.033; NPS: 77 mo *vs* 40 mo, P < 0.001). These preoperative immune-nutritional scores are reliable multidimensional RGC prognostic scoring systems.

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INTRODUCTION

The incidence rate of gastric cancer (GC) ranks fifth among all malignancies, with an annual incidence of more than one million people. Thus far, GC is still one of the diseases that seriously affect the health system[1]. Many high-risk factors contribute to the occurrence of GC, one of which is the remnant stomach after gastrectomy[2]. Remnant GC (RGC) is defined as GC that occurs five years or more after gastrectomy due to benign or malignant lesions. Reports have shown that approximately 2%–3% of remnant stomachs will develop RGC[3,4]. The mechanism of the occurrence and development of RGC remains unclear. Bile reflux, the loss of vagus nerve, and the change in gastric mucosal microenvironment may play important roles in RGC carcinogenesis[5-7].

The treatment of RGC is often comprehensively based on surgery[8,9]. However, the prognosis of RGC is often worse than that of primary GC even after radical gastrectomy[10,11]. Notably, patients often have malnutrition and poor immune status[12,13] after gastrectomy, which may be one of the factors leading to the poor prognosis of RGC patients. Therefore, systematically evaluating the preoperative immune and nutritional status of patients and analyzing its prognostic impact on postoperative RGC patients are crucial.

An increasing number of studies have shown that the immune system plays a crucial role in the tumor microenvironment[14-16]. Meanwhile, the nutritional status of patients often affects tumor growth, metastasis, angiogenesis, and the efficacy of antitumor therapy[17,18]. Prognostic factors related to inflammation and nutrition, including neutrophil to lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, lymphocyte to monocyte ratio (LMR), serum albumin (ALB), and total cholesterol (TC), are

associated with the prognosis of a variety of cancers, including GC, rectal cancer, and breast cancer[19-23].

However, prognostic prediction based on a single marker is often inaccurate and may even be misleading. Therefore, a simple scoring system that combines multiple immune or nutritional indicators to identify nutritional or immune status before surgery is significantly better than single inflammatory or nutritional markers. The prognostic nutritional index (PNI), controlled nutritional status (CONUT), and a new inflammation related prognostic system named Naples prognostic score (NPS) established in recent years by combining preoperative TC content, serum ALB content, LMR, and NLR have been widely used to predict the prognosis of a variety of tumors[24-26]. However, studies on the prognosis of RGC patients predicted by preoperative immune-nutritional score systems are few.

Therefore, this retrospective cohort study aimed to determine the prognostic value of three preoperative immune-nutritional scoring systems, namely, PNI, CONUT, and NPS, in patients with RGC, and to examine their relationship with other clinicopathological features.

MATERIALS AND METHODS

Patients

The medical data of 43 patients with RGC at the First Affiliated Hospital of Nanjing Medical University (Jiangsu Province Hospital) and 11 patients at the Affiliated Suzhou Hospital of Nanjing Medical University (Suzhou Municipal Hospital) from January 2009 to July 2019 were collected. The inclusion criteria of this study were as follows: (1) The patient had a previous history of gastrectomy; (2) The interval from the occurrence of residual GC was five years or more; (3) After admission, the patient underwent radical resection of residual GC; (4) The postoperative pathological diagnosis was gastric adenocarcinoma; (5) The patient did not receive any anticancer treatment from the diagnosis of RGC to surgery; (6) The patient had detailed and extractable medical data and laboratory results; and (7) The patient had survival follow-up data of three years or more. By contrast, participants who met any of the following criteria were excluded from the final analysis: (1) The patient had any clinical evidence of infection or inflammatory disease. Infection was defined in this study as preoperative body temperature ≥ 37.5 °C or increased preoperative C-reactive-protein levels; and (2) The patient had a history of malignant tumors other than GC. This study was approved by the medical ethics committee of Nanjing Medical University. The data were anonymous; therefore, relevant informed consent was not required.

Definition of immune-nutritional prognosis systems

PNI score is defined as serum ALB (g/L) + 5 × Lymphocyte count (× 10^9); a PNI score < 45 indicated that the patient had immune-nutritional risk.

The CONUT score is defined as the sum of the three scores based on serum ALB concentration, lymphocyte count, and TC concentration. A score ≥ 3 was considered to be at immune-nutritional risk. Serum ALB concentration was grouped as > 35, 30–34.9, 25–29.9, and < 25 (g/L), and the scores of the four groups were 0, 2, 4, and 6, respectively. Lymphocyte count was grouped as ≥ 1.6, 1.2–1.5, 0.8–1.1, and < 0.8 (× 10^9), respectively, which had scores of 0, 1, 2, and 3, respectively. TC concentration was divided into groups ≥ 180, 140–179, 100–139, and < 100 mg/dL, with scores of 0, 1, 2, and 3, respectively.

NPS is defined on the basis of the following four parameters: Serum ALB, TC, LMR, and NLR. NLR and LMR are calculated by dividing the neutrophil count by lymphocyte and monocyte counts in routine blood tests, respectively. Patients with serum ALB lower than 40 g/L, TC lower than 180 mg/dL, LMR lower than 4.44, or NLR higher than 2.96 will obtain 1 point; otherwise, it will be regarded as 0. The sum of the scores of the four parameters is an NPS score. Patients with an NPS score of 0 were considered to have non-immune-nutritional risks, those with an NPS of 1 or 2 were regarded have mild immune-nutritional risks, and patients with an NPS of 3 or 4 were considered to have severe immune-nutritional risks. In the actual grouping, patients with an NPS score of 0 (6/54) are few due to the generally poor nutritional status of patients with RGC; however, this score cannot be analyzed alone. Therefore, patients with an NPS score of 0–2 (no or mild immune nutritional risk) were regarded as one group.

Data collection and follow-up

The clinical characteristics and pathological parameters of the patients, including gender, age, histological type, pathological stage, and laboratory data, were retrospectively collected from the hospital information system. Among them, the data of neutrophils, lymphocytes, and monocytes were from routine blood tests, the levels of serum ALB and TC were respectively from liver and kidney function tests, and all blood samples were fasting blood samples. All patients were followed up regularly after radical gastrectomy. This study mainly obtained the survival information of patients through postoperative medical examination or telephone contact. The follow-up interval was once every 6 mo. The patient was followed up to death (event) or the last follow-up (censored).

Statistical analysis

IBM SPSS statistics 23.0 (SPSS, Inc., Chicago, Illinois, United States) and GraphPad prism software (version 5.0) were used for statistical analyses and mapping, respectively. *T*-test or chi-square test was used to analyze the differences in statistical data between various groups. The receiver operating characteristic (ROC) curve was generated to evaluate the difference in survival prediction capability between different scoring systems. The Kaplan–Meier method was used for survival analysis, and log-rank test was employed to compare the difference in prognosis between various immune-nutritional system groups. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics of patients

According to the inclusion and exclusion criteria, a total of 54 patients with RGC were included in this study. Among these patients, 42 were male (77.8%) and 12 were female (22.2%), and the median age was 70.5 years (ranging from 39 to 87 years). A total of 28 patients (51.9%) and 26 patients (48.1%) had better or worse histological differentiation types, respectively. In addition, 26 patients had lymph node metastasis, accounting for 48.1% of all patients. Table 1 describes the potential different immune-nutritional system scoring groups among populations with different clinical characteristics. The results show that no significant correlation existed between most pathological features and immune-nutritional status in patients with RGC.

ROC curve analysis of immune-nutritional systems for predicting postoperative survival

Fasting blood indicators of the patients were used to calculate the immune-nutritional scores. Among these indicators, the average level of serum ALB was 38.75 g/L [95% confidence interval (CI): 35.98–38.93 g/L], TC was 168 mg/dL (95%CI: 157–179 mg/dL), and the average lymphocyte count was 1.30 × 10^9/L (95%CI: 1.16–1.44 × 10^9/L); the average monocyte count was 0.40 × 10^9/L (95%CI: 0.35–0.44 × 10^9/L), the average neutrophil count was 3.61 × 10^9/L (95%CI: 3.04–4.17 × 10^9/L), the calculated NLR was 3.22 (95%CI: 2.45–4.00), and the LMR was 3.71 (95%CI: 2.21–4.21).

The curves of the three immune-nutritional scores for predicting postoperative survival were plotted (Figure 1). NPS was found to have the largest area under the curve (AUC = 0.707; 95%CI: 0.566–0.848; $P = 0.009$). The AUC values of PNI and CONUT were 0.611 (95%CI: 0.460–0.763; $P = 0.161$) and 0.635 (95%CI: 0.485–0.784; $P = 0.090$), respectively.

Analysis of OS

Cox regression analysis showed that tumor gross classification ($P = 0.014$), pathological differentiation type ($P = 0.032$), lymph node metastasis ($P < 0.001$), clinical Tumor-Node-Metastasis status ($P = 0.001$), and three immune-nutritional scoring systems, namely, PNI ($P = 0.002$), CONUT ($P = 0.039$), and NPS ($P < 0.001$), were significantly correlated with OS. In addition, no significant correlation was found between age, sex, primary tumor size, and T stage and OS ($P > 0.05$ for all) (Table 2).

Kaplan–Meier analysis was used to analyze the relationship between PNI, CONUT, and NPS scores and prognosis. The analysis showed that the median OS of patients with a low immune-nutritional risk was significantly higher than that of patients with a high immune-nutritional risk (PNI: 75 mo *vs* 42 mo, $P = 0.001$; CONUT: 69 mo *vs* 48 mo, $P = 0.033$; NPS: 77 mo *vs* 40 mo; $P < 0.001$) (Figure 2). This finding suggests that the three immune-nutritional systems can significantly predict the prognosis of patients. Of note, the NPS system demonstrated the best prediction capability.

DISCUSSION

An increasing number of studies have shown that immunity and nutrition are closely related to the occurrence and development of cancer, which has led to the research and development of biomarkers or prognostic scoring systems based on immunity and nutrition[14-16]. The nutritional status of patients is often worse after partial gastrectomy and frequently combined with poor immune status, leading to the crucial evaluation of immune-nutritional indicators in patients with RGC[12,13]. Appropriate treatment strategies can be formulated by evaluating the relationship between immune-nutritional systems and the postoperative prognosis of patients with RGC. Three immune-nutritional systems are analyzed in the current study based on the calculation of inflammatory cells in routine blood tests and nutritional indicators, such as ALB and TC. The results showed that PNI, CONUT, and NPS can accurately predict the postoperative OS of patients with RGC. Among the three scoring systems, NPS has a superior accuracy.

Inflammatory cells participate in the destruction of tumor cells and angiogenesis in the tumor microenvironment and regulate the sensitivity of tumors to radiotherapy and chemotherapy drugs. Lymphocytes are the main antitumor cells and play an important role in cell-mediated immune

Table 1 Clinical characteristics of patients and three immune-nutritional score systems

Characteristics	Immune–nutritional score systems						
	Values (*n* = 54)	PNI (*n* = 27/27)	*P* value	CONUT (*n* = 34/20)	*P* value	NPS (*n* = 32/22)	*P* value
Age (years)			1.000		0.368		0.047
< 70	26	13/13		18/8		19/7	
≥ 70	28	14/14		16/12		13/15	
Gender			1.000		0.713		0.216
Male	42	21/21		27/15		23/19	
Female	12	6/6		7/5		9/3	
Primary tumor size			0.790		0.581		1.000
≤ 3 cm	27	13/14		18/9		16/11	
> 3 cm	27	14/13		16/11		16/11	
Gross type			0.412		0.313		0.386
Non-ulcerative type	21	12/9		15/6		14/7	
Ulcerative type	33	15/18		19/14		18/15	
Differentiation			0.285		0.449		0.189
Well/Moderate	28	16/12		19/9		19/9	
Poor	26	11/15		15/11		13/13	
T stage			0.588		0.519		0.984
T1/T2	22	12/10		15/7		13/9	
T3/T4	32	15/17		19/13		19/13	
Lymph node metastasis			0.106		0.449		0.445
No	28	17/11		19/9		18/10	
Yes	26	10/16		15/11		14/12	
cTNM status			0.282		0.538		0.075
I/II	30	17/13		20/10		21/9	
III	24	10/14		14/10		11/13	

The number of cases, low risk cases/high risk cases were shown, p-value indicated the significance of different immune-nutritional risk between the patients with different clinical characteristics. PNI: Prognostic nutritional index; CONUT: Controlled nutritional status; NPS: Naples prognostic score; cTNM: Clinical Tumor-Node-Metastasis.

response by recognizing and killing cancer cells[27]. Lymphopenia is related to the adverse reactions and prognosis of a variety of malignant tumors, including GC[28,29]. However, patients with malignant tumor with increased neutrophil infiltration often have poor clinical outcomes. Neutrophils can promote tumor formation by releasing cytokines and stimulate tumor cell proliferation and metastasis [30,31]. Tumor-associated macrophages and blood monocytes are also involved in tumor progression and metastasis and the improvement of tumor microenvironment through a variety of mechanisms[32, 33]. Thus far, an increasing number of immune cell-based prognostic parameters, including NLR and LMR, have been studied and reported[19,20,34]. NLR and LMR are objective markers that reflect the inflammatory and immune status of the host. The increase in NLR and the decrease in LMR in patients are usually associated with a poor prognosis[21,35].

Malnutrition is closely related to tumor growth, angiogenesis, and progression. Serum ALB concentration is an important marker of nutrition. In a variety of tumors, patients with hypoalbuminemia usually represent a high degree of malignancy, which often indicates a poor prognosis[23,36]. Almost all nutritional prognosis scoring systems cover serum ALB levels, such as C-reactive protein to ALB ratio, Glasgow diagnostic score, as well as PNI, CONUT, and NPS discussed in this study, due to its important significance in malignant tumors[37,38]. Simultaneously, TC content is also one of the indicators of tumor prognosis. Hypocholesterolemia is associated with a poor prognosis in many tumors, including prostate cancer and non-small cell lung cancer[22,39]. Cholesterol integrates into

Table 2 Cox regression analysis of overall survival

Characteristic	OS		
	HR	95%CI	*P* value
Age (years)			0.500
< 70	1.000	0.605-2.796	
≥ 70	1.301		
Gender			0.451
Male	1.000	0.261-1.1.816	
Female	0.689		
Primary tumor size			0.926
≤ 3 cm	1.000	0.479-2.242	
> 3 cm	1.037		
Gross type			0.014
Non-ulcerative type	1.000	1.285-8.932	
Ulcerative type	3.388		
Differentiation			0.032
Well/Moderate	1.000	1.083-5.629	
Poor	2.469		
T stage			0.289
T1/T2	1.000	0.671-3.823	
T3/T4	1.601		
Lymph node metastasis			<0.001
No	1.000	1.963-10.472	
Yes	4.534		
cTNM stage			0.001
I/II	1.000	1.734-9.117	
III	3.976		
PNI group			0.002
Low risk	1.000	1.724-10.030	
High risk	4.158		
CONUT group			0.039
Low risk	1.000	1.041-4.666	
High risk	2.204		
NPS group			< 0.001
Low risk	1.000	1.879-9.425	
High risk	4.208		

PNI: Prognostic nutritional index; CONUT: Controlled nutritional status; NPS: Naples prognostic score; cTNM: Clinical Tumor-Node-Metastasis; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval.

specialized lipoprotein membrane domains, forms signal transduction mechanisms, and participates in a variety of key cellular signaling pathways[40].

The scoring system formed by combining immune and nutritional indicators can effectively reflect the physical condition of patients and improve the efficacy of predicting prognosis. This study calculated the PNI, CONUT, and NPS scores of patients according to their blood indicators. Survival analysis revealed that the three scoring systems can show good prediction efficiency. PNI, an index

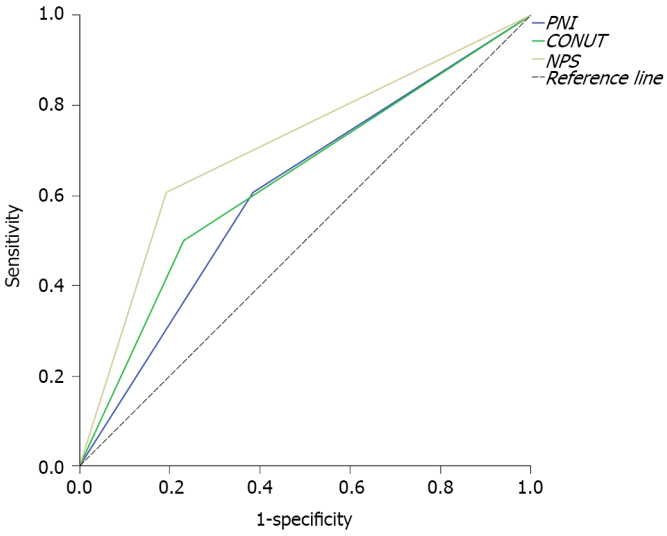

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Figure 1 Receiver operating characteristic curve analyses for prognostic nutritional index, controlled nutritional status, and Naples prognostic score systems. ROC: Receiver operating characteristic; PNI: Prognostic nutritional index; CONUT: Controlled nutritional status; NPS: Naples prognostic score.

related to ALB concentration and lymphocyte count, has been used to predict the risk of postoperative complications and the OS of patients with GC and other cancers[24,41,42]. The CONUT score is an index related to ALB concentration, lymphocyte count, and TC concentration. Studies have shown that the CONUT score is strongly correlated with the survival rate of patients with thyroid cancer; it is also an independent risk factor for lung cancer prognosis[25,43]. NPS is an index related to serum ALB concentration, TC concentration, LMR, and NLR and has been proven to be a predictor of OS in a variety of tumors. NPS has better predictive value than clinical prognostic parameters alone in patients with resected pancreatic cancer[26]. In esophageal cancer, high NPS is associated with a poor prognosis in locally advanced patients[44]. NPS can also predict the prognosis of endometrial cancer patients and may play an important role in clinical guidance[45].

In RGC, the clinical data of immune-nutritional scoring systems are still lacking; particularly, no relevant literature is available for the prediction of postoperative OS. PNI, CONUT, and NPS are comprehensive predictive evaluation methods that are easy to obtain. They represent the entire systemic inflammation and nutritional status of patients with RGC from many aspects. Meanwhile, the results show that NPS has the strongest prediction efficiency among the three prediction systems according to survival analysis.

This study has some limitations. First, the current study is retrospective. Although the data of two institutions were included, the sample size of patients was relatively small and the selection deviation was inevitable due to the low incidence and radical resection rate of RGC, respectively. For example, this study found significant differences in gender between different NPS groups, which may represent a selection bias. This bias may reduce the universality of the research results. Second, the cutoff points of laboratory indicators were obtained from previous literature reports. A new prediction system has not been developed. This system should be established by creating new cutoff points based on RGC, possibly leading to the weakening of the prediction capability of immune-nutritional indicators. However, the predictive significance of the three immune-nutritional systems in the prognosis of patients with RGC still shows considerable value.

CONCLUSION

In this study, the immune-nutritional score systems PNI, CONUT, and NPS were the factors that affected the prognosis of patients with RGC. The results showed that poor immune-nutritional scores were associated with a poor OS. Among the three immune-nutritional scoring systems, the NPS scoring system can more accurately evaluate the prognosis of patients with RGC.

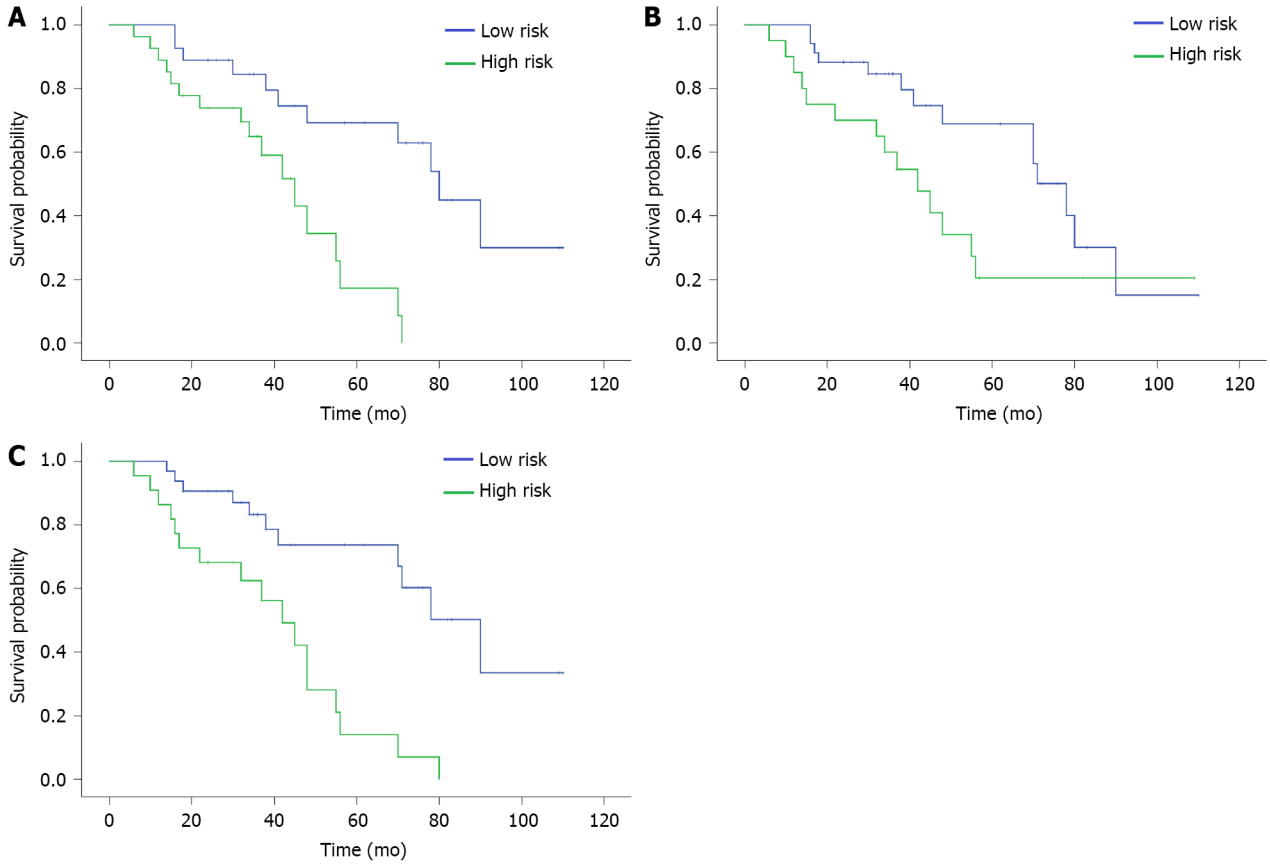

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Figure 2 Kaplan-Meier survival curves for overall survival based on prognostic nutritional index, controlled nutritional status, and Naples prognostic score stratification. A: Prognostic nutritional index; B: Controlled nutritional status; C: Naples prognostic score. PNI: Prognostic nutritional index; CONUT: Controlled nutritional status; NPS: Naples prognostic score.

ARTICLE HIGHLIGHTS

Research background

The mechanism of the occurrence and development of remnant gastric cancer (RGC) remains unclear. Systematically evaluating the preoperative immune and nutritional status of patients and analyzing its prognostic impact on postoperative RGC patients are crucial.

Research motivation

In RGC, the clinical data of immune-nutritional scoring systems are still lacking; particularly, no relevant literature is available for the prediction of postoperative overall survival (OS). Prognostic nutritional index (PNI), controlled nutritional status (CONUT), and Naples prognostic score system (NPS) are comprehensive predictive evaluation methods that are easy to obtain. They represent the entire systemic inflammation and nutritional status of patients with RGC from many aspects.

Research objectives

This retrospective cohort study aimed to determine the prognostic value of three preoperative immune-nutritional score systems, namely, PNI, CONUT, and NPS, in patients with RGC, and to examine their relationship with other clinicopathological features.

Research methods

The curves of the three immune-nutritional scores for predicting postoperative survival were plotted. Kaplan–Meier analysis was used to analyze the relationship between PNI, CONUT, and NPS scores and prognosis.

Research results

NPS was found to have the largest area under the curve [AUC = 0.707; 95% confidence interval (CI): 0.566–0.848; P = 0.009]. The AUC values of PNI and CONUT were 0.611 (95%CI: 0.460–0.763; P = 0.161) and 0.635 (95%CI: 0.485–0.784; P = 0.090), respectively. The three immune-nutritional scoring systems,

PNI (P = 0.002), CONUT (P = 0.039), and NPS (P < 0.001), were significantly correlated with OS. Median OS of patients with a low immune-nutritional risk was significantly higher than that of patients with a high immune-nutritional risk (PNI: 75 mo *vs* 42 mo, P = 0.001; CONUT: 69 mo *vs* 48 mo, P = 0.033; NPS: 77 mo *vs* 40 mo, P < 0.001).

Research conclusions

Poor immune-nutritional scores are associated with a poor OS. Among the three immune-nutritional scoring systems, the NPS scoring system can more accurately evaluate the prognosis of patients with RGC.

Research perspectives

The finding shows that the three immune-nutritional systems can significantly predict the prognosis of patients. Of note, the NPS system demonstrates the best prediction capability.

FOOTNOTES

Author contributions: Zhang Y, Wang LJ, and Xu ZK contributed equally to this work; Gu XH and Xu ZK designed the research study; Zhang Y and Wang LJ performed the research; Li QY contributed analytic tools; Yuan Z, Zhang DC, Xu H, and Yang L analyzed the data and wrote the manuscript; all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Efficacy and safety of preoperative immunotherapy in patients with mismatch repair-deficient or microsatellite instability-high gastrointestinal malignancies

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Abstract

BACKGROUND

Programmed death protein (PD)-1 blockade immunotherapy significantly prolongs survival in patients with metastatic mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) gastrointestinal malignancies such gastric and colorectal cancer. However, the data on preoperative immunotherapy are limited.

AIM

To evaluate the short-term efficacy and toxicity of preoperative PD-1 blockade immunotherapy.

METHODS

In this retrospective study, we enrolled 36 patients with dMMR/MSI-H gastrointestinal malignancies. All the patients received PD-1 blockade with or without chemotherapy of CapOx regime preoperatively. PD1 blockade 200 mg was given intravenously over 30 min on day 1 of each 21-d cycle.

RESULTS

Three patients with locally advanced gastric cancer achieved pathological complete response (pCR). Three patients with locally advanced duodenal carcinoma achieved clinical complete response (cCR), followed by watch and wait. Eight of 16 patients with locally advanced colon cancer achieved pCR. All four patients with liver metastasis from colon cancer reached CR, including three with pCR and one with cCR. pCR was achieved in two of five patients with non-liver metastatic colorectal cancer. CR was achieved in four of five patients with low rectal cancer, including three with cCR and one with pCR. cCR was achieved in seven of 36 cases, among which, six were selected for watch and wait strategy. No cCR was observed in gastric or colon cancer.

CONCLUSION

Preoperative PD-1 blockade immunotherapy in dMMR/MSI-H gastrointestinal malignancies can achieve a high CR, especially in patients with duodenal or low rectal cancer, and can achieve high organ function protection.

Key Words: Preoperative; PD-1 blockade; dMMR/MSI-H; Gastrointestinal malignancies

Core Tip: To the best of our knowledge, this retrospective study is one of the few to summarize mismatch repair-deficient/microsatellite instability-high gastric, duodenal, and colorectal cancers for preoperative immunotherapy. The cohort was a sequential case analysis that only one patient was excluded from the cohort because symptoms disappeared after programmed death protein 1 therapy and she refused to examination and further treatment.

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INTRODUCTION

Many solid tumors have a mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) ratio, and dMMR/MSI-H subtype, as a unique type of tumor, accounts for 5%–15% of solid tumor patients[1]. However, the proportion of dMMR/MSI-H varies significantly among different tumor types, with a high incidence in colorectal, gastric and endometrial cancer, as well as breast cancer, liver cancer, cholangiocarcinoma, pancreatic cancer and other solid tumors[2]. As a distinguished biomarker, dMMR/MSI-H status can accurately predict the efficacy of immunotherapy for many solid tumors[3,4].

MSI-H subtype is one of the molecular subtypes of gastric or colorectal cancer[5,6]. MSI-H is an independent prognostic factor in gastrointestinal tumors, with good prognosis and resistance to conventional chemoradiotherapy[7,8]. Locally advanced gastrointestinal malignancies or surgically resectable metastatic colorectal cancer require preoperative treatment to improve R0 resection rate. However, many studies[9,10] on locally advanced gastric cancer suggest that the pathological complete response (pCR) rate of conventional preoperative neoadjuvant chemotherapy is not high, and dMMR/MSI-H gastric cancer has a worse response to conventional chemotherapy. As with gastric cancer, pancreaticoduodenectomy (Whipple's procedure) for duodenal cancer is a major, invasive procedure that needs to be performed even after preoperative chemotherapy. MSI-H colorectal cancer is resistant to conventional chemotherapy[11] and radiotherapy[12], and low advanced rectal cancer requires R0 resection and organ preservation.

In 2015[13] and 2017, Le *et al*[14] revealed that pembrolizumab [programmed death protein (PD) 1 blockade] achieved a high objective response rate for metastatic dMMR/MSI-H solid malignant tumors, and some patients achieved complete response (CR). In 2017, for the first time, the United States FDA approved pembrolizumab (for immunotherapy of all unresectable, metastatic dMMR/MSI-H solid tumors based on biomarkers instead of tumor types. A series of studies[15-18] on advanced or metastatic dMMR/MSI-h gastrointestinal malignancies such as gastric and colorectal cancer showed that PD1 blockade achieved better therapeutic effects.

This study aimed to evaluate the efficacy and safety of preoperative PD-1 blockade immunotherapy in patients with dMMR/MSI-H locally advanced or metastatic gastrointestinal malignancies.

MATERIALS AND METHODS

Patients

We retrospectively analyzed clinical data of all patients with dMMR/MSI-H gastrointestinal malignancies who received preoperative PD1 blockade immunotherapy with or without chemotherapy in Ward 3, Gastrointestinal Cancer Center, Peking University Cancer Hospital from January 1, 2020 to September 30, 2022. Preoperative PD-1 blockade immunotherapy is recommended for patients with dMMR/MSI-H detected by molecular detection before treatment. This cohort was a series of sequential cases.

The inclusion criteria were: (1) Age ≥ 18 and ≤ 90 years; (2) Eastern Collaborative Oncology Group performance status score 0–2; (3) gastrointestinal malignancies: gastric cancer, duodenal carcinoma, or colorectal cancer; (4) adenocarcinoma or mucous adenocarcinoma confirmed by endoscopic biopsy; (5) clinical stage II–IV according to imaging examinations [spiral computed tomography, magnetic resonance imaging, positron emission tomography–computed tomography (PET-CT) or ultrasound colonoscopy]; and (6) MSI and MMR status confirmed by immumohistochemical staining, polymerase chain reaction (PCR) and next-generation sequencing (NGS). The exclusion criteria included: (1) Initially unresectable metastasis lesion; and (2) diseases of the immune system. This study was approved by the Ethics Committee of Peking University Cancer Hospital (2022YJZ39) and it conformed to the provisions of the Declaration of Helsinki.

Treatment and evaluation

All patients were discussed in a multidisciplinary team conference. All patients received PD1 blockade (PD1 blockade 200 mg intravenously over 30 min on day 1 of each 21-d cycle) preoperative immunotherapy with or without CapOx chemotherapy (oxaliplatin 130 mg/m^2 on day 1 and capecitabine 1000 mg/m^2 twice daily on d 1–14, repeated every 3 wk).

