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OPINION REVIEW

Diverticulitis is a population health problem: Lessons and gaps in strategies to implement and improve contemporary care

Stephanie Lee Stovall, Jennifer A Kaplan, Joanna K Law, David R Flum, Vlad V Simianu

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Abstract

The disease burden of diverticulitis is high across inpatient and outpatient settings, and the prevalence of diverticulitis has increased. Historically, patients with acute diverticulitis were admitted routinely for intravenous antibiotics and many had urgent surgery with colostomy or elective surgery after only a few episodes. Several recent studies have challenged the standards of how acute and recurrent diverticulitis are managed, and many clinical practice guidelines (CPGs) have pivoted to recommend outpatient management and individualized decisions about surgery. Yet the rates of diverticulitis hospitalizations and operations are increasing in the United States, suggesting there is a disconnect from or delay in adoption of CPGs across the spectrum of diverticular disease. In this review, we propose approaching diverticulitis care from a population level to understand the gaps between contemporary studies and real-world practice and suggest strategies to implement and improve future care.

Key Words: Diverticulitis; Hospitalization; Elective; Emergent surgery; Clinical guidelines; Diverticular disease

Core Tip: Diverticulitis-associated hospitalization and colectomy are costly and have increased over the past decade, despite professional society guidelines advocating for outpatient management and individualized decisions about surgery. These trends raise flags about how to best measure guideline-concordant clinical practice in the modern era. Strategies to improve guideline-concordant care may consist of improved population-level data in diverticulitis care, regionalization of care, and system wide quality improvement initiatives for guideline implementation.

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INTRODUCTION

Diverticular disease is the most common benign pathology of the colon and exhibits an unpredictable, relapsing-remitting course[1]. The rate of symptomatic diverticulitis is estimated to range from < 5% to 25%, though its precise incidence is controversial. Of patients with symptomatic disease, 15% will develop acute or chronic complications such as abscess, fistula, obstruction, bleeding, or perforation[2-4]. Advanced age, obesity, smoking, non-steroidal anti-inflammatory drug use, sedentary lifestyle, and Western diets are all risk factors for diverticulitis[1,5-9]. It is unsurprising, therefore, that diverticular disease is pervasive in Western countries and its prevalence has increased in the recent past[1-3,10-12]. Indeed, diverticulitis is one of the top five gastrointestinal admission diagnoses in the United States, accounting for nearly 980000 hospital days, approximately 208000 admissions, and over $5.5 billion in combined inpatient and emergency department costs in 2018[3,12].

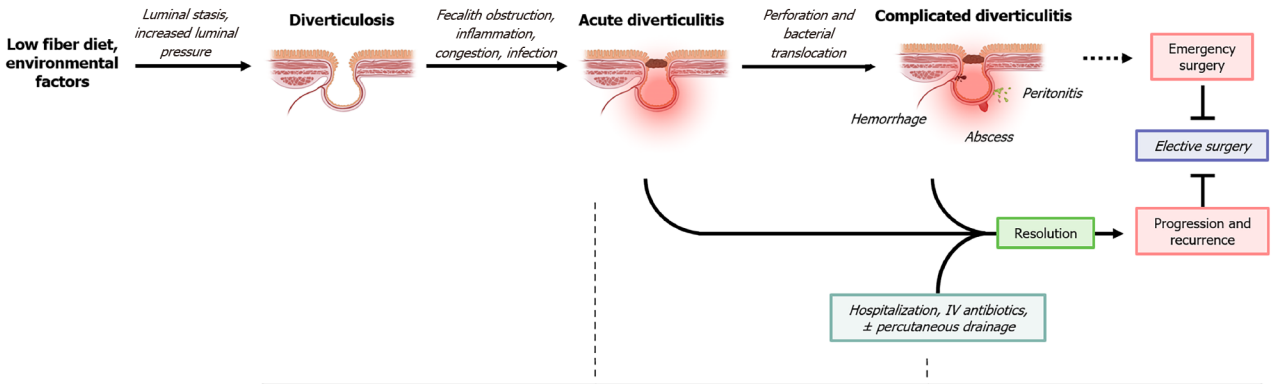
To curb this healthcare burden, several recent studies have challenged the standards of how acute and chronic diverticulitis are managed. The admission rate after selective outpatient management of uncomplicated diverticulitis is low and confers significant healthcare savings, ranging from 42%-82% compared to inpatient care[10,13]. Similarly, recent studies showed no significant difference in the rate of emergency surgery or recurrence after prophylactic colectomy for uncomplicated disease[10,14]. These data prompted many professional societies' clinical practice guidelines (CPGs) to shift toward outpatient management and individualized decisions about surgery[15-19].

Despite these two paradigm shifts over the past decade, the rate of hospitalization and surgery for diverticulitis rose, which lead to an increase in costs for diverticulitis care[3,14,20-22]. The specific factors contributing to this increase in hospitalization, surgery, and costs are poorly understood. It is not clear whether increased hospitalizations and surgery are necessary, driven by patients or their providers, or reflect overuse, under use, or concordance with CPGs across the spectrum of diverticular disease. Hospitalization and surgery are major drivers of healthcare costs and understanding the factors driving their use is necessary to better risk stratify patients, improve quality of care, and control costs. In this review, we propose approaching diverticulitis care from a population level to understand gaps between CPGs and real-world practice and suggest strategies to implement and improve future care.

REFRAMING DIVERTICULITIS FROM PROGRESSIVE TO RELAPSING-REMITTING DISEASE

Diverticular disease was once considered a progressive condition arising from environmental factors, primarily a low fiber diet[1,2]. This model implicated fiber deficiency as a driver of luminal stasis and increased intraluminal pressure leading to the formation of colonic pseudodiverticula. Obstruction of these diverticula by fecaliths was thought to cause inflammation, congestion, inflammation/infection, and eventual microperforation, bacterial translocation, and abscess formation[1,2]. Predicated on this pathogenesis, aggressive care with broad-spectrum IV antibiotics, bowel rest, and hospitalization was the mainstay of diverticulitis treatment. To prevent recurrence, surgical guidelines advocated for early colectomy after two episodes of uncomplicated or a single episode of complicated diverticulitis[23,24]. Epidemiological studies addressing the natural history of diverticular disease, however, do not support this progressive disease model and have called into question the foundation of these guidelines (Figure 1)[25-30].

For example, a progressive disease model predicts more frequent/severe relapses and complications in subsequent diverticulitis episodes. While the risk of recurrence increases, the rate of complicated diverticulitis actually decreases with each subsequent episode in observational studies[3,31]. Addi-



		Diverticulosis	Uncomplicated diverticulitis	Complicated diverticulitis
Progressive disease model	*Medical*	▪ Prevention: High fiber diet ▪ Avoid nuts/seeds	▪ IV antibiotics in all patients ▪ Bowel rest ▪ IV hydration	▪ IV antibiotics in all patients ± percutaneous drainage ▪ Bowel rest ▪ IV hydration
	Inpatient Care	–	▪ Hospitalization in most patients	▪ Hospitalization in most patients
	Surgery	▪ Not indicated if asymptomatic	▪ Indicated electively after two episodes to reduce risk of recurrence[24,25]	▪ Indicated electively after one episode[24,25] ▪ Emergent surgery for peritonitis/treatment failure[24,25]
Challenges to progressive disease model	*Medical*	▪ Associated with other risk factors[38,39] • Genetic factors[36,37,40] • Colonic dysmotility[42,44] • Microbiome[38] • Chronic inflammation ▪ Nuts/seeds not associated with diverticulitis[27]	▪ Equivalent outcomes in immunocompetent patients treated with or without antibiotics in outpatient setting[46-50] ▪ Early enteral nutrition associated with lower morbidity[28,29]	▪ Four days of antibiotics after source control equivalent outcomes to extended course[26]
	Inpatient Care	–	▪ Low risk of admission after outpatient management and equal to inpatient treatment[51]	▪ High rate of recurrent abscess despite percutaneous drainage/antibiotics[30]
	Surgery	–	▪ Elective surgery did not decrease rate of emergency surgery[13] ▪ Equal rates of recurrence with or without surgery[14]	▪ Higher stoma rate, diverticulitis-associated inpatient hospital days, and cost with surgery[71]

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Figure 1 Historical understanding of diverticulitis as a progressive disease and summary of recent challenges to the progressive disease model.

tionally, patients with diverticulitis may develop chronic manifestations of disease that are not the direct result of a single episode (such as fistula or stricture). These chronic symptoms can range from ongoing abdominal pain in the absence of inflammation (symptomatic uncomplicated diverticular disease, incidence: 20%) to refractory symptoms with inflammation/early recurrence (smoldering diverticulitis, incidence: 10%), and cryptogenic segmental colitis associated with diverticulosis (incidence: 1%-11%)[32,33]. Furthermore, our understanding of the development of colonic diverticula, the precursor lesion to diverticulitis, has evolved. Statistical models derived from twin studies estimates that genetic factors account for 40%-50% of the risk of diverticular disease[34,35]. In patients of European ancestry, diverticulitis is almost exclusively in left-sided (> 95% sigmoid) but is mostly right-sided (80%) in patients of Asian descent[36]. Other studies implicate abnormal colonic neuromuscular function, altered microbial metabolism, and chronic inflammation as secondary factors contributing to development of diverticular disease[37-43]. Collectively, these data point to a relapsing-remitting inflammatory model of disease, rather than a progressive, infectious model (Figure 2). These data drove a shift in CPGs away from automatic hospitalization, antibiotics, and surgical intervention in the acute phase[15-19,44].

PROFESSIONAL GUIDELINES PIVOT AWAY FROM ANTIBIOTICS, HOSPITALIZATION, AND SURGERY

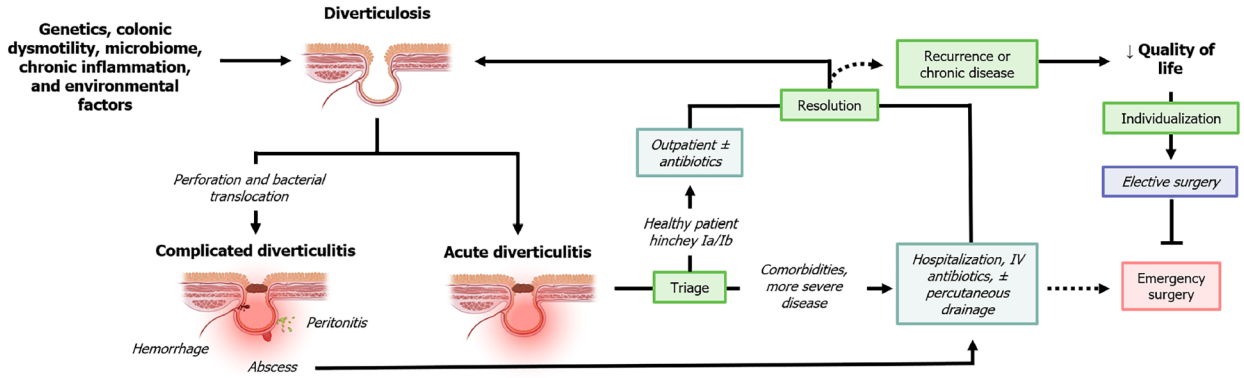
Historically, diverticulitis was considered an infectious process requiring routine antibiotics. However, multiple randomized controlled trials, as well as several metanalyses, have shown no significant difference in outcomes in patients with uncomplicated diverticulitis treated with or without antibiotics [45-49]. In response to these data, the American Gastrological Association (AGA) and American Society of Colon and Rectal Surgeons (ASCRS) now recommend selective use of antibiotics in immunocompetent patients (Table 1)[18,19]. Concurrently, the recommendation for hospitalization in uncomplicated disease was similarly challenged by clinical data showing similar outcomes in select patients receiving

Table 1 Comparison of medical and surgical professional society clinical practice guidelines for diverticular disease

	Medical society guidelines			Surgical society guidelines		
	AGA[19], 2015	AAFP[16], 2013	ACP[17], 2022	ASCRS[18], 2020	SAGES[45], 2019	WSES[15], 2020
Diagnosis and medical management						
Triage to outpatient	-	Recommend outpatient if uncomplicated and mild (level C)	Outpatient in uncomplicated disease as outpatients in absence of SIRS (conditional, low certainty)	-	Selective outpatient in immunocompetent host with uncomplicated diverticulitis (weak, moderate-quality)	Outpatient if uncomplicated without comorbidity, re-evaluate at 7 d (weak, moderate-quality)
Antibiotics						
Use	Selective use in uncomplicated disease (conditional, low-quality)	Enteric coverage if inpatient. Use outpatient if persistent or worsening symptoms (level B)	Omit in healthy, immunocompetent outpatients with uncomplicated disease and no SIRS (conditional, low certainty)	Healthy patients with uncomplicated disease should not be treated with antibiotics (strong, high-quality). May use in non-operative strategies (strong, low-quality)	Selective use in immuno-competent patients with uncomplicated disease (weak, high-quality)	Advise against antibiotics in healthy patients with uncomplicated disease and no SIRS (strong, high-quality)
Duration	-	-	Insufficient data	-	-	-
Percutaneous drainage	-	Consider in presence of abscess. No size recommendation (level C)	Insufficient outcomes data with percutaneous drain	Recommend when abscess > 3 cm (strong, moderate-quality)	Abscess < 4 cm: Trial antibiotics, drain for failure. Abscess > 4 cm: Drain upfront (weak, low-quality)	Abscess 4-5 cm: Trial antibiotics, drain for failure (weak, low-quality). Abscess > 5 cm: Drain upfront (weak, low-quality)
Prevention	Fiber, physical activity (conditional, very low-quality)	Fiber intake, weight loss, smoking cessation	-	Tobacco cessation, limit red meat, physical activity weight loss (strong, low-quality)	-	-
Surgical management						
Emergency surgery						
Indications	-	-	-	Diffuse peritonitis, non-operative treatment failure (strong, low-quality)	Peritonitis - Hinchey class III and IV (strong, low-quality)	
Stoma or no stoma	-	-	-	Restoration of continuity preferred, when possible, based on patient/OR factors, surgeon preference (strong, moderate-quality)	Hartmann's if unstable, or immunocompromise. Sigmoid resection with primary anastomosis and proximal diversion over Hartmann's (weak, moderate-quality)	Critically-ill or major comorbidities: Hartmann's procedure (strong, low-quality). Stable without comorbidities: Primary resection ± diversion (weak, low-quality)
Laparoscopic lavage	-	-	-	Advise against in feculent peritonitis (strong, high-quality). Not preferred in purulent peritonitis (strong, high-quality)	Consider in select Hinchey III with appropriate expertise and intensive monitoring (weak, high-quality)	Reserve for highly selected patients with generalized peritonitis (weak, high-quality)
Elective surgery						
Uncomplicated	Recommends against after single episode of	-	-	Individualize, do not based on age or episodes (strong,	Resect when symptomatic disease decreases-quality of life (strong, moderate-	Recommend elective resection in high-risk patients

	acute diverticulitis, individualize (conditional, very low-quality)			moderate-quality)	quality)	(weak, very low-quality). Individualize, do not base on episodes (weak, low-quality)
Complicated	-	-	-	Consider when diverticular abscess resolved (strong, moderate-quality). Recommend for fistula, obstruction, or structure (strong, moderate-quality)	Minimum six weeks after complicated episode (weak, low-quality)	-

All professional societies agree workup should include a history and physical, laboratory studies, and imaging with contrast-enhanced abdominopelvic computed tomography (CT), if clinically indicated. Societies agree that ultrasound with regional expertise or magnetic resonance imaging are acceptable alternatives in patients in whom contrast-enhanced CT is contraindicated. Similarly, surgical societies agree that using minimally invasive surgery is preferable in emergent and elective surgery when expertise is available. AGA: American Gastroenterological Association; AAFP: American Academy of Family Physicians; ACP: American College of Physicians; ASCRS: American College of Colon and Rectal Surgeons; SAGES: Society of American Gastrointestinal and Endoscopic Surgeons; WSES: World Society of Emergency Surgery.



		Diverticulosis	Uncomplicated diverticulitis	Complicated diverticulitis
Relapsing remitting model	*Medical*	▪ Prevention • High fiber diet • Smoking cession • Weight loss	▪ Selective antibiotic use[15-19,45] ▪ PO antibiotics or early transition to PO[16] ▪ Diet as tolerated	▪ Hospitalization ▪ IV antibiotics ▪ ± percutaneous drainage
	Inpatient care	–	▪ Selective outpatient management[15-17,45]	▪ Hospitalization for many patients
	Surgery	▪ Not indicated in asymptomatic disease ▪ Does not prevent diverticulitis (re)occurrences[15,18,45]	▪ Do not base on age, number recurrences, or any single factor[18] ▪ Individualized decisions about surgery[18]	▪ Recommended selectively after complicated diverticulitis[18]
Current clinical questions	*Medical*	▪ Unknown primary etiology of diverticulosis ▪ Unknown impact of risk reduction strategies to prevent recurrence (*e.g.*, weight loss, dietary modifications)	▪ Definition and optimal management of chronic manifestations of diverticulitis poorly defined ▪ Guideline concordance unknown ▪ No consensus on "best" medical alternative to surgery	▪ Abscess size for percutaneous drainage controversial.
	Inpatient care	–	▪ Proportion and demographics of patients treated outpatient unknown	▪ Guideline concordance unknown
	Surgery	–	▪ Factors to consider in individualizing surgery are unknown ▪ Long-term improvement in quality of life after colectomy unknown[57,58] ▪ Guideline concordance unknown	▪ Is delaying/avoiding elective surgery safe in select patients with complicated disease?

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Figure 2 Modernized understanding of diverticular disease *via* a relapsing-remitting model and summary of ongoing controversies and gaps in the literature in diverticular disease.

outpatient treatment with or without antibiotics[50]. While the ASCRS and AGA do not make explicit recommendations regarding the appropriateness of outpatient management in any subset of diverticular disease, nearly one in five low-risk patients with uncomplicated acute diverticulitis are probably now managed in the outpatient setting[51].

Similarly, there has been insight that early surgical intervention in acute, uncomplicated diverticulitis does not prevent future complications. In their 1995 guidelines, the ASCRS recommended elective

resection after two episodes of uncomplicated diverticulitis, or one episode of diverticulitis in patients < 50 years or complicated disease at presentation[23]. However, the rate of emergency surgery in uncomplicated disease is low (1 in 2000 patient-years), and only 1.8%-7% of patients with recurrent disease will require emergency surgery[52,53]. Contemporary studies showing similar rates of emergency surgery and recurrence-related hospitalization in patients who underwent colectomy (5%-11%) compared to those who did not (4%-13%) further questioned the utility of "prophylactic" colectomy[10,14]. Complications of elective colectomy are rare, but significant, with a "rescue colostomy" rate of 1%-3% for anastomotic leak[54,55]. On the other hand, the DIRECT trial showed that patients with recurrent diverticulitis had improved quality of life (QoL) scores at six months after randomization to sigmoid colectomy. A criticism of this landmark trial is that the non-operative group had a high risk of surgery (23%) and was underpowered. This raised questions about the criteria for patients included in the study, and generalizability of 'early surgery' across a spectrum of diverticulitis presentations[56]. Collectively, these data prompted the CPGs to pivot from recommending surgery based on number of episodes toward "individualized" decisions about surgery. The ongoing Comparison of Surgery and Medicine on the Impact of Diverticulitis trial hopes to address this gap in the literature by evaluating whether elective colectomy is more effective than best medical management at improving patients' QoL in diverticular disease[57].

The management of acute complicated diverticulitis has undergone a similar evolution. While emergency colectomy remains non-controversial in feculent or purulent peritonitis, the routine use of Hartmann's procedure has been increasingly challenged in the past decade. Multiple clinical trials and meta-analyses have demonstrated the safety and efficacy of sigmoid colectomy with primary anastomosis (with or without diverting ostomy) in the short- and long-term[58-65]. In the short-term, morbidity and mortality were equivalent or decreased after resection with primary anastomosis *vs* Hartmann procedure. Despite similar recurrence rates, notable differences between the procedures were seen at follow-up[58-61,63-65]. Specifically, rates of stoma non-reversal were lower and complication rates were higher after reversal in patients who underwent Hartmann procedures, compared to primarily anastomosed patients[29,58,60,62]. The practical implication of these data is that anastomosis should be considered in most emergent cases, rather than defaulting to the traditional Hartmann's. This is particularly important, as Hartmann procedures are associated with a decrease in general QoL compared to primary anastomosis for perforated diverticulitis, and the presence of a stoma was shown to be an independent predictor of lower QoL in one study[62,66]. In the modern era, most CPGs advise against routine use of the Hartmann procedure in stable patients, favoring primary anastomosis with or without proximal diversion. However, data showing whether the practice of routine anastomosis in emergent diverticulitis has been meaningfully implemented is lacking.

CONTEMPORARY PRACTICE OF HOSPITALIZATION AND SURGERY DO NOT LINE UP WITH GUIDELINES

The incidence of diverticulitis has increased dramatically in the United States over the past several decades, and hospitalizations for acute diverticulitis rose by 25%-41% from 2000 to 2010[3,67]. Similarly, the rate of elective colectomy for uncomplicated disease has increased[10,14,20,22]. These increases in healthcare utilization are occurring as data and guidelines are urging a shift away from inpatient care and surgery. One explanation may be that more cases of diverticulitis are driving hospitalization and operations, outpacing the recommendations of CPGs. This argument is supported by two observations: (1) The prevalence of diverticulitis is highest in patients aged 65 years and older, a group whose numbers are predicted to increase by 48% in the United States by 2030[47]. CPGs reserve outpatient management for healthy patients, potentially excluding many older diverticulitis patients from receiving outpatient treatment[15,16,19,44]; and (2) The age-adjusted rate of diverticulitis is also increasing, particularly in adults under 50 years of age wherein the incidence of diverticulitis increased by 132% from 1980 to 2007[3]. Conceptualizing diverticulitis as a progressive disease, rather than relapsing-remitting, may prompt some surgeons to operate on younger patients more frequently; however, the magnitude of this effect on rates of surgery are unknown[22]. Studies evaluating the fundamental epidemiology of diverticular disease are dated, and updated studies are needed to better characterize changes in diverticular disease incidence and distribution. Understanding the interplay between this evolving epidemiology and how diverticulitis is treated across healthcare settings and disease severity is important to contextualizing and optimizing patient care in the modern era.

In addition, better data are needed to assess impact of CPGs on diverticulitis care. Contemporary research shows it takes 17 years to incorporate only 14% of published literature into clinical practice, highlighting the role of CPGs in synthesizing vast bodies of literature, and modernizing practice[68]. When implemented, CPGs have the potential to improve the processes of care and patient outcomes, but are infrequently followed[69-72]. For diverticulitis care, the rising rates of hospitalization and surgery may indicate a delay or disconnect in guideline concordant care. In a recent joint consensus statement by the European Association for Endoscopic Surgery (EAES) and Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), only 65% of providers offered outpatient treatment

to low risk patients with uncomplicated disease[44]. When measured about a decade ago, approximately 1 in 3 patients undergoing elective colectomy in Washington State did not meet CPG criteria for resection and it is unclear whether these data reflect regional practice or larger trends in surgical management of diverticulitis[73]. As such, larger scale studies are needed to assess national trends in diverticulitis surgery, but thus far have been limited by a lack of granularity needed to identify the indication for surgery and, therefore, appropriateness of operation and outcome. Furthermore, when emergent diverticulitis surgery is performed by general surgeons, there is a high, and increasing, rate of ostomy, despite CPG suggesting primary anastomosis is safe[18,74]. Yet, another state-level study suggests that mortality after emergency surgery for perforated diverticulitis (particularly in resection with primary anastomosis) may be higher when performed by general compared to colorectal surgeons. Jointly, these studies offer insight into disconnect with CPGs, but incompletely describe the practice patterns for diverticulitis care and are not generalizable to other clinicians or non-surgical patients. These findings may be explained also by selection bias, isolated regional trends in clinical practice, or standard of care. Indeed, diverticulitis remains a clinical challenge for physicians across specialties, including general practitioners, emergency room physicians, gastroenterologists, and surgeons. Said otherwise, there is a lacking in the definition of "guideline concordant care" for diverticulitis and measures thereof across the spectrum of clinical contexts.

One challenge is many diverticulitis CPGs offer conflicting or vague recommendations, and clinicians are less likely to implement CPGs when they are perceived as lacking clarity or sufficient evidence, offer many weak/conditional recommendations, or are too rigid[71,72,75]. For example, while several studies have indicated that outpatient management for uncomplicated disease in select patients is safe, the incorporation of these findings into modern guidelines is inconsistent (Table 1). The decision whether to operate and what operation to perform is similarly fraught with a lack of consensus, shifting guidelines, and behavioral inertia. No professional society offers discrete indications for elective resection, nor specifies which factors to incorporate into such individualized care. There are also no guidelines for managing chronic manifestations of diverticulitis, such as smoldering disease or chronic pain. The ambiguity of these recommendations likely reflects the complexity of decision-making in diverticulitis and a lack of quality population-level studies that address the fundamental epidemiology of disease. Additionally, it has been long recognized that the staging system for diverticulitis is inaccurate and poorly suited to clinical decision making. For example, the term "complicated disease" spans the spectrum of complex disease, ranging from chronic, QoL-limiting conditions requiring elective surgery (*e.g.*, fistula) and acute, life-threatening disease requiring emergency surgery (*e.g.*, feculent peritonitis). This absence of a clinically relevant classification system could contribute to ambiguous guidelines. Collectively, these factors may contribute to inappropriately heterogeneous and potentially low-value care, particularly considering the persistently high rate of elective colectomy in the United States compared to other Western countries[76].

The absence of clear guidance from professional societies may also explain regional variations in clinical practice that can be driven by patient, hospital, and market factors. For example, referral patterns to surgeons could influence the rate of colectomy *via* physician-induced demand[77]. In this phenomenon, information asymmetry leads to undue physician influence on patient decision making, thereby increasing demand for health services like surgery. Perhaps patients who might not otherwise undergo an operation choose to do so electively because surgery is offered more often than if they never saw a surgeon. Indeed, one study showed the rate of elective colectomy increased linearly with surgeon density, but the observational nature of the study precludes conclusions about causation[78]. This same study showed patients receiving diverticulitis care in large (> 500 beds) metropolitan for-profit hospitals are more likely to undergo elective colectomy compared to smaller, suburban, or rural hospitals[78]. Importantly, these studies do not differentiate the indication for surgery (*e.g.*, stricture/fistula *vs* QoL indication) and thus should be interpreted with caution. These data could reflect national referral patterns of complex patients to metropolitan centers or differences in reginal practice patterns, and whether one practice is more 'guideline concordant' or not is unknown.

PROPOSING NEW, POPULATION-LEVEL STRATEGIES

Reframing diverticulitis as a relapsing-remitting disease has the potential to inform systems-level practices to improve the quality, efficiency, and effectiveness of diverticulitis care. To start, the ubiquity of diverticulitis in the general population coupled with the complexity of medical decision-making raises the question of where patients currently do and/or should receive care. It is well established that medical and surgical outcomes are improved and less costly (*via* economies of scale) when patients with colorectal cancer and inflammatory bowel disease are treated at specialized centers[69,70]. As a result, resources and structures for treating these diseases are concentrated at a few high-volume hospitals, a process called regionalization. To date, no studies have explicitly addressed whether regionalization would produce similar outcomes in diverticulitis, though there is some suggestion that diverticulitis patients may benefit from specialized care. Two separate studies showed that patients undergoing emergent colectomy for complicated diverticulitis undergo fewer Hartmann's procedures when

operated on by fellowship-trained colorectal surgeons compared to general surgeons after controlling for comorbidities and disease severity[74,79]. In one of these studies, patients in the colorectal surgeon group also experienced fewer post-operative complications and had their ostomies reversed sooner[74]. Yet another study suggests patients undergoing a Hartmann's reversal experienced fewer complications when performed by a colorectal surgeon[80]. While it is possible regionalizing care could increase surgeon volume, expertise, and outcomes, there is no agreed upon definition of "high-volume" at the clinician or systems level. Referral patterns, hospital resources, on-call responsibilities, eligible patient population, and numerous other factors may also explain current practice for diverticulitis care. It is, therefore, critical to characterize who is currently providing care across a spectrum of disease and healthcare settings, particularly when considering potential drawbacks of regionalization such as economic cost, travel burden, and healthcare disparities[81]. Importantly, attempts to regionalize diverticulitis care would require a radical shift in the distribution of diverticular disease burden, a sharp transition that brings into question whether any individual or collection of hospital systems can function as high-volume centers. Even if these centers had sufficient capacity, economic and travel burden are significant costs, which if incurred by rural and underserved patients could significantly limit access to care. Given the lack of supporting data and potential challenges of regionalization, more studies should evaluate the distribution of diverticulitis care focusing beyond single institutions and perhaps at the health system or state level. Characterizing distribution of care allows researchers to explore the association of volume and clinical outcomes in diverticulitis. If diverticulitis care is broadly distributed across institutions, this decentralized model of care has profound implications for how diverticular disease is studied and for implementation of quality improvement initiatives. This work should consider also regional practice patterns to better characterize how diverticular disease is actually treated in the general population.

Expanding the use of telemedicine has the potential to alleviate this burden, but a need for in-person consultation, rescue, and follow-up remains a challenge. Telemedicine also offers little to alleviate the travel burden of 19-42 million Americans without reliable access to fixed broadband services, a new frontier of inequity affecting predominantly poor, racial minority, and rural populations[82-84].

If concordance with CPGs leads to improved patient outcomes across a spectrum of medical and surgical disease, then improving existing CPGs or better adherence to them may result better, more cost-effective care. The decision to "individualize" surgery may arise from a composite assessment of patient/surgeon preferences, disease-specific factors, assessments of the "built environment" (*e.g.*, transportation, social support, *etc.*), and continuity of care. Yet, CPG recommendations are made without defining what clinical and external factors should be considered before recommending surgery. The SAGES/EAES guidelines advocate for colectomy when symptomatic disease impacts QoL; however, studies evaluating QoL following elective colectomy exhibit mixed results[44,85-89]. Despite technically successful operations, many patients have recurrent or ongoing symptoms after colectomy [86,87]. These studies are often underpowered, lack standardization of QoL, and do not discuss timing of QoL evaluation[85,90]. Presumably, QoL will be lower near a diverticulitis episode, improving overtime as symptoms resolve. In one prospective study, Droullard *et al*[91] identified four distinct QoL trajectories in diverticulitis patients and found that 40% of patients with unacceptable baseline QoL improved without surgery. These data suggest that phenotyping patient QoL trajectory could aid in the selection of appropriate surgical candidates in diverticulitis, a hypothesis that warrants further study. It is important to note, however, that patients with diverticulosis and no history of diverticulitis may exhibit higher physical and mental QoL scores than patients with symptomatic uncomplicated diverticular disease and those with a history of diverticulitis. However, differences in QoL scores were small (1-3 points) and whether these findings are clinically meaningful is not established[92]. Making comparisons between studies is challenging due to a lack of standardization in assessing QoL in diverticular disease. Some studies rely on more global assessments, such as the highly-validated and global SF-12, whereas others rely on more specific, but less broadly validated, and potentially convoluted measures, such as the diverticulitis QoL scale[44,66,85,86,89-93]. To date, there is no consensus regarding when or how the impact of diverticulitis on QoL should be assessed, and whether the timing of evaluation could change a surgeons' propensity to offer surgery. These global and disease specific QoL metrics need to be validated across a spectrum of diverticular disease patients with consideration paid to clinically meaningful changes for each metric. Consolidating these data and providing an actionable tool for clinicians would likely require consensus and multidisciplinary agreement. As an example, the Pelvic Floor Consortium, a multidisciplinary organization that aims to enhance care of patients with pelvic floor disorders, recently modeled how to establish a combined, validated patient reported outcomes tool to standardize QoL assessments across subspecialties[94]. A consortium of colorectal surgeons, general surgeons, gastroenterologists, and primary care providers could offer similar guidance and allow for longitudinal evaluations of QoL in diverticular disease.

Even in the context of clearer CPGs, measuring their implementation is complex and predicated on provision of clear and actional recommendations. Most studies evaluating other programs to improve guideline concordance are often (and appropriately) narrow in scope and lack conceptual clarity, thereby limiting their general applicability. One study implemented benchmarking and a peer-to-peer messaging initiative that increased guideline concordance among surgeons participating in Washington State's Surgical Care and Outcomes Assessment Program and highlights the potential of regional

initiative to improve guideline concordance[73]. However, this was limited to those patients having surgery, and the appropriateness of 'non-operative' management was not included. Ongoing research by the Expert Recommendations for Implementation Project seeks to define and evaluate discrete generalizable and comprehensive implementation strategies to improve guideline conformity. These research efforts are ongoing and may provide discrete implementation strategies applicable to diverticulitis care[95].

CONCLUSION

Awareness of the healthcare burden of diverticulitis and its distribution of inpatient and outpatient care is critical for cost-containment and improving disease management. Population-level studies provide the best reflection of an increasingly common disease that requires complex clinical decision-making that appears discordant with contemporary CPGs. Based on our current understanding of diverticulitis, the biggest challenges include improving population-level data in diverticulitis care, an evaluation of regionalized care for diverticulitis, and development/implementation of CPG-concordance measures.

FOOTNOTES

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REVIEW

Distal pancreatectomy with or without radical approach, vascular resections and splenectomy: Easier does not always mean easy

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Abstract

Because distal pancreatectomy (DP) has no reconstructive steps and less frequent vascular involvement, it is thought to be the easier counterpart of pancreaticoduodenectomy. This procedure has a high surgical risk and the overall incidences of perioperative morbidity (mainly pancreatic fistula), and mortality are still high, in addition to the challenges that accompany delayed access to adjuvant therapies (if any) and prolonged impairment of daily activities. Moreover, surgery to remove malignancy of the body or tail of the pancreas is associated with poor long-term oncological outcomes. From this perspective, new surgical approaches, and aggressive techniques, such as radical antegrade modular pancreato-splenectomy and DP with celiac axis resection, could lead to improved survival in those affected by more locally advanced tumors. Conversely, minimally invasive approaches such as laparoscopic and robotic surgeries and the avoidance of routine concomitant splenectomy have been developed to reduce the burden of surgical stress. The purpose of ongoing surgical research has been to achieve significant reductions in perioperative complications, length of hospital stays and the time between surgery and the beginning of adjuvant chemotherapy. Because a dedicated multidisciplinary team is crucial to pancreatic surgery, hospital and surgeon volumes have been confirmed to be associated with better outcomes in patients affected by benign, borderline, and malignant diseases of the pancreas. The purpose of this review is to examine the state of the art in distal pancreatectomies, with a special focus on minimally invasive approaches and oncological-directed techniques. The widespread reproducibility, cost-effectiveness and long-term results of each oncological procedure are also taken into deep consideration.

Key Words: Distal pancreatectomy; Minimally invasive; Splenectomy; Laparoscopic

Core Tip: Laparoscopic or robotic distal pancreatectomy is a good option to cure diseases arising from the pancreatic body/tail. The minimally-invasive approach allows to achieve concomitant splenectomy and arterial resections. However, current Literature is still lacking, and the surgical decision is based mainly on the presence of advanced laparoscopic and da Vinci equipment, controlled by skillful experts. A rigorous attention to the general and oncologic principles should be the maintained.

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INTRODUCTION

Distal pancreatectomy (DP) should be defined as resection of the pancreatic gland distal to the left mesenteric vein, including the body and tail of the pancreas. Indications for DP include a wide spectrum of diseases, ranging from benign to highly aggressive neoplasms. In the first group, most cases consist of chronic pancreatitis and benign cysts, while pancreatic adenocarcinoma is the most frequent pathology in the second[1]. In selected cases, DP also often requires concomitant splenectomy as a routine step of the same operation.

For pancreatic cancer, long-term survival after DP remains unsatisfactory, with a median survival time of 17-28 mo and a 5-year overall survival of approximately 20%-30%[2,3]. Despite the highly aggressive nature of the disease and early regional lymph node metastasis, adenocarcinomas of the body and tail of the pancreas have attracted significantly less clinical attention than proximal tumors[4].