The primary tumor response was assessed according to the iRECIST criteria[19]. Acute toxicity was graded according to the NCI Common Terminology Criteria for Adverse Events 4.0[20]. After every one or two cycles of neoadjuvant immunotherapy, all patients had complete assessment including computed tomography (CT), magnetic resonance imaging, PET-CT, blood counts, renal biochemistry, hepatobiliary function, thyroid function, cardiac function, and tumor markers (carcinoembryonic antigen and carbohydrate antigen 19-9) to evaluate the general condition and treatment response. The determination of clinical complete response (cCR) was based on Memorial Sloan Kettering Cancer Center standard[21] and International Watch & Wait Database[22]. The cCR was defined as no evidence of residual tumor determined by rectum MRI, abdomen/pelvis CT and chest CT, endoscopic physical examination, nomarl CEA and/or digital rectal exam. Pathological staging was based on the 8th edition of the American Joint Committee on Cancer TNM staging system[23]. Post-treatment response was assessed by NCCN grading: 0 = complete response (ypCR) with no detectable cancer cells; 1 = major response with few residual cancer cells; 2 = partial response; 3 = no or very little response[24].

Postoperative complications were classified according to the Clavien–Dindo classification[24].

Follow-up and statistical analysis

After initial treatment, all patients were re-examined every 3 mo for the first 2 years, 6-mo intervals for the next 3 years, and yearly thereafter. Clinical data were obtained by laboratory examination records, imaging examination records, pathological examination records, and medical records review. Survival data were obtained from outpatient clinical visit or telephone interview. Analyses were conducted using SPSS for Windows version 19.0. Frequencies and percentages were calculated for categorical variables, and means and standard deviations for continuous variables.

RESULTS

Patient characteristics

From January 1, 2020 to September 30, 2022, 37 patients with dMMR/MSI-H gastrointestinal malignancies finished preoperative PD1 blockade immunotherapy, and one patient with locally advanced colon cancer refused re-examination and treatment after symptom resolution. By September 30, 2022, 36 patients completed PD1 blockade immunotherapy and the treatment results were analyzed.

The clinical features are shown in Tables 1 and 2. Twenty-six men (26/36, 72.2%) and 10 women (10/36, 27.8%) were enrolled and the median age was 52 (26–87) years. Lynch syndrome was diagnosed in 16 patients. Three patients were diagnosed with initially unresectable locally advanced gastric cancer, three with locally advanced duodenal carcinoma, and 30 with colorectal cancer. Among the 30 cases of colorectal cancer, 21 were locally advanced and nine were surgically resectable metastatic colorectal cancer. Twenty-seven patients received single PD-1 blockade as preoperative therapy, and nine with PD1 blockade and CapOx regimen. Of these patients, nine were initially treated with CapOx and two with radiotherapy, which was ineffective and switched to immunotherapy.

Table 1 Patient, tumor and treatment characteristics

All cases	N (%)
Sex, *n* (%)	
Male	26 (72.2)
Female	10 (27.8)
Age, yr (median)	52.0
ECOG	
0	2 (5.6)
1	30 (83.3)
2	4 (11.1)
Tumor location, *n* (%)	
Stomach	3 (8.3)
Duodenum	3 (8.3)
Colorectal cancer	30 (83.3)
Clinical TNM stage, *n* (%)	
II-III	27(75.0)
IV	9 (25.0)
Lynch syndrome	
Yes	16 (44.4)
No	20 (55.6)
No clear	0 (0.0)
MMR and MSI status	
Consistent	30 (83.3)
Inconsistent	6 (16.7)

ECOG: Eastern Cooperative Oncology Group; MMR: Mismatch repair; MSI: Microsatellite instability; TNM: Tumor-node-metastasis.

Efficacy

With a median interval of 2 wk after neoadjuvant immunotherapy (range: 1–4 wk), all patients received imaging evaluation (Table 2). cCR was achieved in seven patients (patient 4, 5, 6, 23, 26, 27, 30), among which six (patient 4, 5, 6, 23, 26, 30) were selected for wait and watch strategy. No cCR was observed in gastric or colon cancer. Thirty patients underwent surgery, including nine laparoscopic operations and 21 Laparotomies. Twenty-nine patients achieved R0 resection according to the postoperative pathological diagnosis (Table 2).

Three patients with locally advanced gastric cancer achieved pathological CR (pCR). Three patients with locally advanced duodenal carcinoma achieved cCR and then watch and wait (Video 1). Eight of 16 patients with locally advanced colon cancer achieved pCR. All four patients with liver metastasis from colon cancer achieved CR, including three pCR and one cCR. pCR was achieved in two of five patients with non-liver metastases from colorectal cancer. CR was achieved in four of five patients with low rectal cancer, including three with cCR and one with pCR. The CR (cCR and pCR) rate was 58.3% (21/36).

No adjuvant therapy was performed after pCR was achieved. Six patients received 2–10 cycles of adjuvant mono-immunotherapy after reaching cCR. The median follow-up was 9.4 (1–29) mo, and final follow-up time was September 30, 2022. pCR and cCR patients had no recurrence during follow-up. No patient died during follow-up.

Safety

Preoperative immunotherapy was well tolerated and there was no interruption caused by immunotherapy-related toxicity. Two patients had grade 3 toxicity that presented as hypothyroidism and hematochezia, and eight patients had grade 1 or 2 toxicity including hypothyroidism, thyroid toxicity, rash, fatigue, reactive cutaneous capillary endothelial proliferation (Table 3). No surgery was delayed, but four patients experienced emergency surgery, of which two had perforated tumor, and two had

Table 2 Details of the 36 patients with neoadjuvant programmed death protein 1 blockade immunotherapy

No.	Tumor location	Clinical stage	MMR status	MSI status	Courses of ICB	Combined treatment	Surgery	Pathological stage
1	Stomach	T4aN2M0	dMMR	MSI-H	Sintilimab × 6	CapeOX	Total gastrectomy	PCR
2	Stomach	T4aN2M0	dMMR	MSI-H	Sintilimab × 5	CapeOX	Total gastrectomy	PCR
3	Stomach	T4aN2M0	dMMR	MSI-H	Sintilimab × 3	CapeOX	Total gastrectomy	PCR
4	Duodenum	T3N0M0	dMMR	MSI-H	Pembrolizumab × 4	-	cCR	-
5	Duodenum	T3N0M0	dMMR	MSI-H	Pembrolizumab × 6	-	cCR	-
6	Duodenum	T4aN0M0	dMMR	MSI-L	Sintilimab × 8	CapeOX	cCR	-
7	LACC	T4aN+M0	dMMR	MSI-H	Pembrolizumab × 2	-	Colectomy	PCR
8	LACC	T3N+M0	dMMR	MSI-H	Sintilimab × 2	-	Colectomy	ypT3N0
9	LACC	T4bN2M0	dMMR	MSI-H	Pembrolizumab × 2	-	Colectomy	PCR
10	LACC	T3N+M0	dMMR	MSI-H	Camrelizumab × 4	CapeOX	Colectomy	PCR
11	LACC	T4bN+M0	dMMR	MSI-H	Pembrolizumab × 1	-	Colectomy	ypT3N0
12	LACC	T3N+M0	dMMR	MSI-H	Camrelizumab × 3	-	Colectomy	ypT2N0
13	LACC	T4bN2bM0	dMMR	MSI-H	Sintilimab × 4	-	Colectomy	ypT1N1b
14	LACC	T4bN+M0	dMMR	MSI-H	Pembrolizumab × 2	-	Colectomy	PCR
15	LACC	T4aN+M0	dMMR	MSS	Sintilimab × 3	CapeOX	Colectomy	ypT3N0
16	LACC	T4aN+M0	dMMR	MSI-H	Toripalimab × 8	-	Colectomy	ypT2N0
17	LACC	T3N0M0	dMMR	MSI-H	Pembrolizumab × 4	-	Colectomy	ypT3N0
18	LACC	T4bN2aM0	dMMR	MSI-H	Sintilimab × 5	-	Colectomy	PCR
19	LACC	T4bN2bM0	dMMR	MSI-H	Sintilimab × 3	-	Colectomy	PCR
20	LACC	T4aN2bM0	dMMR	MSS	Pembrolizumab × 3	-	Colectomy	ypT3N1a
21	LACC	T3N2aM0	pMMR	MSI-H	Pembrolizumab × 3	-	Colectomy	PCR
22	LACC	cT4aN2M0	dMMR	MSI-H	Pembrolizumab × 4	-	Colectomy	PCR
23	Low rectum	T3N1M0	dMMR	MSI-H	Pembrolizumab × 1	-	CCR	-
24	Low rectum	T3N2M0	dMMR	MSI-H	Nivolumab × 3	CapeOX	LAR	PCR
25	Low rectum	T3N+M0	pMMR	MSI-H	Sintilimab × 4	-	LAR	ypT3N0
26	Low rectum	T3N+M0	dMMR	MSI-H	Pembrolizumab × 2	-	CCR	-
27	Low rectum	T3N2M0	pMMR	MSI-H	Camrelizumab × 3	CapeOX	CCR	PCR
28	CLM	M1a	dMMR	MSI-H	Sintilimab × 6	CapeOX	Hepatectomy	PCR
29	CLM	T4bN2M1a	dMMR	MSI-H	Sintilimab × 4	CapeOX	ColectomyHepatectomy	ypT4bN1aM0
30	CLM	M1a	dMMR	MSI-H	Sintilimab × 26	-	CCR	-
31	CLM	T4aN2M1a	dMMR	MSI-H	Pembrolizumab × 4	-	ColectomyHepatectomy	PCR
32	Rectum	T4bN2M1c	dMMR	MSI-H	Pembrolizumab × 1	-	Colectomy	ypT4bN2aM1c
33	Rectum	T4bN2M1a	dMMR	MSI-H	Sintilimab × 6	-	Hartmann	PCR

34	Colon	T4bN2M1c	dMMR	MSI-H	Tislelizumab × 8	-	Colectomy	ypT0N0M1c
35	Colon	T4bN2M1c	dMMR	MSI-H	Sintilimab × 5	CapeOX	Colectomy	ypT3N0M1c
36	Colon	T4aN1M1c	dMMR	MSI-H	Sintilimab × 5	-	Colectomy	PCR

cCR: Clinical complete response; LACC: Locally Advanced Colon Cancer; pMMR: Proficient mismatch repair; dMMR: Different mismatch repair; ICB: Immune checkpoint inhibitor; CLM: Colorectal Liver Metastases; LAR: Low Anterior Resection; PCR: Polymerase chain reaction.

Table 3 Adverse events

Adverse events	No. of patients (%)	No. of patients (%)	No. of patients (%)
Immuno-related	Grade 1	Grade 2	Grade 3
Any	4 (11.1)	4 (11.1)	2 (5.6)
Dermatologic			
Rash	2 (5.6)	0 (0)	0 (0)
RCCEP	1 (2.80)	0 (0)	0 (0)
Endocrine			
Hypothyroidism	2 (5.6)	2 (5.6)	1 (2.80)
Hyperglycemia	0 (0)	0 (0)	0 (0)
Fatigue	3 (8.3)	4(11.1)	0 (0)
Surgery-related			
Any	1 (2.80)	4(11.1)	1 (2.80)
Chylous fistula	0 (0)	2 (5.6)	0 (0)
Anastomosis leakage	0 (0)	2 (5.6)	0 (0)
Fever	1 (2.80)	0 (0)	0 (0)
Intra-abdominal hemorrhage	0 (0)	0 (0)	1 (2.80)

RCCEP: Reactive cutaneous capillary endothelial proliferation.

colonic obstruction. There was no 30-d mortality. Four patients had grade 1 or 2 postoperative complications, including two grade 2 chylous fistula, two grade 2 anastomotic leak, and one grade 1 fever. One patient (case 24) underwent emergency surgery for intestinal obstruction, and received a second operation for postoperative abdominal bleeding (grade 3). All patients recovered well after conservative treatment and only one (anastomotic leak) stayed in hospital > 2 wk after surgery.

DISCUSSION

This retrospective study is one of the few to summarize dMMR/MSI-H gastric, duodenal and colorectal cancers for preoperative immunotherapy. The cohort was a sequential case analysis and only one patient was excluded because her symptoms disappeared after PD1 therapy and she refused further examination and treatment.

The GERCOR NEONIPIGA study[25] reported neoadjuvant nivolumab plus ipilimumab in patients with localized dMMR/MSI-H esophagogastric adenocarcinoma showed a pCR rate of 58.6%. The NICHE study[26] and PICC study[27] of dMMR/MSI-H colon cancer showed a pCR rate of 60% and 65%, respectively. Cercek *et al*[28] reported 14 patients with dMMR/MSI-H rectal cancer using dostarlimab (PD1 blockade); all of whom achieved cCR and avoided surgical treatment.

MSI-H/dMMR tumors are currently the best predictive markers for cancer immunotherapy, but MSI-H tumors are also heterogeneous, and show different incidence, differences in clinical and radiographic responses to immunotherapy in different solid tumors, primary immunotherapy resistance in some patients, and heterogeneity of different stages of the same tumor[1,29-31]. In our cohort three patients with locally advanced gastric cancer achieved pCR. Three patients with locally advanced duodenal carcinoma evaluated as cCR received the watch and wait strategy. Eight of 16 patients with locally advanced colon cancer achieved pCR. All four patients with liver metastatic lesions from colon cancer

reached CR. pCR was achieved in two of five patients with non-liver metastatic colorectal cancer. CR was achieved in four of five patients with low rectal cancer, including three with cCR and one with pCR. No cCR was observed in gastric or colon cancer. Duodenal and low rectal cancers have a high cCR rate, and do not require surgery and achieve organ preservation. Based on such high pCR and cCR rates, some patients can avoid surgery. Eleven of 36 patients in our study underwent routine preoperative chemotherapy and/or radiotherapy, which was unnecessary. Neoadjuvant therapy should be effective, moderate and accurate based on the treatment target. It is necessary to determine the molecular status of patients before treatment.

Different from the prospective clinical study, patients in our cohort underwent surgery and achieved R0 resection on imaging examination. Five patients achieved cCR or pCR within one or two cycles, and 15 patients who achieved pCR did not receive postoperative adjuvant therapy. None of the patients with pCR or cCR had recurrence or metastasis during follow-up. The Keynote 016[13], Keynote 177[2] and CHECKMATE 142[16] studies showed that if MSI-H tumors were highly sensitive to PD1 inhibitors or CTLA4 (cytotoxic T lymphocyte-associated antigen-4, CTLA-4) antibody, the response was rapid, and there was a significant tail effect of immunotherapy after long follow-up. Because of the inaccuracy of conventional imaging in the assessment of immunotherapy, the development of new tests that reflect the pathological response (*e.g.*, metabolic imaging) or molecular features (*e.g.*, liquid biopsy) is needed to better assess the response to treatment[32]. For MSI-H tumors sensitive to PD1 immunotherapy, early and short-term PD1 treatment can achieve a curative effect. It is necessary to clarify the characteristics and immune microenvironment of MSI-H tumors.

Our study and others have shown that preoperative immunotherapy is safe for most patients[33,34]. However, we have seen that there are some hidden dangers in the use of immunotherapy for such patients before surgery, such as stenosis, obstruction and perforation during the treatment of colon cancer. Previous studies[35,36] of neoadjuvant chemotherapy have suggested that obstruction and perforation reflect the poor effect of neoadjuvant therapy and are associated with tumor progression and poor prognosis. Due to immune cell infiltration and other reasons, many patients did not observe tumor remission on imaging-maintained stability or even some enlargement, but pathological examination will find a large number of necrosis tumors and inflammatory immune response[37]. Our study also observed this phenomenon. Our cohort reported four patients with MSI-H colon cancer with obstruction and perforation during PD1 treatment; all of whom had some tumor pathological response after emergency surgery, including one who achieved pCR and three with pathological ratings of TRG2–3. We also observed five patients with regional lymph node enlargement during treatment. Although no trace of metastasis was found after lymph node dissection, it increased the difficulty of surgery and was prone to complications of lymphatic leakage. The incidence of thyroid dysfunction was 22% and three patients required long-term oral thyroxine replacement therapy.

Many studies[2,3,14-18] have reported that 10%–40% of patients with dMMR/MSI-H colorectal cancer developed primary drug resistance when receiving immunotherapy. Cohenet al[38] suggested that primary resistance to PD-1 blockades in dMMR/MSI-H metastatic colorectal cancer can largely be attributed to misdiagnosis of MMR/MSI status. In our cohort, 16.7% (6/36) of patients had MMR and MSI discordance[39,40]. We found that this discordance was test related and in some patients it was related to examination methods, tissue volume, tumor heterogeneity, and examination quality control. Six patients were rediagnosed with MMR and MSI status, and three were found to be consistent (Table 4). Our study and many others have found that intrinsic resistance exists even when MSI is consistent with MMR status[39,40]. Wang *et al*[41] found that combination of AKT1 and CDH1 mutations predicted primary resistance to immunotherapy in dMMR/MSI-H gastrointestinal cancer.

The limitations of this study included its small sample size, retrospective design, short follow-up time, and different neoadjuvant regimens and cycles. However, our study was a real-world clinical study in patients who required preoperative immunotherapy, and the group was a continuous case cohort, with the exception of one patient who declined to be enrolled because of resolution of symptoms. This study compared preoperative immunotherapy for dMMR/MSI-H in different gastrointestinal tumors, and showed that specific treatment strategies could be used for different tumor sites. It was encouraging to find that a high proportion of dMMR/MSI-H duodenal and low rectal cancers did not require surgery after preoperative immunotherapy, and this treatment strategy deserves further investigation.

CONCLUSION

Our study demonstrated that preoperative PD-1 blockade immunotherapy with or without chemotherapy achieved significant results and acceptable adverse events in dMMR/MSI-H gastrointestinal malignancies. Some low cases of low rectal cancer or duodenal cancer can achieve cCR and avoid surgery and achieve organ preservation. Larger clinical trials are needed to conform our results.

Table 4 Details of the 6 patients with inconsistency of dMMR and MSI-H

No.	Tumor location	Clinical stage	Heredity	MMR (IHC)biopsy	MMR (NGS) biopsy	MSI (PCR) biopsy	MSI (NGS) biopsy	MMR (IHC) surgery	MMR (NGS) surgery	MMR (PCR) surgery	MMR (NGS) surgery	Reason
6	Duodenum	T4aN+M0	Lynch	dMMR	dMMR	MSI-L	MSI-L					-
15	Colon	T4aN+M0	No	dMMR	pMMR	MSS	MSS	pMMR	pMMR	MSS	MSS	Tumor hetero-geneity
20	Colon	T4aN2bM0	No	dMMR	dMMR	MSS	MSS	dMMR	dMMR	MSI-H	MSI-H	Low tumor content
21.	Colon	T3N2aM0	No	pMMR	dMMR	MSI-H	MSI-H					Only MSH3 mt
25	Rectum	T3N+M0	No	pMMR	pMMR	MSS	MSI-H	pMMR	pMMR	MSS	MSI-H	DDR mt
27	Rectum	T3N2M0	No	pMMR	pMMR	MSS	MSI-H					DDR mt

IHC: Immunohistochemistry; PCR: Polymerase chain reaction; NGS: Next-generation sequencing; MSH-L: Microsatellite instability-low; pMMR: Proficient mismatch repair; dMMR: Different mismatch repair; WT: Wild type; MT: Mutant type.

ARTICLE HIGHLIGHTS

Research background

Neoadjuvant programmed death protein (PD)-1 blockade immunotheapy has been sufficiently applied in a variety of cancers, but was rare in metastatic mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) gastrointestinal malignancies. Since the NICHE Study have showed their inspiring results that neoadjuvant immunotherapy was an efficient and safe method to improve colon cancer patients' outcome, NCCN guideline then recommend immune checkpoint inhibitors to cT4b gastric or colorectal cancer. However, whether preoperative immunotherapy can expand to other stage gastrointestinal malignancies is still unknown.

Research motivation

We performed this study among 36 initially surgical resected difficult dMMR/MSI-H gastrointestinal malignancies such gastric cancer, duodenal cancer and colorectal cancer patients who received preoperative PD-1 blockade immunotherapy followed by surgery in order to investigate if the indication of preoperative immunotherapy can expand to initially surgical resected difficult dMMR/MSI-H gastrointestinal malignancies and evaluate the safety and efficacy.

Research objectives

To the best of our knowledge, this retrospective study is one of the few to summarize dMMR/MSI-H gastric, duodenal, and colorectal cancers for preoperative immunotherapy. The cohort was a sequential case analysis that only one patient was excluded from the cohort because symptoms disappeared after PD1 therapy and she refused to examination and further treatment.

Research methods

The limitations of this study included its small sample size, retrospective design, short follow-up time, and different neoadjuvant regimens and cycles. However, our study was a real-world clinical study in patients who required preoperative immunotherapy, and the group was a continuous case cohort, with the exception of one patient who declined to be enrolled because of resolution of symptoms.

Research results

Our study demonstrated that preoperative PD-1 blockade immunotherapy with or without chemotherapy could achieve significant effect and acceptable adverse events in dMMR/MSI-H gastrointestinal malignancies.

Research conclusions

Our study demonstrated that preoperative PD-1 blockade immunotherapy with or without chemotherapy could achieve significant effect and acceptable adverse events in dMMR/MSI-H gastrointestinal malignancies. Some low rectal cancer or duodenal cancer can achieve clinical complete response and avoid surgery to achieve organ preservation. Large sample clinical trials are needed.

Research perspectives

This study compared preoperative immunotherapy for dMMR/MSI-H in different gastrointestinal tumors, and showed that specific treatment strategies could be used for different tumor sites. It was encouraging to find that a high proportion of dMMR/MSI-H duodenal and low rectal cancers did not require surgery after preoperative immunotherapy, and this treatment strategy deserves further investigation.

FOOTNOTES

Author contributions: Wu AW contributed to conception and design of the study, draft and final approval of the manuscript; Li YJ contributed to collection of the data, draft the manuscript, study design and statistical analysis; Wu AW, Li YJ, Liu XZ and Yao YF, Li ZW, Zhang XY, Lin XF contributed to quality control of the study especially the surgery part, acquisition of data; All authors approved the final manuscript.

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

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at drwuaw@sina.com.

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ORIGINAL ARTICLE

Observational Study

Hepatobiliary manifestations following two-stages elective laparoscopic restorative proctocolectomy for patients with ulcerative colitis: A prospective observational study

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Abstract

BACKGROUND

Hepatobiliary manifestations occur in ulcerative colitis (UC) patients. The effect of laparoscopic restorative proctocolectomy (LRP) with ileal pouch anal anastomosis (IPAA) on hepatobiliary manifestations is debated.

AIM

To evaluate hepatobiliary changes after two-stages elective laparoscopic restorative proctocolectomy for patients with UC.

METHODS

Between June 2013 and June 2018, 167 patients with hepatobiliary symptoms underwent two-stage elective LRP for UC in a prospective observational study. Patients with UC and having at least one hepatobiliary manifestation who underwent LRP with IPAA were included in the study. The patients were followed up for four years to assess the outcomes of hepatobiliary manifestations.

RESULTS

The patients' mean age was 36 ± 8 years, and males predominated (67.1%). The most common hepatobiliary diagnostic method was liver biopsy (85.6%), followed by Magnetic resonance cholangiopancreatography (63.5%), Antineutrophil cytoplasmic antibodies (62.5%), abdominal ultrasonography (35.9%), and Endoscopic retrograde cholangiopancreatography (6%). The most common hepatobiliary symptom was Primary sclerosing cholangitis (PSC) (62.3%), followed by fatty liver (16.8%) and gallbladder stone (10.2%). 66.4% of patients showed a stable course after surgery. Progressive or regressive courses occurred in 16.8% of each. Mortality was 6%, and recurrence or progression of symptoms required surgery for 15%. Most PSC patients (87.5%) had a stable course, and only 12.5% became worse. Two-thirds (64.3%) of fatty liver patients showed a regressive course, while one-third (35.7%) showed a stable course. Survival rates were 98.8%, 97%, 95.8%, and 94% at 12 mo, 24 mo, 36 mo, and at the end of the follow-up.

CONCLUSION

In patients with UC who had LRP, there is a positive impact on hepatobiliary disease. It caused an improvement in PSC and fatty liver disease. The most prevalent unchanged course was PSC, while the most common improvement was fatty liver disease.

Key Words: Courses; Hepatobiliary manifestations; Primary sclerosing cholangitis; Restorative proctocolectomy

Core Tip: There has been little research on the efficacy of proctocolectomy in ulcerative colitis patients with hepatobiliary manifestations. The course of hepatobiliary symptoms after proctocolectomy is being evaluated prospectively in our study. The main finding of this study was that two-thirds of patients had an unchanged course following surgery, whereas 16.8% had a progressive or regressive course. The mortality rate was 6%, and 15% of patients required surgery due to recurrence or worsening symptoms. Most primary sclerosing cholangitis patients (87.5%) had an unchanged course, with only 12.5% progressing. Two-thirds (64.3%) of fatty liver patients progressed, whereas one-third (35.7%) remained stationary. At 12, 24, 36, and 48 mo, the survival rates were 98.8%, 97%, 95.8%, and 94%, respectively.

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INTRODUCTION

Inflammatory bowel disease (IBD) is expected to affect 1% of the population over the next decade[1]. Although the primary clinical manifestations of IBD are centred on the gastrointestinal tract, 25%–40% of IBD patients develop at least one extraintestinal manifestation (EIM)[2].

Hepatobiliary manifestations constitute one of the most common EIMs in IBD[3]. Primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH), fatty liver, cholelithiasis, primary biliary cholangitis, portal vein thrombosis, and hepatic abscess are the most prevalent hepatobiliary manifestations of ulcerative colitis (UC)[4,5].

Most UC patients can be managed with medications, but minorities require proctocolectomy[6]. Two-stage laparoscopic proctocolectomy (LRP) with ileal pouch-anal anastomosis (IPAA) is a cure for UC, but its effect on hepatobiliary diseases is controversial[6-10]. Therefore, we conducted a prospective observational study to examine the effects of LRP with IPAA on hepatobiliary symptoms to evaluate the role of surgery in preventing or ameliorating liver damage from the disease progression.

MATERIALS AND METHODS

Study design and participants

This is a prospective observational study on 167 patients with hepatobiliary manifestations who underwent two-stage elective LRP with IPAA for UC from June 2013 to June 2018 at our universities' hospitals. Inclusion criteria were all patients between 18 and 69 years; men and women with at least one hepatobiliary manifestation. In patients with UC, surgery was decided according to The European Crohn's and Colitis Organisation guidelines on therapeutics in UC[11]. Exclusion criteria included: Alcohol abuse, severe heart failure or type II diabetes mellitus, complications or death related to LRP operation, liver toxicity of IBD-related medications, active or chronic viral hepatitis, hemochromatosis, Wilson's disease, drugs-induced steatosis (amiodarone or tamoxifen), morbid obesity or patients undergoing bariatric surgery, immunoglobulin G4-related cholangitis; human immunodeficiency virus/acquired immune deficiency syndrome; tuberculosis; secondary sclerosing cholangitis; cholangiocarcinoma; complications of advanced PSC (hepatic encephalopathy, portal hypertension, hepatorenal syndrome, or hepato-pulmonary syndrome; end-stage liver failure), hypercoagulability status (systemic lupus erythematosus, increased von Willebrand factor or increased homocysteine level), oral contraceptive pills, Grave's disease, dyslipidemia, and previous biliary tract surgery including cholecystectomy.

Study ethics

The Institutional Review Board approved the study (Approval No. ZU IRB#9841). Each patient signed a written consent form, and the study followed the rules of the 1975 Declaration of Helsinki principles. In addition, the study was registered on ClinicalTrials.gov (NCT05495178) and done according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Definitions of outcomes and measurements

PSC is progressive biliary fibrosis affecting intra and/or extrahepatic bile ducts[12] and diagnosed by laboratory tests [(cholestasis, Antineutrophil cytoplasmic antibodies (ANCA)], radiology [abdominal ultrasonography (US), abdominal computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP), or magnetic resonance cholangiopancreatography (MRCP)], and liver biopsy. Primary biliary cholangitis (PBC) is characterized by the loss of small and medium-sized bile ducts on liver biopsy, elevated anti-mitochondrial antibodies, and altered gamma-glutamyl transferase and alkaline phosphatase (ALP) levels[13]. Non-alcoholic fatty liver disease (NAFLD) is characterized by fat storage in ≥ 5% of hepatic steatosis in the absence of concomitant liver disease (chronic viral hepatitis), use of steatosis-inducing medications (amiodarone or tamoxifen), autoimmune hepatitis, hemochromatosis, Wilson's disease, or excessive alcohol consumption[14]. Diagnosis of NAFLD was made by liver biopsies or US[15], and the severity score was previously stated[16]. Autoimmune hepatitis

diagnosis based on the International Autoimmune Hepatitis Group criteria with a score of > 15 points consisting of demographic, histologic, and laboratory markers, including antinuclear antibodies with a titer of at least 1:40 and liver histology[17]. An aseptic liver abscess is diagnosed based on IBD history, US, and CT[18]. Ultrasound, colour Doppler, and/or CT scans were used to detect portal vein thrombosis.

Perioperative technique and follow-up after surgery

For patients with UC who require surgery, two stages of LRP with IPAA and a diverting loop ileostomy are the gold standard[19]. The diverting loop ileostomy was reversed 2-3 mo following surgery. Because of the increased risk of thromboembolic events, prophylactic anticoagulation medication was scheduled and continued for six months after surgery. The follow-up period was four years, and cases lost during the follow-up period were excluded from the study.

Follow-up with the clinical progression of patients' conditions and laboratory evaluations was performed at six months, one year, two years, three years, and four years, or at any time of patients' complaint. These data were compared to data obtained immediately before surgery (at the time of surgery). Follow-ups were performed at outpatient clinics, *via* phone, or by email. Laboratory (Liver function tests, antibodies, Cancer antigen 19-9) and radiology (abdominal ultrasonography, colour Doppler, CT, MRCP) tests were performed as part of the follow-up assessments. An endoscopic examination of the ileal pouch on an annual basis was arranged. A liver biopsy was planned at the end of the study.

Statistical methods

Version 28 of SPSS was used for data management and statistical analysis (IBM, Armonk, New York, United States). The normality of quantitative data was evaluated using the Kolmogorov–Smirnov test, the Shapiro-Wilk test, and direct data visualization methods. Means and standard deviations, or medians and ranges based on normality tests, were used to summarize the quantitative data. As a summary of categorical data, numbers and percentages were used. The McNemar test compared laboratory and clinical findings before and after surgery. We used a Kaplan-Meier analysis to estimate overall survival and recurrence-free survival. The independent *t*-test or the Mann-Whitney *U* test for normally and non-normally distributed quantitative variables was used to compare the regression rates of hepatobiliary manifestations in the two groups. We compared categorical data using the Chi-square test. Multivariate logistic regression analysis was done to predict no regression of hepatobiliary manifestations. Each significant variable on the univariate levels was included in a multivariate regression model and adjusted for age, gender, smoking, family history of UC, and UC duration. The odds ratios and confidence intervals at 95% were calculated. All statistical tests were two-sided. *P* values < 0.05 were considered statistically significant.

RESULTS

General characteristics

Figure 1 shows the flow diagram of the inclusion and exclusion criteria of the study cohort. As shown in Table 1, the mean age was 36 ± 8 years, with male predominance (67.1%). The most frequent diagnostic method for hepatobiliary manifestations was liver biopsy (85.6%), followed by MRCP (63.5%), ANCA (62.5%), US (35.9%), and ERCP (6%). Figure 2 shows the frequency of different hepatobiliary manifestations.

Outcomes

After surgery, there were clinical and laboratory improvements (Table 2 and Figure 3). Figure 4 showed that 66.4% of patients had a stationary course. In comparison, 16.8% of patients showed a progressive or regressive course, and there are variations in the courses of different types of hepatobiliary manifestations.

Overall survival and recurrence-free survival using kaplan-meier analysis

The survival rate was 98.8%, 97%, 95.8%, and 94% at 12 mo, 24 mo, 36 mo, and at the end of the follow-up. Regarding the recurrence or progression of symptoms requiring surgery, the recurrence-free rate at 12 mo was 98.2%. At 24 mo, it was 92.8%. At 36 mo, it was 89.2%. At the end of the follow-up, it reached 85% (Figure 5).