Traditionally, DP is considered less challenging than pancreaticoduodenectomy, as proven by the reported lower perioperative morbidity and mortality of patients[5,6] due to the lack of reconstructive steps. Moreover, the most important postoperative complication, pancreatic fistula, is rarely life-threatening (1% mortality)[7,8]. A logical consequence of these issues led to investigating the result of minimally invasive DP (MIDP), which has been widely accepted in the worldwide surgical community [9]. Interestingly, after the first procedure reported by Cuschieri *et al*[10], MIDP has now become the procedure of choice in tertiary referral centers for both benign and malignant lesions of the body and tail of the pancreas[9,11].

Although surgical resection of the body/tail of the pancreas, achieved by an open or minimally invasive approach, is considered a less demanding operation, few evidence-based studies are available, and many issues remain unresolved. The main problems are represented by the development of postoperative pancreatic fistula (POPF) and management of the spleen (splenectomy *vs* preservation)[8,12,13].

The principal aim of this review was to investigate the ongoing surgical approaches to DP, with a special focus on minimally invasive techniques, spleen preservation and extended resections with vascular reconstruction. Endoscopic, percutaneous maneuvers and other nonsurgical maneuvers did not represent the purposes of this article and are not explained.

A web-based search of MEDLINE (accessed through PubMed and Ovid) and Cochrane databases was performed until October 2022. Many cross-matched manual references were also included. Randomized controlled clinical trials (RCTs) or meta-analyses were considered a priority. Data arising from more recent, English-written, multicentric, international studies and those with long-term follow-up and oncologic results were also considered of major interest and included in the study.

The review examines the state of the art in distal pancreatectomies, with a special focus on minimally invasive approaches and oncological-directed techniques.

CURRENT TECHNIQUES OF DP

The operation could be defined as resection of the body-tail of the pancreas (with or without concomitant splenectomy). Globally, it includes more than 20% of all pancreatic resections[14]. The first DP was reported by Lillemoe *et al*[1], although Finney[15] and Mayo[16] collected the first case series with the description of their techniques in 1900. The surgical steps have remained unchanged for decades, and most of them are still in use.

A subcostal left transverse incision is the preferred approach, but upper midline incisions are also employed. After careful exploration, the surgeon begins by accessing the retrocavity by sectioning the greater omentum, cutting some short gastric vessels to increase the surgical view and expose the anterior surface of the pancreas. The celiac axis is then identified and dissected, and the splenic artery is transected. The pancreatic neck is gently detached from the portomesenteric confluence using a finger

or blunt forceps.

The next step includes complete distal pancreatic detachment, securing each vessel originating from the splenic vein or maintaining some short gastric vessel, in the case of spleen preservation, while splenic mobilization could be achieved from left parietal ligaments in the case of concomitant splenectomy. The splenic vein should be transected distal from the inferior mesenteric vein confluence. The pancreatic neck is then transected with a selective ductal closure, and the specimen is removed. Some upgrades include vessel and/or pancreatic transection with a linear stapler, the use of a harmonic scalpel, and the employment of surgical clips[17,18].

Conventionally, DP and splenectomy have been performed to treat pancreatic cancer of the body and tail in a left-to-right retrograde fashion, in which mobilization of the spleen and pancreas is followed by vascular control and division of the pancreas[19].

After its first introduction in clinical practice, DP has substantially remained unmodified for 100 years [20,21]. In recent decades, some steps forward have been made to overcome some limits of DP and to obtain better oncological results. The most influential advances are presented below.

RADICAL ANTEGRADE MODULAR PANCREATO-SPLENECTOMY

Recently, the routes of lymphatic drainage have been investigated deeply to minimize the risk factors for margin positivity and to enhance survival after DP. The acronym Radical antegrade modular pancreatosplenectomy (RAMPS) was introduced by Strasberg *et al*[20] to address some of these important issues. His technique had the goal of achieving systematic and radical surgical dissection during DP, leading to maximum rates of negative resection margins and complete regional lymph node dissection [19].

From a technical perspective, RAMPS is a "no-touch" isolation approach to control major blood vessels, such as the splenic, renal, and adrenal vessels, by early separation of the pancreatic neck from the pancreas to the spleen[22]. The major anatomic landmarks include the left-sided portal vein, the aorta, the celiac axis, the mesenteric artery, the left-sided borders and the left kidney vein and the diaphragm. The posterior margin varies according to the location and extension of the pancreatic tumor, introducing some different subclassifications of the proper "RAMPS"[23]. In detail, anterior RAMPS includes the dissection of Gerota's fascia, the prerenal fat on the surface of the adrenal gland and the upper half of the kidney, while so-called posterior RAMPS involves the asportation of the left adrenal gland and the retroperitoneal fat tissue, with the muscle layer of the posterior abdominal wall limiting the surgical field[24].

The first published experiences reported a negative resection margin rate of up to 90%[20], although the influence of asymptomatic recurrence-free survival on overall survival remains controversial[25,26]. The systematic adoption of the RAMPS procedure has been increasing, particularly in Japan and Korea [4]. The number of patients eligible for RAMPS is small, and only recently have some prospective randomized trials of RAMPS *vs* the standard procedure been started[4,27,28]. These studies are still enrolling patients, and no definitive results are available yet. Consequently, the evidence is largely based on prospective, not randomized, studies.

Interestingly, compared to standard retrograde pancreato-splenectomy (SRPS), RAMPS has been demonstrated to reduce intraoperative bleeding[29,30] and increase R0 resection rates[4,29,30], the number of lymph nodes harvested[4,29,30] and the local recurrence rate (23.6% *vs* 49.6%; $P = 0.019$)[31], but no statistically significant difference has been found in terms of overall survival and disease-free survival[4,32]. Nevertheless, in the most recent systematic literature reviews and meta-analyses, the evidence tended to favor RAMPS in terms of safety and effectiveness (including both outcomes and overall survival)[29,33-35] with respect to SRPS, while another recent meta-analytic study suggested that RAMPS may have little effect on disease-free survival and overall survival[19].

DP WITH CELIAC AXIS RESECTION

Locally advanced disease is present in up to 40%[36,37] of patients affected by pancreatic cancer, with a median survival reported between 6 mo to 24 mo, and the longer survival time was obtained after a somewhat systematic approach[38]. However, the surgeon may also help to obtain a more radical procedure, achieving negative margins at the price of higher complication rates. A clear benefit of more aggressive surgery has not yet been proven, and the best management is driven by the application of standardized, recognized, international guidelines that propose a chemotherapy or radio-chemotherapy approach for locally advanced cancers[39,40]. More frequently, patients undergo chemotherapy plus radiotherapy to obtain regression, with reported conversion rates (unresectable to resectable) of 33%-50% and R0 resection rates comparable to standard resections[41-44].

Based on these assumptions, demolitive surgeries, such as DP with celiac axis resection (DP-CAR), have become a therapeutic option in recent decades[45]. Nimura *et al*[46] introduced a formal DP-CAR as a modified gastric-sparing approach of the Appleby procedure[47]. It consists of concomitant DP and

celiac axis resection, with the perfusion of the liver and stomach guaranteed by retrograde flow *via* the superior mesenteric artery, pancreatoduodenal arcades, and the gastroduodenal artery[48].

If venous infiltration is no longer an absolute contraindication to surgery, arterial infiltration is considered an unresectability criterion, both for technical challenges and for poor prognosis[49]. The so-called "artery-first" approach is useful as an initial surgical step to clarify arterial infiltration along the superior mesenteric artery[49]. Nevertheless, some selected patients could benefit from arterial resection if R0 margins could be obtained, with a median overall survival comparable to that of patients with localized pancreatic cancer[45,47,48,50-53]. Unfortunately, such radical surgery has high rates of morbidity (50%-80%) and mortality (3.5%-17.0%), mostly related to the liver[54] and gastric ischemia[55, 56].

A systematic review by Klompmaker *et al*[48] collected the results of 19 retrospective studies published between 1975 and 2014, including a total of 240 patients. Radical resection was obtained in 75% of patients, with 27% of patients who experienced complications, with a median overall survival of 14.4[9-48] mo. Although these results were highly flawed because the percentages of neoadjuvant chemotherapy administered differed, the sample size was small, and the enrollment period was long, the conclusion is that a subgroup of patients could benefit from by this approach[47].

Interestingly, the introduction of the FOLFIRINOX chemotherapeutic schedule (folic acid, fluorouracil, irinotecan, oxaliplatin) has enhanced the neoadjuvant approach with a more aggressive approach[57,58], leading to a higher rate of resection, clear margins and significantly better survival [59]. The assumptions imply that some older surgical experiences, including aggressive vascular resections (such as DP-CAR), could have obtained suboptimal results[47].

Klompmaker *et al*[48] reported the results of an international multicenter (20 high-volume pancreatic centers) study, including a total of 68 patients with exocrine pancreatic cancer treated from 2000 to 2016. Half of them received neoadjuvant radiochemotherapy, with more than half resulting in clear margins. Additional results from this study included the following: A 25% rate of POPF, 17 d of hospital stay, and a 90-d mortality of 16%. The median overall survival was 18 mo. The authors concluded that DP-CAR offers a survival benefit in selected patients with otherwise unresectable pancreatic cancer treated by highly skilled surgical teams working at high-volume centers[47]. The best results were achieved by combining DP-CAR with chemotherapy.

Interestingly, some pioneering experiences introduced the application of the robotic platform to overcome some of the technical limitations of laparoscopic vascular resections during pancreatic surgery (Robotic DP-CAR)[47].

One of the largest reviews comparing DP-CAR and traditional DP was published by Nigri *et al*[45]. A total of 24 articles, including 1077 patients who were divided into two groups, showed a higher percentage of T4 tumors in the DP-CAR group. Perioperative outcomes were similar in terms of POPF, complications and mortality. Patients treated with DP-CAR were more likely to have positive resection margins but less likely to receive adjuvant treatments. The overall survival at one year was similar in the two groups[45]. The authors concluded that celiac axis involvement should no longer be considered a strict contraindication to surgery in patients with locally advanced pancreatic adenocarcinoma. However, a direct comparison of DP-CAR and palliative approaches should be more informative, together with a somewhat randomized design or propensity score matching. Liu *et al*[60] reported the results of a very accurate systematic review, including 11 high-quality studies and 1072 patients, concluding that DP-CAR has worse efficacy and prognosis and is more dangerous than standard DP, but it can improve survival and quality of life than palliative treatment.

Future studies should also investigate the extent of surgical volumes and the enhanced median survival in comparison to upfront resectable pancreatic cancer.

LAPAROSCOPIC DP

The first laparoscopic DP (LDP) was performed by Gagner *et al*[61] in the mid-nineties. Since then, laparoscopy has been widely demonstrated to reduce pain, decrease blood loss, shorten hospital stay, enhance the postoperative course, provide better cosmesis and reduce costs in many abdominal procedures[62-64]. Laparoscopic techniques have also been progressively applied in DP at the price of increased cost[64,65] and with less enthusiasm because of the position and anatomical relations with major vessels[66] when compared to open surgery. Currently, LDP has been progressively becoming the preferred approach in most centers[11].

The indications for LDP are the same as those for open DP[67-69], including benign, borderline, or malignant tumors, pancreatic injury and chronic or acute pancreatitis with pseudocysts located in the pancreatic body and tail. The invasion of the surrounding organs, vascular involvement, the presence of distant spread in cancer, or acute pancreatitis are current contraindications to a robotic approach in most centers. The minimally invasive approach should be considered more challenging in a morbidly obese patient, although skilled surgeons have reported opposite conclusions[70].

The main steps of the surgical technique are similar to those of open surgery, but no formal clear standardization of the technique has been published[71,72]. The patients are usually approached in the

supine positions and tilted on the left side, and a minimum of 4 trocars are employed. Intraoperative ultrasound is recommended to identify the location of the lesion. After gentle pancreatic mobilization, the splenic vessels are identified and secured by a stapler, clips, or ligation. The pancreas is then transected using a stapler or energy device (in this case, selective duct closure is mandatory)[71].

Unfortunately, most evidence is derived from retrospective experiences, and few randomized studies have compared the minimally invasive technique with the open technique, demonstrating the superiority of MIDP in terms of reduced delayed gastric emptying, quality of life, functional recovery, reduced hospital stay, and costs[73,74]. A Cochrane review published in 2016 collected data from 12 non-RCT retrospective studies, including 1576 participants (394 LDP). No clear evidence has been reported between the two approaches in terms of short- to long-term morality and severe complications [11]. Similar conclusions were driven by the Application of the International Study Group on Pancreatic Fistula (2017) criteria, with LDP having surgical outcomes comparable with those of open DP (ODP). However, LDP resulted in lower blood loss, fewer complications, and shorter hospital stay[75].

Interestingly, LDP is underused in clinical practice[76], while ODP is still considered the standard procedure by most surgeons, including the publication of widely recognized benchmarks[77]. Despite the scarce evidence available, the application rate of LDP varied over time and differed between countries. Data extracted from nationwide database analysis reported the application of LDP in 26% of cases between 1998-2009 in the United States[78], and this rate did not exceed 10% from 2005-2013 in the Netherlands[79]. Moreover, a more recent publication from the Norwegian Patient Register reported a laparoscopic approach in 59% of DP procedures between 2012 and 2016[80].

A possible explanation of these risks could be related to the concentration of casistic in few specialized centers, which offer the maximum expertise in pancreatic pathology and highly expensive updated instrumentation. Specific participation in the training course could improve both the use and outcomes of LDP, while the initial introduction of the technique implies careful patient selection[81]. The learning curve to gain sufficient skills is reported to range between 11 and 40 procedures[81-84], and the lack of reconstructive time contributed to feeling that LDP was much more feasible than laparoscopic duodenopancreatectomy[65]. Interestingly, some authors reported similar operative times with respect to open procedures, considering it a surrogate parameter of proficiency[85,86].

Nevertheless, another possible limitation to the widespread application of LDP is the cost-effectiveness, although the balance remains difficult to evaluate due to the variability of health systems between countries and the different costs of disposable surgical devices[86]. The supposed gain in terms of the reduced hospitalization, incidence of complications, and reduction of days off-work are often misinterpreted if not available in many publications.

In 2020, an international panel of expert surgeons published guidelines for the application of minimally invasive techniques to pancreatic surgery in an attempt to overcome the uncertainties about this issue in terms of benefits and applicability and to standardize most of the indications[9,73].

The risk of POPF is the major impacting complication after open and laparoscopic DP and is highly related to prolonged intra-abdominal drainage, hemorrhage, readmissions, sepsis and certainly mortality[87,88]. Older studies reported a higher rate (39%) of POPF after minimally invasive DP compared to open DP[89], but others failed to find significant differences after careful statistical patient stratification and homogenization[90]. Moreover, in 2021, a new POPF risk score (ua-FRS) was validated for minimally invasive pancreatic surgery[91], with a reported global incidence rate of 21%. A careful surgical technique, independent of the approach (open or minimally invasive), is the best option to minimize the risk of POPF[91]. Many different approaches (some comparative) to pancreatic transection have been published, including scalpel, electrocautery, ultrasonic/harmonic, and laparoscopic staplers [92-97], but no evidence is available to support one method over another, and most evidence is derived from ODP studies. The use of fibrin sealants and similar products has little effect on POPF in people undergoing DP[96,97].

Many researchers hypothesize some advantages of MIS in decreasing the proinflammatory and immunologic response to surgical trauma[98,99] that is associated with a superior oncologic result, while a robust meta-analysis demonstrated that LDP might be safer with regard to the oncological outcomes of pancreatic ductal adenocarcinoma patients[100]. A study by Shin *et al*[101] specifically compared LDP and ODP in 150 cancerous patients, with oncologic adequacy considered the primary endpoint. The authors reported a 5-year survival rate, the length of surgery, the number of harvested lymph nodes, the resection margin status, and the incidence of POPF to be similar between the two groups.

Spleen preservation is considered to be mandatory for patients operated on for IPMN or less aggressive neuroendocrine tumors located in the pancreatic body and tail, leading to a reduction in both blood loss and postoperative complications[102-108]. Warshaw[109] described a technique in which splenic vessels are ligated with the preservation of the short gastric and left gastroepiploic vessels, while Kimura spared the splenic vessels by careful detachment of pancreatic vessels from the major trunks [110]. Although this concept has recently been discussed, the two available spleen-preservation techniques[111,112] are feasible by laparoscopy in the hands of experienced surgeons[111]. Most published papers reported similar rates of spleen preservation[103,105,106].

Table 1 State of the art of distal pancreatectomy and future directions

Planned operation	To be considered	Present	Ongoing research	To be matched with
DP	Age, comorbidities	Laparoscopic	Robotic	Laparoscopy
DP + splenectomy	Age, comorbidities, cancer, local anatomy	Laparoscopic	Robotic	Laparoscopy
RAMPS	Age, comorbidities, cancer	Laparoscopic, open	Robotic	Open surgery
DP-CAR	Age, comorbidities, cancer	Open	Laparoscopic, robotic	Open surgery

DP: Distal pancreatectomy; RAMPS: Radical proximal-distal modular pancreatosplenectomy; DP-CAR: Distal pancreatectomy with celiac axis resection.

ROBOTIC DP

The recent, widespread introduction of the da Vinci® Surgical Systems (Intuitive Surgical, Inc., Sunnyvale, CA, United States) robot has led many surgeons to address pancreatic disease with this technology[113]. If minimally invasive pancreaticoduodenectomy (laparoscopic, hybrid, or robotic) is far from routinely adopted in the community, robotic-assisted distal pancreatic resection (RDP) should potentially resolve many of the major issues of pure laparoscopy, including the preservation of the spleen[114]. For example, few retrospective series have reported the percentages of the spleen left in situ (when indicated) in up to 90% of cases[115,116], while neither the traditional open nor laparoscopic approach has been reported to reach 90%[117]. In addition, robotic articulated stable instrumentation could help the surgeon improve tissue dissection and lymphadenectomy when treating pancreatic cancer[118-120]. Nevertheless, definitive data on the robotic approach are still needed.

A meta-analysis by Zhang *et al*[121], which included seven trials, examined 137 robotic and 203 open pancreatectomies. Many of the analyzed parameters, such as morbidity, blood loss and length of hospital stay, favored robotic procedures, but none of the differences reached statistical significance. The incidence of POPF was similar.

Another more recent meta-analysis by Feng *et al*[122] reported better results of RDP compared to LDP in terms of operative time, tumor size, and lymph node dissection, with a higher R0 resection rate ($P < 0.0001$)[122]. Other meta-analyses comparing RDP and LDP reported the former as safe and feasible, with a low rate of conversion to open surgery, blood loss, a shorter length of stay and an increased rate of spleen preservation[117,123]. However, demographic discrepancies, underpowered RDP samples and differences in oncological burden do not permit certain conclusions regarding the oncological safety of RDP and LDP for pancreatic adenocarcinoma[123]. The oncological safety of robotic DP compared to LDP has been demonstrated[2] in a national database and is currently being evaluated in a multicenter European randomized trial (DIPLOMA trial)[124].

In conclusion, robotic DP is a safe and feasible procedure with perioperative and oncological outcomes comparable to those of LDP and open traditional surgery. Many technical advantages seem to permit the surgeon to overcome many of the drawbacks of pure laparoscopy, including a steep learning curve, complex dissection and ergonomic issues, maintaining the same advantages of a minimally invasive procedure (reduced blood loss, shorter hospitalization and improved cosmetic results)[113]. Costs and availability remain the main limitations of the robotic approach[125] (Table 1).

CONCLUSION

Surgical resection has the best chance to cure pancreatic disease, including malignancy, precancerous lesions, and inflammatory involvement. Nevertheless, pancreatic surgery has high morbidity and mortality rates and is especially challenging for surgeons operating on elderly surgical patients. Therefore, the purpose of ongoing research and surgical efforts is to reduce the impact of surgical trauma through minimally invasive approaches, spleen preservation when indicated, and maintaining and improving the accuracy of oncologic dissection (*i.e.*, clear margins and proper lymphadenectomy). All the issues mentioned above can be addressed by laparoscopic and robotic surgeries, which have been well established for distal pancreatic resections. However, such procedures require excellent surgical skill, training experience with proctors, and case-load concentration in high-volume hospitals with the best resources. In conclusion, if DP with or without a radical approach, vascular resection or splenectomy is thought to be easier than cephalic resection, it should not be considered easy in every case.

FOOTNOTES

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MINIREVIEWS

Endoscopic ultrasound-guided portal pressure gradient measurement in managing portal hypertension

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Abstract

Portal hypertension (PH) is still a challenging clinical condition due to its silent manifestations in the early stage and needs to be measured accurately for early detection. Hepatic vein pressure gradient measurement has been considered as the gold standard measurement for PH; however, it needs special skill, experience, and high expertise. Recently, there has been an innovative development in using endoscopic ultrasound (EUS) for the diagnosis and management of liver diseases, including portal pressure measurement, which is commonly known as EUS-guided portal pressure gradient (EUS-PPG) mea-surement. EUS-PPG measurement can be performed concomitantly with EUS evaluation for deep esophageal varices, EUS-guided liver biopsy, and EUS-guided cyanoacrylate injection. However, there are still major issues, such as different etiologies of liver disease, procedural training, expertise, availability, and cost-effectiveness in several situations with regard to the standard management.

Key Words: Portal hypertension; Hepatic vein; Endoscopic ultrasound; Portal pressure

Core Tip: Portal hypertension (PH) is a challenging clinical condition due to its silent manifestations in the early stage. Hepatic vein pressure gradient measurement is still the gold standard for PH diagnosis; however, it is not recommended for a routine measurement in daily practice. Esophagogastroduodenoscopy is still the main procedure for variceal screening due to PH. Recently, there has been a development in using endoscopic ultrasound (EUS) for managing liver diseases. EUS-guided portal pressure gradient measurement seems to be a promising method in the future for early detection and management of PH.

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INTRODUCTION

Portal hypertension (PH) is a challenging clinical condition due to its silent manifestations in the early stage and it needs to be measured accurately for early diagnosis. PH is defined when there is an increase of portal pressure above 5 mmHg. Clinically significant PH (CSPH) is defined when the portal pressure reaches 10 mmHg and above. CSPH is an important clinical condition because of its clinical consequences, such as the presence of esophageal and gastric varices, ascites, kidney dysfunction, as well as cardiopulmonary complications. These conditions are mostly observed in liver cirrhotic patients with liver disease progression, even though there are non-cirrhotic conditions with PH[1,2]. Hepatic vein pressure gradient (HVPG) measurement has been considered as the gold standard measurement for PH; however, it needs special skill, experience, and high expertise. This procedure also needs to be performed in a dedicated catheterization procedure room[3]. Esophagogastroduodenoscopy (EGD) is a standard procedure for early detection of PH complications, *i.e.*, the presence of varices[4,5]. A major drawback is that these two procedures might not be performed in the same session. Another issue in clinical practice is that not all cases might have accurate portal pressure measurement through this indirect measurement procedure due to the pathology of the portal vein (PV), which does not include the liver architecture disturbance[6,7]. Recently, there has been innovation for portal pressure measurement through endoscopic ultrasound (EUS). The liver images as well as the liver vascularity will be shown clearly for puncture location. However, it needs special skill and knowledge to perform the procedure[8]. In our center, this procedure is also only performed by endoscopists with more than ten years of clinical experience (Figures 1A and B). This review will discuss the role of EUS in portal pressure measurement and its impact in clinical practice.

PH, portal pressure measurement, and issues in clinical practice

PH has been divided into prehepatic, intrahepatic, and post-hepatic. This condition happens due to increased portal blood flow resistance, where it is mostly caused by intrahepatic vascular resistance in chronic liver disturbances. Imbalanced activation between vasoconstrictors and vasodilators due to liver architectural disturbance is the main key to the development of PH. In non-cirrhotic condition, or commonly known as non-cirrhotic PH (NCPH), PV fibrosis or thrombosis is the main issue[9,10].

HVPG measurement is the gold standard for PH assessment. This measurement technique is considered safer than direct measurement *via* transhepatic or transvenous catheterization because a more advanced approach to the inferior vena cava will be required for portal pressure gradient (PPG) measurement. HVPG has been considered as a safe procedure. However, there are several patient conditions which need special attention, such as cardiopulmonary disorders, hepatic encephalopathy, history of cardiac arrhythmias, and evidence of vena cava thrombosis. There are also some possible conditions which can happen during the procedure itself, such as allergic reaction to contrast agent, cardiac arrhythmia during catheter insertion *via* the transjugular route, and bleeding in patients with a very low platelet count or prolonged international normalized ratio[11,12]. On the other hand, this procedure is preferable in patients with significant ascites[3]. Based on HVPG measurement, the strategy of further management has been clearly defined with possible mortality rate. In the early stage, CSPH complications can be prevented with early medication. A randomized controlled trial of carvedilol *vs* endoscopic band ligation (EBL) by Tripathi *et al*[4] has showed that carvedilol has the same efficacy as EBL primary prophylaxis in terms of bleeding prevention. This study has also been supported by another more recent study by Shah *et al*[13] in a multicentre randomized controlled trial. A recent systematic review and meta-analysis by Dwinata *et al*[14] showed that carvedilol had similar efficacy to EBL for primary variceal bleeding prevention. Follow-up HVPG value can also be used to determine the response to the treatment and change to another strategy if needed. In the late stage of the disease or decompensated condition, more advanced complication prevention or advanced mana-

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Figure 1 Endoscopic ultrasound procedure. A: Endoscopic ultrasound evaluation in a liver cirrhosis patient with portal hypertension; B: Endoscopic ultrasound-guided portal pressure gradient measurement. Non-surgical Integrated Procedural Room, Hepatobiliary Endoscopy Unit, Dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia.

gement can be decided based on HVPG value[2]. Moitinho *et al*[15] showed the usefulness of early portal pressure measurement in acute variceal bleeding scenario. This prospective study concluded that higher HVPG value is associated with a longer interval between each hospital admission and lower mortality rate. Another study conducted by Ripoll *et al*[16] on 213 liver cirrhosis (LC) patients within a 6-year period showed that HVPG value with a 10 mmHg cut-off can be a good predictor of liver decompensation. The hazard ratio for liver decompensation of HVPG is higher than those of albumin level and model for end-stage liver disease score.

There has been a development of non-invasive methods for PH assessment. A prospective study by Bureau *et al*[17] on the use of transient elastography for PH prediction showed that there was a good correlation between liver stiffness and HVPG ($P < 0.001$). However, based on further analysis, the sensitivity and specificity were becoming higher in line with the increase of the liver stiffness. The main issues were the high value of liver stiffness due to the severity of liver fibrosis condition and varied etiologies of liver diseases[17]. Another prospective study conducted by Palaniyappan *et al*[18] on patients with advanced liver disease using magnetic resonance imaging (MRI) parameters, where the patients also underwent liver stiffness measurement (LSM) before the MRI examination, showed that two MRI parameters, *i.e.*, liver T1 relaxation time and splenic artery velocity, were significantly associated with HVPG values ($r = 0.90$, $P < 0.001$). Even though the LSM was significantly correlated to HVPG ($r = 0.791$, $P < 0.001$), no significant correlation was found in the subgroup of patients with an HVPG value more than 10 mmHg[18]. Another innovation of non-invasive method for assessing PH in clinical practice has been showed in a study by Frankova *et al*[19], where liver stiffness measured by ultrasound-based shear-wave elastography has been correlated well with HVPG values in all LC patients as well as in a subgroup of patients. The liver stiffness values of 16 and 20 mmHg were considered as the best predictive values associated with HVPG. In daily practice, non-invasive methods are still debatable due to their different study results and early detection for PH. MRI examination is also a major issue at present as a routine follow-up examination due to its cost, availability, and patients' comfort[20].

Metabolic condition, such as non-alcoholic fatty liver disease (NAFLD), now well-known as metabolic dysfunction associated fatty liver disease, might be a new challenge in the field of hepatology. It has been postulated that this condition might not have liver fibrosis progression and PH condition in the same line[21]. A prospective study published by Hirooka *et al*[22] revealed that there was a hemodynamic change in early course of the disease process in NAFLD patients, where patients were still in the early liver fibrosis condition based on the median hepatic arterioportal ratio together with splenic elasticity evaluation. Another database study conducted by Mendes *et al*[23] on 354 NAFLD patients showed that 6% of NAFLD patients without evidence of LC had PH complications. NCPH is another issue, where HVPG measurement may not be as good as it is. The complexity of the vascular system and liver pathology assessment for confirming diagnosis have been a challenging issue in clinical practice[24].

EGD is still the main procedure in daily practice to diagnose PH condition based on the presence of esophageal or gastric varices[25,26]. However, luminal evaluation does not always show a significant parameter for the presence of PH as well as in further management for PH[27].

EUS-PPG measurement in PH

Recently, there has been an innovative development in using EUS for diagnosis and management of liver diseases. It has been proposed as "endo-hepatology", where endoscopic technique innovation can be used in the field of hepatology. It is started from EUS-guided liver biopsy, followed by the use of

EUS for abdominal fluid paracentesis, portal circulation, and EUS-guided intravascular injection for gastroesophageal varices[28,29].

The initial animal study by Lai *et al*[30] on feasibility of EUS-guided PV catheterization showed a good correlation between PV pressure (PVP) obtained through EUS procedure and *via* the transhepatic route (r = 0.91). Giday *et al*[31] conducted EUS-guided direct PVP measurement in pigs, and this study showed that there has been consistency in the pressure results, and no evidence of complications was recorded. Another pioneered animal study which used a novel device (compact manometer) was published by Huang *et al*[32], where the authors were able to show a good correlation between EUS approach and transjugular approach for right hepatic vein, PV, and aorta pressure measurements (r = 0.985). An innovative animal study on EUS-PPG measurement using a digital pressure wire showed that this method was safe, and there were no complications such as thrombus or bleeding[33]. A human pilot study was subsequently published by Huang *et al*[34], where 28 patients underwent EUS-PPG without any complications. The technical success rate was 100% and the PPG had a good correlation with varices (P = 0.002), low platelet count (P = 0.036), and gastropathy (P = 0.007). A recent study was conducted by Zhang *et al*[35] on the role of EUS-PPG measurement in patients with acute or subacute PH. In this study, the technical success was achieved in 91.7% of the cases, where EUS-PPG measurement had a higher success rate than HVPG measurement. A good correlation was showed through the manometry result between EUS-PPG value and HVPG value (r = 0.852). No adverse events were observed during examination. Recently, a retrospective study conducted by Choi *et al*[36] was looking at the correlation between portal pressure and clinical manifestations of PH. In that study, the PPG value was significantly higher in patients with LC (9.46 *vs* 3.61 mmHg; P < 0.0001), presence of gastroesophageal varices (13.88 *vs* 4.34 mmHg; P < 0.0001), and low platelet count (9.25 *vs* 4.71 mmHg; P = 0.0022). Seventy-one of 83 subjects underwent liver biopsy through EUS. No adverse events or complications were observed during and after the procedures. Lesmana[37] has recently published a technique innovation where EUS-PPG was conducted by using a standard manometer set in 13 patients diagnosed with PH. In this case series, two LC patients with Child-Pugh C liver function were included. One patient was diagnosed with NCPH. There were no adverse events or complications occurring during and after the procedure. Another more recent case report using a standard pressure monitor was published just to show the procedural steps and safety[38]. A systematic review and meta-analysis on EUS-PPG to diagnose cirrhosis showed that successful portal pressure measurement was achieved in 91.61% of the cases, with no post-procedural complications, such as bleeding, perforation, and infection (95% confidence interval: 0-2.85). However, based on pooled analysis, abdominal pain developed in 6.15% of cases, emergency department visit in 3.11%, and sore throat in 2.82%[39]. A very recent publication from Lei *et al*[40] on EUS-PPG in 52 LC patients showed that this method was successfully performed in 98% of the cases. The authors showed an innovative puncture location, *i.e.*, transduodenal route, where it can be an alternative location if conventional puncture location was difficult. This study also showed that none of the patients experienced any adverse event (Table 1).

Future directions

EUS-PPG measurement is a better method in portal pressure measurement and diagnosing all PH conditions, not limited to chronic liver disease patients only. However, there are several issues that still need to be discussed before it becomes a clinical recommendation in daily practice. First, EUS-PPG measurement can be performed concomitantly with EUS evaluation for the presence of deep esophageal varices or gastroesophageal varices. The clinical impact of EUS evaluation in the presence of deep esophageal varices in naïve patients as well as in patients with recurrent esophageal varices has been reported in several studies[41-43]. However, whether EUS evaluation is needed in the first setting in all patients with LC for deep varices evaluation is still debatable because there is no strong clinical evidence yet regarding its impact as the first-line examination, and there is a different course of liver disease progression based on each etiology. Second, EUS-PPG measurement can be performed together with EUS-guided liver biopsy; however, EUS-guided liver biopsy is not considered as a routine procedure yet in clinical practice due to the unavailability of standard training, limited experience and availability, and high cost when compared to percutaneous liver biopsy[44,45]. Last but not least, EUS-PPG measurement can be performed and then followed by EUS-guided cyanoacrylate injection for large or deep gastroesophageal varices as well as isolated gastric varices[37,46]. However, the need of EUS approach in acute variceal bleeding and the impact of interventional radiology procedures, such as transjugular intrahepatic porto-systemic shunt or balloon-occluded retrograde transvenous obliteration, are still becoming a long way discussion for managing PH complications[30,47].

CONCLUSION

EUS-PPG is a promising method in future clinical practice for managing PH condition and complications. However, it needs further studies and re-evaluation before it can be recommended as a routine clinical procedure.

Table 1 Endoscopic ultrasound portal pressure gradient study for portal hypertension assessment

Ref.	Type of study	Study design	Results	Technical success rate	Adverse events
Lai *et al*[30], 2004	Animal	Experimental	EUS-PVP correlated well with transhepatic catheterization (r = 0.91)	100%	None
Giday *et al*[31], 2008	Animal	Experimental	Consistent results of portal pressure measurements for 1 h	100%	None
Huang *et al*[32], 2016	Animal	Experimental	Excellent correlation between EUS and IR methods in all pressure range (r = 0.985-0.99)	100%	None
Schulman *et al*[33], 2017	Animal	Experimental	EUS-PPG results did not differ from transhepatic portal venule measurement	100%	None
Huang *et al*[34], 2017	Human (n = 28)	Pilot	EUS-PPG had an excellent correlation with clinical parameters of portal hypertension (P < 0.05)	100%	None
Zhang *et al*[35], 2021	Human (n = 12)	Cohort prospective	Good correlation between EUS-PPG and HVPG (r = 0.923)	91.7%	None
Choi *et al*[36], 2022	Human (n = 83)	Retrospective	EUS-PPG correlates well with clinical markers of portal hypertension (P < 0.05)	100%	None
Lesmana[37], 2022	Human (n = 13)	Case series	EUS-PPG showed consistent pattern of portal pressure	100%	None
Reddy *et al*[39], 2022	Human (n = 128)	Systematic review and meta-analysis	Good correlation between clinical portal hypertension and portal pressure gradients	91.61%	None
Lei *et al*[40], 2023	Human (n = 52)	Case series	EUS-PPG results are significantly higher in patients with a history of gastro-esophageal bleeding (P < 0.05)	98%	None

EUS-PPG: Endoscopic ultrasound portal pressure gradient; HVPG: Hepatic vein pressure gradient; PVP: Portal vein pressure; IR: Interventional radiology.

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FOOTNOTES

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MINIREVIEWS

Robotic surgery in elderly patients with colorectal cancer: Review of the current literature

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Abstract

With an ageing global population, we will see an increasing number of elderly patients with colorectal cancer (CRC) requiring surgery. However, it should be recognized that the elderly are a heterogenous group, with varying physiological and functional status. While traditionally viewed to be associated with frailty, comorbidities, and a higher risk of post operative morbidity, the advancements in minimally invasive surgery (MIS) and improvements in perioperative care have allowed CRC surgery to be safe and feasible in the elderly - chronological age alone should therefore not strictly be an exclusion criterion for curative surgery. However, as a form of MIS, laparoscopic assisted colorectal surgery (LACS) has the inherent disadvantages of: (1) Dependence on a trained assistant for retraction and laparoscope control; (2) The loss of wristed movement with reduced dexterity and suboptimal ergonomics; (3) A lack of intuitive movement due to the levering effect of trocars; and (4) An amplification of physiological tremors. Representing a technical evolution of LACS, robotic assisted colorectal surgery was introduced to overcome these limitations. In this minireview, we examine the evidence for robotic surgery in the elderly with CRC.