Factors affecting regression of hepatobiliary manifestations

Patients with no regression (stationary and progressive course) demonstrated higher use of anti-Tumor necrosis factor (15.1% *vs* 0%, $P = 0.028$), corticosteroids (43.2% *vs* 17.9%, $P = 0.012$), and hepatobiliary treatment (80.6% *vs* 7.1%, $P < 0.001$). In addition, they demonstrated higher percentages of high alanine transaminase (ALT) (74.8 *vs* 39.3%, $P < 0.001$), high aspartate aminotransferase (AST) (75.5% *vs* 57.1%, *P*

Table 1 General characteristics of the studied patients, *n* (%)

General characteristics	
Age (yr) (mean ± SD)	36 ± 8
Sex	
Male	112 (67.1)
Female	55 (32.9)
Smoking	50 (29.9)
Family history of ulcerative colitis	35 (21.0)
Ulcerative colitis disease duration before surgery (mo)	39 (4 - 90)
Treatment of ulcerative colitis	
Mesalazine	137 (82.0)
Sulphasalazine	30 (18.0)
Anti-TNF	21 (12.6)
Corticosteroids	65 (38.9)
Type of PSC[1]	
Large duct PSC	83 (79.8)
Small duct PSC	21 (20.2)
Family history of PSC	14 (8.4)
Diagnosis and treatment of hepatobiliary manifestations	
Diagnostic methods	
ANCA	104 (62.3)
MRCP	106 (63.5)
ERCP	10 (6.0)
Liver biopsy	143 (85.6)
Ultrasound	60 (35.9)
Treatment	
UDCA	106 (63.5)
LMWH	6 (3.6)
Steroid	2 (1.2)
Obeticholic acid	2 (1.2)
Sonar guided drainage	1 (0.6)
Fibrates	2 (1.2)
Azathioprine	1 (0.6)

[1]Percentages calculated based on a total of 104 patients with PSC.
Data were presented as mean ± SD, median (min-max), or number (percentage).
Anti-TNF: Anti-tumour necrosis factor; PSC: Primary sclerosing cholangitis; ANCA: Antineutrophil cytoplasmic antibodies; MRCP: Magnetic resonance cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatography; UDCA: Ursodeoxycholic acid; LMWH: Low-molecular-weight heparin.

= 0.047), high alkaline phosphatase (71.2% *vs* 3.6%, $P < 0.001$), jaundice (67.6% *vs* 46.4%, $P = 0.033$), pruritus (59% *vs* 14.3%, $P < 0.001$), and fever (24.5% *vs* 3.6%, $P = 0.013$). Age ($P = 0.578$), gender ($P = 0.327$), smoking ($P = 0.780$), family history ($P = 0.278$), duration of UC ($P = 0.877$), treatment for UC ($P = 0.601$), family history of PSC ($P = 0.079$), pain ($P = 0.496$), and fatty liver score ($P = 0.121$) were not found to be significantly different (Table 3).

Prediction of no regression of hepatobiliary symptoms

The predictors of no regression were steroid treatment (OR = 3.68, 95%CI = 1.29 – 10.45, $P = 0.015$), high

Table 2 Laboratory and clinical findings before (immediately before surgery) and after surgery (at the end of the study), *n* (%)

		P value
High ALT		
Before surgery	115 (68.9)	< 0.001[1]
After surgery	54 (32.3)	
High AST		
Before surgery	121 (72.5)	< 0.001[1]
After surgery	68 (40.7)	
High alkaline phosphatase		
Before surgery	100 (59.9)	< 0.001[1]
After surgery	63 (37.7)	
High bilirubin		
Before surgery	114 (68.3)	< 0.001[1]
After surgery	74 (44.3)	
Pain		
Before surgery	110 (65.9)	< 0.001[1]
After surgery	71 (42.5)	
Jaundice		
Before surgery	107 (64.1)	< 0.001[1]
After surgery	73 (43.7)	
Pruritus		
Before surgery	86 (51.5)	< 0.001[1]
After surgery	59 (35.3)	
Fever		
Before surgery	35 (21.0)	< 0.001[1]
After surgery	21 (12.6)	
Fatty liver score		
Before surgery	2 (1- 3)	< 0.001[1]
After surgery	1 (0-3)	

[1]Significant bilirubin (normal range < 20 mmol/L) alanine aminotransferase (ALAT) (normal range < 39 U/L, gamma-glutamyl transpeptidase (GGT) (normal range < 42 U/L), alkaline phosphatase (ALP) (normal range 60-275 U/L).
Data were presented as number (percentage) or median (min-max).
ALT: Alanine aminotransferase; AST: Aspartate transaminase ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transpeptidase; ALAT: Alanine aminotransferase.

ALT (OR = 5.39, 95%CI = 2.19 – 13.28, $P < 0.001$), high AST (OR = 2.59, 95%CI = 1.08 – 6.2, $P = 0.032$), high ALP (OR = 73.59, 95%CI = 9.52 – 568.93, $P < 0.001$), high bilirubin (OR = 2.72, 95%CI = 1.16 – 6.4, $P = 0.022$), jaundice (OR = 2.49, 95%CI = 1.07 – 5.8, $P = 0.034$), pruritus (OR = 9.75, 95%CI = 3.12 – 30.5, $P < 0.001$), and fever (OR = 9.7, 95%CI = 1.25 – 75.03, $P = 0.029$). The predictors with their odds ratios and 95% confidence intervals are illustrated in Table 4.

DISCUSSION

To the best of our knowledge, this is the first current study to investigate the course of hepatobiliary symptoms in patients with UC after elective two-stage LRP with IPAA. Colectomy was correlated to a considerably low rate of progressive course in this study of 167 patients: 66.4% for an unchanged course, 16.8% for a regressive course, and 16.8% for a progressive course. There were not many changes for PSC

Table 3 Factors affecting regression of hepatobiliary manifestations, *n* (%)

	Manifestations regression		*P* value
	Yes (*n* = 28)	No (*n* = 139)	
Age (yr)	37 ± 7	36 ± 8	0.578
Sex			
Males	21 (75)	91 (65.5)	0.327
Females	7 (25)	48 (34.5)	
Smoking	9 (32.1)	41 (29.5)	0.780
Family history	8 (28.6)	27 (19.4)	0.278
UC duration (mo)	37 (7-81)	40 (4-90)	0.877
UC treatment			
Mesalazine	22 (78.6)	115 (82.7)	0.601
Sulphasalazine	6 (21.4)	24 (17.3)	
Anti-TNF	0 (0)	21 (15.1)	0.028[1]
Corticosteroids	5 (17.9)	60 (43.2)	0.012[1]
Hepatobiliary manifestations			
Autoimmune hepatitis	1 (3.6)	0 (0)	NA
Fatty liver	18 (64.3)	10 (7.2)	
Gall bladder stone	0 (0)	17 (12.2)	
Liver abscess	0 (0)	1 (0.7)	
Primary biliary cholangitis	1 (3.6)	1 (0.7)	
PSC	0 (0)	104 (74.8)	
Portal vein thrombosis	0 (0)	6 (4.3)	
Reactive hepatitis	8 (28.6)	0 (0)	
Type of PSC			
Large duct PSC	0 (0)	83 (79.8)	NA
Small duct PSC	0 (0)	21 (20.2)	
Family history of PSC	0 (0)	14 (10.1)	0.079
Hepatobiliary treatment	2 (7.1)	112 (80.6)	< 0.001[1]
High ALT	11 (39.3)	104 (74.8)	< 0.001[1]
High AST	16 (57.1)	105 (75.5)	0.047[1]
High Alkaline phosphatase	1 (3.6)	99 (71.2)	< 0.001[1]
High bilirubin	14 (50)	100 (71.9)	0.023[1]
Pain	20 (71.4)	90 (64.7)	0.496
Jaundice	13 (46.4)	94 (67.6)	0.033[1]
Pruritus	4 (14.3)	82 (59)	< 0.001[1]
Fever	1 (3.6)	34 (24.5)	0.013[1]
Fatty liver score	2 (1-3)	2 (2-3)	0.121

[1]Significant.
Data were presented as mean ± SD, number (percentage), or median (min-max).
PSC: Primary sclerosing cholangitis; NA: Not applicable; Anti-TNF: Anti-tumour necrosis factor; UC: Ulcerative colitis; ALT: Alanine aminotransferase; AST: Aspartate transaminase.

Table 4 Multivariate logistic regression analysis to predict no regression of hepatobiliary symptoms

	OR (95%CI)[2]	*P* value
Steroid treatment	3.68 (1.29-10.45)	0.015[1]
High ALT	5.39 (2.19-13.28)	< 0.001[1]
High AST	2.59 (1.08-6.20)	0.032[1]
High ALP	73.59 (9.52-568.93)	< 0.001[1]
High bilirubin	2.72 (1.16-6.4)	0.022[1]
Jaundice	2.49 (1.07-5.8)	0.034[1]
Pruritus	9.75 (3.12-30.50)	< 0.001[1]
Fever	9.7 (1.25-75.03)	0.029[1]

[1]Significant.
[2]Adjusted for age, gender, smoking, family history of UC, and UC duration; OR: Odds ratio; 95%CI: 95% confidence interval.
UC: Ulcerative colitis; ALT: Alanine aminotransferase; AST: Aspartate transaminase ALP: Alkaline phosphatase.

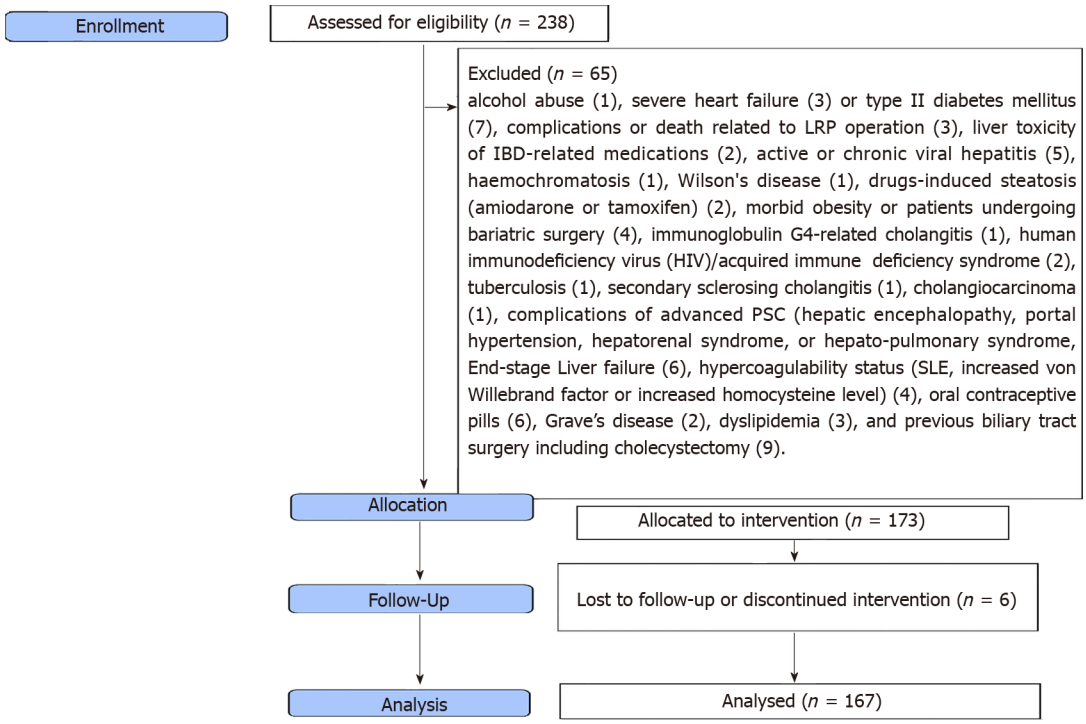

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Figure 1 Flow diagram of inclusion and exclusion criteria of the studied patients. IBD: Inflammatory bowel disease; HIV: Human immunodeficiency virus; SLE: Systemic lupus erythematosus; PSC: Primary sclerosing cholangitis.

(91/104, 87.5%), while the most progressive cases were gallbladder disorders (12/17, 70.5%), and the most regressive cases were fatty liver (18/28, 64.3%).

Many theories have been proposed to explain the course of PSC after LRP with IPAA, including autoimmune phenomena[20], liver-gut crosstalk[21], the influence of saturated fat on changes in the bile acid pool, with an increase in the taurocholic acid[22], and bacterial translocation or absorption of bacterial endotoxins into the portal circulation *via* a chronically inflamed bowel with Kupffer cell activation[23-26]. The effects of colectomy on PSC have been documented in conflicting ways. Colectomy was beneficial according to a study by Lepistö *et al*[6] that stated that PSC severity increased in four (13%) patients, regressed in 15 (50%), and stayed stationary in 11 (37%).Regarding the incidence of progression, our findings are identical to those of this study, but not in the incidence of stationary and regressive courses. Our stationary course of PSC is higher (87.5% *vs* 37%), and none of the cases in our study demonstrated a regression course. We performed liver biopsies and MRCP on all PSC patients prior to surgery and during the follow-up period, whereas the previous study relied on liver function

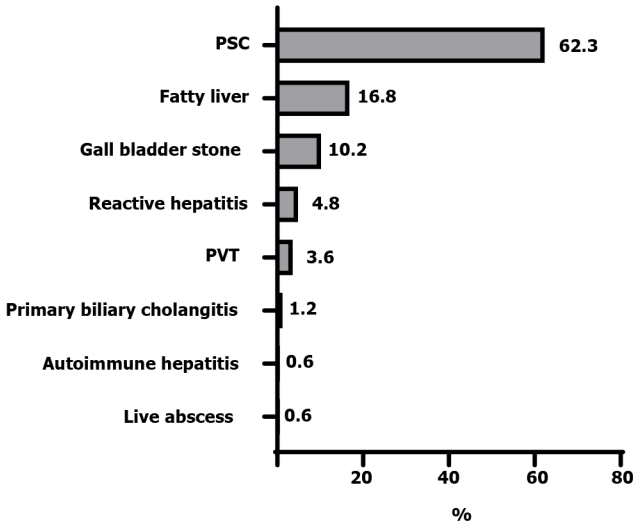

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Figure 2 Hepatobiliary manifestations of the studied patients. PSC: Primary sclerosing cholangitis.; PVT: Portal vein thrombosis.

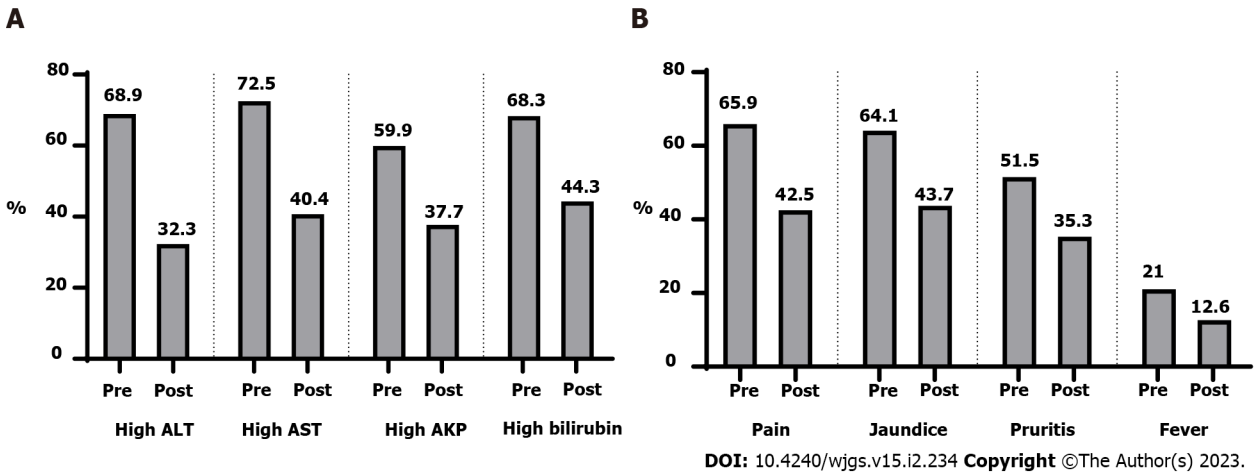

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Figure 3 Laboratory and clinical findings before and after surgery. A: Laboratory findings before and after surgery; B: Clinical findings before and after surgery. ALT: Alanine transaminase; AST: Aaspartate aminotransferase; AKP: Alkaline phosphatase.

for diagnosis and did not perform liver biopsies on all patients. Furthermore, our study had a large number of patients, and cases lost to follow-up were excluded from our study (in comparison to earlier study). Our study's higher stable course of PSC may be attributable to Ursodeoxycholic acid (UDCA) (15 mg/kg/day) in all patients after LRP, whereas only 9/30 patients had UDCA following colectomy in the prior study. Treatment with UDCA has a beneficial effect on the course of PSC; studies have demonstrated efficacy[27-30]. A good proportion of PSC cases not progressing to a more severe form is associated with the absence of pouchitis in all of our patients' ileoanal pouch anastomosis. The study corroborated our conclusion that pouchitis may aggravate PSC[31].

In contrast, another study by Cangemi *et al*[7] stated that proctocolectomy exerted no beneficial effect on PSC, the stage of which has remained unchanged or has progressed with no statistically significant improvements in liver function test values[7]. On the contrary, our results showed a statistically significant improvement in liver function test values after surgery. Variations in the results could be attributed to methodological differences, diagnostic procedures (liver biopsy in 71% of cases only), and the number of cases. Perhaps, the effect of LRP on PSC is beneficial, as evidenced by the higher percentage of stable disease and smaller progressive cases. Another study by Treeprasertsuk *et al*[32] discovered that proctocolectomy had no benefit and a lower survival rate than expected. They experienced only progressive courses with higher mortality rates; LCF, acute cholangitis, right hepatic vein thrombosis with liver infarcts, and many cases that needed liver transplantation. The poor prognosis could be attributed to the study's small sample size, open approach, surgical difficulties, and heterogeneity in selection criteria, particularly the inclusion of cirrhotic patients with low platelet counts and albumin levels.

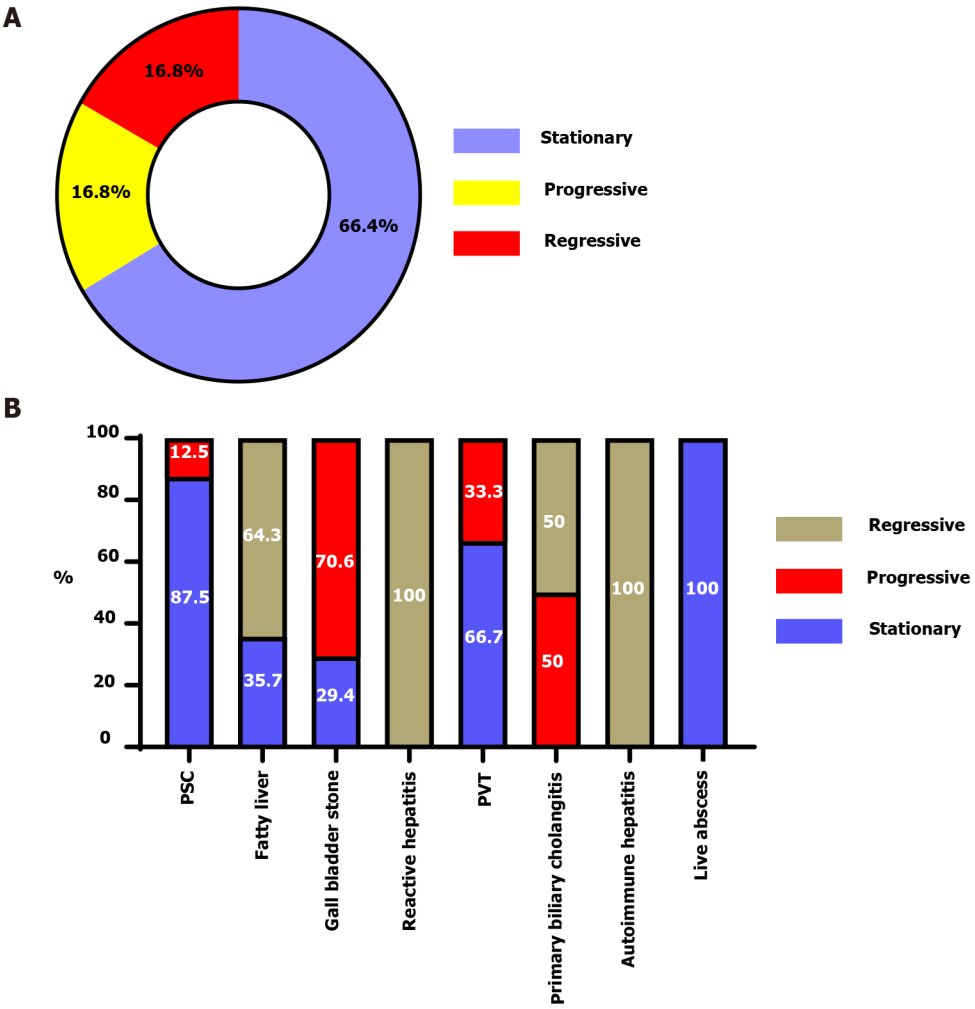

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Figure 4 The course and outcome of each hepatobiliary manifestations. A: Hepatobiliary manifestations course in the studied patients; B: The outcome for each hepatobiliary manifestation. PSC: Primary sclerosing cholangitis.; PVT: Portal vein thrombosis.

In patients with LRP, resection of a short segment of the ileum and the entire colon inhibits bile acid absorption, resulting in supersaturation of biliary cholesterol[8], pouch metaplasia with decreased primary bile acid absorption[33], and delayed gall bladder emptying[34]. We found a high incidence of recurrent biliary colic requiring surgery (12/17, 70.5%), while the remaining five cases had a stationary course without symptoms. Concomitant cholecystectomy with LRP may prolong the operative time (nearly 40 min) and add more risk of complications. However, it saves the patient from going through more difficult cholecystectomy operation /gallstone complications in the future[35]. There were no cases of gallbladder cancer in our study. This is because most gallstone cases develop symptoms following LRP, necessitating cholecystectomy. Another problem is the short duration of follow-up (4 years).

Multiple studies showed that proctocolectomy could help with fatty liver regression[7,36,37]. We agree with prior evidence that proctocolectomy is favourable for NAFLD. LRP had a positive effect on fatty liver, with 18 cases (18/28, 64%) showing complete regression to normal liver and the remaining ten patients (36%) showing a stationary course. This improvement is due to improvements in malnutrition, anaemia, and a reduction in corticosteroid dosage during the surgical follow-up period, as supported by a study[38]. NAFLD progression was not observed in our cases due to the absence of pouchitis. As a result, we concluded that proctocolectomy plays a definitive role in the management of NAFLD-complicating UC, as evidenced by radiology and liver biopsy (improvement of fatty liver score from a median of 2 (range 1-3) in preoperative biopsies to a median of 1 (range 0-3) in postoperative biopsies).

High incidence of portal vein thrombosis (PVT) in IBD may be due to increased factors V and VIII levels, platelet counts, fibrinogen levels, or decreased antithrombin III levels[39,40]. In our study, we identified six patients with PVT: Four cases before surgery, no recurrence after surgery, and two patients who developed PVT after surgery. One of the two postoperative PVT cases exhibited partial portal vein obstruction, which was treated with anticoagulants. In contrast, the second case exhibited complete obstruction of PVT with intestinal gangrene, necessitating resection of the majority of the

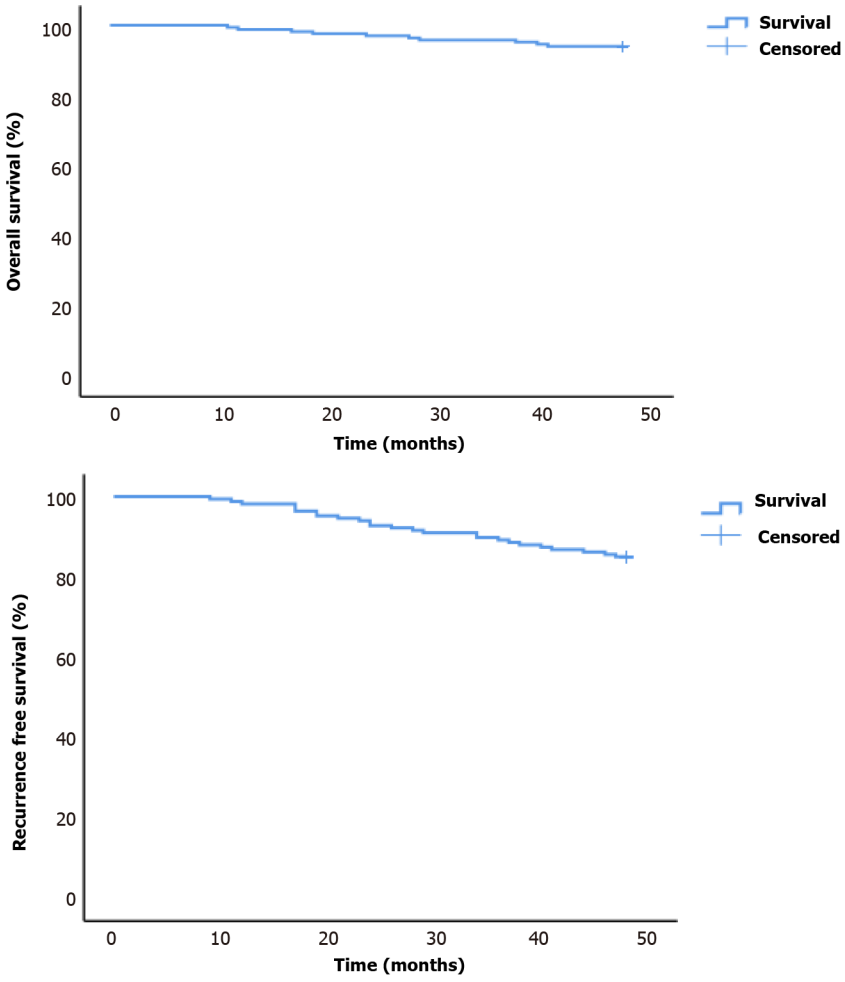

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Figure 5 Overall and recurrence-free survival of the studied patients.

small intestine with short bowel syndrome, and died two months later. The low incidence of postoperative PVT can be due to the small number of cases, the routine use of low molecular heparin in the postoperative period for six months in all cases according to the current society guidelines and expert opinion[40], absence of pouchitis which increases the incidence of PVT[41], and the possible occurrence of PVT not associated with specific symptoms or asymptomatic[42]. The use of abdominal ultrasound and colored Doppler at regular intervals unquestionably aided in detecting asymptomatic cases. We concluded that proctocolectomy decreases the incidence but not the severity of PVT with an unfavorable outcome, despite the small number of cases, with a mortality rate of 50% among those who developed PVT is similar to the findings of other studies[43].

Two isolated PBC accidentally discovered cases were included; one regressed to normal liver condition, while the other progressed to liver cell failure and required liver transplantation without mortality. We thought that the excellent prognosis was due to obeticholic acid that improved the course of the disease[44], removal of the colon, the site of antibody production, which helped make the prognosis better after surgery, and absence of pouchitis[9].

One patient with UC developed a liver abscess before surgery, whereas no such case was reported after LRP. We concur with the pathogenesis that liver abscess may be caused by antibodies produced by patients with UC attacking the liver, resulting in necrosis and abscess formation that was negative for bacteria[45]. Proctocolectomy permanently eliminates the site of antibody production. Furthermore, postoperative corticosteroids help to prevent recurrence[46]. Proctocolectomy prevents liver abscesses, according to our findings.

One case of AIH was diagnosed before surgery and regressed to normal following LRP with a favourable prognosis, demonstrating the positive effects of proctocolectomy[47]. The favorable prognosis of our patient was likely due to the removal of the inflamed colon and steroid-based immunosuppressive therapy[10].

An earlier study confirmed the efficacy of proctocolectomy for nonspecific reactive hepatitis[7]. In accordance with the previous study's findings, we diagnosed 8 patients with nonspecific reactive hepatitis, and complete regression in every case was confirmed.

Strengths and limitations

This is a large prospective multicenter study of different hepatobiliary manifestations assessment after LRP with a relatively long duration of patient follow-up. We also included comprehensive clinical points evaluating different courses of hepatobiliary manifestations. A prospective study prevents selection bias with accurate results that could be generalized.

However, our study has some limitations. One is the lack a control group of patients that were not operated on. Therefore, this study did not handle the severity of preoperative colitis and its effect on the course of hepatobiliary manifestations in the postoperative period. Another limitation is that it did not evaluate the disease course after liver transplantation. Another limitation is that we did not evaluate the treatment of both UC and hepatobiliary manifestations during the postoperative course. Finally, we did not evaluate the causes of the high incidence of symptomatic gallbladder stones.

CONCLUSION

This is a large prospective multicenter study of different hepatobiliary manifestations assessment after LRP with a relatively long duration of patient follow-up. We also included comprehensive clinical points evaluating different courses of hepatobiliary manifestations. A prospective study prevents selection bias with accurate results that could be generalized.

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ARTICLE HIGHLIGHTS

Research background

Inflammatory bowel disease (IBD) is expected to affect 1% of the population over the next decade. Hepatobiliary manifestations constitute one of the most common extraintestinal manifestations in IBD. Primary sclerosing cholangitis (PSC), autoimmune hepatitis, fatty liver, cholelithiasis, primary biliary cholangitis, portal vein thrombosis, and hepatic abscess are the most prevalent hepatobiliary manifestations of ulcerative colitis (UC). Most UC patients can be managed with medications, but minorities require proctocolectomy.

Research motivation

Two-stage laparoscopic proctocolectomy (LRP) with ileal pouch-anal anastomosis (IPAA) is a cure for UC, but its effect on hepatobiliary diseases is controversial.

Research objectives

Therefore, we conducted a prospective observational study to examine the effects of LRP with IPAA on hepatobiliary symptoms to evaluate the role of surgery in preventing or ameliorating liver damage from the disease progression.

Research methods

This is a prospective observational study on 167 patients with hepatobiliary manifestations who underwent two-stage elective LRP with IPAA for UC We examined the effects of LRP with IPAA on hepatobiliary symptoms to evaluate the role of surgery in preventing or ameliorating liver damage from the disease progression.

Research results

The course of hepatobiliary manifestations after surgery is improved in most forms. Most PSC patients had a stable course, Two-thirds of fatty liver patients showed a regressive course with an improved survival rate at the end of the study.

Research conclusions

Our study emphasized the positive and improving effects of surgery on hepatobiliary manifestations in patients with UC.

Research perspectives

Further studies are required in a larger sample size to evaluate the effect of surgery on different forms of hepatobiliary manifestations in patients with UC. further studies are required to compare the effect of surgery and effects of medical treatment.

FOOTNOTES

Author contributions: Habeeb TAAM is the corresponding author and is responsible for patient recruitment; Habeeb TAAM, Hussain A, Podda M, Cianci P, Ramshaw B, Safwat K, Amr WM, Wasefy T, Fiad AA, Mansour MI, Moursi AM, Osman G, Qasem A, Fawzy M, Alsaad MIA, Kalmoush A, Nassar MS, Mustafa FM, Badawy MHM, Hamdy A, Elbelkasi H, Mousa B, Metwalli AM, Mawla WA, Elaidy MM, Baghdadi MA, Raafat A shared data collection, data analysis, study design, and writing up the first draft and final form of the manuscript; All authors accept the final version of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Zagazig University Institutional Review Board (Approval No. ZU IRB#9841).

Informed consent statement: Informed written consent was obtained from the patient and her family for publication of this report and any accompanying images.

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SYSTEMATIC REVIEWS

Hypophosphatemia as a prognostic tool for post-hepatectomy liver failure: A systematic review

Romualdas Riauka, Povilas Ignatavicius, Giedrius Barauskas

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Peer-review model: Single blind

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Abstract

BACKGROUND

Post-hepatectomy liver failure (PHLF) is one of the main causes of postoperative mortality and is challenging to predict early in patients after liver resection. Some studies suggest that the postoperative serum phosphorus might predict outcomes in these patients.

AIM

To perform a systematic literature review on hypophosphatemia and evaluate it as a prognostic factor for PHLF and overall morbidity.

METHODS

This systematic review was performed according to preferred reporting items for systematic reviews and meta-analyses statement. A study protocol for the review was registered in the International Prospective Register of Systematic Reviews database. PubMed, Cochrane and Lippincott Williams & Wilkins databases were systematically searched up to March 31, 2022 for studies analyzing postoperative hypophosphatemia as a prognostic factor for PHLF, overall postoperative morbidity and liver regeneration. The quality assessment of the included cohort studies was performed according to the Newcastle-Ottawa Scale.

RESULTS

After final assessment, nine studies (eight retrospective and one prospective cohort study) with 1677 patients were included in the systematic review. All selected studies scored ≥ 6 points according to the Newcastle-Ottawa Scale. Cutoff values of hypophosphatemia varied from < 1 mg/dL to ≤ 2.5 mg/dL in selected studies with ≤ 2.5 mg/dL being the most used defining value. Five studies analyzed PHLF, while the remaining four analyzed overall complications as a main outcome associated with hypophosphatemia. Only two of the selected studies analyzed postoperative liver regeneration, with reported better postoperative liver regeneration in cases of postoperative hypophosphatemia. In three studies hypophosphatemia was associated with better postoperative

outcomes, while six studies revealed hypophosphatemia as a predictive factor for worse patient outcomes.

CONCLUSION

Changes of the postoperative serum phosphorus level might be useful for predicting outcomes after liver resection. However, routine measurement of perioperative serum phosphorus levels remains questionable and should be evaluated individually.

Key Words: Hypophosphatemia; Post-hepatectomy liver failure; Liver regeneration; Serum phosphorus; Literature review

Core Tip: A systematic literature review on hypophosphatemia and its value as a prognostic factor for post-hepatectomy liver failure and overall morbidity after liver surgery was performed. In three of nine included studies hypophosphatemia was associated with better postoperative outcomes, while six studies revealed hypophosphatemia as a predictive factor for worse patient outcomes. Data show that postoperative hypophosphatemia and changes of postoperative serum phosphorus might be used as a predictor after liver surgery. However, to be implemented in clinical practice as routine measurement more studies and data are needed.

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INTRODUCTION

Post-hepatectomy liver failure (PHLF) is a severe and lethal complication occurring in patients after partial liver resection and defined by derangement of liver function, coagulopathy, high lactate and encephalopathy[1]. Incidence of PHLF varies from 1% to 32% with reported perioperative mortality up to 60%[2,3]. PHLF is a significant complication and one of the main causes of mortality in patients after liver resection even with advancing surgical techniques and perioperative management[4,5]. A wide variety of preoperative predictive factors, such as patient-related (male sex, older age, obesity), hepatic parenchyma-related (cirrhosis, fibrosis, steatosis, preoperative chemotherapy, cholestasis), surgery-related (high blood loss, extended liver resection, prolonged inflow occlusion and operating time) and postoperative course-related (hemorrhage, infections), might contribute to PHLF[4,6,7]. Despite various scoring systems for standardizing PHLF and predicting postoperative morbidity and mortality, early identification of patients, who will develop PHLF remains challenging[8].

Regenerative potential of hepatocytes and the compensatory capacity of the functional liver remnant allow resection of up to 80% of the healthy liver[9,10]. Patients at risk of PHLF do not exhibit a normal regenerative response and may present with early disorders in normal metabolic responses, such as failure to utilize serum phosphorus postoperatively[11,12]. Consequently, absence of a decrease in postoperative serum phosphorus might be an early predictive factor of PHLF. Organic phosphate is part of several important biological processes such as signal transduction, energy transfer and formation of high-energy bonds and is critical to multiple metabolic processes[13]. Blood phosphate levels are regulated by various organs such as bone, parathyroid glands, small intestine, kidneys and liver, thus the pathophysiology of postoperative hypophosphatemia is multifactorial[14,15].

According to Woodard *et al*[16] liver tissue contains approximately 0.3% phosphorus by weight. Low serum phosphate levels after major liver resection might be associated with removal of liver mass containing phosphorus, resulting in blood phosphate movement into the hepatocytes and, subsequently, better liver regeneration[17,18]. Some studies suggested that postoperative serum hypophosphatemia might predict better outcomes in patients with acute liver failure[19,20]. Absence of hypophosphatemia after major liver resections might help identify patients with an increased chance of PHLF.

Several studies present contradictory results. Postoperative hypophosphatemia was reported to be associated with a higher risk of postoperative complications, thus refuting the previous statements[21-23]. It is hypothesized that liver regeneration after major hepatectomy results in serum phosphorus replenishing intracellular phosphorus levels needed for ATP synthesis and further regeneration processes. Therefore, low serum phosphorus levels impair liver regeneration, resulting in liver

dysfunction and failure[24,25]. Therefore, data on postoperative hypophosphatemia as a prognostic factor for PHLF are yet to be systemically analyzed. Our aim was to perform a systematic literature review of hypophosphatemia as a prognostic tool for PHLF and overall morbidity.

MATERIALS AND METHODS

This systematic review was performed according to the preferred reporting items for systematic reviews and meta-analyses statement[26]. A study protocol for the review was registered in the International Prospective Register of Systematic Reviews database: CRD42020197717.

Search strategies

PubMed, Cochrane, Lippincott Williams & Wilkins and *Reference Citation Analysis* databases were searched up to March 31, 2022. Our search terms included: (hypophosphatemia OR phosphorus) AND (hepatectomy OR liver resection) AND (post-operative hepatic insufficiency OR mortality OR complications OR liver failure OR liver insufficiency). After checking titles and abstracts, inappropriate studies were excluded. The remaining full-text articles were reviewed carefully. Additionally, reference lists of selected articles were reviewed for eligible studies.

Study selection

Inclusion criteria for selected studies were: (1) Studies written in English language; and (2) Studies analyzing postoperative hypophosphatemia as a prognostic factor for PHLF, overall postoperative morbidity and liver regeneration (patients after different types of liver resections, including living-donor liver donation). Exclusion criteria were as follows: (1) Abstracts, case reports, editorials, letters, systematic reviews and meta-analyses; (2) Studies with incomplete data for further analysis (studies with no reported postoperative complications or phosphorus, studies analyzing postoperative hypophosphatemia in liver transplant recipients); (3) Duplicate studies; and (4) Studies in languages other than English.

Data extraction and quality assessment

Selected studies were evaluated by two investigators independently, and necessary data was extracted including name of the first author, year of publication, type of study, number of patients included in the study, study population (type of surgery performed), postoperative phosphorus, main and secondary outcomes (PHLF, overall postoperative morbidity and liver regeneration) and their correlation with postoperative hypophosphatemia. In cases of disagreement, differences in opinion were resolved by a third author.

The quality assessment of the included cohort studies was performed according to the Newcastle-Ottawa Scale[27]. Evaluation ranged from 0 to 9 points, and studies with a Newcastle-Ottawa Scale score of ≥ 6 were considered as high quality. Due to heterogeneity of included studies and analyzed populations meta-analysis and subgroup analysis was not conducted.

RESULTS

PubMed, Cochrane, and Lippincott Williams & Wilkins databases were searched, and 264 articles were initially retrieved. After removing 45 duplicates, 219 articles were left for screening. One hundred ninety-six articles were removed after screening titles and abstracts due to inappropriate topics, leaving 23 full-text articles for further assessment. After final assessment, nine studies (eight retrospective and one prospective cohort study) with 1677 patients were included in the systematic review (Table 1). The selection process is summarized by preferred reporting items for systematic reviews and meta-analyses flow diagram (Figure 1).

The majority of included studies were characterized by wide variation (inconsistency) of the extent of performed liver resections[11,21-23,28-30]. Indications for liver surgery [colorectal cancer liver metastases, metastatic neuroendocrine tumors, cholangiocarcinoma, hepatocellular carcinoma, sarcoma, metastases of other primary tumors and benign diseases (hemangiomas, cysts, primary sclerosing cholangitis)] were also different. Patients with local ablation of liver tumors were included in one study [21]. Hypophosphatemia after living-donor liver donation was analyzed in 2 studies[24,31]. Quality of the selected studies was evaluated by two investigators independently according to the Newcastle-Ottawa Scale. All selected studies scored ≥ 6 points with the of the studies (6) scoring 7 points, making them eligible to be included in further analysis (Table 1).

Postoperative outcomes

PHLF as the main outcome associated with postoperative hypophosphatemia was analyzed in five out of nine included studies[11,24,29-31]. Liver failure in selected studies was defined using 50-50 criteria

Table 1 Characteristics of included studies

Ref.	Study type	NOS	*N*	Study population	Cutoff phosphorus level	Main outcomes	Results	Conclusions
George *et al* [28], 1992	Retrospective	6	44	Liver resections	≤ 2.5 mg/dL	Postoperative complications	Profound HP group had higher frequency rate of postoperative complications (P < 0.005)	Hypophosphatemia increased risk of postoperative complications
Buell *et al* [21], 1998	Retrospective	6	35	Liver resections and cryosurgery	< 2.5 mg/dL	Postoperative complications	More complications in HP group (80% *vs* 28%; P < 0.05)	Hypophosphatemia increased risk of postoperative complications
Giovannini *et al*[22], 2002	Retrospective	7	59	Liver resections	≤ 2.5 mg/dL	Postoperative complications	HP (< 1.5 mg/dL) associated with increase in rate of complications (P < 0.001)	Hypophosphatemia increased risk of postoperative complications
Smyrniotis *et al*[23], 2003	Prospective	7	30	Liver resections	< 1.5 mg/dL	Postoperative complications	Patients with HP (< 1.5 mg/dL) had more complications	Hypophosphatemia increased risk of postoperative complications
Yuan *et al* [24], 2011	Retrospective	6	132	LDLT	< 1 mg/dL	Liver insufficiency	MV binary logistic regression: Postoperative nadir serum phosphorus (P = 0.01) was independently related to hepatic functional impairment (ß = -5.927, odds ratio 0.003; 95%CI: 0.000-0.239). Postoperative nadir of serum phosphorus < 1 mg/dL (P = 0.006, AUC = 0.731) led to more severe hepatic dysfunction	Hypophosphatemia increased risk of postoperative liver insufficiency
Squires *et al* [11], 2014	Retrospective	7	719	Liver resections	< 2.4 mg/dL	Liver insufficiency	UV: Patients with POD2 phosphorus > 2.4 demonstrated a significantly increased risk of PHLF (P = 0.020). MV: POD2 phosphorus > 2.4 mg/dL remained independently associated with a significantly increased risk of PHLF (HR = 1.78; 95%CI: 1.02-3.17; P = 0.048)	Absence of postoperative hypophosphatemia increased risk of postoperative complications and liver insufficiency
Hallet *et al* [29], 2016	Retrospective	7	402	Liver resections	≤ 2.01 mg/dL	Liver insufficiency	More patients with HP recovered from LI compared to those with NP (90.9% *vs* 65.0%, P = 0.03)	Postoperative hypophosphatemia associated with better recovery from PHLF
Margonis *et al*[30], 2016	Retrospective	7	95	Liver resections	≤ 2.4 mg/dL	Liver insufficiency	LI was lower in patients with HP (P = 0.01). MV analysis: Normal/high serum phosphorus on POD2 (HR = 3.24, 95%CI: 1.23-8.56; P = 0.02) remained independently associated with a worse OS	Postoperative hypophosphatemia associated with better OS, better liver regeneration and lower rate of liver insufficiency
Serrano *et al* [31], 2019	Retrospective	7	161	LDLT	≤ 2.5 mg/dL	Liver insufficiency	LI 1.77 mg/dL *vs* no LI 2.01 mg/dL for no LI cohort at a median of 1.6 d (38 h) postoperatively (P = 0.003). ROC postoperative phosphate levels through the first 38 h best predicted LI (sensitivity, 90%; specificity, 55.6%; positive predictive value, 11.8%; negative predictive value, 98.8%; AUC, 0.731)	Hypophosphatemia increased risk of postoperative liver insufficiency

AUC: Area under the receiver operating characteristic curve; CI: Confidence interval; HP: Hypophosphatemia; HR: Hazards ratio; LDLT: Living donor liver transplantation; LI: Liver insufficiency; MV: Multivariate; NP: Normophosphatemia; OS: Overall survival; PHLF: Post-hepatectomy liver failure; POD: Postoperative day; NOS: Newcastle-Ottawa Scale; ROC: Receiver operating characteristic; UV: Univariate.

introduced by Balzan *et al*[8] [prothrombin time < 50% and serum bilirubin > 50 μmol/L on postoperative day 5 (the 50-50 criteria)] or Mullen *et al*[32] (peak postoperative serum bilirubin > 7.0 mg/dL). In the four remaining studies, general postoperative complications (intraabdominal or

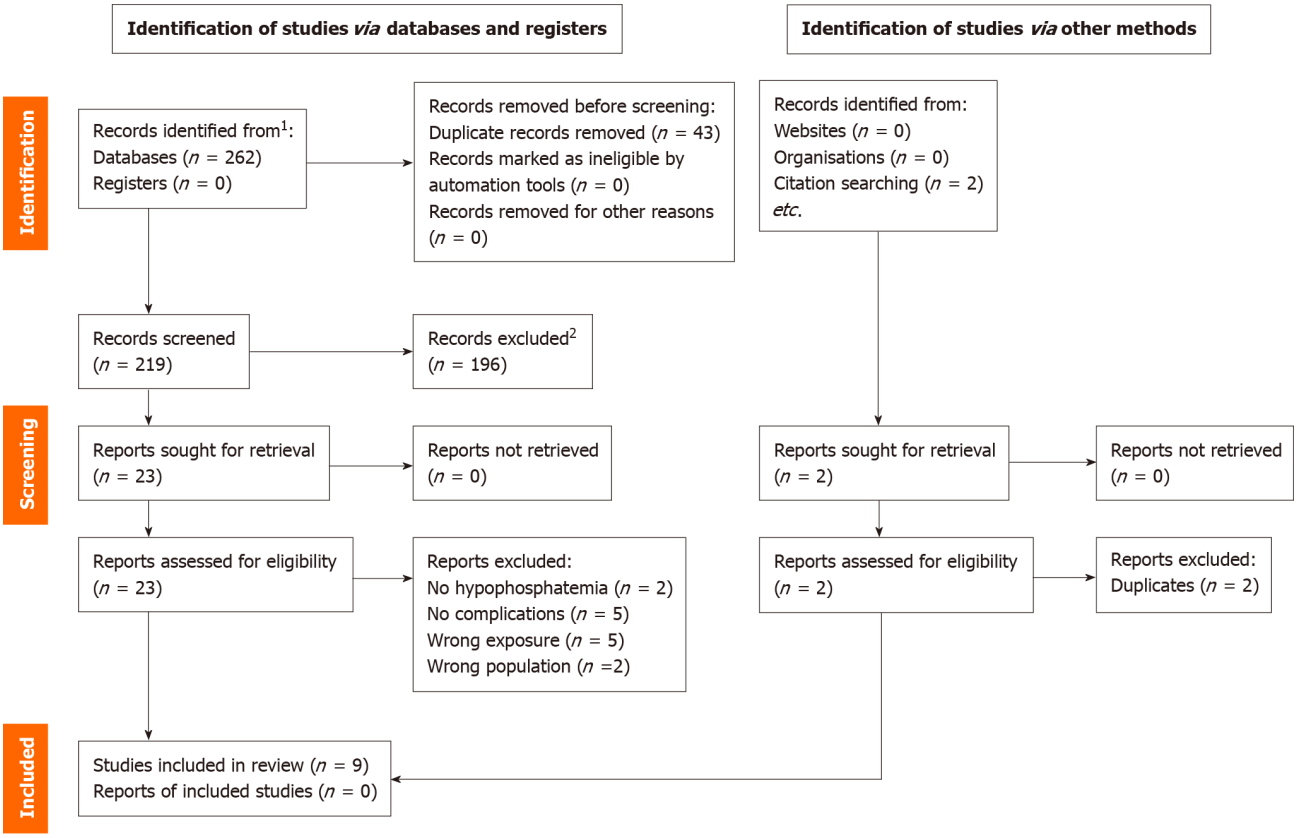

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Figure 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram for new systematic reviews, which included searches of databases, registers and other sources. [1]PubMed, Cochrane, Lippincott Williams & Wilkins and *Reference Citation Analysis* databases. [2]Recording excluded due to wrong topic, wrong language, unsuitable title, abstracts and case reports.

gastrointestinal bleeding, intraabdominal abscess, pneumonia, pleural effusion, pancreatitis, biliary fistula, neurological disorders, *etc*) with no or inadequate data on liver failure were analyzed[21-23,28]. Only two of the included studies analyzed serum phosphorus levels in relation to postoperative liver regeneration[29,30]. The extensive analysis of the included studies is presented in Table 1.

Cutoff values of hypophosphatemia varied from < 1 mg/dL to ≤ 2.5 mg/dL in selected studies with ≤ 2.5 mg/dL being the most used defining value (3 studies[22,28,31]). Only four of the included studies utilized hypophosphatemia values based on previous studies[11,28-30]. Phosphate concentration in the majority of the selected studies was measured daily starting with postoperative day 1 and was measured up to 10 d postoperatively with days 1, 2 and 3 after the operation being the most popular. In two studies the timing of serum phosphorus measurements was not reported[24,29].

DISCUSSION

This is the first systematic review including 1677 patients and analyzing postoperative serum phosphorus levels in correlation with PHLF and general surgical complications. In our systematic review we found that changes in postoperative serum phosphorus concentration may be useful for predicting outcomes of patients after extensive liver resections. However, each case and result need to be analyzed individually.

One of the first published studies on the topic reported that patients with more severe hypophosphatemia experienced a significantly higher rate of postoperative complications compared to patients with milder levels of phosphorus decrease[28]. Similar results were reported by Buell *et al*[21] analyzing clinical implications of hypophosphatemia following major hepatic resection or cryosurgery for liver tumors. The incidence of surgery-related complications was greater in patients with hypophosphatemia compared to patients without phosphorus decrease. Interestingly, hypophosphatemia did not increase complication rates or intensive care and hospital stay in patients undergoing cryotherapy. Two other studies by Giovannini *et al*[22] and Smyrniotis *et al*[23] reported similar outcomes. Patients with severe hypophosphatemia developed more complications and experienced a longer intensive care stay compared with patients with milder hypophosphatemia levels.

Similarly, Yuan *et al*[24] reported postoperative serum phosphorus nadir was independently associated with severe hepatic dysfunction. Authors of the study hypothesized that low serum phosphorus levels may be responsible for impaired intracellular regeneration processes resulting in further hepatic dysfunction. Hypophosphatemia as a predictive factor for PHLF was reported in a recent study by Serrano *et al*[31]. Patients with liver failure had significantly lower serum phosphorus levels at a median 38 h after operation.

In contrast, Squires *et al*[11], Hallet *et al*[29] and Margonis *et al*[30] revealed that patients with an absence of postoperative hypophosphatemia were more likely to experience higher rates of complications, liver insufficiency and even worse overall survival. Additionally, Hallet *et al*[29] and Margonis *et al*[30] reported better recovery from PHLF in patients with hypophosphatemia compared to patients with normophosphatemia. Only two of the selected studies (Hallet *et al*[29] and Margonis *et al*[30]) analyzed liver regeneration and reported better postoperative liver regeneration in cases of postoperative hypophosphatemia. The association between liver regeneration and postoperative serum hypophosphatemia relates to high energy consumption during the hepatocyte regeneration processes. Serum phosphorus is primarily used to foster liver recovery processes, such as DNA synthesis, reaching its maximum during the first 72 h after liver resection; however, it takes about 7 d for bone phosphorus to be mobilized into the blood[13,29,30,33].

Moreover, according to Margonis *et al*[30], patients who developed hyperphosphatemia after surgery had a worse overall survival, a higher risk of death and a worse liver regeneration index reaching up to 7 mo after liver surgery with exact mechanisms still uncertain. It is of interest to mention, that the latter three studies advocating the idea of a positive influence of hypophosphatemia on liver regeneration were published in the last 5 years and analyzed more than 70% (n = 1216) of patients from all included studies (n = 1677).

By analyzing the proposed mechanisms of phosphorus influence, it becomes evident that both hypotheses are based on the fact that phosphorus is needed to foster regenerative response. The difference is in the details. The first theory emphasizes the failure of cells to utilize phosphorus, and the second theory proposes that there is a lack of phosphorus to be utilized. Data on the dynamics of phosphorus concentrations in the pre- and postoperative periods could help understand the meaning of hypophosphatemia. Unfortunately, only two of the included studies provided data on preoperative phosphorus levels[22,24].

Phosphate is an essential element, necessary in a number of physiological processes such as skeletal mineralization and development, nucleotide structuring, membrane composition, *etc*[34,35]. Most phosphorus (85%) in the human body is found in the skeleton and maintained through the bone-kidney-intestine homeostatic network[36]. The outcome of this homeostatic network is a dynamic balance between urinary phosphate losses, intestinal phosphate absorption and reabsorption from bones, regulated by parathyroid hormone, fibroblast growth factor 23 and vitamin D.

The main reasons of non-surgery related hypophosphatemia are redistribution of phosphorus from extracellular fluids into cells, decreased intestinal absorption, high renal phosphate excretion and decreased proximal reabsorption with reduced activation of vitamin D[37]. For many years, increased liver regeneration and associated metabolic processes were thought to be the main reason of surgery-related hypophosphatemia. However, some authors have suggested that the severity of postoperative hypophosphatemia may not depend on just the extent of serum phosphorus uptake by the regenerating liver[13]. Studies by Salem *et al*[38] and Nafidi *et al*[39] revealed that phosphate renal loss was a more credible cause of postoperative hypophosphatemia than phosphorus consumption by the regenerating liver in their patients. Nomura *et al*[40] reported that liver surgery-related hypophosphatemia and hyperphosphaturia were associated with abnormal urinary nicotinamide metabolism in the liver and kidneys. The results were drawn from *in vitro* studies with opossum kidney cells and an animal model. However, exact mechanisms and factors of renal phosphaturia are yet to be investigated, analyzed and adapted for clinical use. Further studies are needed to better understand homeostasis of phosphorus to optimize patient outcomes.

The present systematic review has several limitations. First, only nine studies with a relatively small number of patients were eligible for inclusion in this systematic review. Second, eight out of nine included studies were of a retrospective design with a potential source of bias, while only one was a prospective cohort study. Differences between size of the investigated groups, different phosphorus cutoff values, the extent of liver resection not clearly defined, varying primary and secondary outcomes, varying statistical methods and phosphorus measurement days and intervals were other factors further contributing to increased heterogeneity. Finally, due to high heterogeneity between included studies there were not enough data to perform the appropriate meta-analysis.

CONCLUSION

We present the first systematic review analyzing postoperative serum phosphorus correlation with PHLF and general surgical complications. Changes in postoperative serum phosphorus concentrations may be useful for predicting outcomes of patients after extensive liver resections. However, it is

inconclusive whether the incidence or absence of post-hepatectomy hypophosphatemia is related to a better postoperative outcome. In our opinion, routine measurement of perioperative serum phosphorus levels remains questionable, and results should be evaluated individually to prevent PHLF and reduce overall liver surgery-related patient morbidity.

ARTICLE HIGHLIGHTS

Research background

Post-hepatectomy liver failure (PHLF) is a severe and serious complication occurring after high-volume liver resections and presenting with high perioperative mortality rates. There are contradictory results regarding serum phosphorus association with postoperative outcomes. Changes in serum phosphorus levels might predict development of PHLF and improve its treatment results.

Research motivation

Data of serum phosphorus level changes as a prognostic tool for PHLF is scarce and needs to be systemically analyzed.

Research objectives

To perform the first systematic review analyzing hypophosphatemia as a prognostic tool for PHLF and general complications.

Research methods

Study protocol for the review was registered in the International Prospective Register of Systematic Reviews database (D42020197717). This systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analyses guidelines. PubMed, Cochrane and Lippincott Williams & Wilkins databases were searched up to March 31, 2022 using relevant search terms.

Research results

After thorough research, nine studies with 1677 patients were included in the systematic review. The majority of the included studies were retrospective. However, due to high heterogeneity between included studies there were not enough data to perform appropriate the meta-analysis.

Research conclusions

Changes of postoperative serum phosphorus concentration may be useful for predicting outcomes of patients after extensive liver resections. However, the decision to measure and interpret results needs to be considered individually with routine phosphorus level measurements, and its benefits remain questionable.

Research perspectives

Further high volume, non-randomized studies are needed to better analyze postoperative hypophosphatemia as a predictive factor for PHLF and general surgical outcomes.

FOOTNOTES

Author contributions: Riauka R, Ignatavicius P and Barauskas G contributed to study design and conception, data collection, analysis and interpretation and writing the draft of the manuscript; and all authors read and approved the published version of the manuscript.

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META-ANALYSIS

Network meta-analysis of the prognosis of curative treatment strategies for recurrent hepatocellular carcinoma after hepatectomy

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Abstract

BACKGROUND

Recurrent hepatocellular carcinoma (rHCC) is a common outcome after curative treatment. Retreatment for rHCC is recommended, but no guidelines exist.

AIM

To compare curative treatments such as repeated hepatectomy (RH), radiofrequency ablation (RFA), transarterial chemoembolization (TACE) and liver transplantation (LT) for patients with rHCC after primary hepatectomy by conducting a network meta-analysis (NMA).

METHODS

From 2011 to 2021, 30 articles involving patients with rHCC after primary liver resection were retrieved for this NMA. The Q test was used to assess heterogeneity among studies, and Egger's test was used to assess publication bias. The efficacy of rHCC treatment was assessed using disease-free survival (DFS) and overall survival (OS).

RESULTS

From 30 articles, a total of 17, 11, 8, and 12 arms of RH, RFA, TACE, and LT subgroups were collected for analysis. Forest plot analysis revealed that the LT subgroup had a better cumulative DFS and 1-year OS than the RH subgroup, with an odds ratio (OR) of 0.96 (95%CI: 0.31-2.96). However, the RH subgroup had a better 3-year and 5-year OS compared to the LT, RFA, and TACE subgroups. Hierarchic step diagram of different subgroups measured by the Wald test yielded the same results as the forest plot analysis. LT had a better 1-year OS (OR: 1.04, 95%CI: 0.34-03.20), and LT was inferior to RH in 3-year OS (OR: 10.61, 95%CI: 0.21-1.73) and 5-year OS (OR: 0.95, 95%CI: 0.39-2.34). According to the predictive P score evaluation, the LT subgroup had a better DFS, and RH had the

best OS. However, meta-regression analysis revealed that LT had a better DFS ($P < 0.001$) as well as 3-year OS ($P = 0.881$) and 5-year OS ($P = 0.188$). The differences in superiority between DFS and OS were due to the different testing methods used.

CONCLUSION

According to this NMA, RH and LT had better DFS and OS for rHCC than RFA and TACE. However, treatment strategies should be determined by the recurrent tumor characteristics, the patient's general health status, and the care program at each institution.

Key Words: Hepatocellular carcinoma; Recurrence; Network meta-analysis; Curative treatment; Outcome; Survival rate

Core Tip: Network meta-analysis was used to compare treatments for recurrent hepatocellular carcinoma including repeated hepatectomy, radiofrequency ablation, transarterial chemoembolization, and liver transplantation. Thirty articles published from 2012-2021 were included in the analysis. Disease-free survival and overall survival were compared using forest plot analysis and hierarchic step diagram of subgroups by the Wald test, forest plot analysis, and predictive *P* score for subgroup analysis. Repeated hepatectomy or liver transplantation had better disease-free survival and overall survival compared to the others based on the testing methods from this network meta-analysis.

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INTRODUCTION

In Taiwan, hepatocellular carcinoma (HCC) was one of the most common causes of cancer-related deaths in 2019, ranking second in men and fourth in women[1]. Despite improvements in hepatitis control and care programs in Taiwan through antiviral therapy and vaccination projects, HCC remains a critical public health issue with a poor prognosis. Recurrent HCC (rHCC) after primary treatment is common in most patients, often resulting in a life-threatening situation and a major global health problem. According to Eastern and Western studies, the recurrence rates after primary hepatectomy are 70% or higher within 5 years[2-6]. Retreatment methods are crucial for improved survival, but the option of a retreatment method should be established where possible[7].

Currently, a precise treatment strategy for rHCC, including surgical or non-surgical methods, is controversial[8-10]. However, once an rHCC lesion is diagnosed during an imaging study, an effective treatment method should be implemented without delay. The therapeutic options for primary HCC are clearly dependent on the specified staging and international guidelines. Curative techniques such as liver transplantation (LT), hepatectomy, and radiofrequency ablation (RFA), among others, have been established[11-13]. Consequently, rHCC management necessitates specific guidance based on risk factors such as recurrence time, tumor nature, and the patient profile[13]. Therefore, a better treatment option for rHCC would be advantageous, but a guideline for clinical decision-making is still lacking.

In evidence-based medicine, network meta-analysis (NMA) of clinical studies is used to reach a conclusion based on multiple treatment comparisons[14]. It quickly garners insight for clinical decision-making by synthesizing both direct evidence from head-to-head trials and indirect evidence from indirect comparisons with treatment comparators[15-17]. The majority of studies are traditional two-arm meta-analyses, but NMA integrates multiple arms, including surgical and non-surgical arms, and provides a useful ranking of intervention methods for patients with rHCC[18]. Many institutions have adopted the consensus guidelines for primary HCC[11,12,19,20]. However, these guidelines are not useful for rHCC.

Treatment options for rHCC include repeated hepatectomy (RH), RFA, transarterial chemoembolization (TACE), LT, radiation therapy, and systemic target or immunotherapy[21-24]. When compared with other treatments, LT resulted in better overall survival (OS) in rHCC, whereas TACE was significantly worse than LT, RH, and RFA[8]. Accordingly, treatment strategies should be chosen based on the tumor characteristics and the patient profile at the time of recurrence.

In the recent decade, many studies comparing different treatment options for rHCC have been published. Four curative retreatment methods, including RH, RFA, TACE, and LT, are now routinely adopted in current practice and are coded globally[8,9,25-27]. Therefore, we aimed to conduct an NMA to compare four curative retreatment methods for patients with rHCC after primary hepatectomy.

MATERIALS AND METHODS

Search strategy and data extraction

A systematic search for rHCC treatment on PubMed, EMBASE, and the Cochrane Library Databases from 2012 to 2021 was conducted, and all relevant clinical cohorts or observational studies were identified. The keywords of article searching were HCC, recurrent hepatocellular carcinoma, liver cancer, recurrence, liver resection, hepatectomy, repeated hepatectomy, repeated liver resection, radiofrequency ablation, RFA, trans-arterial chemo-embolization, TACE, chemotherapy, chemoembolization, or liver transplantation. In this NMA, articles included should meet the following criteria: (1) Patients had an intrahepatic rHCC after initial liver resection; (2) Randomized controlled or observational clinical studies; (3) Must compare one of the four curative rHCC treatments, including RH, RFA, TACE, and LT; and (4) Have prognosis or outcome results. The exclusion criteria were as follows: (1) Conference abstracts, commentaries, case reports, reviews, or meta-analyses; and (2) Insufficient main outcome data for data extraction. If there were more than two studies from the same institution, the data were extracted from the most recent one. After reviewing the retrieved full articles, a final decision on eligibility for analysis was made.