Key Words: Robotic surgery; Minimally invasive surgery; Colorectal cancer; Elderly; Geriatric; Frailty

Core Tip: Robotic assisted colorectal surgery (RACS) is safe and feasible in the elderly. Despite an increased operative time, it potentially confers the benefit of lower conversion, earlier return of gut function and shorter length of stay with comparable oncological outcomes. As such, age alone should not be a specific exclusion criterion for RACS.

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INTRODUCTION

Globally, life expectancy has increased by more than 6 years between 2000 and 2019 - from 66.8 years in 2000 to 73.4 years in 2019. As such, the geriatric (age 65 and older) population is expected to expand exponentially[1]. The incidence of colorectal cancer (CRC) increases with age and the peak incidence has been reported to be between the 7th and 8th decade of life[2]. An estimate from the Surveillance, Epidemiology, and End Results database shows that approximately 70% of CRC develop over the age of 65, and about 40% of patients are over 75 years old[3]. Combining this age-specific incidence with a rapidly ageing population will result in a growing number of elderly patients with newly diagnosed CRC requiring surgery.

Despite being associated with multiple comorbidities[4], frailty[5], and sarcopenia[6], improvements in surgical technique and peri-operative care have made curative resection in the elderly safe and feasible[7]. One of these technological advancements is minimally invasive surgery (MIS). Studies have shown that the benefits of laparoscopy over open colorectal surgery are more pronounced in the elderly and the former has now become the standard of care in many countries[8,9]. However, the data for robotic colorectal surgery in the elderly remains comparatively scarce due to its slower uptake. This is partly due to concerns of adverse outcomes in the elderly from increased operative time and prolonged pneumoperitoneum associated with robotic surgery. In this review, we examine the operative and oncological outcomes for robotic colorectal surgery in elderly patients with CRC. Literature search was performed electronically using PubMed (MEDLINE) and the *Reference Citation Analysis* (https://www.referencecitationanalysis.com) was applied. The search terms were as follows: Elderly or old, CRC or colon cancer, and robotic surgery or robotic colectomy in combination with Boolean operators AND or OR. All studies published in English were extracted for review by the authors.

THE FRAIL ELDERLY AND RISK OF SURGERY

Most reports concur that CRC surgery in the elderly is associated with greater risks than in younger patients. The CRC Collaborative Group found that compared with their younger counterparts, the elderly tend to have more comorbidities and are more likely to present with late-stage disease requiring emergency surgery. These risk factors contribute to post operative morbidity and mortality[10]. They are also more likely to have had previous abdominal surgery, resulting in intra-abdominal adhesions that prolong operative time and increase the risk of iatrogenic injury[11].

Frailty is common in the elderly and is associated with an increased incidence of post-operative complications, prolonged hospitalization, greater 30-d mortality, and poorer overall survival (OS)[12]. Though there is no consensus definition of frailty, it is used to describe the syndrome of multisystem decline in physiological reserve which results in general debility, cognitive impairment, fatigue, weight loss, sarcopenia, low levels of physical activity, and progressive decline in body function and consequently the increased susceptibility of the patient to stress which can result in poor health outcomes[13-15].

However, it is important to note that frailty goes beyond age. Although it has been previously reported that advanced age itself is an independent risk factor for adverse outcomes, recent evidence suggests that it is not the chronological age of the patient but rather the quality of aging and the functional status that defines frailty and constitute a risk for surgery[16]. There is significant heterogeneity in the elderly with varying functional and physiological reserve and co-morbid states, hence tolerance to surgical stress can vary[17].

Comprehensive metrics have been used to distinguish between ''frail'' and ''non-frail'' patients to risk stratify elderly patients for surgery. At present, the Comprehensive Geriatric Assessment (CGA) is viewed as the gold standard for diagnosing frailty[18], and is recommended by the International Society of Geriatric Oncology. However, the CGA is time consuming and requires special training to assess. Other rapid frailty screening tools such as the image based Canadian Study of Health and Aging-Clinical Frailty Scale have been developed and can be utilized in the routine outpatient setting[19]. Risk stratification and medical optimization are important because it has been shown that a complicated postoperative course in the elderly has an adverse impact on survival in the first year after surgery[20], and for survivors of this early post-operative period of 1 year, cancer-related survival of the elderly is comparable to their younger counterparts[21,22].

While chronological age should not be a strict exclusion criterion for curative surgery in elderly patients with CRC, it should be recognized that the elderly patient has a more diverse and complex range of problems that puts him or her at an increased risk for surgery. As such, the importance of patient selection and treatment individualization cannot be overemphasized. For the frail elderly with limited life expectancy and poor functional reserve, it is perhaps reasonable to adopt a less aggressive approach to avoid the risks associated with radical surgery. Examples include palliative stoma or stenting for malignant large bowel obstruction, a watch and wait strategy after chemoradiation for rectal cancer, or surveillance in lieu of surgery for those with complete endoscopic removal of a malignant polyp. However, for those with a reasonable life expectancy and functional status, there is no compelling reason to deny them curative surgery based on age alone. If planned for surgery, this group of patients will benefit from multidisciplinary collaborative care involving geriatricians, anaesthetists, rehabilitation physicians, dieticians, and physiotherapists to deliver frailty targeted intervention programs to achieve better outcomes[23].

SURGICAL OPTIONS FOR CRC IN ELDERLY PATIENTS

The adage "Nothing beats good surgery!" holds true particularly for the elderly. The ideal operation for CRC would be one that: (1) Expedient; (2) Low morbidity; (3) Early return of gut function; (4) Acceptable pain profile that allows early ambulation; and (5) Good oncological outcome. When compared to open surgery, laparoscopic assisted colorectal surgery (LACS) for the elderly has been shown to be safe and feasible. Notwithstanding longer operative times, LACS conferred the benefits of less blood loss, reduced morbidity, faster return of bowel function and a shorter length of stay[24,25]. There was no difference in lymph node yield, disease specific survival and OS[25]. Studies by Frasson *et al*[8] and Hamaker *et al*[9] showed that the benefits of LACS were more pronounced in the elderly.

Unfortunately, there are inherent disadvantages in LACS. These include an unstable assistant-dependant view, loss of wristed movement with reduced dexterity, lack of intuitive movement due to the levering effect of trocars, and the amplification of tremors[26]. Also reported are poor ergonomic positions resulting in operator strain and lack of control over assistant's traction[27]. These drawbacks are particularly apparent when performing total mesorectal excision (TME) in the narrow confines of the pelvis, resulting in a high rate of open conversion and potentially negating the benefits of MIS[28].

Representing a technical evolution of LACS, robotic assisted colorectal surgery (RACS) overcame many of its limitations. These include a stable surgeon-controlled 3D view, tremor elimination, increased manoeuvrability with EndoWrist technology, fixed stable traction, less physical strain and movement scaling which allows for greater precision in dissection and improved ergonomics for the surgeon[29,30]. Applied to TME, these advantages have been shown to reduce the risk of open conversion, post-operative complication, and length of stay[31]. Other studies have also shown that RACS provides superior visualization and more dynamic assistance than conventional laparoscopy in hemicolectomies[32]. It is therefore unsurprising that the uptake of RACS has increased dramatically over the past decade[33,34].

However, when compared to the general population, the uptake of RACS in the elderly has not been as rapid. This is due to concerns of the elderly being more susceptible to the stress of prolonged pneumoperitoneum from the increased operative time. Coupled with the steep Trendelenburg position required for rectal surgery, this can potentially result in adverse cardiovascular and respiratory complications[35]. Prolonged steep Trendelenburg has also been reported to result in ischemic optic neuropathy and raised intraocular pressure that potentially increase the risk of vision loss, especially in the elderly with pre-existing glaucoma[36].

SURGICAL OUTCOMES OF RACS IN THE ELDERLY

Despite these concerns, contemporary data seem to suggest that they are unfounded. We summarize the post operative outcomes of the available comparative studies between RACS and LACS in the elderly in Table 1[37,38] and with their younger counterparts in Table 2[39-42]. de'Angelis *et al*[38] reported that RACS took longer but Palomba *et al*[37] found that when subdivided by procedure, only colectomies had a longer operative time and there was no difference when TME was required. Despite this increase in operative time, no commensurate rise in intraoperative or postoperative cardio-respiratory complications or reports of vision loss were noted[37,38]. Furthermore, when compared to their younger counterparts, the elderly did not have a more complicated post operative course and there was no difference in 30-d mortality between the groups[39-42]. It is however important to note that these studies were limited by their retrospective nature and small numbers and were prone to bias. Till more conclusive data is available, it is prudent to ensure careful patient selection and medical optimization in the elderly.

Table 1 Robotic *versus* laparoscopic colorectal surgery in elderly studies

Ref.	Study type	Age cut-off	Number patients		Complication (%)			Conversion (%)			Operative time (min)			LOS (d)			Adequacy of resection and oncological outcomes
			RACS	LACS	RACS	LACS	*P* value	RACS	LACS	*P* value	RACS	LACS	*P* value	RACS	LACS	*P* value	
Palomba *et al* [37], 2022	Retrospective, comparative	65	32	51	25	29.4	0.66	3.1	13.7	0.35	RC = 238.5	RC = 183.5	0.004[a]	RC = 6.6	RC = 6.3	0.26	No difference in LN yield and length of specimen
											LC = 249.6	LC = 211.7	0.003[a]	LC = 4.2	LC = 5.8	0.004[a]	
											RS = 276	RS = 270	0.87	RS = 3.7	RS = 6.2	0.003[a]	
											RR = 302.8	RR = 291.7	0.12	RR = 5	RR = 7.1	0.003[a]	
de'Angelis *et al* [38], 2018	Retrospective, PSM comparative	65	43	43	37.2	44.2	0.66	0	0	NA	300.6	214.5	0.034	11.7	14.8	0.079	No difference in LN yield. No difference in R0 resection. No difference in OS, DFS at 1,2 and 3 yr

[a]*P* values < 0.05 were considered statistically significant.

LOS: Length of stay; LN: Lymph node; OS: Overall survival; DFS: Disease free survival; PSM: Propensity score matched; RACS: Robotic assisted colorectal surgery; LACS: Laparoscopic assisted colorectal surgery; RC: Right colectomy; LC: Left colectomy; RS: Rectosigmoid colectomy; RR: Rectal resection; NA: Not available.

Although not statistically significant, the open conversion rate was 4 times more for LACS (13.7% *vs* 3.1%) in Palomba *et al*[37]'s series. Similar trends have also been reported in the general adult population[26,31]. Intra-abdominal adhesions are often cited as a common reason for open conversion. In addition, adhesions increase operative time and the risk of iatrogenic bowel injury[11]. In this aspect, the elderly patient is particularly disadvantaged. Firstly, they are more likely to have had previous open surgery given that MIS was only mainstream in the past couple of decades, and secondly, they have an increased risk of adverse outcomes in the event of surgical complications and open conversion[20]. RACS has been shown to reduce the rates of open conversion in both colectomies[26] and TME surgery [31], especially in the setting of patients with intra-abdominal adhesions[43]. This potentially allows more elderly patients to benefit from MIS.

Compared to LACS, Palomba *et al*[37] reported a faster return of bowel function and reduced length of stay for left sided resection and those requiring TME. This is consistent with the results seen in the general adult population[31] and is probably a reflection of the superiority of the robotic platform in the narrow confines of the pelvis. These benefits have also been reported in robotic hemicolectomies and are theorized to be a consequence of greater precision of dissection, less bowel manipulation, and reduced tissue trauma when compared to the open or laparoscopic approaches. Furthermore, the reduced pain associated with more pivotal rather than tractional port manipulation results in less opiate use in RACS, allowing for an earlier recovery of gut function. The advantages of the robotic platform also lend itself well to intracorporeal anastomosis, which has been shown to reduce extraction site morbidity and

Table 2 Robotic colorectal surgery in elderly *versus* non-elderly

Ref.	Study type	Age cut-off	Number patients		Operative time (min)			Complication (%)			LOS (d)			Oncological outcomes
			ELD	NELD	ELD	NELD	*P* value	ELD	NELD	*P* value	ELD	NELD	*P* value	
Hannan *et al*[39], 2022	Retrospective, comparative	65	89	73	228	254	0.09	30.3	26	0.2	7	6	0.007[a]	No difference in LN yield. No difference in R0 resection
Su *et al*[40], 2021	Retrospective, comparative	70	30	126	320	280	0.187	16.7	20.6	0.002[a]	7	6	0.084	No difference in LN yield. No difference in R0 resection. No difference in OS and DFS
Oldani *et al*[41], 2017	Retrospective, comparative	70	RC = 9	RC = 6	NI	NI	NI	0	0	NI	5.22	5.66	NI	No difference in LN yield
			LC = 5	LC = 15				0	6.7		6.75	6.4		
			RR = 8	RR = 7				0	14.3		5.75	9.0		
Cuellar-Gomez *et al*[42], 2022	Retrospective, comparative	YO: 75-80; MO: 81-85; OO: ≥ 86	YO: 48; MO: 19; OO: 9		YO: 280; MO: 290; OO: 253		0.538	YO: 27.2; MO: 52.6; OO: 44.4		0.144	YO: 13.77; MO: 13.58; OO: 18.22		0.579	No difference in LN yield

[a]*P* values < 0.05 were considered statistically significant.

ELD: Elderly; NELD: Non-elderly; LOS: Length of stay; LN: Lymph node; OS: Overall survival; DFS: Disease free survival; RC: Right hemicolectomy; LC: Left hemicolectomy: RR: Rectal resection; NI: No information; YO: Youngest-old; MO: Middle-old; OO: Oldest-old.

shorten the length of stay[44].

Oncological surgery should not be compromised in the elderly. In fact, some may argue that it is perhaps more essential given that pre-existing comorbidities may preclude them from adjuvant systemic therapy. The adequacy of resection for RACS is comparable to LACS in terms of lymph node yield and the percentage of R0 resections in the elderly[37,38]. de'Angelis *et al*[38] also reported no differences in OS and disease-free survival (DFS) up till 3 years. This is in keeping with current evidence for RACS in the adult population, which show no difference in terms of 5-year OS, DFS and local recurrence[45,46]. Complete mesocolic excision (CME) with central vascular ligation (CVL) for colonic cancer was first described by Hohenberger *et al*[47] and has been shown to have better quality surgical specimens and is associated with superior long term oncological outcomes[48]. The superior optics, stable retraction and dexterous dissection provided by the robotic platform makes it well suited to perform CME and CVL safely[49].

CONCLUSION

Early results from comparative studies show that RACS is safe and feasible in the elderly and despite an increased operative time, it potentially confers the benefit of lower conversion, earlier return of gut

function and shorter length of stay with comparable oncological outcomes. As such, age alone should not be a strict exclusion criterion for RACS.

FOOTNOTES

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MINIREVIEWS

Median arcuate ligament syndrome often poses a diagnostic challenge: A literature review with a scope of our own experience

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Abstract

The median arcuate ligament syndrome (MALS) is recognized as a rare clinical entity, characterized by chronic post-prandial abdominal pain, nausea, vomiting, and unintentional weight loss. Due to its vague symptomatology, it is mainly regarded as a diagnosis of exclusion. Patients can often be misdiagnosed for several years before a correct diagnosis is established, also due to a medical team's clinical suspicion. We present a case series of two patients who suffered from MALS and were treated successfully. The first patient is a 32-year-old woman, presenting with post-prandial abdominal pain and weight loss that have lasted for the past ten years. The second patient, a 50-year-old woman, presented with similar symptomatology, with the symptoms lasting for the last five years. Both cases were treated by laparoscopic division of the median arcuate ligament fibers, which alleviated extrinsic pressure from the celiac artery. Previous cases of MALS were retrieved from PubMed, to assemble a better diagnostic algorithm and propose a treatment method of choice. The literature review suggests an angiography with a respiratory variation protocol as the diagnostic modality of choice, along with the laparoscopic division of the median arcuate ligament fibers as the proposed treatment of choice.

Key Words: Median arcuate ligament syndrome; Dunbar syndrome; Celiac trunk compression syndrome; Celiac artery compression syndrome; Case series; Review

Core Tip: Due to its rarity, reviews, meta-analyses, and guidelines regarding median arcuate ligament syndrome (MALS) are rare. Most data can be extracted by individual case reports and case series. Even though MALS has a low frequency among the general population, more and more studies continue to support the claim that an increasing percentage of people may be prone to present characteristics of the syndrome. Thus, using this case series of patients as an example, we explore the literature with an aim to propose an improved diagnostic algorithm and treatment of choice.

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INTRODUCTION

The median arcuate ligament syndrome (MALS) does not represent a common clinical entity; however, its prevalence might be higher than previously considered[1]. The European Society for Vascular Surgery guidelines regarding diseases of the mesenteric arteries and veins, state that MALS is the most common cause of single vessel abdominal arterial stenosis[2]. It is characterized by recurrent episodes of post-prandial abdominal pain, nausea, vomiting, weight loss, and other more uncommon, but certainly potentially dangerous complications[3]. Due to the confusing overlapping symptomatology between MALS and other chronic mesenteric ischemic clinical entities, many researchers believe that the syndrome may be under-diagnosed, as is the case in many patients with chronic mesenteric ischemia due to diagnostic delay[4]. These factors have contributed to the lack of clinical studies and consensus guidelines for the diagnosis and treatment of this syndrome. Most clinical guidelines come from the systematic review and meta-analyses based on individual case reports and case series[5,6]. In this paper, we present two patients who were laparoscopically treated for MALS. In addition, we attempt to add a narrative review of the literature regarding diagnostic workup and treatment options for this syndrome.

LITERATURE REVIEW

We conducted a review of the literature of the past 3 years throughout the PubMed database, using the terms "median arcuate ligament syndrome", "MALS", "median arcuate ligament syndrome case report", "median arcuate ligament syndrome diagnosis", and "median arcuate ligament syndrome treatment".

PRESENTATION OF CASE 1

A 32-year-old woman presented to the outpatient clinic, complaining of abdominal pain, nausea, vomiting, and diarrhea. She had a ten-year history of recurrent post-prandial abdominal pain and weight loss. The symptoms have caused her to reduce her food intake and sometimes skip meals entirely. Her past medical history was unremarkable. She was not taking any prescribed medication and reported no allergies. The patient had never smoked and reported no significant alcohol consumption. Physical examination findings were unremarkable, other than the patient's weight at 38 kg and her height at 160 cm [body mass index (BMI) = 14.8 kg/m^2]. An abdominal X-ray showed gastric distension and no other remarkable findings. The magnetic resonance imaging (MRI) study performed with a respiratory variation protocol showed post-stenotic dilation of the celiac artery during expiration, along with a "J-shaped" or "hook-shaped" celiac artery (Figure 1).