The topics of each article were appropriately categorized in order to select the articles concerned with the retreatment methods of RH, RFA, TACE, or LT. For each study arm's outcome, the title, first author, publication year, intervention methods, outcomes, and associated risk factors, if available, were extracted. The study's endpoints were the disease-free survival (DFS) and OS rates for each subgroup. In addition, data for DFS were collected from 49 arms pooled for comparison in all studies, including recurrence-free survival in one arm of RH and RFA and two arms of LT, progression-free survival in one arm of TACE, and tumor-free survival in one arm of LT.

In addition, we conducted a relevant search by Reference Citation Analysis (https://www.referencecitationanalysis.com/) to supplement the latest cutting-edge research results.

Quality assessment

For quality assessment in the meta-analysis, two statistical models based on heterogeneity could be used: the fixed effects and random effects models. In the fixed effects model, all studies in the meta-analysis shared the same true effect size, whereas in the random effects model the true effect size varies from study to study. The heterogeneity among trials was assessed using the Q test with I^2 values, which represents the proportion of total variation in studies based on estimated heterogeneity[28]. An I^2 statistic of more than 50% or a P value of less than 0.05 indicated significant heterogeneity among trials, and the random effects model was used. The overall heterogeneity and publication bias of the effects model were used to assess the size deviation of the inconsistency in the variance parameter. After comparing each subgroup, ranking diagrams of presumed therapeutic effects were created based on the probability of superiority.

Statistical analysis

In this NMA, the data were analyzed using R software (version 3.0.2; R Foundation, Vienna, Austria) and comprehensive meta-analysis (Biostat Inc., 4 North Dean Street, Englewood, NJ, United States). The Q test is the sum of a heterogeneity measurement, which represents the variability of treatment effect between direct and indirect comparisons in a meta-analysis based on an I^2 statistic of more than 50% or P value[28]. A frequent analog to the surface under the cumulative ranking curve could be replaced by a P score, which measured whether a treatment was better than the comparative treatments[14,16]. Another predictive P score was 100% when a treatment was certain to be the best and 0% when it was certain to be the worst[16,29]. The forest plot displayed a summary of the overall estimation and was compared by treatment method subgroup. A hierarchic step diagram of the cumulative comparative efficacy of treatment methods based on effect size was displayed with odds ratios (OR) and 95%CI, which were used to measure superiority in decision-making with the Wald test[30]. For each arm, publication bias was assessed using Egger's test and illustrated with a funnel plot analysis[31,32]. The statistically significant level was set at 0.05 for all treatment comparisons.

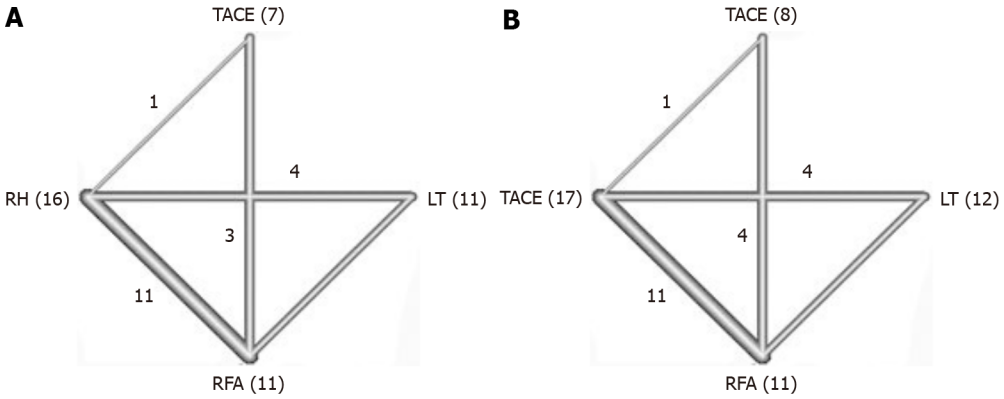

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Figure 1 Network graph of study number. Numbers appeared on the line of paired studies, and numbers with parenthesis at the angles of connected line were the cumulative number of subgroup of treatment methods in all studies. A: One-year and three-year overall survival (OS); B: Five-year OS. LT: Liver transplantation; RFA: Radiofrequency ablation; RH: Repeat hepatectomy; TACE: Transarterial chemoembolization.

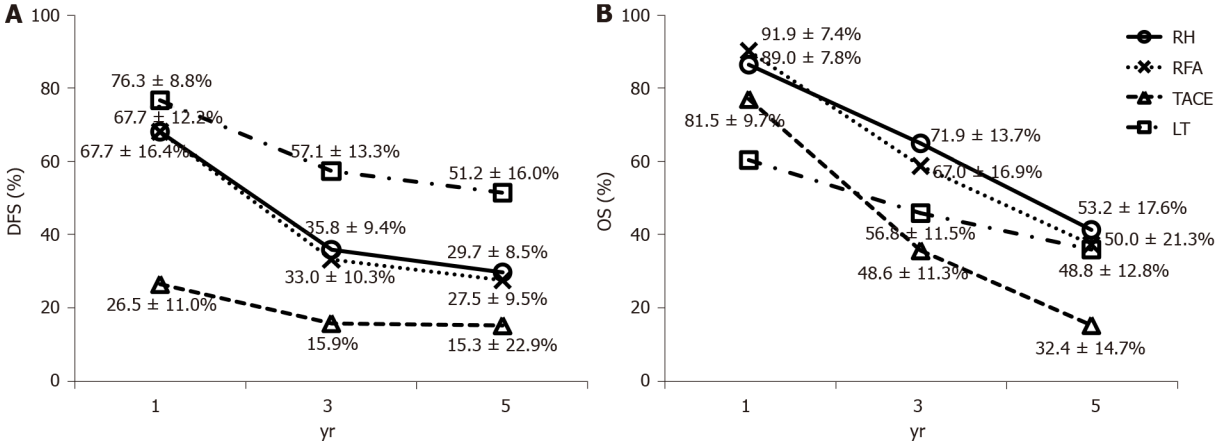

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Figure 2 Pooled mean survival rates of disease-free and overall survival of the patients treated by repeated hepatectomy, radiofrequency ablation, transarterial chemoembolization, or liver transplantation in recurrent hepatocellular carcinoma from all studies. A and B: The results of transarterial chemoembolization (TACE) disclosed the inferiority to other treatment options in disease-free survival (DFS) (A) or overall survival (B). The data of DFS were recorded and pooled together from recurrent-free survival in one arm of repeated hepatectomy and radiofrequency ablation and two arms of liver transplantation (LT), progression-free survival in one arm of TACE, and tumor-free rate in one arm of LT. DFS: Disease-free survival; LT: Liver transplantation; OS: Overall survival; RH: Repeated hepatectomy; RFA: Radiofrequency ablation; TACE: Transarterial chemoembolization.

RESULTS

Profiles of eligible articles of treatment methods in all studies

After the initial search, a total of 2671 published articles relating to rHCC treatment from 2012 to 2021 were retrieved. After duplicate removal and initial screening, 157 relevant articles were selected based on the selection criteria. Finally, 30 articles involving patients with intrahepatic rHCC after primary liver resection were included. Data were extracted from these studies and pooled for analysis. There were 4, 10, and 16 studies, with three, two, and one arm, respectively. These 30 articles were assembled and divided into 17, 11, 8, and 12 subgroups with the interventions RH, RFA, TACE, and LT, respectively, as shown in Figure 1. The basic characteristics of all studies are listed in Supplementary Table 1[3,6,9,21-22,24,26-27,33-54]. There were 14, 4, 4, 5, 2, and 1 articles from China, Taiwan, Korea, Japan, France, and Germany, respectively. The patients' characteristics and the cumulative mean value of the subgroups are summarized in Table 1. The total numbers of patients were 1405, 1013, 1123, and 1484 in the RH, RFA, TACE, and LT subgroups, respectively. Males were dominant in all groups, with prevalence ranging from 79.9% to 89.1%. The mean recurrence times after primary liver resection were 26.0 ± 8.3, 18.1 ± 6.5, 14.7 ± 6.6, and 19.4 ± 10.4 mo in the RH, RFA, TACE, and LT subgroups, respectively. The other relative factors of patients in each subgroup are listed in Table 1.

Table 1 Cumulative mean value of 49 arms of studies and patient profiles from 30 articles of curative treatment of recurrent hepatocellular carcinoma after primary liver resection

Arm in study, *n*	Patient, *n* [1]	Male %	Age in yr	HBV (+) %	HCV (+) %	Cirrhosis %	MVI (+) %	rChild A %	Time to recurrence in mo	rTumor size in mm	rTumor (*n* = 1) %
RH = 17	1405	79.9	56.5 ± 6.8	68.6	33.3	55.8	29.8	78.7	26.0 ± 8.3	25.3 ± 6.8	76.2
RFA = 11	1013	83.2	56.4 ± 5.5	78.5	12.4	59.0	26.6	94.9	18.1 ± 6.5	21.5 ± 4.0	78.6
TACE = 8	1123	86.5	54.6 ± 8.7	73.4	21.7	49.3	30.7	91.7	14.7 ± 6.6	32.2 ± 16.1	62.3
LT = 12	1484	89.1	53.6 ± 5.3	81.7	9.3	68.4	31.6	76.9	19.4 ± 10.4	27.1 ± 8.0	62.2

[1]Patients *n*, cumulated number of patients in subgroup from all studies.

Details of each study are listed in Supplementary Table 1. RH: Repeated hepatectomy; RFA: Radiofrequency ablation; TACE: Transarterial chemoembolization; LT: Liver transplantation; r: Recurrent; HBV: Hepatitis B virus; HCV: Hepatitis C virus; MVI: Microvascular invasion.

DFS and OS of rHCC after retreatment

The cumulative means of DFS and OS rates were assessed using the Wilcoxon rank sum test, as illustrated in Figure 2. The pooled 1-year, 3-year, and 5-year DFS in patients with rHCC were found to be the best in the LT subgroup, with 76.3 ± 8.8%, 57.1 ± 13.3%, and 51.2 ± 16.0%, respectively (Figure 2A). The pooled OS rates were found to be better in the RFA subgroup, with a 1-year OS of 91.1 ± 7.4%, and in the RH subgroup, with a 3-year OS of 71.9 ± 13.7% and a 5-year OS of 53.2 ± 17.6% (Figure 2B), with a significant difference in the 5-year OS between the RH and LT subgroups (P = 0.019). However, TACE was found to be inferior in both DFS and OS rates.

Comparison favorability of pooled outcome displayed with forest plot

The forest plot analysis revealed that LT had a higher DFS than other treatment methods (Figure 3A-C). In addition, the RH subgroup had a better 1-year OS than the LT (OR: 0.96, 95%CI: 0.31-2.96), RFA (OR: 1.19, 95%CI: 2.71-2.00), and TACE (OR: 2.56, 95%CI: 1.26-5.20) subgroups (Figure 3D). RH subgroup had a more favorable 3-year and 5-year OS than the LT (OR: 1.64, 95%CI: 0.56-4.66 and OR: 1.05, 95%CI: 0.43-2.56), RFA, and TACE subgroups (Figure 3E and F).

Hierarchic step diagram for comparison with the Wald test

The Wald test was used to compare the OS between the four interventional arms: RH, RFA, TACE, and LT. The results of cumulative comparisons between each treatment were displayed using a hierarchical step diagram in Figure 4. Compared to other treatments, RH had an expressed ranking probability with OR and 95%CI. LT had the better in 1-year OS (OR: 1.04, 95%CI: 0.34-03.20), and RH had a higher ranking probability based on 3-year OS (OR: 0.61, 95%CI: 0.21-1.73) or 5-year OS (OR: 0.95, 95%CI: 0.39-2.34), while TACE had the lowest probability of the better OS.

Predictive P score

Based on the predictive P score evaluation, the LT group had the best 1-year, 3-year, and 5-year DFS (Table 2). TACE data were insufficient for DFS analysis. In terms of OS, RH had the highest P scores of 0.739, 0.932, and 0.8331 for 1-year, 3-year, and 5-year OS, respectively. TACE had the lowest P scores for OS.

Meta-regression analysis

Meta-regression analysis provided a sensitivity analysis for model specification[29]. Compared to other treatments, LT had better results than RH in 1-year, 3-year, and 5-year DFS with β = 0.93 (P = 0.001), β = 1.181 (P < 0.001), and β = 1.258 (P < 0.001) respectively. LT compared with RH was inferior for 1-year OS with β = -0.036 (P = 0.913) but superior for 3-year OS with β = 0.04 (P = 0.881) and 5-year OS with β = 0.392 (P = 0.188), respectively. From this study, LT had better results for DFS (P < 0.001) and 3-year and 5-year overall survival (P > 0.05). RH had a better result for 1-year OS (P > 0.05) than other treatment options (Table 3).

Heterogeneity and publication bias

The heterogeneity among studies was estimated based on I^2 values using the Q test. The I^2 values for 1-year, 3-year, and 5-year DFS were 86.65%, 94.86%, and 95.81%, respectively, and for 1-year, 3-year, and 5-year OS, they were 79.07%, 89.72%, and 93.43%, respectively (Table 4). Therefore, the random effects

Table 2 Predictive P score for each treatment method for recurrent hepatocellular carcinoma

P score/subgroup	1-yr DFS	3-yr DFS	5-yr DFS	1-yr OS	3-yr OS	5-yr OS
RH	0.6470	0.4999	0.5100	0.7390[1]	0.9320[1]	0.8331[1]
LT	0.9986[1]	0.9998[1]	0.9820[1]	0.6980	0.5470	0.7505
RFA	0.3531	0.0003	0.0080	0.5340	0.5090	0.4159
TACE	0.0012	NA	NA	0.0300	0.0130	0.0500

[1]Best treatment option.

DFS: Disease-free survival; NA: Not available; LT: Liver transplantation; OS: Overall survival; RFA: Radio-frequency ablation; RH: Repeated hepatectomy; TACE: Transarterial chemoembolization.

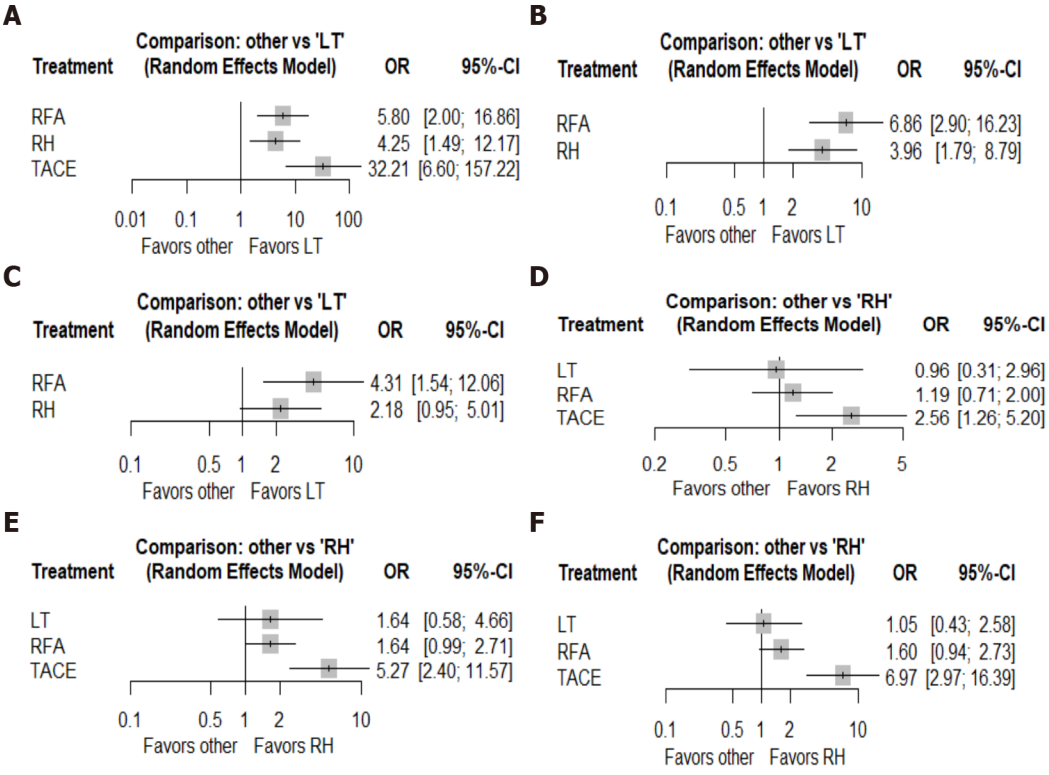

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Figure 3 Forest plot analysis demonstrated the odds ratio (95%CI) of 1-year, 3-year, and 5-year disease-free survival in the liver transplantation subgroup compared with repeated hepatectomy, radiofrequency ablation, and transarterial chemoembolization and 1-year, 3-year, and 5-year overall survivalin the repeated hepatectomy subgroup compared with liver transplantation, radiofrequency ablation, and transarterial chemoembolization with the random effects model. A: One-year disease-free survival (DFS); B: Three-year DFS; C: Five-year DFS; D: One-year overall survival (OS); E: Three-year OS; F: Five-year OS. RFA: Radiofrequency ablation; RH: Repeated hepatectomy; LT: Liver transplantation; OR: Odds ratio; TACE: Transarterial chemoembolization.

models were used for analysis based on a P value of less than 0.05 obtained from the I^2 value among retreatment methods. The Z value indicated the pooled effect size of all subgroups, and further details are listed in Supplementary Table 2. A detailed analysis of heterogeneity using a forest plot for DFS and OS is available in Supplementary Figures 1-6. The publication bias was assessed by Egger's regression test and resulted in 1-year, 3-year, and 5-year OS P values of 0.8459, 0.0562, and 0.3574, respectively. Funnel plot graphs were used for displaying publication bias among all studies. The number of potential missing studies for the association between analysis of treatment methods of 1-year, 3-year, and 5-year OS were depicted in the Figure 5A-C.

DFS and OS summary of subgroups among all testing methods

The best-pooled outcomes of the four retreatment methods analyzed by multiple testing methods are summarized in Table 5. In general, the LT subgroup had superior DFS ($P < 0.001$), whereas the RH subgroup had superior OS without a significant difference compared to other treatments.

Table 3 Meta-regression analysis for comparison of subgroups

Subgroup	β	SE	95%CI		Z value	P value
			Lower limit	Upper limit		
1-yr DFS						
Intercept	0.658	0.177	0.311	1.005	3.720	< 0.001
LT *vs* RH	0.930[1]	0.283	0.376	1.485	3.290	0.001
RFA *vs* RH	-0.315	0.272	-0.848	0.217	-1.160	0.246
TACE *vs* RH	-1.823	0.447	-2.699	-0.946	-4.080	< 0.001
3-yr DFS						
Intercept	-0.353	0.212	-0.769	0.063	-1.660	0.096
RFA *vs* RH	-0.609	0.335	-1.266	0.049	-1.810	0.070
TACE *vs* RH	-2.235	0.751	-3.707	-0.763	-2.980	0.003
LT *vs* RH	1.181[1]	0.322	0.550	1.812	3.670	< 0.001
5-yr DFS						
Intercept	-0.748	0.216	-1.171	-0.325	-3.460	0.001
RFA *vs* RH	-0.834	0.366	-1.552	-0.116	-2.280	0.023
TACE *vs* RH	-0.762	0.577	-1.893	0.369	-1.320	0.186
LT *vs* RH	1.258[1]	0.324	0.623	1.893	3.880	< 0.001
1-yr OS						
Intercept	2.185	0.208	1.777	2.594	10.480	< 0.001
LT *vs* RH	-0.036[1]	0.332	-0.687	0.614	-0.110	0.913
RFA *vs* RH	-0.041	0.325	-0.677	0.596	-0.130	0.900
TACE *vs* RH	-0.614	0.332	-1.264	0.036	-1.850	0.064
3-yr OS						
Intercept	0.996	0.162	0.679	1.313	6.150	< 0.001
RFA *vs* RH	-0.394	0.251	-0.885	0.098	-1.570	0.116
TACE *vs* RH	-1.114	0.287	-1.676	-0.551	-3.880	< 0.001
LT *vs* RH	0.040[1]	0.265	-0.479	0.558	0.150	0.881
5-yr OS						
Intercept	0.204	0.185	-0.158	0.565	1.100	0.270
RFA *vs* RH	-0.317	0.293	-0.890	0.257	-1.080	0.279
TACE *vs* RH	-0.917	0.328	-1.559	-0.275	-2.800	0.005
LT *vs* RH	0.392[1]	0.298	-0.192	0.975	1.320	0.188

[1]Best treatment option.

DFS: Disease-free survival; LT: Liver transplantation; OS: Overall survival; RFA: Radiofrequency ablation; RH: Repeated hepatectomy; SE: Standard error; TACE: Transarterial chemoembolization.

DISCUSSION

NMA models are simple to implement in clinical decision-making as a treatment strategy for patients with rHCC after primary liver resection[8,55]. The high recurrence rate has consistently undermined patient survival, making rHCC a major global healthcare problem. In terms of the optimal strategy for rHCC, LT had the best OS, followed by RH and RFA, while TACE had the worst[8]. Compared to RH and RFA, the LT subgroup had a superior DFS but not OS[42,45,47,56]. However, patients with rHCC treated with RH had a better OS, with no significant difference between the testing methods in our study, which is consistent with other studies[9]. The salvage LT group had a significantly higher 3-year and 5-year DFS than the RH subgroup with significant difference[57]. Although LT appears to have

Table 4 Overall heterogeneity of outcome measured by Q test with random effects model and pooled effect size of each subgroup

Outcome	Heterogeneity				Pooled effect (overall)		
	Q value	df (Q)	*P* value	I^2	*Z* value	95%CI	*P* value
1-yr DFS	224.670	30	< 0.001	86.65	0.672	0.625-0.716	*P* < 0.001
3-yr DFS	583.665	30	< 0.001	94.86	0.414	0.370-0.46	*P* < 0.001
5-yr DFS	764.476	32	< 0.001	95.81	0.315	0.276-0.357	*P* < 0.001
1-yr OS	219.820	46	< 0.001	79.07	0.874	0.850-0.895	*P* < 0.001
3-yr OS	437.662	45	0.002	89.72	0.642	0.642-0.714	*P* < 0.001
5-yr OS	730.285	48	< 0.001	93.43	0.546	0.497-0.594	*P* = 0.068

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

Table 5 Summary of the better pooled outcome of treatments depended on the analysis method

Test method	1-yr DFS	3-yr DFS	5-yr DFS	1-yr OS	3-yr OS	5-yr OS
Wilcoxon rank sum test	LT	LT	LT	RFA	RH	RH
Forest plot analysis	LT	LT	LT	LT	RH	RH
Wald test	LT	LT	LT	LT	RH	RH
P score	LT	LT	LT	RH	RH	RH
Meta-regression analysis	LT	LT	LT	RH	LT	LT

DFS: Disease-free survival; LT: Liver transplantation; RFA: Radio-frequency ablation; RH: Repeated hepatectomy; OS: Overall survival.

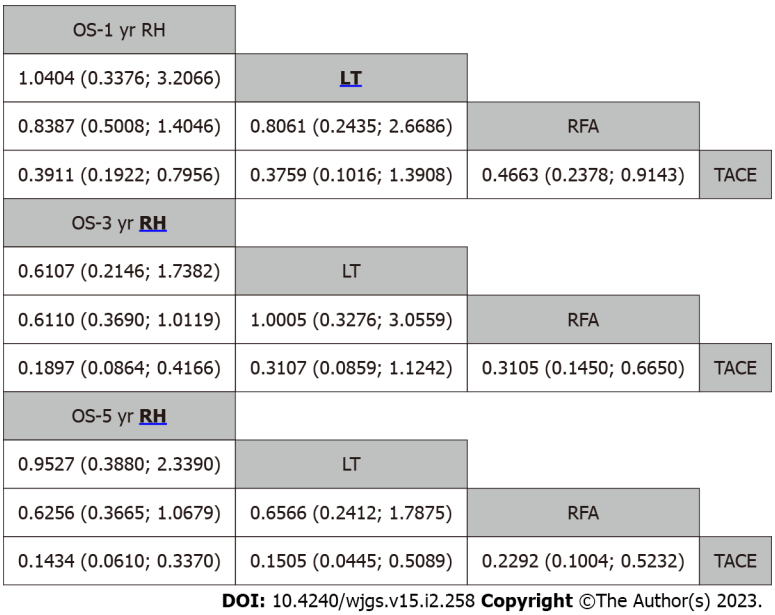

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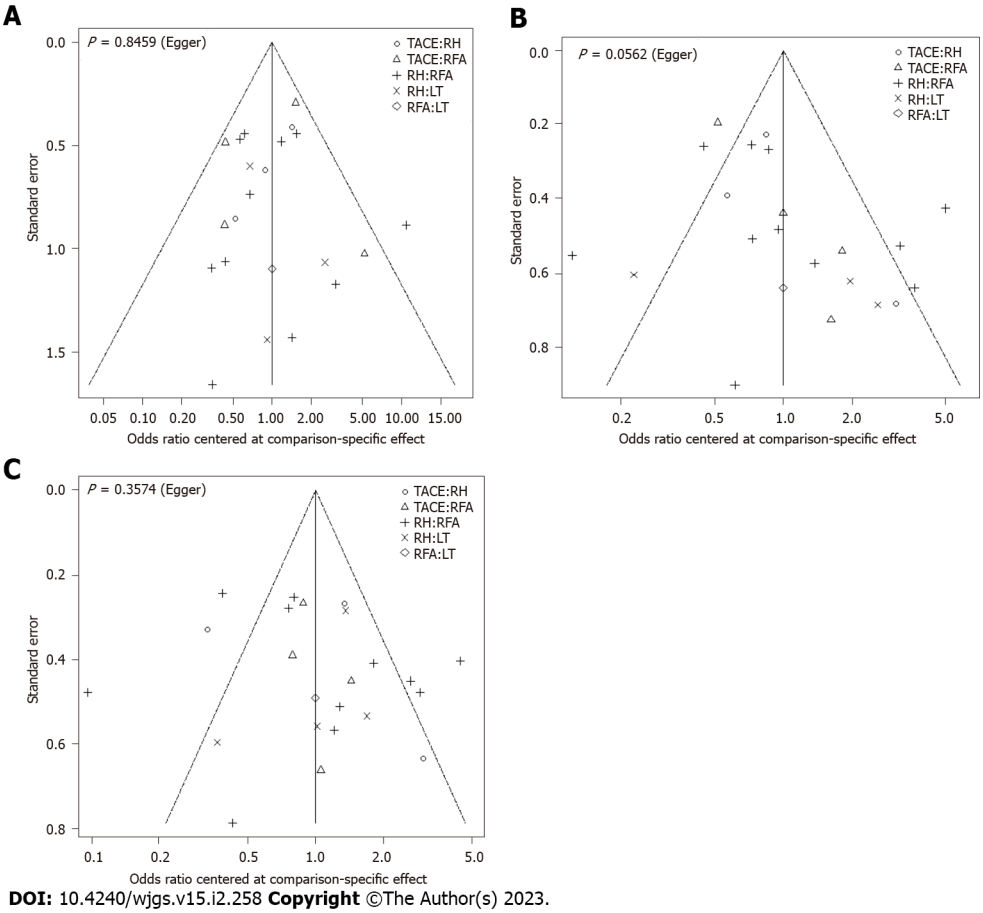
Figure 4 Hierarchic step diagram of cumulative comparative efficacy of treatment methods based on the effect size displayed with the odds ratio and corresponding 95% confidence interval of the 1-year, 3-year, and 5-year overall survival. All results were presented as the ratio of the x-axis over the y-axis with the Wald test. The better option had an underline and TextTitle letter. LT: Liver transplantation; OS: Overall survival; RFA: Radiofrequency ablation; RH: Repeated hepatectomy; TACE: Transarterial chemoembolization.

better survival, operative mortality still existed and ranged from 1.9% to 11.0%, which is higher than that in the RH group (ranging from 0% to 6.0%), with a significant difference[22,42,45,47].

Currently, LT is considered the best treatment for rHCC, but it is challenging due to organ shortages. Therefore, the number of patients who meet the transplantation criteria at the time of recurrence is low,



DOI: 10.4240/wjgs.v15.i2.258

Figure 5 Publication bias measured by the comparison of the specific effect for 1-year, 3-year, and 5-year overall survival. $P > 0.05$ were obtained among all studies after Egger's regression test. A: One-year overall survival (OS); B: Three-year OS; C: Five-year OS. LT: Liver transplantation; RFA: Radiofrequency ablation; RH: Repeated hepatectomy; TACE: Transarterial chemoembolization.

particularly in Asian countries[40,42,45,58]. There was no significant difference in DFS or OS between the patients who underwent primary LT and those who underwent primary resection and LT performed after recurrence from primary resection[27]. Surgical resection has been shown to be a viable procedure in the treatment of primary HCC or rHCC, with better survival than non-surgical methods in general[9,52,53].

The patients with rHCC who were treated again with a curative RH or LT approach had evident survival advantages. When the Japan Society of Hepatology guideline for primary HCC is applied to rHCC, either RFA or TACE are generally indicated in Child-Pugh Class A or B patients with 2-3 tumors of 3 cm or less in diameter or 4 tumors or more, and TACE may be indicated in some patients even with minor vascular invasion[12]. According to the European Association for the Study of the Liver guideline for primary HCC, most patients with rHCC had a similar recurrent tumor burden, favoring non-surgical treatment[59]. In this study, the cumulative means of recurrent tumor size and the percentage of single nodules were 21.5-32.2 mm and 62.2%-78.6%, respectively. Recurrent tumor size is one of the most significant prognostic factors associated with survival[6,9,60]. Currently, surgical resection is the first option in both primary and rHCC. An NMA revealed that RH is the most feasible intervention for recurrence after primary resection and is widely used to compare other treatments[8]. Nevertheless, RFA or TACE are less invasive and have fewer complications but have a lower survival rate.

Tumor recurrence after HCC resection has been proven to be unpreventable[13]. Based on the retreatment methods, the recurrence time after primary resection had a strong impact on survival. There is no universal definition of early and late recurrence after resection, and recurrence time ranges from 8 to 24 mo[13,61-64]. According to an international study, curative procedures mostly benefited patients who relapsed after 8 mo[61]. However, Yamashita *et al*[42] reported that the recurrence time may effectively identify patients with a poor prognosis who relapse before 17 mo. Because intrahepatic recurrence is often associated with aggressive cancer cell biological behavior and a poor prognosis[62,64], the potential effect of curative procedures such as RH, LT, or RFA may be considered, especially when the recurrence is within 1 year[35,65].

On the basis of ongoing hepatocarcinogenesis, late rHCC occurring more than 1 year after primary resection in the context of cirrhosis is regarded as a de novo tumor occurrence of different clonal origin [64,66,67]. In addition, before deciding on retreatment methods, it is possible to overlook de novo

minute nodules. In this situation, TACE will have unexpected benefits for the simultaneous treatment of ignored minute nodules alongside the main recurrent tumor. Therefore, the 5-year OS is significantly lower in patients with early recurrence and ranges from 4.5%-15.4% to 27.1%-36.3% compared to late recurrence, according to previous studies[64,68,69].

For patients with intrahepatic rHCC, a multicentric occurrence pattern is associated with better long-term outcomes than the intrahepatic metastasis pattern. LT is the preferred option for intrahepatic rHCC, especially for multicentric occurrence patients[70]. Appropriate rHCC management strategies are important for improving long-term survival if available data can be used to aid clinical decision-making [7]. Nevertheless, in most institutions, treatment strategy with RH and RFA could be the first-line treatment for rHCC. There is no difference between the LT and curative locoregional therapy (RFA or TACE) groups regarding 1-year and 3-year OS. However, the 5-year OS and 1-year, 3-year, and 5-year DFS were significantly higher after salvage LT than after locoregional therapy[57]. The feasibility of a retreatment method is determined by the number and location of the recurrent tumor, liver function, remnant liver volume, and the patient's general health status at the time of recurrence.