After careful investigation of the patient's history and examination of the physical and radiologic findings, a diagnosis of MALS was established. The patient was scheduled for a laparoscopic median arcuate ligament release.

For the laparoscopic surgery, the patient is placed in a reverse Trendelenburg position with the legs being apart. The surgeon is standing between the patient's legs, a camera port is placed through the umbilicus, and four more ports are also inserted into the upper abdomen. The main goal of the procedure is to sustain a good view of the operative anatomy. The left and right diaphragmatic crura

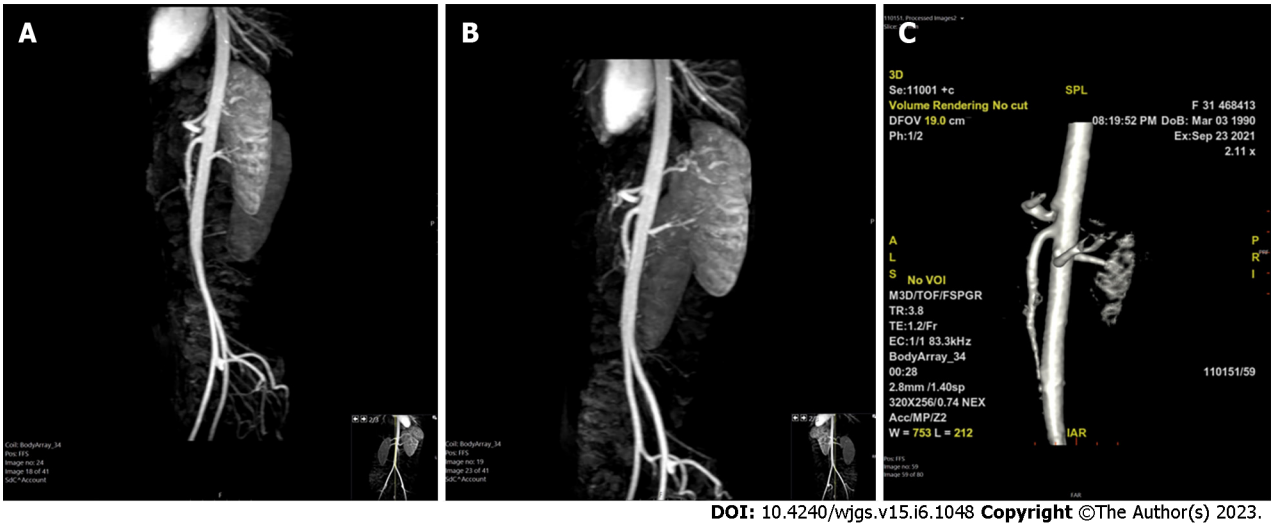

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Figure 1 Magnetic resonance angiography with a respiratory variation protocol. A-C: Evident stenosis of the celiac artery and post-stenotic dilatation.

are exposed to achieve good view of the surgical field prior to the division of the median arcuate ligament fibers. The dissection of the diaphragmatic crura is continued cranially with the intention of identifying the branches of the celiac artery (common hepatic artery, left gastric artery and splenic artery). The left gastric artery is controlled with the use of a vessel loop and with significant traction, to prevent injuries upon the left gastric artery and maintain adequate view of the surgical field. The dissection continues until the plane of the abdominal aorta. At this point, it is easier to identify the connective tissue comprising the median arcuate ligament, along with fibers from the celiac plexus. Using hook diathermy and a laparoscopic dissector with diathermy, the median arcuate ligament fibers are excised. Inadvertently, some fibers from the celiac plexus are also cauterized, further adding to the main goal, which is reduction of the pressure upon the celiac artery, as well as dissecting the sympathetic pain fibers of the celiac plexus. During the procedure for case 1 specifically, an aberrant blood vessel heading towards the liver was recognized and carefully preserved. This further supports the theory of development of collateral blood vessels to compensate for the reduced flow through the celiac artery (Figure 2).

PRESENTATION OF CASE 2

A 50-year-old woman presented to the outpatient clinic complaining of abdominal pain, nausea, and vomiting, with a 5-year history of post-prandial abdominal pain. She added that she had been losing weight over the referred time period. She also stated that she had undergone an extensive diagnostic workup in the past, for the same symptoms, but no diagnosis could be reached. Her past medical history was unremarkable. She was not taking any prescribed medication and reported no allergies. The patient had never smoked and reported no significant alcohol consumption. Physical examination findings were unremarkable and her BMI was in normal range (21 kg/m^2). An abdominal X-ray showed gastric distension and no other remarkable findings. After reviewing her past diagnostic workups, an MRI with a respiratory variation protocol was performed. Similar to the first case, the patient's celiac artery showed post-stenotic dilation during expiration, with a characteristic "J-shape". A diagnosis of MALS was established and the patient underwent laparoscopic division of the median arcuate ligament fibers, thus relieving the pressure from the celiac artery. The surgical technique for case 2 was similar to that described earlier.

During subsequent follow-up checks, the most recent being a year after the procedures, both patients presented well. Physical examination and history did not reveal any findings or referred symptoms. The patients have gained weight and do not present any postoperative complications or symptoms.

DISCUSSION

The MALS, or otherwise called Dunbar syndrome, remains a rare clinical entity. Diagnosing the syndrome is a difficult task, due to the overlapping symptomatology among many other clinical entities [1]. Even though the syndrome presents a low prevalence in the population, the anatomical variations responsible for the syndrome are present at a rather large portion of the population. Normally, the branches of the celiac artery arise from the abdominal aorta at the level of the T11-L1 vertebrae, while

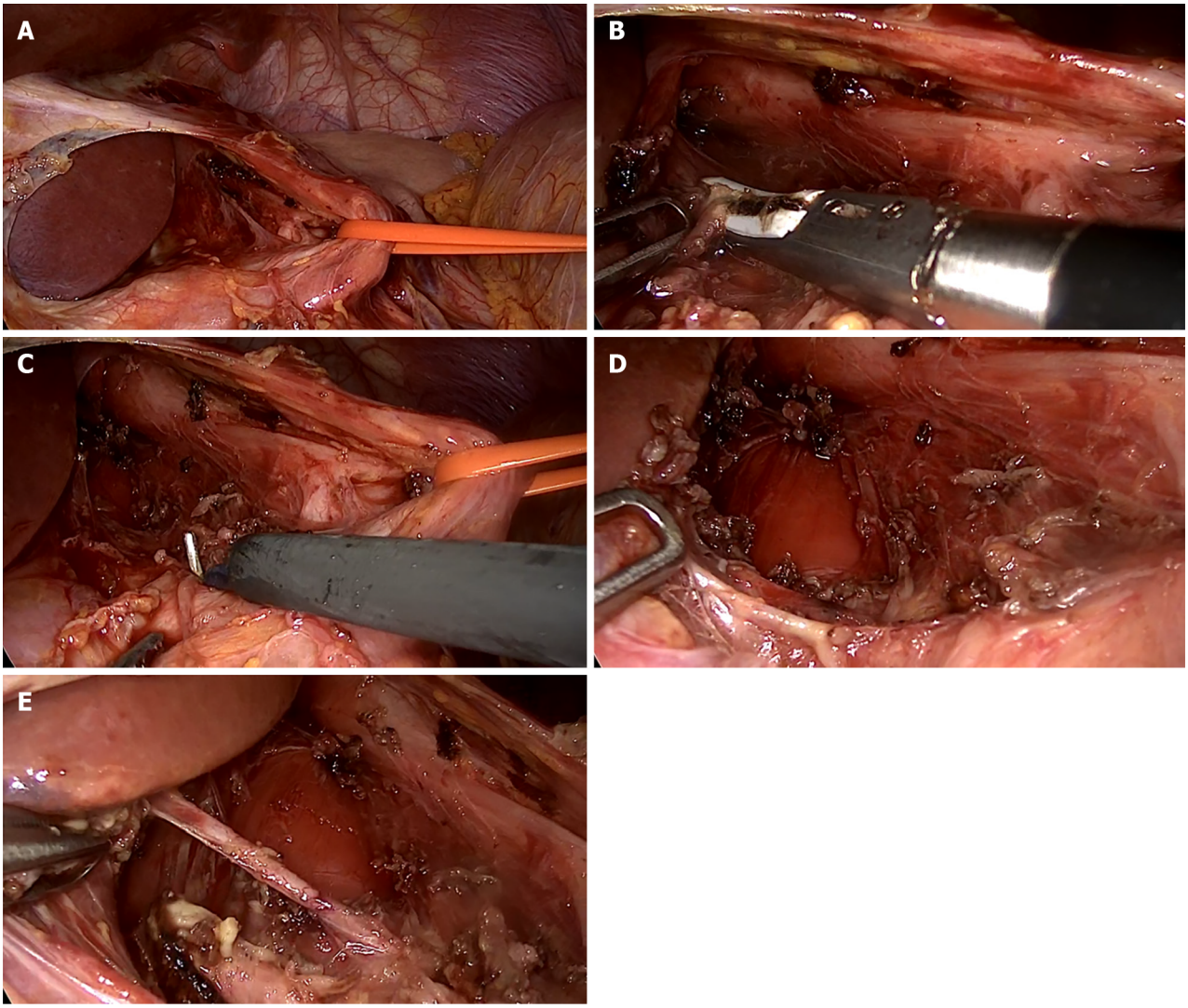

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Figure 2 Intraoperative images. A: Vessel loop around the left gastric artery; B: Careful dissection along the diaphragmatic crura; C: Dissection continues as the aorta is starting to be exposed and relieved from the extrinsic pressure of the diaphragmatic crura and the median arcuate ligament; D: Exposure of the abdominal aorta after the dissection of the diaphragmatic crura, the median arcuate ligament, and the neural fibers of the celiac plexus; E: Final look of the abdominal aorta along with the recognition of an aberrant blood vessel towards the liver.

the diaphragmatic crura arise from the level of L1-L4[7]. At that same level is where the median arcuate ligament connects the two parts of the diaphragmatic crura. In many people, a variation of the celiac artery arising at a higher level, or the diaphragmatic crura originating at a lower level, sets the circumstances for celiac artery compression. These anatomical prerequisites are found in 10%-24% of the population[1]. Based on this percentage, MALS could be responsible for more cases of chronic mesenteric ischemia than previously thought. This vascular compression theory is accompanied by some other researchers who support that extrinsic pressure upon the celiac plexus from the median arcuate ligament may also play a role in the pathophysiology of the syndrome[4]. The patients from the cases presented fit the characteristics of MALS, but the syndrome remains mostly a diagnosis of exclusion. The patient typically presents with postprandial abdominal pain, weight loss, nausea, vomiting, and diarrhea, among other complaints[8]. From the physical examination, it is reported that in up to 35% of patients, an epigastric bruit can be heard on auscultation, but it certainly is not pathognomonic[6]. These symptoms characterize a vast variety of diseases and syndromes throughout medicine, and certainly MALS is not the most common cause behind them[5]. Due to its rarity and relatively low prevalence, a radiologist may not always have this specific diagnosis in mind and thus miss the characteristic findings in routine computed tomography (CT)[9]. A study by Skeik *et al*[10] stated that the prevalence for MALS among other non-atherosclerotic abdominal arterial vasculopathies was found to be around 15.3%. Mainly, the diagnosis of MALS requires careful examination of the physical, clinical, and imaging findings by a team of experienced physicians and radiologists. The diagnostic modalities that are more commonly used include CT of the abdomen with IV contrast, magnetic resonance angiography (MRA), or Doppler ultrasound with a respiratory variation protocol

[4]. However, the diagnosis may not be so simple in some cases, especially when the clinical presentation is not typical. One common complication of MALS due to the increased flow speed through the celiac trunk is the subsequent development of collateral blood vessels. This process causes damage to the endothelium of the arteries comprising the celiac trunk. One manifestation of this complication can be a spectrum of coagulopathies or vasculopathies, mainly affecting the organs supplied by the celiac trunk. For instance, a patient with symptomatology consistent with chronic mesenteric ischemia, along with splenic infarcts or pancreaticoduodenal aneurysms, superior mesenteric artery (SMA) thrombus, and retroperitoneal hemorrhage, should raise a question about examining the vasculature of the area for other abnormalities, to reach a definite diagnosis, which could include MALS, and also, treat the accompanying disease either *via* surgery or *via* interventional radiologic methods[11-15]. All these complications and clinical presentations from MALS are reported in the literature, and as the cases of MALS increase, more complications could be associated with it. Another reason why the diagnosis of MALS may not be as easy as perhaps expected, is because it may even coincide with other vascular anomalies, such as a common origin of the SMA with the celiac trunk, or the co-incidence of syndromes such as the SMA syndrome or the nutcracker syndrome[16,17]. A radiologist or a physician interpreting diagnostic imaging must always have in mind the case of aberrant anatomy when trying to reach a diagnosis.

In many cases, MALS may not be identified prior to other medical or surgical interventions, which could be the cause of many complex and threatening complications. During our search in the literature, in many cases the missed diagnosis caused a halt to the operative actions to re-evaluate pre-operative diagnostic imaging, thus prolonging operative time[18]. In these cases, the decreased flow through the celiac trunk branches may cause postoperative complications, either medical or surgical, some of them even endangering the viability of other abdominal organs, as is the case in the reversal of flow in the hepatic artery causing liver ischemia[18].

Another important consideration about MALS occurs in the case of orthotopic liver transplantation. In these patients, MALS is considered a predisposing factor for hepatic artery thrombosis, due to the hemodynamic compromises in the hepatic artery[19]. Specifically, the compression from the median arcuate ligament is responsible for a reduction of blood velocities in the hepatic artery. This vascular compromise may contribute to reduced blood supply to the liver graft, biliary complications, and hepatic artery thrombosis[20]. In a recent retrospective study regarding patients receiving orthotopic liver transplantation, the presence of MALS dictated different management for the graft to be preserved and the procedure to be a success[19]. According to Li *et al*[19], if flow from the hepatic artery is found to be reduced, the gastroduodenal arteries and the collateral branches should be preserved. Still, there is much debate regarding the surgical technique used in patients receiving orthotopic liver transplantation while suffering from MALS.

To prevent the mentioned complications and operative risks, a definitive diagnosis should be established in patients presenting with chronic mesenteric ischemic symptoms. Because these symptoms are non-specific, an extensive workup must be ordered, including right upper quadrant ultrasonography, abdominal CT, and upper endoscopy. Due to the prevalence of the disease, consensus guidelines for the diagnosis of MALS specifically are not reported. There have been some attempts to study a cohort of patients who have adhered to a strict plan for potential diagnosis and treatment of MALS, such as a recent study by Gerull *et al*[21]. Mostly, patients undergo an extensive workup to exclude other diseases which are easier to definitively diagnose. A diagnostic modality that has been shown to have good efficiency and sensitivity is abdominal Doppler ultrasound, but it remains an operator dependent examination. A cut-off point that has been shown to have better efficiency is at 350 cm/s during the expiratory phase. Except for this cut-off, it has been reported that the difference in speed between the expiratory and inspiratory phase more than 50% has contributed towards the diagnosis of the syndrome[21]. Even without the use of MRI or CT angiography, the characteristic "J-shape" of the celiac artery can be evident with the use of Doppler ultrasound[22]. However, given the fact that Doppler ultrasound is operator dependent, it may not ultimately be the most accurate way of setting the diagnosis of MALS. So, keeping in mind that most patients have undergone an extensive diagnostic workup in the past, as was the case in our patients presented earlier, from our experience, our suggestion is to perform tests and diagnostic imaging that provide clear results. Thus, we consider MRA with a respiratory variation protocol to be the diagnostic modality of choice in patients undergoing a workup for MALS.

As far as the treatment options are concerned, procedures have varied throughout the years. Even when endovascular or other angioplasty techniques are considered as possible choices, it is possible that a surgical operation, preferably a laparoscopic procedure, is still superior to other approaches. This conclusion is evident from the cases where a surgical operation was required to treat the patients who initially underwent angioplasty procedures but were actually not relieved or did not show any sign of improvement. The main cause for the deficiencies of angioplasties to provide symptom relief is the inability to pass the guide wire through the stenosis formed from the median arcuate ligament and the diaphragmatic crura[23]. Other than laparoscopic surgery, robotically assisted surgery is being considered as an alternative. However, data is scarce mainly due to the rarity of the syndrome and the limited experience with robotically assisted surgery in many hospitals. From studies regarding the postoperative outcomes, robotically assisted surgery is an acceptable option, providing treatment and

good quality of life, as is evident from the good scores in questionnaires based on the patient's experience[24,25].

A study by the American College of Surgeons National Surgical Quality Improvement Program which spanned for 10 years depicted that the patients in the laparoscopic group had lower length of stay, lower major complication rates, and lower reoperation rates[26]. Even though the studies comparing robotically assisted surgery with laparoscopic surgery for MALS are rare, it has been stated that the abdominal pain associated with MALS was relieved more often in the group receiving the robotically assisted operation[27].

A very recent report from an expert panel on interventional radiology, regarding the topic of mesenteric ischemia, included MALS in their attempt to provide concise and evidence-based instructions for the diagnosis and treatment of mesenteric ischemia[28]. From their recommendations, the selection of mesenteric angiography in lateral projection with a respiratory variation protocol (during both inspiration and expiration) is critical to the diagnosis of MALS and the depiction of the abdominal vascular anatomy. The development of collateral vessels, which is a complication from the celiac artery stenosis, has been found to be a poor prognostic factor in patients with MALS[28,29]. The expert panel has also provided advice regarding the angioplasty *vs* surgical treatment options. According to their recommendations, transluminal angioplasty with the use of a stent should be reserved for patients whose symptoms and clinical presentation have not been resolved after a surgical division of the median arcuate ligament[28,30].

We acknowledge limitations in our mini-case series presentation and literature review. Our perspective originates from the diagnostic workup and treatment of two cases, which is still a relatively small number. Even though the diagnostic pathway and treatment used were successful, the collective study of more MALS cases can yield more definite results. Our review is based on recent studies and cases, and as the reported instances of the syndrome rise, more findings and guidelines can be published in the future.