In this study, about one-third of the patients at the time of recurrence had multiple or moderate-to-large nodular tumors, impaired liver function, or were unable to receive surgical curative treatment. rHCC patients treated by a palliative approach (TACE or target therapy) or having a median size of the recurrent nodule > 5 cm have a significantly decreased OS compared with curative treatment methods [58]. Non-surgical methods such as RFA or TACE were effective as non-radical treatments for these patients. TACE, while not as effective as other curative treatments, significantly improves survival in patients with unresectable rHCC[41,49,54]. TACE was also recommended in rHCC as a treatment for downstaging before curative LT, according to the treatment flowchart based on the Barcelona Clinic Liver Cancer staging and treatment strategy published in 2022[59].

rHCC can be caused by multicentric carcinogenesis or inadequate initial treatment. Prevention of rHCC necessitates early diagnosis and complete anatomic resection of primary HCC lesions with a safety margin[71]. Currently, there are no solid and effective chemotherapeutic agents available to prevent rHCC. However, molecularly targeted drugs and anti-hepatitis B/C virus oral nucleoside/nucleotide analogs agents are recommended, but they are expensive and not promising. Therefore, the only option is to detect tumors as early as possible, and tumors can be treated based on the facilities at each institution.

The most common limitation of NMA is unexplained heterogeneity for available pairwise comparisons, which random effects meta-analysis models can accommodate[72]. In NMA studies, we should place more emphasis on treatment effects and consider the possibility of uncertainty with less emphasis on the probabilities of an NMA output. Clinical decision-making highlights the complexities of recommending a treatment method at the individual level based on tumor burden and patient condition.

CONCLUSION

In conclusion, patients with rHCC treated with RH or LT had comparably favorable DFS and OS. Currently, no solid algorithm can be expected to provide a guideline for patients with rHCC. Treatment strategies with RH, LT, RFA, or TACE are determined by factors such as liver function, tumor burden, metastasis, vascular invasion, and others. A multiparametric evaluation should be in place for personalized treatment of patients with rHCC, and it should be integrated into multidisciplinary tumor boards and partners in care programs at each institution.

ARTICLE HIGHLIGHTS

Research background

Recurrent hepatocellular carcinoma (rHCC) is a common outcome after curative treatment. Retreatment for rHCC is controversial, and no guidelines are currently available.

Research motivation

Acceptable decision making for treatment of rHCC patients is a priority.

Research objectives

Our objectives were to conduct a network meta-analysis (NMA) to compare curative treatments including repeated hepatectomy (RH), radiofrequency ablation, transarterial chemoembolization (TACE), and liver transplantation (LT) for patients with rHCC after primary hepatectomy.

Research methods

There were 30 articles involving patients with rHCC after primary liver resection from 2011 to 2021 that were retrieved for this NMA.

Research results

The best-pooled outcomes of four retreatment methods were analyzed by multiple testing methods. In general, the LT subgroup had superior disease-free survival (DFS) ($P < 0.001$), whereas the RH subgroup had superior overall survival (OS) without significant differences compared to other treatments.

Research conclusions

RH and LT had better DFS and OS for rHCC than radiofrequency ablation and TACE. However, treatment strategies should be determined by the recurrent tumor characteristics, the patient's general health status, and the care program of each institution.

Research perspectives

Retreatment with RH, LT, radiofrequency ablation, or TACE are determined by factors such as liver function, tumor burden, metastasis, vascular invasion, and others. A multiparametric evaluation should be in place for personalized treatment of patients with rHCC and re-evaluated in the future.

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FOOTNOTES

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META-ANALYSIS

Does size matter for resection of giant versus non-giant hepatocellular carcinoma? A meta-analysis

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Abstract

BACKGROUND

Research on long-term survival after resection of giant (≥ 10 cm) and non-giant hepatocellular carcinoma (HCC) (< 10 cm) has produced conflicting results.

AIM

This study aimed to investigate whether oncological outcomes and safety profiles of resection differ between giant and non-giant HCC.

METHODS

PubMed, MEDLINE, EMBASE, and Cochrane databases were searched. Studies designed to investigate the outcomes of giant *vs* non-giant HCC were included. The primary endpoints were overall survival (OS) and disease-free survival (DFS). The secondary endpoints were postoperative complications and mortality rates. All studies were assessed for bias using the Newcastle–Ottawa Scale.

RESULTS

24 retrospective cohort studies involving 23747 patients (giant = 3326; non-giant = 20421) who underwent HCC resection were included. OS was reported in 24 studies, DFS in 17 studies, 30-d mortality rate in 18 studies, postoperative complications in 15 studies, and post-hepatectomy liver failure (PHLF) in six studies. The HR was significantly lower for non-giant HCC in both OS (HR 0.53, 95%CI: 0.50-0.55, $P < 0.001$) and DFS (HR 0.62, 95%CI: 0.58-0.84, $P < 0.001$). No

significant difference was found for 30-d mortality rate (OR 0.73, 95%CI: 0.50-1.08, P = 0.116), postoperative complications (OR 0.81, 95%CI: 0.62-1.06, P = 0.140), and PHLF (OR 0.81, 95%CI: 0.62-1.06, P = 0.140).

CONCLUSION

Resection of giant HCC is associated with poorer long-term outcomes. The safety profile of resection was similar in both groups; however, this may have been confounded by reporting bias. HCC staging systems should account for the size differences.

Key Words: Hepatectomy; Giant hepatocellular carcinoma; Resection; Meta-analysis

Core Tip: Resection of giant hepatocellular carcinoma (HCC) is associated with poorer long-term outcomes, with a safety profile similar to that of resection of non-giant HCC. The importance of this is that HCC staging systems should account for the size differences.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most prevalent type of primary liver cancer[1]. It is the third most common cause of cancer-related deaths worldwide and has the fifth-highest incidence rate of cancers[2]. Currently, most HCCs develop secondary to underlying liver disease, often due to chronic hepatitis B or C virus infection[3]. Most developed countries have surveillance programs that identify HCC early, resulting in potentially curative treatment for 40%–50% of patients[4,5]. For patients who do not qualify for curative treatment, locoregional or systemic treatments can be used, depending on the stage of the disease[4]. Despite early detection and advances in management, HCC has a 5-year survival rate of 18%[6].

In cancer management, prognostic factors are used in staging systems to help recommend appropriate treatment strategies and counsel patients on recurrence risk and survival estimates[7]. Key predictors of prognosis in patients with HCC include the extent of liver dysfunction, tumor burden, and patient performance status[8]. Tumor size, one of the determinants of tumor burden, has been identified as an independent predictor of overall survival, with larger tumors generally predicting poorer outcomes[9,10]. Despite this, there is currently no consensus on the inclusion of tumor size in HCC staging systems. Some systems, such as the Barcelona Clinic Liver Cancer (BCLC) system[11] and American Joint Committee on Cancer (AJCC) 8th edition staging system[12], include size, while others, such as the Hong Kong Liver Cancer (HKLC) classification[13], do not. Furthermore, the size cut-off may vary in systems that incorporate tumor size, and when used to guide management, such as in the BCLC system, surgical resection remains the primary treatment modality for patients with a single tumor, regardless of tumor size.

Despite being recommended as the first-line treatment for early-stage tumors, resection is still contentious for giant HCC (≥ 10 cm in diameter). Studies on the long-term survival rates after resection of giant and non-giant HCCs have yielded conflicting results. In studies by Noh *et al*[14] and Allemann *et al*[15], no significant difference in survival was found between patients with giant and non-giant HCC. Conversely, studies by Fang *et al*[16] and Lee *et al*[17] found poorer survival outcomes in patients with giant HCC. Furthermore, the prognosis after resection of single large HCCs (≥ 5 cm) has been shown to be closer to intermediate-stage tumors than single tumors of smaller size[18,19]. In light of conflicting evidence, this study aimed to investigate whether oncological outcomes and safety profiles of surgical resection differ between giant and non-giant HCC.

MATERIALS AND METHODS

Search strategy and selection criteria

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic

Reviews and Meta-Analyses guidelines. A search was conducted using PubMed, MEDLINE (via Ovid), EMBASE, and Cochrane Central databases, from inception to 17 December 2021. A combination of search terms such as “HCC" or "liver cancer", "surgical resection" or “hepatectomy” or “liver resection”, “giant” or “huge” or "10 cm" was used. Only English studies were shortlisted for screening purposes. The articles were first screened by their titles and abstracts. Subsequently, full texts of suitable articles were reviewed for inclusion. The search, article review, quality assessment, and data extraction were conducted independently by two authors (Lee AJ and Wu AG). All disagreements were resolved by consensus or by appeal to a senior author. The study protocol was registered with PROSPERO (Number: CRD42022297772).

Inclusion criteria

Cohort and case-control studies were included. Only studies designed to compare the outcomes of resection of giant *vs* non-giant HCC and provided Kaplan-Meier curves for overall survival (OS) or disease-free survival (DFS) were included. In duplicate studies, the most recent study was chosen.

Exclusion criteria

Old studies published before 2000 were excluded from the meta-analysis to ensure that this study was relevant to current practice, as surgical techniques have been refined since then. Studies with a high risk of publication bias such as case reports and series were excluded. Reviews, editorials, conference abstracts, and non-human studies were excluded from the meta-analysis.

Quality assessment

The quality of all the studies was assessed using the Newcastle – Ottawa scale for cohort studies. Studies that scored 7–9 points, 4–6 points, and 3 or fewer points were considered to have a low, moderate, and high risk of bias, respectively.

Data extraction and reconstruction of individual patient data

Two review authors (Lee AJ and Wu AG) independently extracted the publication details (name of the first author, year of publication, and country) and study characteristics (patient demographics, tumor characteristics, Child Pugh score, OS, DFS, hospital mortality, and postoperative complications) from each study. The Child–Pugh score was dichotomized into Child’s A *vs* Child’s B or higher. Individual patient data (IPD) were reconstructed from available Kaplan-Meier survival curves using an iterative algorithm initially proposed by Guyot *et al*[20].

Data Synthesis

The primary endpoints of this study were OS and DFS, while the secondary endpoints were postoperative complications and mortality. Additionally, we investigated whether non-size tumor and liver characteristics such as vascular invasion, multinodularity and presence of Child’s B or higher cirrhosis in non-giant tumors with respect to giant tumors. After extracting the relevant information on OS and DFS from the published survival curves, a one-stage analysis was performed using Cox proportional hazard models based on the shared frailty model. The frailty model was chosen to account for study heterogeneity by incorporating a random-effects term that modelled patients within each study as failure-prone, similar to other individuals in the same study. Stratified Cox models were generated for sensitivity analysis. The stratified Cox models were adjusted for inter-study heterogeneity by allowing patients from a study to share a baseline hazard unique only to the study while constraining partial likelihood estimates of the Cox coefficients to be equal across strata. As the proportional hazard assumption was not upheld at a longer follow-up duration, the restricted mean survival time (RMST) at various time points was also calculated as an alternative measure of treatment effect that does not require model assumptions. Additionally, a two-stage analysis was performed using inverse-variance weighted random-effects meta-analysis.

HR will be presented for the primary endpoints of DFS and OS, and OR for the secondary dichotomous outcomes with their respective 95%CI. Random-effects models were used for all analyses because of the high heterogeneity among the studies.

All analyses were performed using R (version 4.1.2), with statistical significance set at $P < 0.05$.

RESULTS

The search yielded 1682 potentially relevant studies. After duplicate removal and abstract screening, 153 full-text articles were reviewed, of which 24 studies[14-17,21-40] were deemed eligible for meta-analysis. All 24 studies obtained a score of 7 or higher on the Newcastle-Ottawa scale, indicating that they were of high quality. In the overall cohort of 23747 patients, there were 3326 patients in the giant HCC (≥ 10 cm) group and 20421 patients in the non-giant HCC (< 10 cm) group (Figure 1). A summary of the study’s characteristics is provided in Table 1 and 2.

Table 1 Basic characteristics of included studies, hepatocellular carcinoma < 10 cm

Study	Year	Follow-up, mo	No.	Age, yr	Sex (M/F)	Tumour size, cm	Cirrhosis, *n* (%)	Child-Pugh class, *n* (%)	
								A	B + C
Allemann *et al*[15]	2013	25	79	67 (21-85)	NA	4.9 (1-9)	61 (77)	75 (95)	4 (5)
Chang *et al*[21]	2016	72.5	10167	NA	7618/2711	NA	1114 (11)	NA	NA
Choi *et al*[22]	2009	36	447	53.3 (9.7)	344/103	NA	244 (55)	443 (99)	4 (1)
Fang *et al*[16]	2019	20	104	NA	85/19	NA	93 (89)	101 (97)	3 (3)
Giuliante *et al*[23]	2013	NA	28	65.8 (8.8)	22/6	7.9 (7-8.1)	NA	28 (100)	0 (0)
Huang *et al*[24]	2016	26	272	NA	242/30	NA	90 (82)	NA	NA
Jo *et al*[25]	2011	30	40	54.6 (10.5)	36/4	3.81 (2.06)	NA	35 (88)	5 (13)
Lee *et al*[17]	2021	NA	3559	59.1 (12.1)	2716/843	3.36 (2.14)	NA	NA	NA
Lewis *et al*[26]	2019	22	26	NA	NA	NA	NA	NA	NA
Liau *et al*[27]	2005	27	111	63.0 (12.0)	80/31	6.1 (2.5)	40 (36)	104 (94)	7 (6)
Nagano *et al*[28]	2005	NA	143	62.0 (9.0)	112/31	3.25 (1.2-9.5)	81 (57)	101 (71)	NA
Noh *et al*[14]	2016	26.4	73	56.85 (10.7)	56/17	NA	NA	NA	NA
Poon *et al*[29]	2002	56	368	54.1 (12.2)	295/73	5.4 (2.6)	203 (55)	NA	NA
Shah *et al*[30]	2007	34	165	62.0 (14.0)	NA	4.7 (2.2)	NA	145 (88)	14 (8)
Tanaka *et al*[31]	2015	39	291	67 (61-73)	220/71	4 (2.3 – 5)	134 (46)	270 (93)	21 (7)
Taniai *et al*[32]	2008	22.5	291	64.1 (8.7)	225/66	3.71 (1.91)	156 (54)	209 (72)	82 (28)
Thng *et al*[33]	2015	22	63	59 (27-81)	50/13	NA	NA	60 (95)	3 (5)
Wakayama *et al*[34]	2017	57	521	62.8 (10.1)	427/94	4 (2.1)	NA	511 (98)	8 (2)
Yamashita *et al*[35]	2011	NA	412	64.0 (3.0)	328/84	3.8 (2.2)	NA	246 (60)	166 (40)
Yang *et al*[37]	2013	NA	293	47.0 (13.0)	263/57	6.7 (3.8)	201 (69)	231 (79)	62 (21)
Yang *et al*[36]	2014	NA	781	NA	635/146	NA	NA	768 (98)	51 (7)
Yeh *et al*[38]	2003	16.4	985	55.7 (13.11)	776/209	4.5 (2.4)	NA	NA	NA
Zhong *et al*[39]	2017	NA	707	NA	612/95	NA	520 (74)	672 (95)	35 (5)
Zhu *et al*[40]	2015	29.4	495	50.3 (11.2)	436/59	4.8 (2.3)	129 (26)	431 (87)	64 (13)

HCC: Hepatocellular carcinoma; NA: Not available; M: Male; F: Female.

Primary outcomes

Among the included studies, all 24 had extractable data for OS. Non-giant HCC had a lower HR at 0.53 (95%CI: 0.50-0.55, $P < 0.001$; Figure 2) with the one-stage frailty model, and a similarly significant trend was seen with the stratified HR at 0.53 (95%CI: 0.50-0.55, $P < 0.001$; Figure 2). RMST at 1-, 5- and 10-years showed significantly increased hazards for giant HCC. The estimated 1-year OS from the reconstructed IPD was 90.1% for non-giant HCC and 69.5% for giant HCC (RMST 0.91, 95%CI: 0.90-0.92, $P < 0.001$; Figure 2). Two-stage meta-analysis showed that non-giant HCC has a HR of 0.60 (95%CI: 0.50-0.72, $P < 0.01$; Figure 2).

Among the included studies, 17 studies[14-17,22,25-27,29-32,34,35,37,40] had extractable data for DFS. Non-giant HCC had a lower HR at 0.62 (95%CI: 0.58-0.84, $P < 0.001$; Figure 3) in the one-stage frailty model, and a similarly significant trend was seen with the stratified HR at 0.61 (95%CI: 0.57-0.65, $P < 0.001$; Figure 3). RMST at 1-, 5- and 10-years all shown significantly increased hazards for giant HCC. The estimated 1-year DFS from the reconstructed IPD was 58.9% for non-giant HCC and 35.7% for giant HCC (RMST 0.82, 95%CI: 0.80-0.84, $P < 0.001$; Figure 3). Two-stage meta-analysis showed that non-giant HCC has a HR of 0.63 (95%CI: 0.52-0.76, $P < 0.01$; Figure 3).

Secondary outcomes

Among the included studies, 18 studies[15,17,22,24,25,27-32,34-40] reported 30-d mortality rates whereas only two studies[36,39] reported 90-d mortality rates (Figure 4). While resection of non-giant HCC had lower odds of death within the first 30 d after surgery, the difference was not statistically

Table 2 Basic characteristics of included studies, hepatocellular carcinoma ≥ 10 cm

Study	Year	Follow-up, mo	No.	Age, yr	Sex (M/F)	Tumour size, cm	Cirrhosis, *n* (%)	Child-Pugh class, *n* (%)	
								A	B + C
Allemann *et al*[15]	2013	25	22	72 (36-88)	NA	13.5 (10-21)	9 (41)	22 (100)	0 (0)
Chang *et al*[21]	2016	72.5	912	NA	740/162	NA	166 (18)	NA	NA
Choi *et al*[22]	2009	36	50	50.8 (12.5)	34/16	NA	13 (26)	48 (96)	2 (4)
Fang *et al*[16]	2019	20	84	NA	76/8	NA	72 (86)	77 (92)	7 (8)
Giuliante *et al*[23]	2013	NA	37	62.2 (11)	28/9	12 (11-15)	NA	36 (97)	1 (3)
Huang *et al*[24]	2016	26	127	NA	114/13	NA	90 (71)	NA	NA
Jo *et al*[25]	2011	30	11	52.4 (8.4)	6/5	14.5 (4.11)	NA	11 (100)	0 (0)
Lee *et al*[17]	2021	NA	426	55.7 (14.3)	345/81	13.14 (4.95)	NA	NA	NA
Lewis *et al*[26]	2019	22	16	NA	NA	NA	NA	NA	NA
Liau *et al*[27]	2005	27	82	62.0 (14.0)	48/34	14.7 (4.1)	8 (10)	73 (89)	5 (6)
Nagano *et al*[28]	2005	NA	26	56.2 (12.2)	19/7	14.8 (10-30)	5 (19)	22 (85)	NA
Noh *et al*[14]	2016	26.4	41	55.1 (10.8)	33/8	NA	NA	NA	NA
Poon *et al*[29]	2002	56	120	50.9 (12.8)	99/21	13.8 (3)	32 (27)	NA	NA
Shah *et al*[30]	2007	34	24	57.0 (15.0)	NA	13.1 (2.9)	NA	24 (100)	0 (0)
Tanaka *et al*[31]	2015	39	24	64.5 (54-71)	20/4	13 (11.2-14.1)	7 (29)	20 (83)	1 (4)
Taniai *et al*[32]	2008	22.5	29	62.0 (9.4)	26/3	13.45 (2.77)	12 (41)	23 (79)	6 (21)
Thng *et al*[33]	2015	22	23	63 (34-84)	20/3	NA	NA	20 (87)	3 (13)
Wakayama *et al*[34]	2017	57	54	63.9 (12.7)	43/10	12.4 (3.7)	NA	49 (92)	4 (8)
Yamashita *et al*[35]	2011	NA	53	60.0 (2.0)	48/5	13.2 (0.4)	NA	38 (72)	15 (28)
Yang *et al*[37]	2013	NA	258	45.0 (12)	212/46	13.2 (4.1)	171 (66)	217 (84)	41 (16)
Yang *et al*[36]	2014	NA	304	NA	242/62	NA	NA	250 (83)	16 (5)
Yeh *et al*[38]	2003	16.4	211	47.8 (13.4)	164/74	13.9 (3.4)	NA	NA	NA
Zhong *et al*[39]	2017	NA	150	47.3 (10.9)	123/27	12.4 (2.5)	88 (59)	142 (95)	8 (5)
Zhu *et al*[40]	2015	29.4	244	46.8 (11.3)	209/35	12 (2.3)	67 (27)	210 (86)	34 (14)

HCC: Hepatocellular carcinoma; NA: Not available; M: Male; F: Female.

significant (OR 0.73, 95%CI: 0.50-1.08, $P = 0.116$). No significant heterogeneity was observed ($I^2 = 0\%$, $P = 0.60$). In the two studies that reported the 90-d mortality rate, the 90-d mortality rate was higher than the 30-d mortality rate; however, no significant difference was found between the different tumor size groups.

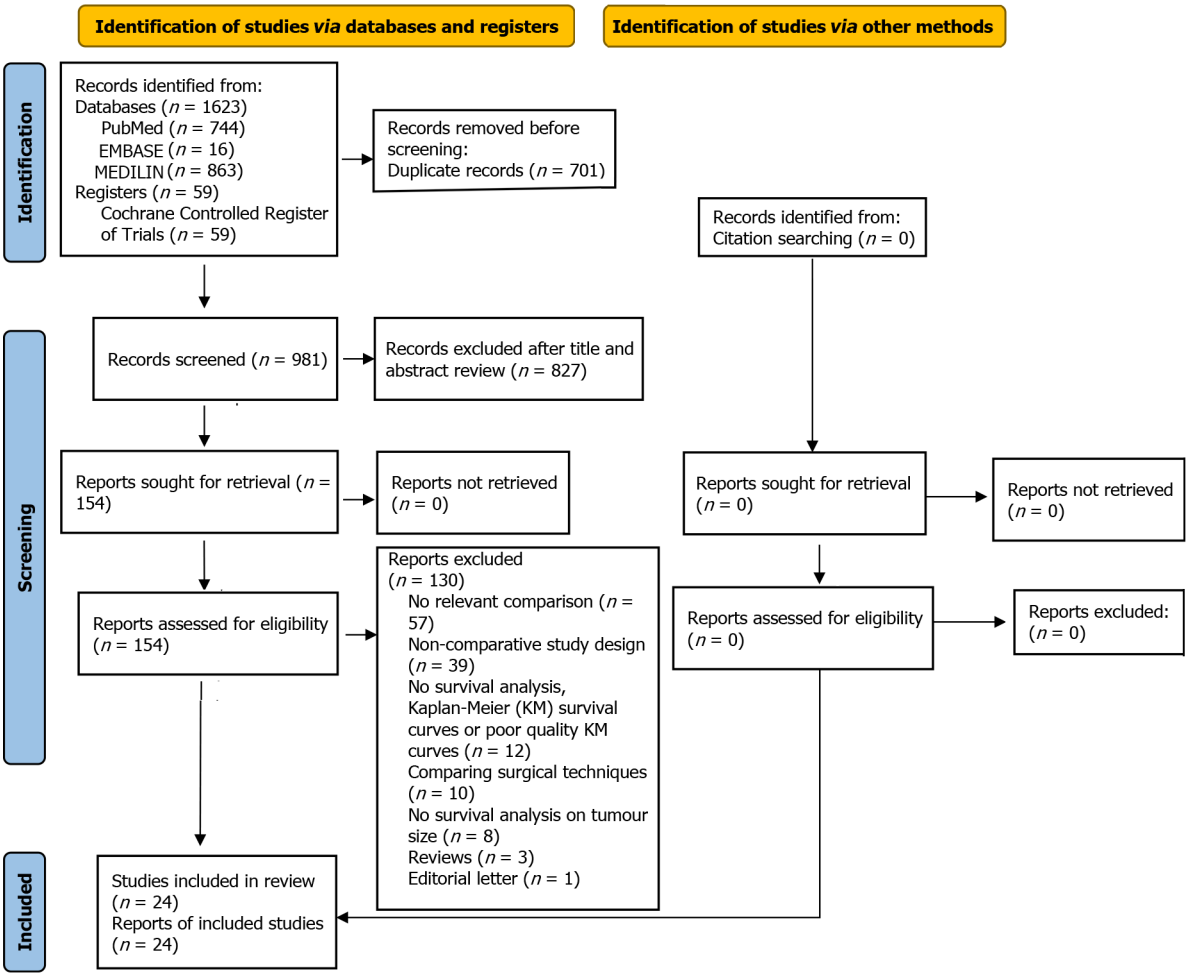
Among the studies included, 15 studies[15,22,25,27-32,35-40] reported major postoperative complications (Figure 4). While resection of non-giant HCC had lower odds of major postoperative complications, the difference was not statistically significant (OR 0.81, 95%CI: 0.62-1.06, $P = 0.140$). Substantial heterogeneity was observed among the included studies ($I^2 = 71\%$, $P < 0.01$).

Among the included studies, six studies[22,27,30,31,34,37] reported post-hepatectomy liver failure (PHLF) (Figure 4). While resection of non-giant HCC had lower odds of PHLF, the difference was not statistically significant (OR 0.59, 95%CI: 0.17-2.05, $P = 0.41$). No significant heterogeneity was observed ($I^2 = 45\%$, $P = 0.10$).

Among the included studies, 20 studies[14-16,21-25,27-34,36-38,40] reported on vascular invasion, 13 studies[15,16,21,22,24,27-29,31,32,37,39,40] on cirrhosis, 16 studies[15,16,22,23,25,27,28,30-37,39,40] on Child Pugh's score and 9 studies[21,22,24,27,29,32,34,37,40] on tumor number (Table 3). While non-giant HCC was found to have significantly lower odds of vascular invasion (OR 0.367, 95%CI: 0.236-0.572, $P < 0.0001$) and multinodular tumors (OR 0.592, 95%CI: 0.376-0.939, $P < 0.0259$), it was found to have significantly higher odds of cirrhosis (OR 1.955, 95%CI: 1.317-2.903, $P = 0.0009$). No significant difference was found between the different tumor size groups for presence of Child-Pugh B and above (OR 1.008, 95%CI: 0.745-1.364, $P = 0.9592$).

Table 3 Comparison of tumor characteristics and liver function

Factor	OR	95%CI	*P* value
Vascular invasion	0.367	0.236-0.572	< 0.0001
Multinodular	0.592	0.374-0.939	0.0259
Child-Pugh score	1.008	0.745-1.364	0.9592
Cirrhosis	1.955	1.317-2.903	0.0009



DOI: 10.4240/wjgs.v15.i2.273

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram.

DISCUSSION

In this meta-analysis of 23747 patients, surgical resection of non-giant HCC was associated with approximately half the rate of death from any cause and a lower rate of disease recurrence than surgical resection of giant HCC. These pooled associations showed a significant disparity in long-term outcomes between the two groups despite the use of the same treatment modality. Furthermore, giant HCC is shown to be associated with higher odds of vascular invasion and multinodular tumors, factors that have been shown to be associated with poorer outcomes[41,42]. In contrast, the short-term perioperative outcomes and safety profiles, measured by 30-d mortality and postoperative complications, respectively, did not differ significantly between the two groups. Hence, while HCC size may not affect the safety and efficacy of surgical resection in the short term, this study illustrates not only a possible correlation between a larger tumor size and poorer outcomes, but also demonstrates that giant HCC have different tumor characteristics from non-giant HCC. Therefore, giant HCC should be staged differently because they are associated with poorer outcomes and prognostically poorer tumor characteristics.

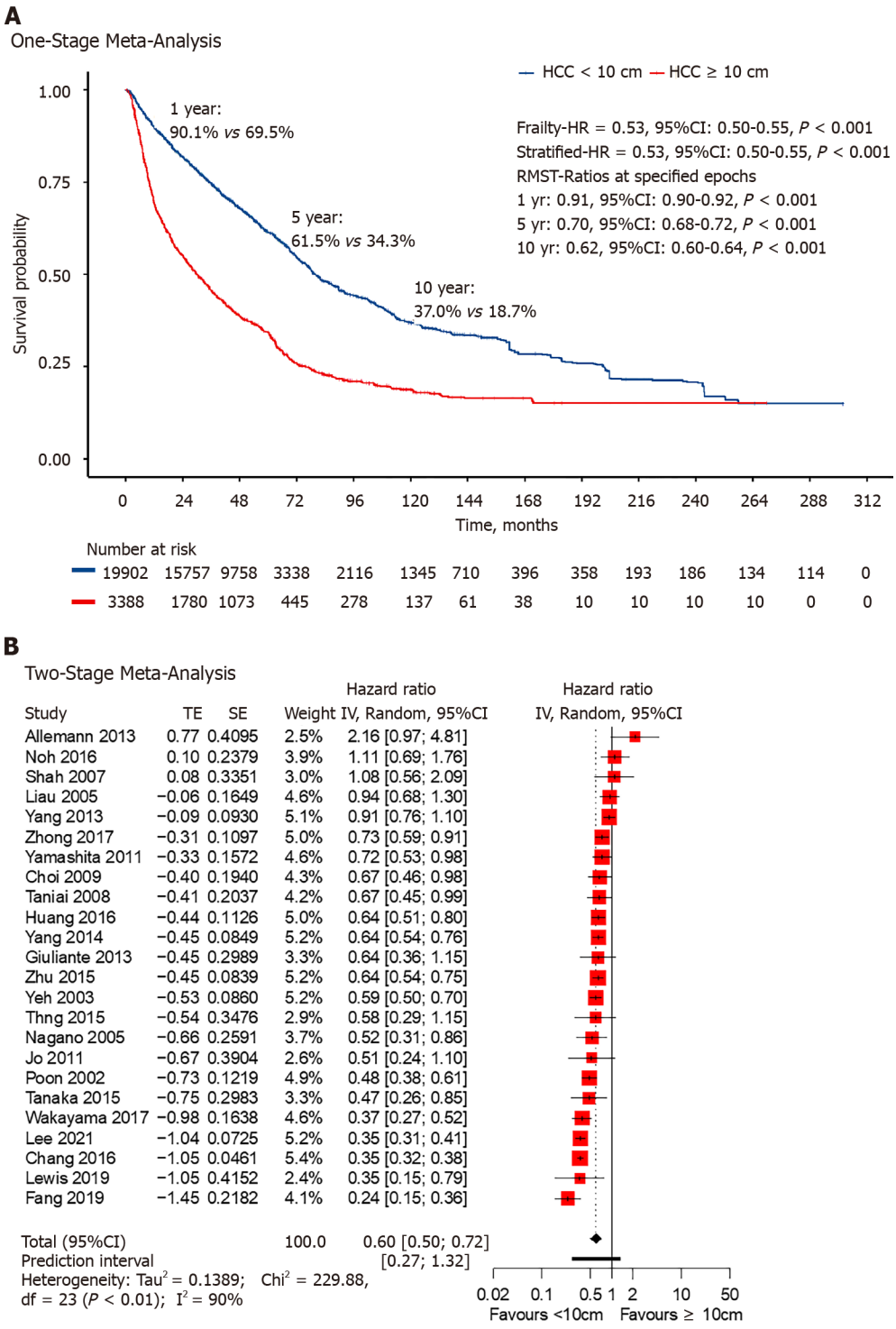


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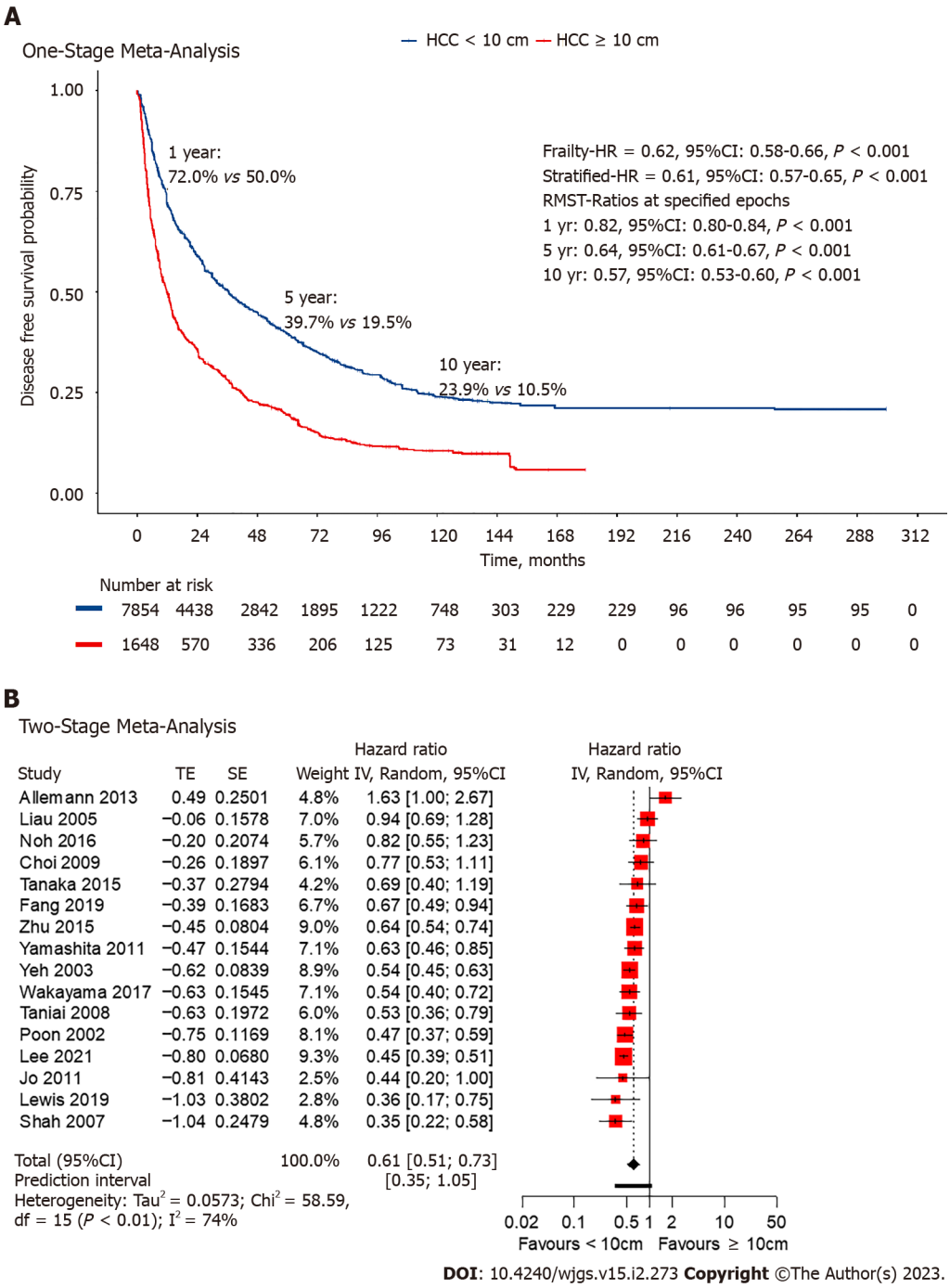
Figure 2 Overall survival curves, numbers-at-risk table and Forest plot. A: Overall survival (OS) curves and numbers-at-risk table for giant *vs* non-giant hepatocellular carcinoma from reconstructed individual patient data; B: OS forest plot. HCC: Hepatocellular carcinoma; HR: Hazard ratio; RMST: Restricted mean survival time.