CONCLUSION

Even though MALS is considered a diagnosis of exclusion, it should be considered in patients who seem to suffer from chronic mesenteric ischemic symptoms, but without a definite diagnosis. These patients have often already undergone an extensive workup, so it is important to choose the correct diagnostic approach, to provide definitive results. In our experience, the best options remain abdominal Doppler ultrasound and MRA with a respiratory variation protocol, with an extra advantage of the MRA as being non-operator dependent. Treatment should primarily focus on surgical release of the celiac artery, either laparoscopically or robotically assisted. Endovascular techniques should be reserved for patients who have already undergone a surgical procedure with no postoperative alleviation of symptoms.

FOOTNOTES

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MINIREVIEWS

Surgical complications of oncological treatments: A narrative review

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Abstract

Gastrointestinal complications are common in patients undergoing various forms of cancer treatments, including chemotherapy, radiation therapy, and molecular-targeted therapies. Surgical complications of oncologic therapies can occur in the upper gastrointestinal tract, small bowel, colon, and rectum. The mechanisms of action of these therapies are different. Chemotherapy includes cytotoxic drugs, which block the activity of cancer cells by targeting intracellular DNA, RNA, or proteins. Gastrointestinal symptoms are very common during chemotherapy, due to a direct effect on the intestinal mucosa resulting in edema, inflammation, ulceration, and stricture. Serious adverse events have been described as complications of molecular targeted therapies, including bowel perforation, bleeding, and pneumatosis intestinalis, which may require surgical evaluation. Radiotherapy is a local anti-cancer therapy, which uses ionizing radiation to cause inhibition of cell division and ultimately lead to cell death. Complications related to radiotherapy can be both acute and chronic. Ablative therapies, including radiofrequency, laser, microwave, cryoablation, and chemical ablation with acetic acid or ethanol, can cause thermal or chemical injuries to the nearby structures. Treatment of the different gastrointestinal complications should be tailored to the individual patient and based on the underlying pathophysiology of the complication. Furthermore, it is important to know the stage and prognosis of the disease, and a multidisciplinary approach is necessary to personalize the surgical treatment. The purpose of this narrative review is to describe complications related to different oncologic therapies that may require surgical interventions.

Key Words: Cancer; Chemotherapy; Radiotherapy; Complications; Bowel perforation;

Gastrointestinal bleeding

Core Tip: Gastrointestinal complications are common in patients undergoing various forms of cancer treatments, including chemotherapy, radiation therapy, and molecular-targeted therapies. Surgical complications of oncologic therapies can occur in the upper gastrointestinal tract, small bowel, colon, and rectum. Treatment of the different gastrointestinal complications should be tailored to the individual patient and based on the underlying pathophysiology of the complication.

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INTRODUCTION

Oncological treatments have greatly improved in the past few decades, thanks to the introduction of new therapies, such as immunologic agents or molecular targeted therapies, used alone or in combination with traditional chemotherapy and radiotherapy. The mechanisms of action of the various cancer therapies are different. Chemotherapy includes cytotoxic drugs, which block the activity of cancer cells by targeting intracellular DNA, RNA, or proteins[1,2].

Gastrointestinal symptoms are very common during chemotherapy, due to a direct effect on the intestinal mucosa resulting in edema, inflammation, ulceration, and stricture[3].

The development of molecular targeted therapies was due to the advances in oncological molecular biology. They include monoclonal antibody to vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR), and tyrosine kinase inhibitors[1]. These drugs modify biological characteristics of tumor cells and have a key role to selectively block some mechanisms related to cell growth, proliferation, and invasion[2]. Serious adverse events have been described as complications of molecular targeted therapies, including bowel perforation, bleeding, and pneumatosis intestinalis (PI), which may require surgical evaluation[2,4-10].

To date, immunotherapy represents the standard of care for different types of cancer. Several agents, such as cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and inhibitors of programmed cell death protein-1 (PD-1) and its ligand (PD-L1), inhibit tumor growth through the stimulation of the body's immune system against cancer. Immune-related adverse events mostly affect the gastrointestinal system, with heterogeneous symptoms that evolve into bowel ischemia or perforation, rarely[11,12].

Radiotherapy is a local anti-cancer therapy, which uses ionizing radiation to cause inhibition of cell division and ultimately lead to cell death[1]. Complications related to radiotherapy can be both acute and chronic. Acute symptoms occur within 2 mo and usually resolve in 3 mo[13,14]. Chronic symptoms, instead, occur months to years after radiotherapy. A high radiation dose, wide radiation area, long-term radiotherapy, and concurrent chemotherapy, are the factors related to an increased risk of toxicity[15]. The incidence of severe intestinal injury after abdominopelvic radiotherapy is about 4%-8%, and the main potentially surgical complications are perforation, strictures, abscesses, fistulas, and bleeding[16].

Ablative therapies, such as radiofrequency, laser, microwave, cryoablation, and chemical ablation with acetic acid or ethanol, can cause thermal or chemical injuries to the nearby structures[2].

As cancer treatments improve and new drugs are introduced, complications associated with oncologic therapies also increase. Many of these complications are life-threatening and have a high morbidity. As such, they require a prompt diagnosis. Therefore, it is crucial for surgeons to know the different complications and the therapies that can cause them, in order to ensure an immediate surgical treatment, if needed. In addition, knowing the stage and the prognosis of the disease is fundamental, and a multidisciplinary approach is necessary in order to personalize the surgical treatment. The purpose of this narrative review is to describe the complications related to different oncologic therapies that may require surgical interventions.

ENTEROCOLITIS

Neutropenic enterocolitis or typhlitis is typically diagnosed in patients with severe neutropenia related to oncologic treatment. This is a clinical syndrome characterized by abdominal pain, especially in the

right lower quadrant, and fever. A systematic review by Gorschlüter *et al*[17] showed an incidence of 5.3% of neutropenic enterocolitis in patients treated for hematologic cancers or treated with high dose chemotherapy for solid tumors. Moreover, 7.0% of individuals undergoing myelosuppressive chemotherapy courses for hematologic malignancies will develop *Clostridium difficile*–associated diarrhea, of whom 8.2% will develop severe enterocolitis, compared with the 2.8% incidence in general inpatient cohorts[18,19].

On computed tomography (CT), the cecum is most frequently affected by circumferential wall thickening with involvement of pericolonic fat. The most severe form of neutropenic enterocolitis can be characterized by bowel necrosis and perforation. Therefore, a right colectomy should be performed to prevent complications, if there is no improvement in clinical condition within 2-3 d of conservative treatment[20,21].

Radiotherapy can also cause enterocolitis, and the sigmoid colon and rectum are the most affected segments in patients treated for pelvic cancers. Acute enterocolitis, due to edema, inflammation, and atrophy related to mucosal stem cell damage, manifests with abdominal pain, nausea, and diarrhea, and it is usually self-limiting in 2-6 wk with symptomatic treatments[1,15,22].

The pathophysiological mechanism that determines the development of chronic enterocolitis is based on the gradual increase in fibrosis of the intestinal wall, due to collagen deposition[22]. Radiotherapy-related vascular injury causing ischemia is another significant factor.

Chronic radiation enteritis affects 5% of patients treated with a dose of 45 Gy, reaching 50% in those treated with 65 Gy[23,24], and the terminal ileum is more commonly affected (Figure 1). Chronic radiation colitis occurs in 1%-5% of patients[25] and symptoms usually develop 6-12 mo after treatment. Bleeding, fistulas, abscesses, and stricture causing intestinal obstruction are the clinical manifestations of radiotherapy-related enterocolitis that may involve the surgeon.

Patients undergoing chemotherapy may develop *Clostridium difficile* colitis (Figure 2), especially when treated with cyclophosphamide, methotrexate, fluorouracil, and doxorubicin[26]. Indications for surgery are the same as for antibiotic-related pseudomembranous colitis (*i.e.*, perforation, fulminant toxic megacolon, and organ failure).

The most common gastrointestinal complications in case of treatment with checkpoint inhibitors are diarrhea and colitis, mainly in patients treated with anti-CTLA-4 (ipilimumab)[27]. Enterocolitis associated with immunotherapy has an incidence of 2.0%[28], which increases to 40.0% in patients on ipilimumab[29], and usually develops after 6-7 wk of treatment. Bowel perforation and death occur respectively in 1.0% and 0.8% of patients[27-31].

To sum up, surgery is required in all the enterocolitis cases consequent to oncological treatment if there is evidence of persistent bleeding, ischemia, perforation, or clinical worsening despite conservative treatment.

PNEUMATOSIS

PI is a rare clinical condition characterized by the presence of air in the thickness of the intestinal wall. It is difficult to estimate the incidence of PI, as it is very often asymptomatic. However, its overall incidence, based on autopsy findings, is 0.03%[32].

PI can be idiopathic (about 15% of cases), when a cause cannot be identified, or secondary (about 85% of cases)[33]. In these cases, PI is associated with gastrointestinal or pulmonary diseases, mechanical ventilation, endoscopic procedures, infections, and drugs.

PI (Figure 3) can also occur as a complication of oncological medical therapies, including cytotoxic agents (cyclophosphamide, cytarabine, vincristine, doxorubicina, etoposide, docetaxel, irinotecan, and cisplatin) and molecular targeted agents (tyrosine kinase inhibitors such as imatinib, sunitinib, lenvatinib, and erlotinib; anti-VEGF monoclonal antibodies such as bevacizumab or anti-EGFR monoclonal antibodies such as cetuximab)[34,35].

The pathophysiological mechanisms underlying intestinal pneumatosis are not yet completely understood. As regards chemotherapeutic drugs, the most probable pathogenetic mechanism is the cytotoxic or ischemic damage caused by these drugs to the mucous layer of the intestinal wall. This damage would lead to the entry of gas, which is physiologically contained in the intestinal lumen, into the intestinal wall[36].

Chemotherapy-induced PI is also due to the myelosuppressive effects of drugs, which induce bone marrow aplasia and inhibit the regeneration process of damaged tissue[6]. Targeted therapies, on the other hand, are specific drugs that act as anti-VEGF/VEGFR, anti-EGFR, anti-PDGFR, and c-KIT inhibitors. These can determine a decrease in capillary density causing ischemia (anti-VEGF/VEGFR), a decrease in the efficiency in repairing intestinal damage (anti-EGFR, anti-PDGRF, and c-KIT inhibitors), and a reduction in intestinal motility (c-KIT inhibitors) by acting on Cajal cells[22,37-39].

According to a recent paper by Gazzaniga *et al*[6], PI mainly occurs in stage IV cancer patients (69.4% *vs* 11.1% of patients treated with a neoadjuvant therapy and 2.8% in adjuvant setting), and with the use of targeted therapies. PI is asymptomatic in most cases, and it is very often an occasional finding on CT performed in oncologic patients to monitor response to chemotherapy. No therapy is required in

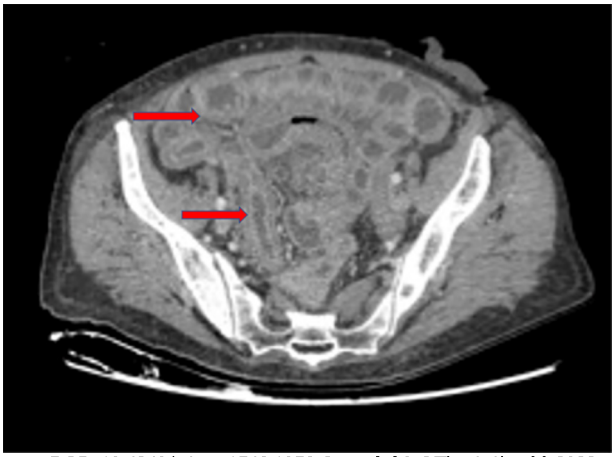

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Figure 1 Chronic radiation enteritis in a 62-year-old woman with anal cancer. Red arrows indicate regions where radiation enteritis is most evident (personal observation).

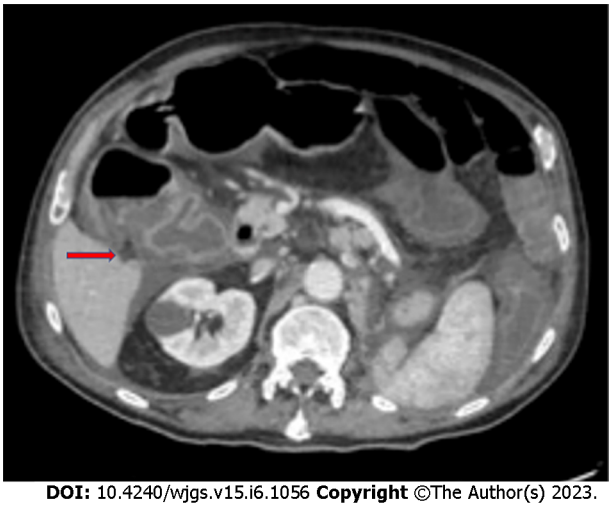

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Figure 2 *Clostridium difficile* colitis (red arrow) in a 78-year-old man with a malignant tumor of the lung treated with cyclophosphamide. (personal observation).

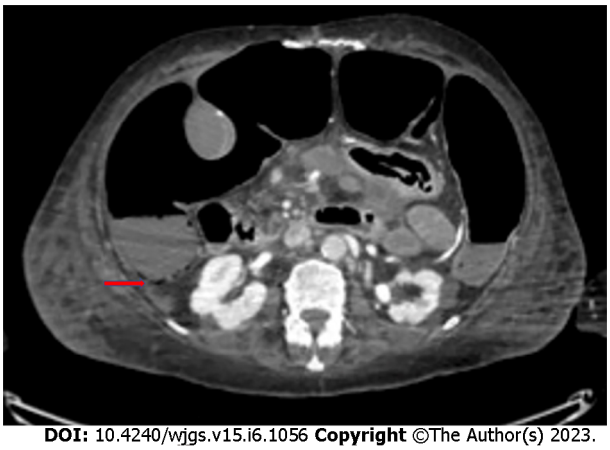

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Figure 3 Bevacizumab-related intestinal pneumatosis with right colon ischemia in a 69-year-old woman being treated for breast cancer. Red arrows indicate regions where pneumatosis is most evident (personal observation).

asymptomatic patients with PI. If present, symptoms can be extremely variable and may be indicative of bowel ischemia. The presence of hepatic and portomesenteric venous gas on a CT scan, associated with abdominal pain and alterations of blood tests and vital parameters, can be indicative of an ischemic pathology[40]. Hence, they require a prompt surgical exploration.

In fact, several studies in the literature demonstrated that the presence of gas in the portal vein is correlated to a transmural bowel ischemia in more than 90% of patients, and it is linked to a poor prognosis[41,42].

Therefore, it is very important to discriminate the cases in which surgery is necessary, to perform an immediate laparoscopy or laparotomy to avoid the progression of necrosis.

OBSTRUCTION

Intestinal obstructions represent an extremely common clinical condition in cancer patients, and they are caused by the tumor mass in most cases. Nevertheless, they can also be an effect of oncological therapies. Radiotherapy can induce a process of fibro-apoptosis which reduces the elasticity of the wall of the hollow viscera until it determines a stenosis. Small bowel strictures consequent to radiation therapy are a rare complication, caused by wall thickening and edema, which develop in 6-12 mo and occur especially in the terminal ileum, owing to its fixed position[22,43]. Intestinal obstructions caused by chronic radiation enteritis should be initially treated conservatively by fluid infusion, nasogastric tube placement, and possible use of laxatives[4,5].

Surgical treatment is indicated if there is no clinical response to medical therapy. One-third of patients with chronic radiation enteritis require surgery, approximately. Surgery is associated with a high morbidity rate and a high risk of reoperation. It is fundamental to resect the entire bowel involved in the stricture to prevent recurrence of obstruction, and to reduce complication and mortality rates[24]. Radiation therapy can also cause strictures of the esophagus and rectum[44,45]. In these cases, endoscopy is the treatment of choice with endoscopic dilatation and placement of self-expanding stents. Intestinal strictures caused by cytotoxic drugs, such as 5-fluorouracil and monoclonal antibodies (*i.e.*, nivolumab) are extremely rare, but described in the literature[46,47].

PERFORATION

Bowel perforation is a rare but serious complication of cancer treatments. It has been reported in association with chemotherapy, molecular targeted therapies, immunotherapy, ablative techniques for solid tumors, and radiation therapy. Several mechanisms may be responsible for gastrointestinal perforation from oncologic treatments. Anticancer drugs induce vascular damage by thrombosis and thromboembolism, and when intestinal vessels are involved, bowel ischemia with perforation may occur[12]. Perforation of the gastrointestinal tract can also occur after prolonged obstruction[48] or due to treatment responses with tumor lysis, as in cases of lymphomas or gastrointestinal stromal tumors [20]. Finally, bowel perforation can be a result of other complications of oncologic therapies, like pneumatosis or enterocolitis. Management of perforation with no generalized peritonitis may be based on placement of image-guided percutaneous drainage in case of fluid collections. If there is a free perforation, instead, urgent laparotomy is needed, primarily to limit septic complications, which are characterized by a very high mortality rate in patients with neutropenia[20]. Gastrointestinal perforation has been reported in the literature with several chemotherapy agents, including fluorouracil, taxols, cisplatin, interleukin-2, and mytomicin[49-52]. Among the molecular targeted therapies, bevacizumab is most commonly associated with gastrointestinal perforation (Figure 4), with an incidence of 0.9%[53], and a correlation with late anastomotic leakage[54]. Risk factors for bevacizumab-related perforation are specific tumors (colorectal, prostate, and gynecological cancers), combination with other treatments, such as oxaliplatin and taxanes, presence of a primary tumor *in situ*, and recent history of endoscopy or abdominal radiotherapy[53,55-57].

Bowel perforation occurs in 80% of patients during the first 6 mo after bevacizumab administration [58], and the most common sites of perforation are the colon, small intestine and stomach[9]. The pathophysiological mechanisms underlying bowel perforation from molecular targeted therapy are different: The antiangiogenic action, which reduces capillary density of the mucosa layer and compromises intestinal wall integrity; the tumor lysis, in response to treatment; the increased risk of thromboembolic events in mesenteric vessels; and the regression of normal blood vessels[8,59].