Despite being a major risk factor for the development of HCC[43], cirrhosis and cirrhotic severity were not found to be associated with larger tumor size. In this study, non-giant HCC were found to have a higher risk of developing cirrhosis. A possible explanation for this is that cirrhotic patients are more likely receiving 6 moly ultrasound scan surveillance[44]. Therefore, tumors are likely to be detected before they reach larger sizes. Similarly, no association was found between the presence of Child-Pugh B cirrhosis and higher and larger tumor sizes. This shows that larger tumor size may not be correlated with greater odds of cirrhosis or more severe cirrhosis.



DOI: 10.4240/wjgs.v15.i2.273

Figure 3 Disease-free survival curve, numbers-at-risk table and Forest plot. A: Disease-free survival (DFS) curves and numbers-at-risk table for giant *vs* non-giant hepatocellular carcinoma from reconstructed individual patient data; B: DFS forest plot. HCC: Hepatocellular carcinoma; HR: Hazard ratio; RMST: Restricted mean survival time.

The myriad of HCC staging systems testifies that no single system is 'ideal'. The BCLC staging system is widely accepted in clinical practice and classifies patients into stages based on their performance status (PS) and Child-Pugh score[11]. The BCLC staging system does not place sufficient importance on tumor size when stratifying patients. Tumor size only plays a role in sorting patients with a single tumor, PS 0, and Child-Pugh A into very early stage (0) and early-stage (A), for which < 2 cm is the cut-off set for being classified as stage 0. However, this classification into stages 0 and A seems inconsequential for patients with single tumors, since the final determinant of management options in this group of patients is portal pressure and bilirubin levels, with no consideration given to size. This is evident because surgical resection is the first option for patients with normal total bilirubin levels and no evidence of clinically significant portal hypertension. Given the findings of this study, BCLC stage A patients with single tumors should be further classified, based on tumor size, into giant and non-giant subgroups since survival after surgical resection differs significantly between these two groups. As a cut-off size of 10 cm was used, this study was unable to determine the exact size beyond which the

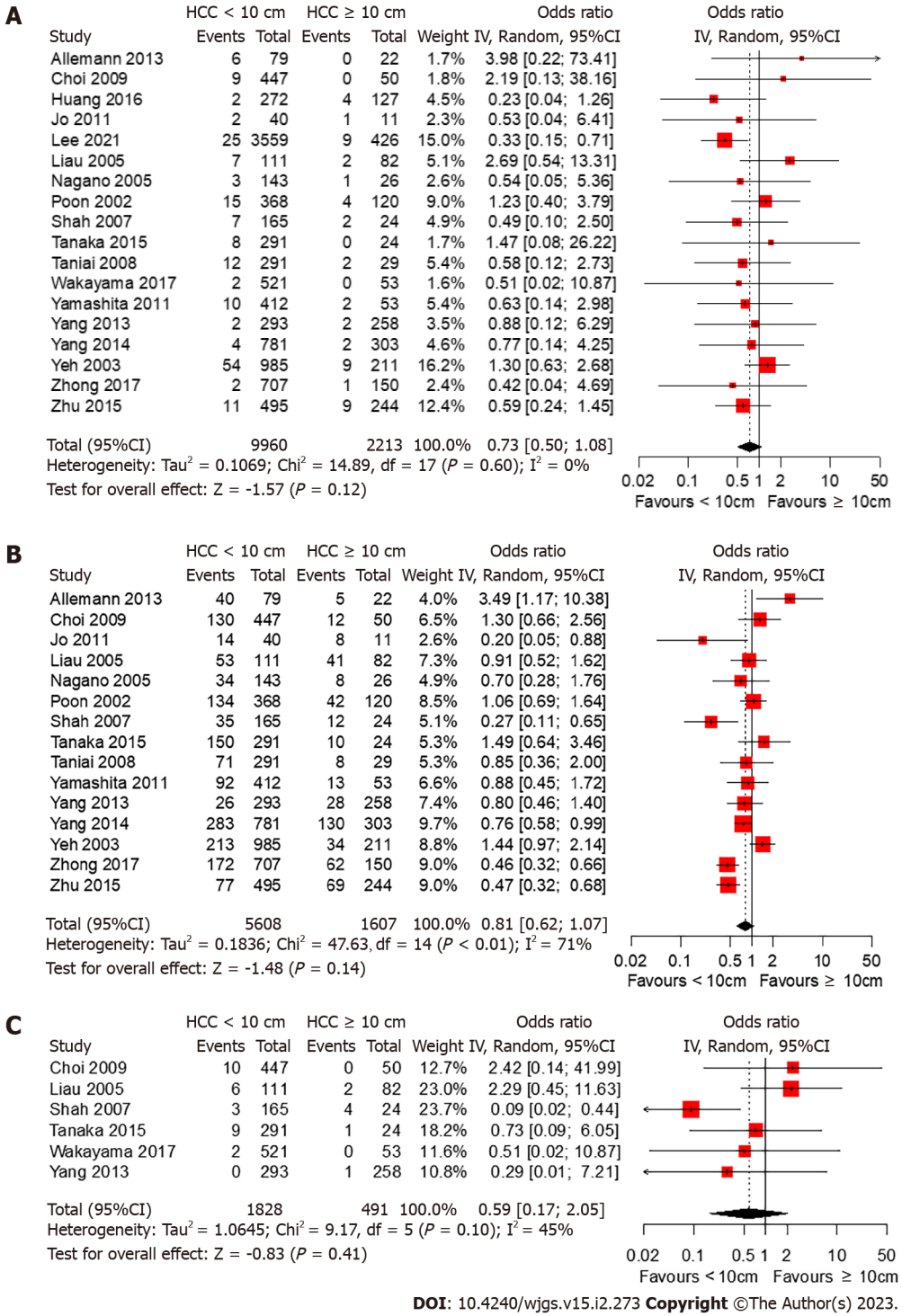


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Figure 4 Forest plots for morbidity and 30-d mortality. A: Forest plot of the 30-d mortality rate; B: Forest plot of the postoperative complication rate; C: Forest plot of post-hepatic liver failure rate. HCC: Hepatocellular carcinoma.

oncological prognosis was inferior.

Similarly, in other staging systems, other prognostic factors have taken precedence over tumor size. In the latest AJCC 8th edition staging system[12], solitary tumors ≤ 2 cm are now staged as T1a regardless of microvascular invasion, which differs from the 7th edition, where microvascular invasion determines whether the tumor is T1 or T2. However, for tumors > 2 cm in diameter, vascular invasion and multifocality play a larger role in staging; the absence of these factors would place the tumor in T1b, regardless of tumor size. In both the Cancer of the Liver Italian Program score[45,46] and Okuda staging system[47], the criteria for tumor size are ambiguous, using relative tumor size compared to the liver (tumor burden) as the cut-off. In contrast, the HKLC classification was constructed solely based on PS, Child-Pugh score, liver tumor status, and the presence of extrahepatic vascular invasion or metastasis, without considering size[13]. Hence, many of the current staging systems ignore tumor size, and even in

those that include size, size plays a limited role in staging the tumors. However, as giant HCC has been shown to be associated with vascular invasion and multinodular tumors, these factors should not be treated as mutually exclusive. From a technical perspective, the surgical resection of giant HCC is challenging. A large tumor size limits the surgical working space, increases the risk of tumor seeding from surgical manipulation, and distorts liver anatomy, thus potentially increasing operative difficulty. Further, it is likely that resection of large tumor entails dissection zone in proximity to hilum or major vessels, thus increasing the likelihood of bleeding or bile leak. In addition, surgical resection of giant HCC is in general entails major hepatectomy with small future liver remnant and associated risk of PHLF.

Although both groups had similar 30-d postoperative mortality and major complication rates, these may not accurately reflect the safety profile of surgical resection in each group. As the 90-d postoperative mortality rate has rarely been reported, only the 30-d mortality rate could be used as an indicator of postoperative mortality. However, a review by Egger *et al*[48] found that most studies reported an approximate doubling of mortality rates between 30 and 90 d following surgery. As the findings of this study were based on 30-d mortality rates, they may not accurately reflect the safety profile of surgical resection. Additionally, many studies did not specify which postoperative complications the patients experienced, and only 6 of the 24 studies[22,27,30,31,34,37] specified if the patients developed PHLF. Since PHLF has been found to be an independent predictor of mortality[2], the development of PHLF after HCC resection may be more indicative of the safety profile than complication rates alone. Thus, to improve the safety profile assessment of surgical resection, more precise reporting of major postoperative complications, particularly PHLF, and reporting of the 90-d mortality rate are required.

Although long-term outcomes for giant HCCs are significantly worse than those for non-giant HCCs, surgery continues to be the preferred treatment option. There is consensus that non-surgical treatment options for single giant HCC are associated with poorer outcomes than surgical resection, although many studies supporting surgical resection in the management of giant HCC have used transarterial chemoembolization (TACE) as a comparison[49-51]. In a recent meta-analysis of 1892 patients, Gui *et al*[52] found that TACE + radiofrequency ablation offers oncological outcomes comparable to surgical resection with lower morbidity. Although the meta-analysis was not specific to the treatment of giant HCC, it opens up the possibility of exploring the multimodal and combination approaches in patients with giant HCC. While surgical resection remains the current preferred treatment option for patients with giant HCC, future prospective studies should investigate different modalities of intervention for single or multiple giant HCC to determine whether these treatments can provide better quality of life outcomes with low therapy-associated morbidity. In addition, with scientific progress and innovation, radiation therapies including external beam radiation and selective internal radiation therapy, have a complementary role in the multidisciplinary care of patients with HCC[53].

This study has several limitations that should be considered. First, all included studies were retrospective studies with a risk of selection bias. As such, the favorable safety profile of giant HCC resection and the similar liver function in both giant and non-giant HCC may in part be due to the selection of younger and fitter patients with well-preserved liver function, or a publication bias. Second, there was a high degree of heterogeneity among studies. Hence, caution should be exercised when interpreting the results. Third, survival data, such as OS and DFS, were manually extracted from the survival curves. Hence, the possibility of errors during the data extraction cannot be eliminated. Fourth, although the algorithm used allows for a close approximation of the original IPD, it does not provide further details, such as patient-level covariates, which may provide greater insight. Lastly, this study was not able to assess whether total tumor volume (calculated by the equation $(4\pi \times r1 \times r2 \times r3)/3$; where r1, r2, and r3 are half of the largest, intermediate, and shortest tumor dimensions respectively) could be a prognosticator of oncological outcomes.

CONCLUSION

In summary, the results of this study show that surgical resection of giant HCC is associated with poorer long-term survival outcomes and should therefore be treated as a separate disease entity. While it was found that surgical resection of both giant and non-giant HCC had similar safety profiles, this may be confounded by poor reporting of the 90-d mortality rate. HCC staging systems should account for these size differences.

ARTICLE HIGHLIGHTS

Research background

There is currently no consensus on the inclusion of tumor size in hepatocellular carcinoma (HCC) staging systems. Furthermore, the size cut-off may vary in systems that incorporate tumor size, and a

consensus is warranted for inclusion of size into the staging criteria with cut-off to be determined by multi-center collaborative clinical studies.

Research motivation

Research on long-term survival after resection of giant (≥ 10 cm) and non-giant HCC (< 10 cm) has produced conflicting results.

Research objectives

This study aimed to investigate whether oncological outcomes and safety profiles of resection differ between giant and non-giant HCC.

Research methods

PubMed, MEDLINE, EMBASE, and Cochrane databases were searched. Studies designed to investigate the outcomes of giant *vs* non-giant HCC were included. The primary endpoints were overall survival (OS) and disease-free survival (DFS). The secondary endpoints were postoperative complications and mortality rates. All studies were assessed for bias using the Newcastle–Ottawa Scale.

Research results

24 retrospective cohort studies involving 23747 patients (giant = 3326; non-giant = 20421) who underwent HCC resection were included. OS was reported in 24 studies, DFS in 17 studies, 30-d mortality rate in 18 studies, postoperative complications in 15 studies, and post-hepatectomy liver failure (PHLF) in six studies. The HR was significantly lower for non-giant HCC in both OS (HR 0.53, 95%CI: 0.50-0.55, $P < 0.001$) and DFS (HR 0.62, 95%CI: 0.58-0.84, $P < 0.001$). No significant difference was found for 30-d mortality rate (OR 0.73, 95%CI: 0.50-1.08, $P = 0.116$), postoperative complications (OR 0.81, 95%CI: 0.62-1.06, $P = 0.140$), and PHLF (OR 0.81, 95%CI: 0.62-1.06, $P = 0.140$).

Research conclusions

Resection of giant HCC is associated with poorer long-term outcomes. The safety profile of resection was similar in both groups; however, this may have been confounded by reporting bias. HCC staging systems should account for the size differences.

Research perspectives

Future prospective studies should investigate different modalities of intervention for giant HCC to determine whether these treatments can provide better quality of life outcomes with low therapy-associated morbidity.

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FOOTNOTES

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CASE REPORT

Primary malignant melanoma of the esophagus combined with squamous cell carcinoma: A case report

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Abstract

BACKGROUND

Primary malignant melanoma of the esophagus is a rare malignant tumor of the esophagus, and its combination with squamous cell carcinoma is also rare. Here, we report the diagnosis and treatment of a case of primary esophageal malignant melanoma combined with squamous cell carcinoma.

CASE SUMMARY

A middle-aged man underwent gastroscopy for dysphagia. Gastroscopy revealed multiple bulging esophageal lesions, and after pathologic and immunohistochemical analyses, the patient was finally diagnosed with "malignant melanoma with squamous cell carcinoma". This patient received comprehensive treatment. After one year of follow-up, the patient was in good condition, and the esophageal lesions seen on gastroscopy were controlled, but unfortunately, liver metastasis occurred.

CONCLUSION

When multiple esophageal lesions are present, the possibility of multiple pathological sources should be considered. This patient was diagnosed with primary esophageal malignant melanoma combined with squamous cell carcinoma.

Key Words: Squamous cell carcinoma; Primary malignant melanoma; Endoscopy; Case

report

Core Tip: Here, we report a 53-year-old man with primary malignant melanoma of the esophagus combined with squamous cell carcinoma diagnosed by endoscopy, biopsy, imaging evaluation, and physical examination; this diagnosis was confirmed by immunohistochemistry. The patient was treated with immunotherapy, radiotherapy, and chemotherapy. As of now, the patient has recovered well.

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INTRODUCTION

Among malignant tumors, esophageal cancer currently ranks seventh worldwide in terms of incidence and sixth in terms of mortality rate. More than 90% of esophageal cancers in China are of the esophageal squamous cell carcinoma pathological type. In contrast, melanoma accounts for only 0.1% of all esophageal malignancies[1]. Although both types of malignant tumors can occur in the esophagus, no case of esophageal malignant melanoma combined with squamous cell carcinoma has been reported. Here, a case of primary esophageal malignant melanoma combined with squamous cell carcinoma is reported.

CASE PRESENTATION

Chief complaints

A 53-year-old man underwent esophagogastroduodenoscopy for dysphagia.

History of present illness

The patient had a history of progressive dysphagia for more than 1 mo.

History of past illness

The patient had no past medical problems.

Personal and family history

He smoked 30 cigarettes per day for 30 years but only rare drinks alcohol. He is a farmer by profession and has other bad habits. No significant personal or family history was noted.

Physical examination

He was 1.76 m tall, weighs 72 Kg and has a BMI of 23.2 Kg/m^2. During physical examination, no specific physical signs were found.

Laboratory examinations

Routine blood, liver function, renal function and prothrombin tests were normal. Alpha-fetoprotein, carcinoembryonic antigen, carbohydrate antigen 19-9, carbohydrate antigen 724, neuron-specific enolase and cytokeratin-19-fragment were normal.

Imaging examinations

Chest and enhanced abdominal computed tomography (CT) indicated upper and lower esophageal wall thickening, and the lumen was narrow. Enhanced scanning showed the enhancement of the wall. The mediastinal lymph nodes were enlarged. Multiple small nodules were seen in both lungs, and emphysema, liver cysts, and cholecystitis were also observed (Figure 1).

Gastroscopy observation showed irregular hyperplasia at 23-27 cm from the incisor, with no melanin deposition; hemispherical bulges at 29 cm and 32 cm from the incisor; and irregular hyperplasia at 39-43 cm from the incisor, indicating ulcers with a small amount of melanin deposition. Biopsies were performed at 23-27 cm, 32 cm, and 39-43 cm (Figure 2).

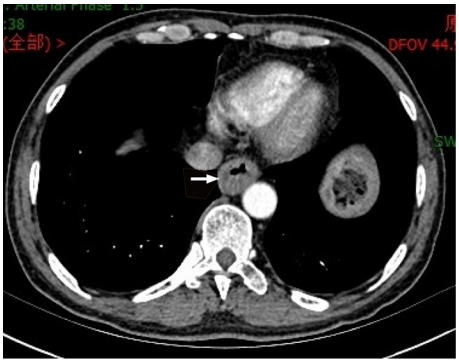

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Figure 1 Computed tomography indicates thickening of the esophageal wall.

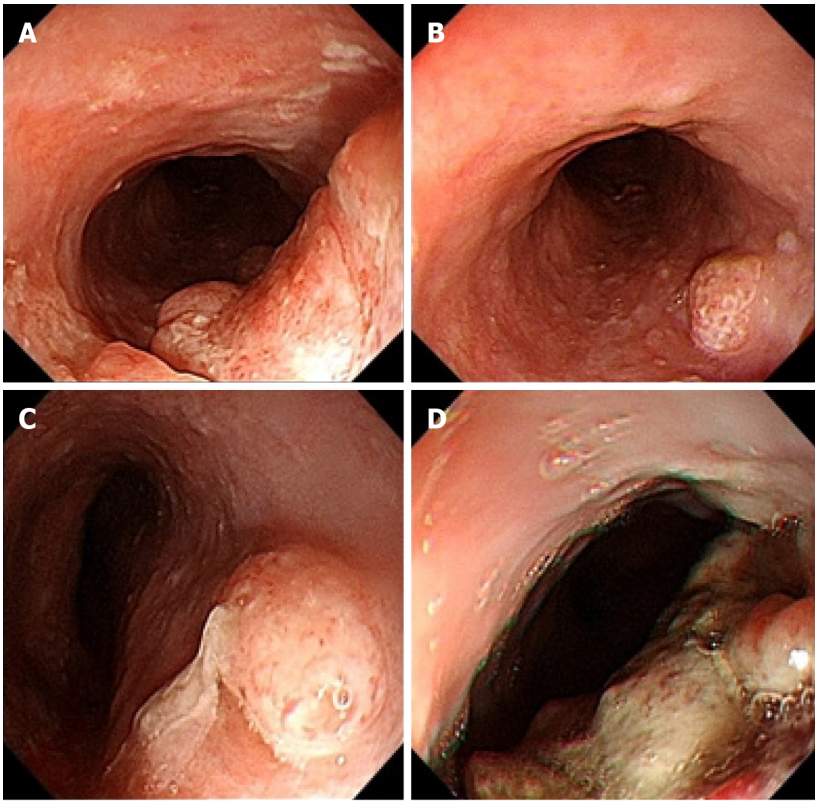

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Figure 2 Gastroscopy suggested multiple lesions of the esophagus. A: 23–27 cm from the incisor; B: 29 cm from the incisor; C: 32 cm from the incisor; D: 39–43 cm from the incisor.

Pathologic analysis indicated malignant melanoma (23–27 cm from the incisor, 39–43 cm from the incisor) combined with squamous cell carcinoma (23–27 cm from the incisor) and solitary squamous cell carcinoma (32 cm from the incisor). Immunohistochemistry showed the following: Vimentin(+), HMB45(+), Melan-A(+), S-100(focus+); squamous cell carcinoma CK5/6(+), P40(+), P63(+), LCK(+), CD56(-), CgA(-), and Syn(-); and Ki-67(+) was approximately 30% (Figure 3).

Upper gastrointestinal imaging revealed irregular filling defects approximately 4.5 cm and 5.7 cm in length in the upper and lower sections, respectively, which were accompanied by tube wall stiffness, poor expansion, restricted passage of contrast agent, and disruption of the continuity of the mucosa (Figure 4).

Positron emission tomography/computed tomography (PET/CT) showed thickening of the upper and lower thoracic walls of the esophagus, an abnormal increase in fluorodeoxyglucose (FDG) metabolism, and multiple enlarged lymph nodes in the mediastinum and right axilla. Multiple small nodules were observed in both lungs, and the FDG metabolism was increased.

No metastatic lesions were observed on brain magnetic resonance imaging (MRI).

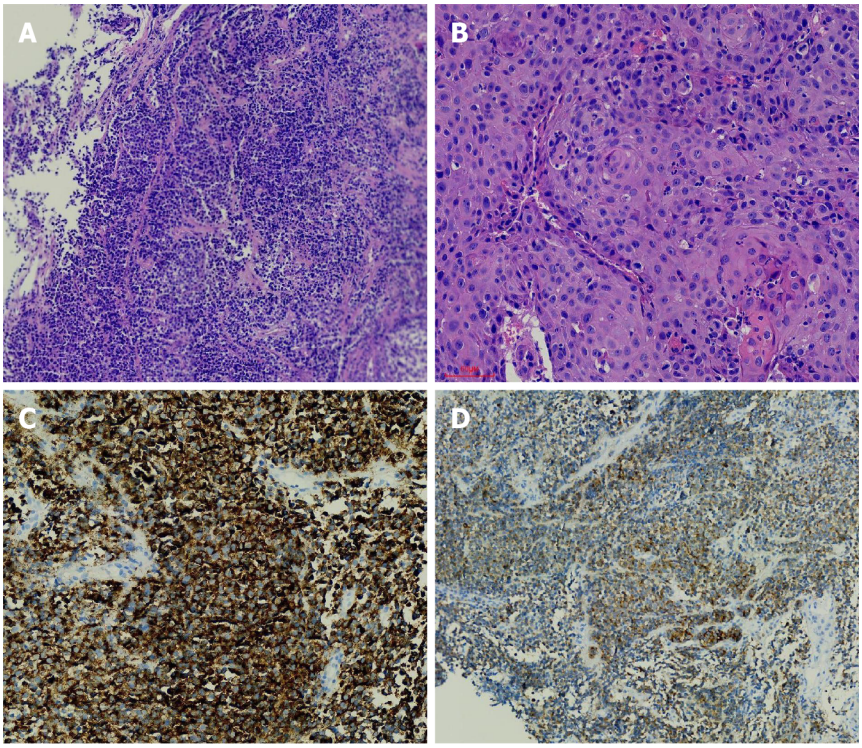

Figure 3 Endoscopic biopsy. A: HE staining of malignant melanoma; B: HE-stained squamous cell carcinoma; C: Immunohistochemical HMB45 positivity; D: Immunohistochemical Melan-A positivity.

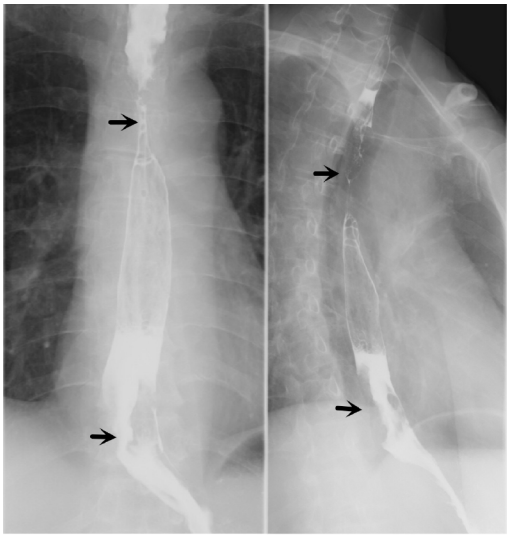

Figure 4 Esophageal barium swallow (the arrow indicates the location of the lesion).

The microsatellite instability results were MSS. Programmed death ligand-1 immunohistochemistry 22C3: The tumour proportion score results were 1%-2% (Figure 5).

FINAL DIAGNOSIS

The final diagnosis was esophageal malignant melanoma, esophageal squamous cell carcinoma (stage IV), bilateral lung metastases, and metastases in the mediastinal lymph nodes and right axillary lymph nodes.

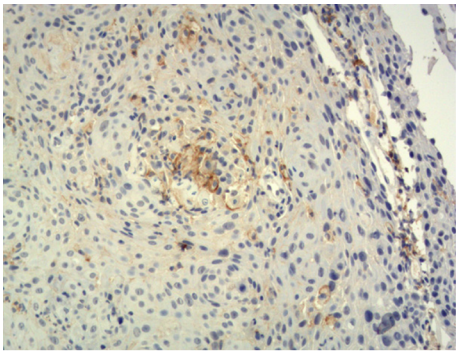

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Figure 5 Programmed death ligand-1 immunohistochemistry 22C3: The tumour proportion score results were 1%-2%.

TREATMENT

The patient was first treated with 1 cycle of 200-mg camrelizumab, followed by 2 cycles of 300-mg nab-paclitaxel. Later, the patient was administered local radiotherapy, which was terminated because the patient could not tolerate it. Subsequently, he was given 2 cycles of 200-mg camrelizumab and 300-mg nab-paclitaxel.

OUTCOME AND FOLLOW-UP

The patient underwent another gastroscopy six months later, and no obvious space-occupying lesion was observed in the esophagus, while only a small amount of melanin deposition was seen (Figure 6). Regrettably, both enhanced CT and enhanced MRI of the patient's abdomen suggested liver metastasis. It is recommended that patients continue treatment with camrelizumab combined with apatinib. The current case has been followed-up for approximately 1 year, and he has not experienced dysphagia.

DISCUSSION

Primary malignant melanoma of the esophagus (PMME) is a rare disease that accounts for 0.5% of all nonskin melanomas[2]. Primary melanin-free melanoma is also extremely rare, with slightly more than 20 cases reported thus far[3], and combined esophageal squamous cell carcinoma is even rarer.

The average age of patients with PMME is 60.5 years, and the incidence rate is higher in male patients than in female patients, with a ratio of 2:1[4,5]. The degree of PMME malignancy is high and is associated with a poor prognosis; PMME has a median survival rate of 18.1 mo and a 5-year survival rate of less than 10%[6].

The clinical manifestations of PMME are similar to those of esophageal squamous cell carcinoma, and most patients experience the following symptoms: Dysphagia, poststernal pain, and weight loss. Hematemesis and melena are rare. Typical PMME on endoscopy is a lobular or polyp-like tumor with clear boundaries and pigmentation. More than 90% of PMME lesions are located in the distal 2/3 of the esophagus[7]. Approximately 10% to 25% of PMME cases have lesions that are different colors, including purple, brown, and white, depending on the amount of melanin[8,9]. Some tumors are composed of melanin-free cells, and the identification of other tumors by endoscopy is difficult. The pathological manifestations of primary malignant melanoma in the esophagus can represent the superficial spreading type or a nodule-like growth pattern, and a distinct Peyer's patch-like or freckle-like melanocyte nest invasion is observed in adjacent squamous epithelium. Tumor cells are primarily composed of epithelial-like mole-like cells, which are round, oval, polygonal, or shuttle shaped and have large nuclei and large, clear nucleoli. Base film samples are dyed to show thick-walled blood vessels and tubes, which are significant features of melanoma[10]. HMB-45, S-100, vimentin, and melanoma-specific antigen (Melan-A) are specific to this diagnosis[11].

PMME mainly occurs through hematogenous metastasis and lymphatic metastasis, and common sites of metastases include the liver (31%), mediastinum (29%), lung (18%), and brain (13%)[12]. Whether mediastinal invasion, lymphadenopathy, and distant metastasis are present can be determined through chest and abdominal CT, which can be used to show and determine the stages of lesions. PET-CT plays an important role in the diagnosis of metastatic lesions.

Esophageal malignant melanoma has no specific treatment, and complete surgical removal of lesions is preferred, along with lymph node clearing. Four to six cycles of temozolomide/dacarbazine (DTIC)-based auxiliary chemotherapy are recommended. Radiation therapy is also a possibility. DTIC is the

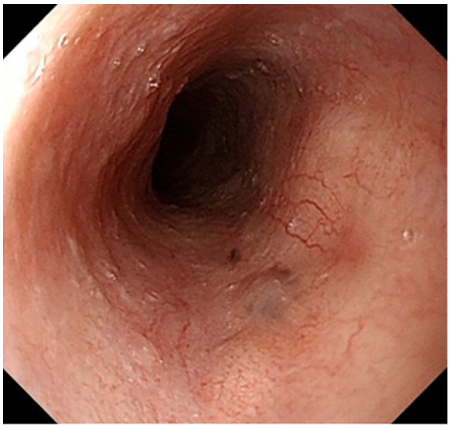

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Figure 6 Gastroscopy review.

"gold standard" for the medical treatment of advanced melanoma, but its overall efficacy is poor. For targeted therapy, ipilimumab can be used to treat advanced melanoma. Anti-PD-1 and anti-CTLA-4 drugs and IL-2 are FDA-approved immunotherapy drugs that result in significant survival benefits in patients with advanced skin melanoma, but their effects on esophageal malignant melanoma require further investigation[13-15].

Esophageal squamous cell carcinoma is the most common malignant tumor of the esophagus. Patients are located in cities in China with a high incidence of esophageal cancer[16,17], which is mainly associated with diet and lifestyle habits. Radical surgery is the main approach for treating esophageal squamous cell carcinoma. PD-1 inhibitors are currently the first-line drugs for advanced melanoma and have been shown to be effective in treating squamous cell carcinoma of the esophagus[18]. Although radiotherapy and chemotherapy are not sensitive to malignant melanoma of the esophagus, the patient was treated with nab-paclitaxel in combination with squamous cell carcinoma of the esophagus and 40 Gy/20 F radiotherapy to the esophageal lesion and mediastinal lymph node area. Overall, our treatment was effective.

CONCLUSION

In this case, many lesions indicative of esophageal disease were found by gastroscopy. The lesions contained no melanin on their surfaces and were thus unsuitable for endoscopy-based diagnosis and identification. Through pathology and immunohistochemistry, esophageal malignant melanoma combined with esophageal squamous cell carcinoma was diagnosed. This case demonstrated that multiple lesions in the same location can represent different pathologies.

We report a very rare case of primary malignant melanoma of the oesophagus combined with squamous cell carcinoma. Although we do not have much experience in treating this disease, the patient's oesophageal lesions were well controlled through aggressive treatment. We hope this will provide an insight into the diagnosis and treatment of this type of disease.

FOOTNOTES

Author contributions: Zhu ML and Wang LY contributed equally to this work; Zhu ML, Liu XY, Wang LY designed the research report; Bai XQ provided pathological diagnosis and pictures, Zhu ML and Wu C analyzed the data and wrote the manuscript; Wang LY and Liu XY guided and reviewed this article; All authors have read and approved the final manuscript.

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CASE REPORT

Mesh erosion into the colon following repair of parastomal hernia: A case report

Yu Zhang, Han Lin, Jia-Ming Liu, Xin Wang, Yi-Feng Cui, Zhao-Yang Lu

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Abstract

BACKGROUND

In recent years, mesh has become a standard repair method for parastomal hernia surgery due to its low recurrence rate and low postoperative pain. However, using mesh to repair parastomal hernias also carries potential dangers. One of these dangers is mesh erosion, a rare but serious complication following hernia surgery, particularly parastomal hernia surgery, and has attracted the attention of surgeons in recent years.

CASE SUMMARY

Herein, we report the case of a 67-year-old woman with mesh erosion after parastomal hernia surgery. The patient, who underwent parastomal hernia repair surgery 3 years prior, presented to the surgery clinic with a complaint of chronic abdominal pain upon resuming defecation through the anus. Three months later, a portion of the mesh was excreted from the patient's anus and was removed by a doctor. Imaging revealed that the patient's colon had formed a t-branch tube structure, which was formed by the mesh erosion. The surgery reconstructed the structure of the colon and eliminated potential bowel perforation.

CONCLUSION

Surgeons should consider mesh erosion since it has an insidious development and is difficult to diagnose at the early stage.

Key Words: Mesh erosion; Mesh migration; Parastomal hernia; Intestinal fistula; Intestinal internal fistula; Case report

Core Tip: In recent years, mesh has become a standard repair method for parastomal hernia surgery because it has the advantages of a low recurrence rate and low postoperative pain. However, using mesh to repair parastomal hernias also carries potential dangers. We report a case of a rare complication caused by mesh erosion 3 years after parastomal hernia repair using the keyhole method. Its atypical symptoms and imaging findings complicated the diagnosis. The aim of this case report was to raise awareness of this rare complication among surgeons.

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INTRODUCTION

Although the incidence of parastomal hernias remains unknown, it is predicted to be > 30% at 1 year, > 40% at 2 years, and ≥ 50% after many years thereafter[1]. Suture repair is undoubtedly the simplest method for parastomal hernia repair, but its recurrence rate has been reported to be higher than that of mesh repair[2]. Hence, mesh repair remains the mainstream method for treating parastomal hernias. Mesh repair can reduce the recurrence rate but may cause potential mesh-related complications. Currently, there is a lack of comparative evidence between the different mesh types for parastomal hernia repair. However, synthetic uncoated mesh types are generally not considered for intraperitoneal use because of the risk of adhesion, intestinal erosion, and stenosis[1].

Here, we present the case of a patient who underwent parastomal hernia repair with intraperitoneal onlay mesh repair mesh and developed a rare complication 3 years after the procedure. We reviewed 137 cases in 132 case reports of mesh erosion from 1973 to 2022 by searching the keywords, "Mesh Erosion" and "Mesh migration" in PubMed.

CASE PRESENTATION

Chief complaints

In January 2021, a 67-year-old female who had undergone parastomal hernia repair surgery 3 years prior began experiencing chronic abdominal pain upon resuming defecation through the anus.

History of present illness

In January 2021, she underwent abdominal computed tomography (CT) for initial workup, which revealed a foreign material located in the distal colon (Figure 1A). Three months later, in April 2021, a portion of the foreign material was excreted from the patient's anus. The patient consulted our center in an emergency and underwent CT examination again (Figure 1B). The foreign material was removed by a doctor who confirmed the foreign material as the mesh used in a parastomal hernia (Figure 1C and D).

History of past illness

The patient underwent anus-preserving radical resection (Dixon operation) for rectal cancer in November 2010. The pathological diagnosis revealed rectal villous tubular adenocarcinoma with negative margins and no lymph node metastasis. Four months later, she was admitted to the hospital because of difficulty with defecation and was diagnosed with postoperative anastomotic stenosis. The stenosis was removed using a colonoscope. Recurrent defecation difficulties for 3 years led to an emergency colostomy for intestinal obstruction. According to the surgical records, the distal colon was removed and closed from the peritoneal reflection. In January 2018, the patient was admitted to our center and underwent parastomal hernia mesh repair (keyhole, Shanshi, China) for an emerging parastomal hernia.

Personal and family history

The patient underwent anus-preserving radical resection (Dixon operation) for rectal cancer in November 2010.

Physical examination

A portion of the foreign material was excreted from the patient's anus. The foreign material was removed by a doctor who confirmed the foreign material as the mesh used in a parastomal hernia.

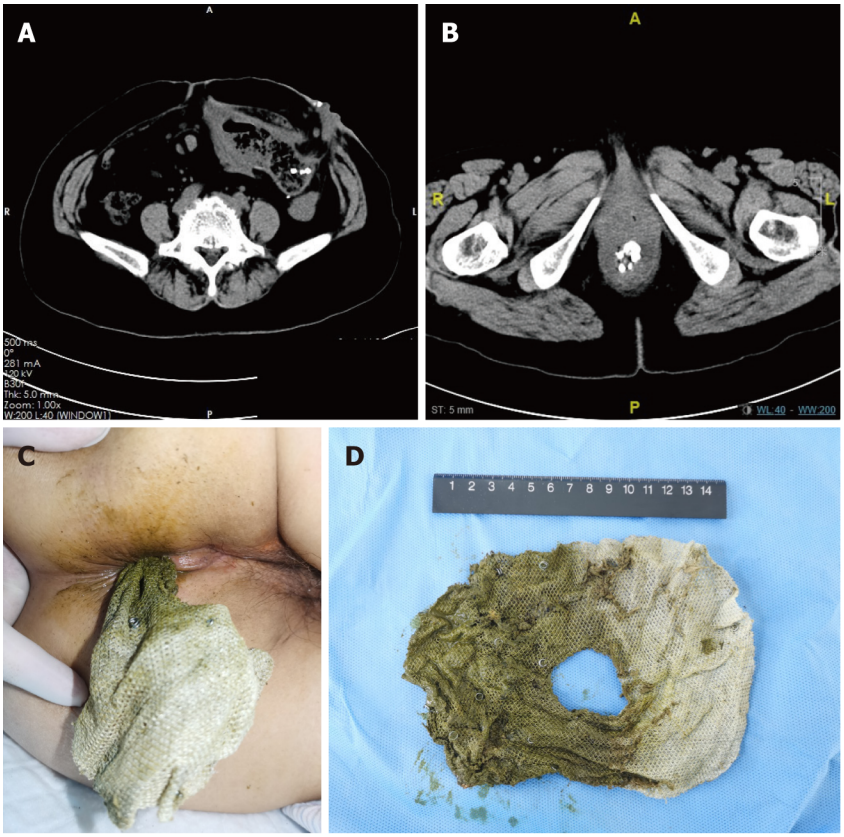

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Figure 1 The computed tomography images and the mesh. A: The computed tomography (CT) images were taken in January 2021; B: The CT images were taken before hospitalization in April 2021. In A and B metal tackers were seen entering the intestine with the mesh located near the anus; C: After hospitalization, the mesh was partially excreted through the anus; D: The mesh was excreted intact along with its metal tackers.

Laboratory examinations

Laboratory tests were unremarkable.

Imaging examinations

We performed gastrointestinal contrast, where a contrast agent was injected through the stoma revealing a t-branch tube structure in the enterocoelia (Figure 2). Transanal colonoscopy was performed and revealed stenosis blocking the passage of the colonoscope. Severe inflammation triggered by the mesh of the parastomal hernia was observed. Due to severe stenosis at the anastomosis, the t-branch tube structure could not be seen in this direction (Figure 3).

FINAL DIAGNOSIS

Mesh erosion into the colon secondary to bowel perforation.

TREATMENT

The patient was considered to have a potential intraperitoneal enteral leakage and consented to the elective operation. Midline abdominal incision was created, and the t-branch tube structure formed from the colon near the stoma, proximal and distal colons, and the lateral wall of the small intestine (Figure 4). The t-branch tube and unduly long colon was excised, and the original stoma was closed. A colostomy was reconstructed on the right side of the abdominal wall.

OUTCOME AND FOLLOW-UP

Pathological examination revealed granulomatous inflammation without tumor recurrence. The patient

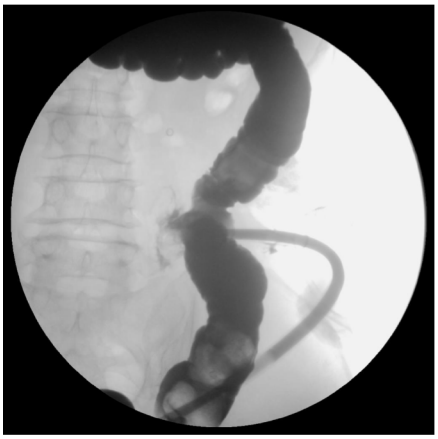

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Figure 2 The contrast agent was injected through the drainage tube placed through the stoma. The intestinal tube formed a t-branch tube structure.

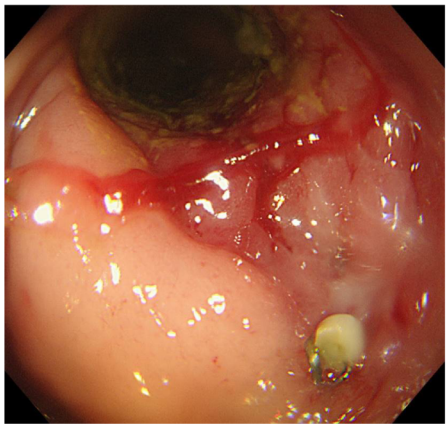

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Figure 3 Transanal colonoscopy revealed the stenosis. Metal tackers that have not yet been excreted can be seen.

was discharged 10 d after the surgery. The patient showed no discomfort after discharge and continued receiving follow-up care on an outpatient basis.

DISCUSSION

According to the European Hernia Society guidelines on the prevention and treatment of parastomal hernias, the incidence of parastomal hernia is more than 30% 1 year after fistulization, more than 40% after 2 years, and can reach 50% or even higher over time[1]. In China, the number of patients undergoing abdominal surgery has increased, and the number of patients with parastomal hernias has gradually increased[2]. Due to the higher risk of recurrence after suture repair, mesh repair is still the best way to repair a parastomal hernia[1]. Common complications of a parastomal hernia repair include seroma, intestinal injury, intraoperative and postoperative bleeding, bowel perforation, hernia recurrence, intestinal obstruction, mesh contamination or infection, and chronic pain.

Mesh erosion is commonly considered a rare complication[3]. According to Jeans *et al*[4], the incidence of mesh erosion after inguinal hernia repair is less than 1%[4]. However, Hamouda *et al*[5] suggested that this percentage is significantly underestimated[5,6]. Targarona *et al*[7] reported that the incidence of graft erosion after hiatal hernia surgery was approximately 2.3%[7]. Unlike hiatal hernia, diaphragm movement is the primary cause of mesh migration and erosion[8]. Therefore, we hypothesized that the incidence of mesh erosion after parastomal hernia surgery would be lower than that after hiatal hernia surgery.

In our literature review, there was only one report of mesh erosion after parastomal hernia surgery [9]. There were only a few cases of parastomal hernia and a low incidence of mesh erosion occurring after various hernia surgeries. Particularly, mesh erosions after parastomal hernia surgeries are even more scarce. In addition, the initial symptoms are usually hematochezia, intestinal obstruction, or other

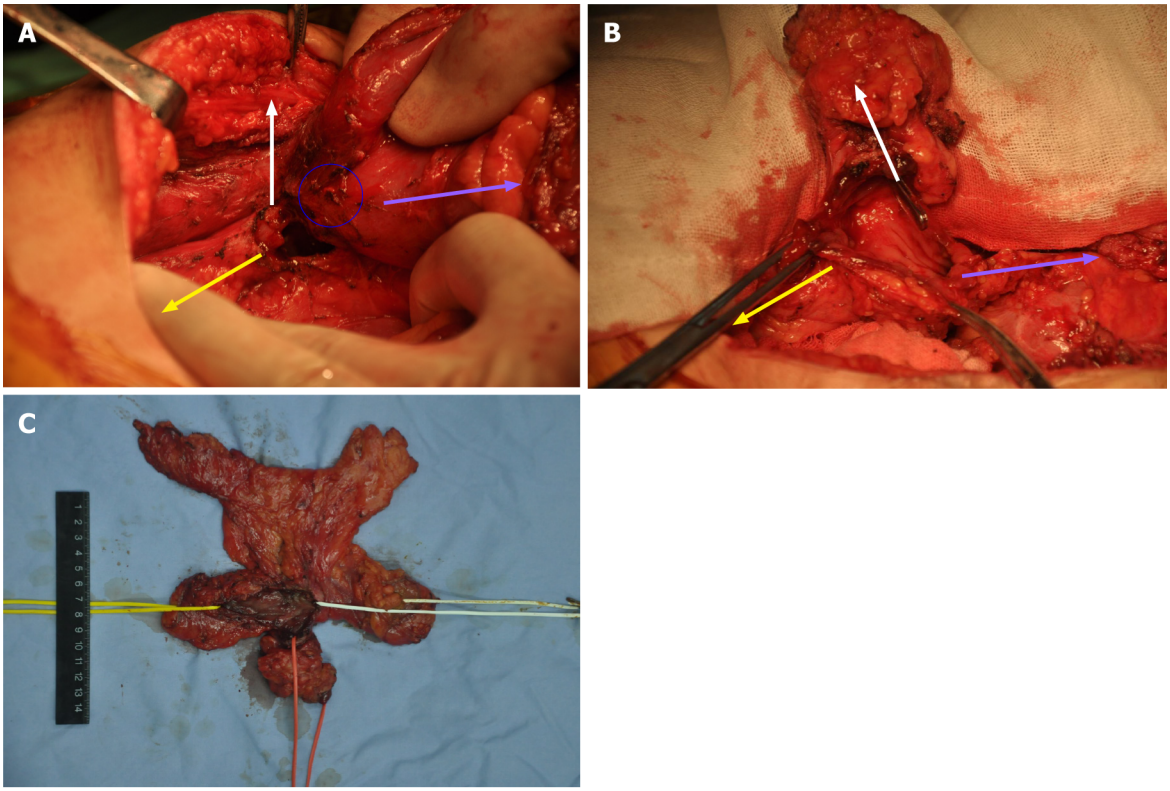

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Figure 4 The structure of the t-branch tube. A: The yellow arrow indicates the proximal colon, the white arrow indicates the colostomy colon, the purple arrow indicates the distal colon, and the blue circle indicates the small intestinal wall. Intraoperative exploration confirmed that the t-branch tube was composed of the distal colon, proximal colon, colostomy colon, and small intestinal wall; B: After separating the small intestinal wall, the structure of the t-branch tube could be more clearly identified; C: Surgical removal of the t-branch tube structure of the colon. The yellow marker shows the proximal colon, the green marker indicates the distal colon, the orange marker shows the original stoma, and the defect is the original small intestinal wall.

digestive system symptoms. Therefore, patients often seek treatment from gastroenterology or gastrointestinal surgery causing underreporting of mesh erosion. Moreover, the primary disease leading to a stoma can shorten the lifespan of patients, which may explain why parastomal hernias are uncommon.

We used "Mesh Erosion" and "Mesh migration" as the keywords to search in PubMed. The reference lists from the extracted studies were manually reviewed to identify additional potentially eligible studies. A total of 132 reports describing 137 cases of mesh erosion from 1973 to 2022 were reviewed (Table 1). All abdominal hernia types except hiatal hernia were included. Erosion caused by mesh placement due to pelvic floor prolapse and other diseases was excluded. The selected studies included 96 cases of mesh erosion of digestive organs, 42 cases of urinary system erosion (including 8 cases of both digestive system and urinary system erosion), and 7 cases of other systems (including 1 case of the inguinal region, 1 case of the testis, 3 cases of migration of only non-eroded organs, 1 case of a uterine adnexa, and 1 case of the heart).

Agrawal and Avill[10] believed that there are two main methods of mesh migration[10]. The first is the mesh migration along the path of least resistance caused by inadequate fixation or external forces. The second is the slow and gradual migration across the anatomical plane. The mesh may be displaced initially and then eroded into adjacent tissues, which is the erosion and migration of the mesh caused by a foreign body reaction[10]. Local tissue destruction from the inflammatory response, granulation tissue proliferation, and repetition of these two processes results in mesh erosion of the intestine. This process can take several years to occur.

Pathology and colonoscopy in the case reports of Millas *et al*[11], Celik *et al*[12], and Riaz *et al*[13] confirmed granulomatous inflammation at the lesion site, which proves the existence of this process and is consistent with the present case. According to Losanoff *et al*[14] and Hamouda *et al*[5], mesh erosion after inguinal hernia surgery is caused by direct contact between the rough mesh surface and organs such as the intestine. The parastomal hernia mesh includes a polyvinylidene difluoride and polyester layer and biological mesh. It is a basic requirement for a parastomal hernia mesh to contact the intestine; therefore, the effect of mesh material on intestinal erosion is irrelevant.

Riaz *et al*[13] suggested that trimming the sharpened edges of the mesh could prevent damage to the surface of the organs and prevent an inflammatory response that could lead to weakness and mesh erosion[13]. We agree with their opinion that an appropriate mesh should be selected to reduce the

Table 1 General information of the patients included in the review

Patient information		Number of cases
Sex	Male	110
	Female	27
Age	≤ 60 years old	57
	> 60 years old	80
Mesh erosion time	≤ 6 mo	22
	> 6 mo	114
Type of hernia	Inguinal hernia	83
	Incision hernia	33
	Umbilical hernia	10
	Parastomal hernia	1
	Obturator hernia	1
	Abdominal wall strengthening	5
	Abdominal wall hernia not specified	5
History of abdominal surgery other than hernia repair		56
Symptoms of prior mesh infection		17
Condition of hernia after mesh erosion	Hernia recurrence	17
	Incisional hernia	3
History of chemotherapy and immune-suppressive therapy		8

The time of invasion was not specified in 1 case. Incisional hernia occurred in 1 case after umbilical hernia repair, and invasion occurred after secondary hernia repair. Due to various emphases in the case reports, it was impossible to judge whether the items not mentioned were negative, so only positive results were counted.

necessary trimming. Particularly in cases of parastomal hernia, the central pore should be trimmed to minimize mechanical damage caused by friction between the mesh and intestine.

Goswami *et al*[15] reported a case of cecal erosion after transabdominal preperitoneal for a right inguinal hernia in a patient with a history of appendectomy before transabdominal preperitoneal[15]. Goswami *et al*[15] indicated that the adhesion caused by the patient's previous appendectomy predisposed the patient to further adhesion between the mesh and organ, which eventually promoted mesh erosion. Abdominal adhesions caused by previous surgeries cause the intestine to lose its ability to avoid injury. Moreover, repeated friction between the fixed intestine and the foreign body causes local tissue damage, leading to mesh erosion. Patients with parastomal hernias have had at least one or several previous operations. For a parastomal hernia, more attention should be paid to adhesions caused by previous operations on mesh erosion.

According to Yang[16], titanium tackers used to fix mesh are more likely to adhere to the intestine, which Hollinsky *et al*[17] confirmed through animal experiments. In our experience, titanium tackers also cause serious adhesions. Persistent inflammation may increase the risk of postoperative hernia mesh erosion and migration[11]. Parastomal hernias involve stomas; therefore, the surgical field is not as sterile as other hernia procedures, potentially leading to mesh erosion. Benedett *et al*[18] recommended that chemotherapy could lead to intestinal perforation and a difficult postoperative period[18]. Patients with parastomal hernia commonly have intestinal tumors, and the state of immunological prostration induced by chemotherapy should not be disregarded.

In our case, another cause that should not be overlooked is the potential iatrogenic causes. The surgeon who performed the stoma may have intended to perform secondary intestinal anastomosis; therefore, the distal colon of the closed loop was over reserved. Preoperative examination before the parastomal hernia repair did not reveal the status of a closed loop intestine. Irregular operation and incomplete preliminary examination before parastomal hernia repair are also important reasons for t-branch tube formation.

It is difficult to diagnose mesh erosion because of the level of damage needed for a patient to feel symptoms, which can vary and take many years to develop. In our review, we observed 96 bowel mesh erosion cases (Table 2). The symptoms of mesh erosion include chronic abdominal pain, vomiting, digestive tract hemorrhage, bowel perforation, and intestinal obstruction. In patients who may have one

Table 2 Diagnostic methods of mesh erosion of the intestinal tract in literature review

Examinations			Number of cases
First radiographic diagnosis	Positive	Mesh erosion	0
	Negative	Foreign body	1
		Other lesions	13
		No abnormal	3
First CT diagnosis	Positive	Mesh erosion	4
	Negative	Mesh migration	2
		Foreign body	4
		Other lesions	44
		No abnormal	6
First gastrointestinal angiography diagnosis	Positive	Mesh erosion	1
	Negative	Foreign body	0
		bowel perforation	12
		Other lesions	8
		No abnormal	1
First colonoscopy diagnosis	Positive	Mesh erosion	11
	Negative	Foreign body	3
		Other lesions	17
		No abnormal	6
Ultrasonic diagnosis	Positive	Mesh erosion	0
	Negative	Mesh migration	1
		Foreign body	1
		Other lesions	4
		No abnormal	2
MRI	Positive	Mesh erosion	0
	Negative	Foreign body	0
		Other lesions	2
		No abnormal	0

CT: Computed tomography; MRI: Magnetic resonance imaging.

or more of these symptoms, a negative fecal occult blood test may occur[12]. Determining mesh status using radiography is also difficult[19]. Among the 96 cases reviewed, the diagnosis was established during surgery in 74 cases, on the first endoscopy in 10 cases, on at least the second endoscopy in 7 cases, and by other means such as CT in 7 cases. A convenient and inexpensive objective assessment of mesh behavior after mesh placement is difficult because there are no routinely available mesh products with unique radiographic labels[20].

Our literature review concluded that radiography, CT, and gastrointestinal angiography could only diagnose intestinal obstruction and leakage, although identifying the actual cause was still difficult. Doppler ultrasound is only performed after clinical judgment of a doctor to determine the mesh location. In our case, because the metal tackers moved into the intestine with the mesh, the CT scan alone could diagnose mesh erosion in the intestine. Early colonoscopy can only detect inflammation, intestinal polyps, or diverticulum; therefore, it may be wrongly interpreted and misdiagnosed as a malignant tumor[21-23]. The actual cause can only be determined when patients undergo more than one colonoscopy or abdominal exploration after experiencing severe symptoms. The early diagnosis of mesh erosion is complex, and the history of hernia repair should not be ignored when a patient presents with abdominal symptoms.

In our literature review, only 9 patients did not receive surgical treatment, and the remaining patients with mesh erosions received surgical treatment. In the 9 cases opting for non-surgical treatment, some authors believed that surgery should still be performed[24-26]. Previous studies discussed that patients usually refuse surgical treatment at the onset of their symptoms but finally receive surgical treatment once they worsen[27,28]. Therefore, mesh erosion after parastomal hernia surgery should be actively treated. Due to the small number of cases, it was inconclusive if the mesh of a parastomal hernia erosion or the bowel loops should be removed and the stoma rebuilt. We believe that mesh erosion, especially penetration into the intestine, necessitates the removal of some or all of the mesh into the intestinal loops. The segment of the intestinal loop should be resected, and the stoma rebuilt. Owing to repeated operations at the original stoma, local skin scars cause difficulties in care of the stoma. Re-stoma reduces the possibility of postoperative intestinal leakage and improves the future nursing of patients.

CONCLUSION

Mesh erosion is a rare complication, but its real incidence may be higher than the reported incidence. Previous studies have speculated on the etiology, many of which are more prominent in patients with parastomal hernia after surgery. Mesh erosion has no typical clinical manifestations, imaging, and endoscopy characteristics. With its insidious behavior, mesh erosion is difficult to diagnose at an early stage. Surgeons should be aware of the surgical history of hernia repair especially when the patient with mesh presents with abdominal symptoms.

FOOTNOTES

Author contributions: Zhang Y contributed to the conceptualization and methodology, wrote the original draft, reviewed, and edited; Lin H contributed to the conceptualization and methodology and collated the patient's data; Liu JM and Wang X collated the patient's data, reviewed, and edited; Cui YF reviewed, edited, and contributed to supervision; Lu ZY contributed to conceptualization, methodology, and supervision; All authors have read and approved the final manuscript.

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LETTER TO THE EDITOR

Fecal microbiota transplantation as potential first-line treatment for patients with *Clostridioides difficile* infection and prior appendectomy

Jing-Wen Zhao, Bing Chang, Li-Xuan Sang

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Peer-review model: Single blind

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Abstract

Clostridioides difficile infection (CDI) is a global health problem. The association of appendectomy on the severity and prognosis of CDI has been reported in many literatures, but there are still contradictions. In a retrospective study entitled "Patients with Closterium diffuse infection and prior appendectomy may be prone to word outcomes" published in *World J Gastrointest Surg* 2021, the author found that prior appendectomy affects the severity of CDI. Appendectomy may be a risk factor for increasing the severity of CDI. Therefore, it is necessary to seek alternative treatment for patients with prior appendectomy when they are more likely to have severe or fulminant CDI.

Key Words: *Clostridioides difficile* infection; Appendectomy; Fecal microbiota transplantation; Intestinal microbiota; Toxic megacolon; Colectomy

Core Tip: The fecal microbiota transplantation (FMT) is a universally approved treatment plan for recurrent *Clostridioides difficile* infection (CDI). We believe that early FMT is a better choice for patients with CDI and prior appendectomy even if they are not diagnosed as recurrent CDI. FMT can change the composition of patients' intestinal microbiota in a lasting way to prevent worse outcomes.

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TO THE EDITOR

We read with great interest the article by Shaikh *et al*[1] entitled patients with "Clostridium difficile infection and prior appendectomy may be prone to worse outcomes". They studied the association of appendectomy on the severity and prognosis of *Clostridioides difficile* infection (CDI). CDI remains a major health care problem globally. Due to super virulent strains and the abuse of antibiotics, the incidence and severity of CDI have been increasing since 2000[2].

We found that there were contradictions in the discussion of the role of prior appendectomy on CDI in the previous literature. The sample size of this article is much larger than that of previous studies, which is one of its strengths, thus providing more powerful evidence for future research on the relationship between prior appendectomy and CDI. This study did not prove that the risk of CDI recurrence in patients with prior appendectomy was increased. However, appendectomy affected the severity of CDI and was also related to toxic megacolon and colectomy, which was consistent with the conclusion of Yong *et al*[3], who stated that appendectomy may be a risk factor for the increase in CDI severity. The specific reason still needs to be determined *via* experimental and clinical research. It is speculated that the appendix is the "safe house" of normal colon bacteria[4], and appendectomy may reduce intestinal immune reactivity, which may reduce intestinal resistance to *Clostridioides difficile* and lead to a worse outcome of CDI. To further confirm and validate the results of this paper, a larger prospective study is needed.

It is necessary to seek a new treatment plan when patients with prior appendectomy are more likely to have severe or fulminant CDI. The fecal microbiota transplantation (FMT) is a method approved by most international guidelines for recurrent CDI[5,6]. Although FMT has been proven to be safe and effective in recurrent infections, its efficacy in severe or fulminant CDI is still unclear. A series of studies show that FMT combined with antibiotics can reduce the mortality of severe and fulminant CDI[7] and reduces the occurrence of surgery[8]. Early FMT can improve the survival rate of patients with severe CDI. Severe CDI patients without FMT have a serious prognosis and a very high mortality rate (30%-60%)[9]. FMT treatment in primary severe CDI has a very low disease recurrence rate[10]. Tixier *et al*[11] provided low-quality evidence to support FMT as a safe and effective treatment for adult severe and fulminant CDI. At present, some scholars believe that FMT can be used as the first-line treatment for severe and fulminant CDI[12], but more evidence is needed.

FMT should be performed by an experienced team after a thorough risk assessment. In clinical practice, the need for FMT or even multiple FMTs can be assessed by establishing a risk assessment system that includes prior appendectomy as a risk factor. Additionally, it has been demonstrated that the presence of pseudomembranous lesions under colonoscopy and highly pathogenic CDI strains are predictors of FMT failure, so patients with severe or fulminant CDI may require multiple FMTs until the pseudomembranous lesions disappear and clinical remission is achieved[13]. We believe that early FMT is a better option to modify the composition of the patient's gut microbiota in a durable way, prophylactically reducing the incidence of toxic megacolon as well as colectomy.

Many risk factors for CDI are immutable (such as advanced age)[14]. The current prevention strategies mainly focus on improving hand hygiene, contact isolation, environmental purification and antibiotic management plans[15]. These strategies have been proven to be effective but still have limitations. Shaikh made us realize that new strategies are needed to prevent CDI when dealing with specific patients. Although probiotics are not included in the guidelines for the prevention and treatment of CDI, some probiotic such as strains from Saccharomyces, Bifidobacterium, or Lactobacillus genera have potential protective effect against *Clostridioides difficile*[16]. For patients who have undergone prior appendectomy, preventive improvement of intestinal flora is the key to avoid worse outcomes.

Many studies have confirmed the long-term safety of FMT for recurrent CDI[17]. A multicenter long-term follow-up study also showed that FMT is successful and safe for patients with severe or refractory CDI[18]. These findings all emphasize the value of FMT in avoiding the repeated use of antibiotics which may cause dysbiosis of the intestinal microbial community permanently. FMT can restore the biological diversity of intestinal microbiota to restore the normal intestinal function. All these enlighten us that FMT has the potential to be the first-line treatment for patients with CDI and prior appendectomy.

FOOTNOTES

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