Several studies in the literature also show an association between gastrointestinal perforation and antiangiogenic tyrosine kinase inhibitors, like erlotinib, regorafenib, sunitinib, and sorafenib[10,60-64] (Figure 5).

The incidence of tyrosine kinase inhibitors-related bowel perforation is still unknown, since there are mainly case reports in the literature. Intestinal perforation after immunotherapy is a rare event (Figure 6). A case report by Patel *et al*[31] described a jejunal perforation after treatment with ipilimumab and nivolumab for metastatic melanoma, related to tumor regression. Another paper by

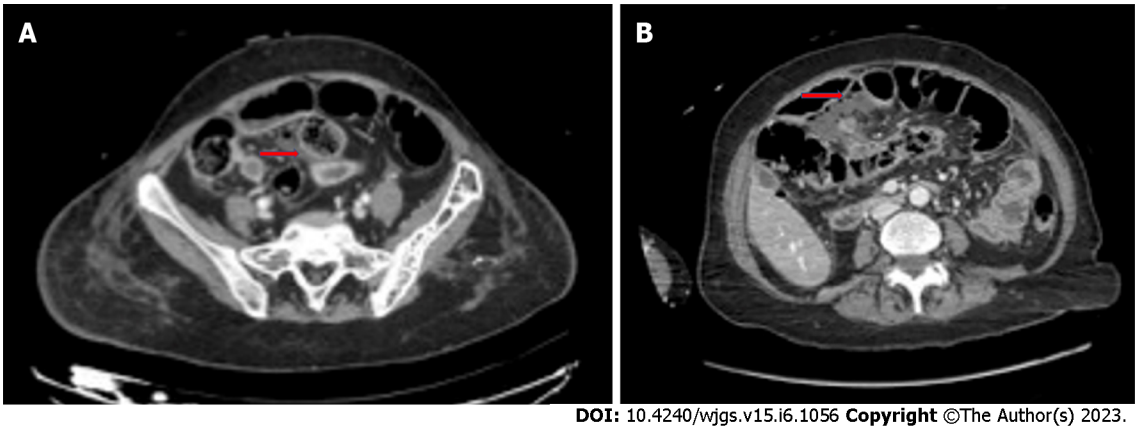

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Figure 4 Computed tomography images. A: Bevacizumab-related small bowel perforation in a 49-year-old female patient with breast cancer (red arrow); B: Bevacizumab-related late anastomotic leakage (red arrow) in a 72-year-old female colon cancer patient (personal observation).

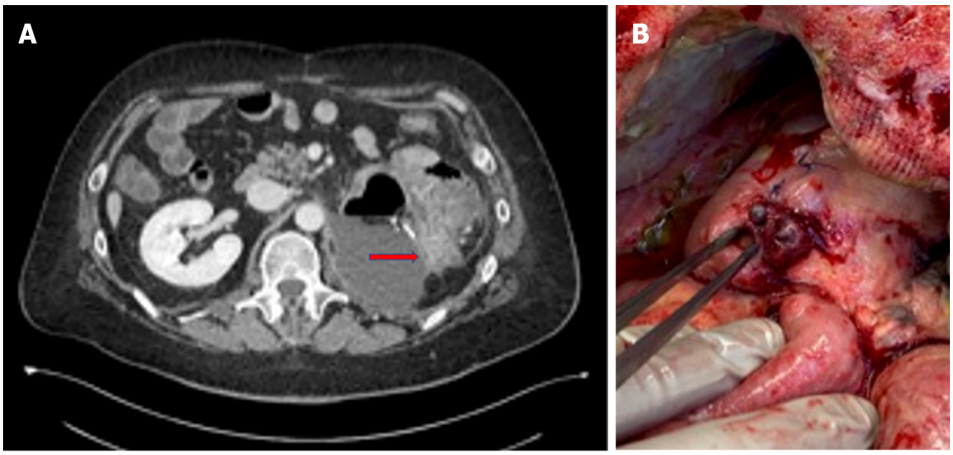

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Figure 5 Computed tomography and intraoperative findings. A: Computed tomography scan of bowel perforation (red arrow) in a 56-year-old male patient undergoing molecular targeted therapy with capozatinib for metastatic renal cell carcinoma; B: Intraoperative findings in the same clinical case (personal observation).

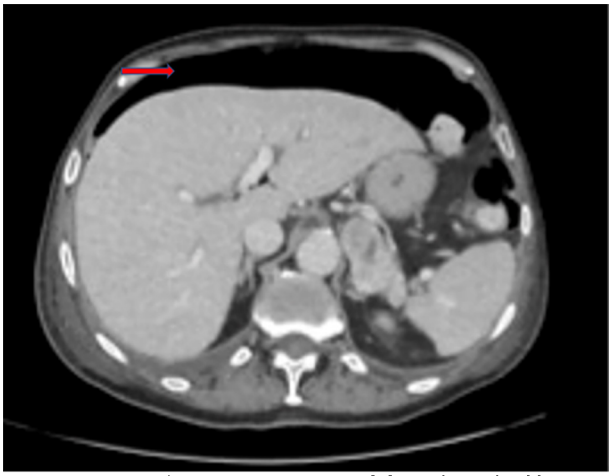

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Figure 6 Bowel perforation in a 73-year-old male lung cancer patient undergoing immunotherapy with atezolizumab. The red arrow indicates subdiaphragmatic free air (personal observation).

Romano *et al*[65] reported a small bowel perforation in a patient treated with nivolumab for metastatic lung cancer.Radiofrequency or micro-wave ablation can cause injuries to nearby organs. Bowel perforation with formation of abscesses and fistulas or free peritonitis, can be due to ablative therapies on liver cancer or, to a greater extent, on solid renal tumors, for direct thermal or chemical injuries[2,3]. In the literature, 4%-8% of patients treated with abdominopelvic radiation therapy can develop serious complications such as fistulas, perforation, or abscesses[16,66].

A recent paper by Zhan *et al*[67] showed that both long course and short course radiotherapy as neoadjuvant treatment for locally advanced rectal cancer increased the risk of anastomotic leakage, without a rise in postoperative mortality.

Risk factors for bowel perforation following radiotherapy are radiation dose, size of irradiation field, and the combination with other cancer treatments[14]. Several studies describe cases of intestinal perforation following the use of radiotherapy together with antiangiogenetic agents, like dabrafenib and trametinib for pelvic bone melanoma metastases[68], sorafenib in renal cancer patients[69], and gefitinib in a patient with lung cancer receiving lumbar irradiation[70]. The precise pathophysiology of radiotherapy-related bowel perforation is still unclear, but stem-cell and microvascular damage seems to have a pivotal role in gastrointestinal injuries affecting these patients.

BLEEDING

Bleeding events in cancer patients can be caused by the disease itself or by medical treatments and require a surgical intervention, rarely. However, the surgeon may be involved in the multidisciplinary management of the patient or in case of failure of conservative treatments. Oncological therapies can affect the risk of hemorrhage both through alteration of the number or function of platelets and effect on the coagulation process. Some chemotherapeutic agents and anti-angiogenic targeted therapies are associated with increased bleeding tendency. For example, gastrointestinal bleeding has been described in patients receiving bevacizumab or in patients with gastrointestinal stromal tumors receiving imatinib or sunitinib[71,72].

Patients may present with different severity symptoms: Visible bleeding such as hematemesis, melaena, and hematuria, or occult bleeding for intraperitoneal or retroperitoneal hemorrhages. Treatment includes initial management by fluid infusion and blood transfusion. Endoscopy is a minimally invasive method to control the bleeding in the gastrointestinal tract, lungs, and bladder[73].

Angiography and interventional radiologic embolization of blood vessels represent additional minimally invasive bleeding control techniques. Nevertheless, these techniques present some technical issues: Accessibility of target blood vessels, subsequent ischemia of important non-target organs, and the availability of appropriate expertise[4,5]. Surgical treatment is reserved for patients with hemodynamic instability or in case of failure of other bleeding control techniques.

Rectal bleeding has been reported to occur in up to 53% of patients who received pelvic radiotherapy, but only 6% of these cases require interventions. The dose of radiotherapy is closely related to the risk of bleeding. The onset of rectal bleeding is described in the literature from 3 mo to 12 mo after radiotherapy.

Medical treatments for rectal bleeding after radiation therapy include sucralfate enemas, long term treatment with metronidazole, vitamin A, and hyperbaric oxygen therapy[74]. Endoscopic thermal therapies are frequently used in rectal bleeding and among these, argon plasma coagulation is the treatment of choice[75]. Radiologic embolization and surgery are required very rarely.

OTHER COMPLICATIONS

Granulocyte growth factor (G-CSF), also known as colony stimulating factor 3 (CSF 3), is a glycoprotein that stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream. This drug is widely used to treat neutropenia, a frequent side effect of many chemotherapy drugs[76]. It is also used to increase the content of hematopoietic stem cells before a bone marrow donation. Although G-CSF is generally well tolerated, a rare side effect of this drug is splenic rupture[77]. The mechanism underlying splenic damage is likely related to massive extramedullary hematopoiesis resulting in splenomegaly, splenic congestion, and nontraumatic rupture of the viscera. The patients generally present abdominal pain, mostly reported in the left hypochondrium, tenderness, anemia on blood tests and, in the most severe cases, hemodynamic instability. If a splenic rupture is suspected, a CT scan of the abdomen is required. Embolization of the splenic vessels is a valid option for stable patients and in hospital centers with the availability of interventional radiology. On the other hand, splenic rupture represents a surgical emergency for patients with hemodynamic instability. Splenic damage is also reported in the literature in patients treated with imatinib or idarubicin[78,79].

Non-occlusive mesenteric ischemia (NOMI) is another rare but serious complication of oncological treatments. A recent paper by Nagano *et al*[80] describes three cases of NOMI in patients undergoing chemotherapy for head and neck cancers. Prompt diagnosis and emergency surgical treatment are

needed to reduce mortality rate and improve prognosis of patients with NOMI and bowel necrosis. Acute cholecystitis has been described in patients undergoing oncological therapies with antiangiogenetic targeted agents, including sunitinib, sorafenib, and bevacizumab[81]. Furthermore, a case of acute cholecystitis in a patient with metastatic renal cell carcinoma during therapy with everolimus, an inhibitor of the mammalian target of rapamycin, is reported in the literature[82]. Alithiasic cholecystitis has been described in patients with hematological diseases treated with vincristine, cyclophosphamide, or cytosine-arabinoside[83]. The proposed pathogenetic mechanism for the onset of acute cholecystitis during oncological therapies is related to the presence of microvascular ischemia or to an altered lipid metabolism, with consequent formation of gallstones. Symptoms and ultrasonographic findings, which include gallbladder distension, edema, hyperemia, pericholecystic fluid, and stranding, are analogous to those found in acute cholecystitis due to another etiology. In patients with acute cholecystitis, it is necessary to suspend cancer therapy temporarily or permanently. Some patients were treated exclusively with antibiotic therapy until symptoms resolved, and others underwent urgent cholecystectomy. However, for high risk, immune deficient, or severely ill patients, less invasive image guided percutaneous cholecystostomy must be considered as a bridge to surgery or as a definitive treatment. Finally, acute cholecystitis can also be a complication of locoregional treatments for liver cancer[84]. When hepatic ablation is performed near to the gallbladder, cystic duct stricture can cause acute cholecystitis[85]. Ablative techniques can also cause diaphragmatic injuries, if target lesion is in the high hepatic dome[85].

SECOND CANCER

The development of specific cancer treatments has improved long-term survival in cancer patients. As a result, the risk of developing a second cancer after a primary oncologic treatment also increases, especially in long-survivor cancer patients.

The risk of a second tumor after radiotherapy is reported to be 0.1% to 1.0%[1] and radiation-induced cancers can be sarcomas, lymphomas, mesotheliomas, and carcinomas. The time to develop a post-radiation sarcoma is estimated to be 4-17 years[86]. Tamoxifen, a selective estrogen receptor modulator, is a chemotherapeutic agent used for the treatment of breast cancer. It is well known that tamoxifen is associated with an increased risk of endometrial cancer (two-to-three times higher than that in normal population)[87] and uterine sarcoma in postmenopausal patients. The onset of both tumors is related to the dose and time of therapy[88], and for this reason it is more frequent in long-survivor breast cancer patients for this reason.

CONCLUSION

Oncologic therapies have greatly improved over the past few years. As a result, complications related to cancer treatments have also increased. Gastrointestinal complications that most frequently require surgery are bowel perforations and obstructions (if conservative treatment fails). However, even for rarer complications, such as splenic rupture or diaphragmatic injury, emergency surgical treatment is necessary. Hence, it is essential for surgeons to be aware of new cancer therapies and their side effects, in order to act promptly if surgery is needed. It is also essential to keep in mind that the treatment of different gastrointestinal complications should be tailored to the individual patient and based on the underlying pathophysiology of the complication.

FOOTNOTES

Author contributions: Fico V and Altieri GM equally contributed to the drafting of the manuscript; Fico V, Altieri G, Tropeano G, Di Grezia M, Bianchi V, Chiarello MM, and Brisinda G designed the research; Bianchi V, Pepe G, Fico V, and Altieri G performed the research; Fico V, Altieri G, Tropeano G, and Di Grezia M analyzed the data; Fico V, Altieri G, Pepe G, and Brisinda G wrote the paper; all the authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Basic Study

Impact of interstitial cells of Cajal on slow wave and gallbladder contractility in a guinea pig model of acute cholecystitis

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Abstract

BACKGROUND

Impaired interstitial cells of Cajal (ICCs) are central to the pathophysiology of acute cholecystitis (AC). Common bile duct ligation is a common model of AC, producing acute inflammatory changes and decrease in gallbladder contractility.

AIM

To investigate the origin of slow wave (SW) in the gallbladder and the effect of ICCs on gallbladder contractions during the process of AC.

METHODS

Methylene blue (MB) with light was used to establish selective impaired ICCs gallbladder tissue. Gallbladder motility was assessed using the frequency of SW and gallbladder muscle contractility *in vitro* in normal control (NC), AC12h, AC24h, and AC48h groups of guinea pigs. Hematoxylin and eosin and Masson-stained gallbladder tissues were scored for inflammatory changes. ICCs pathological changes alterations were estimated using immunohistochemistry and transmission electron microscopy. The alterations of c-Kit, α-SMA, cholecystokinin A receptor (CCKAR), and connexin 43 (CX43) were assessed using Western blot.

RESULTS

Impaired ICCs muscle strips resulted in the decrease in gallbladder SW frequency and contractility. The frequency of SW and gallbladder contractility were significantly lower in the AC12h group. Compared with the NC group, the density and ultrastructure of ICCs were remarkably impaired in the AC groups, especially in the AC12h group. The protein expression levels of c-Kit were significantly decreased in the AC12h group, while CCKAR and CX43 protein expression levels were significantly decreased in the AC48h group.

CONCLUSION

Loss ICCs could lead to a decrease in gallbladder SW frequency and contractility. The density and ultrastructure of ICCs were clearly impaired in the early stage of AC, while CCKAR and CX43 were significantly reduced at end stage.

Key Words: Interstitial cells of Cajal; Acute cholecystitis; Slow wave; Gallbladder; Contractility

Core Tip: Acute cholecystitis (AC) is inflammation of the gallbladder. In this study, we found that loss interstitial cells of Cajal (ICCs) could lead to the decreased of gallbladder slow wave (SW) and contractility. Acute inflammation can cause a reduction in the SW and gallbladder motility deficiency by damaging the density and function of ICCs during early AC stage. At the end stage of AC, the decrease of cholecystokinin A receptor and gap junction leads to the further decrease in gallbladder contractility and electrical conductivity.

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INTRODUCTION

Acute cholecystitis (AC) is a common acute inflammatory disease of gallbladder, which occurs in the cystic duct in approximately 90% to 95% of patient, typically caused by gallstone obstruction[1]. In contrast, acute acalculous cholecystitis is another specific type of acute inflammatory disease of the gallbladder without evidence of gallstones, which is present in approximately 5% to 10% of AC[2]. The main pathogenesis of AC is bile ducts obstruction induced by gallstones, bile sludge or lithogenic bile. The extent and duration of biliary obstruction determines the degree of progression of AC and the severity of gallbladder inflammation. More importantly, gallbladder dysmotility is the most critical pathogenic factor, as it could lead to gallstones, cholestasis, secondary bacterial infection, and even gallbladder ischemia[3].

In gastrointestinal (GI) tracts, interstitial cells of Cajal (ICCs), which characterized by rhythmic, spontaneous depolarization potentials, act as the pacemaker cells that generate and propagate the slow wave (SW). SW has been proven to play a significant role in the regulation of GI motility[4]. The waveform, frequency, amplitude, and duration of SW varies in different species and even in different regions of the GI tract, however the electrophysiological properties of SW always trigger resting membrane potentials of smooth muscle cells (SMCs) into the range of action potentials thus causing GI peristalsis. Thus, the loss of ICCs or disruption of ICCs networks might result in GI motility disorders [5].

Like GI smooth muscle, this spontaneous periodic electrical activity is also present in gallbladder smooth muscle (GBSM), yet the underlying mechanism is not clear. Recently, the distribution of ICCs has been demonstrated in the muscular layers of the gallbladder and biliary system[6,7]. In cholesterol stones of a guinea pig model, the reduced density of gallbladder ICCs could further cause the dysfunction of gallbladder motility[8]. Furthermore, destroying ICCs *in vitro* can significantly induce impairment of gallbladder motility[9]. Together, these results indicate that ICCs might contribute to regulation of the spontaneous rhythmic contractions and progression of gallbladder motility disorders. However, there is still a lack of studies of SW in the gallbladder. The relationship between ICCs and SW of the gallbladder remains unclear.

In this study, we firstly recorded gallbladder SW *in vivo* and *in vitro* and discussed the relationship between SW and ICCs. Then we investigated the alterations of ICCs, SW of gallbladder, and gallbladder motility in the guinea pigs of AC model. Additionally, we examined changes in the expression levels of

c-Kit, α-SMA, cholecystokinin A receptor (CCKAR) and connexin 43 (CX43) protein in the gallbladder of guinea pigs during AC progression.

MATERIALS AND METHODS

Animal model and experimental trials

Adult male guinea pigs (200-250 g) were obtained from Shanghai JieSiJie Laboratory Animal Co., Ltd. (Shanghai, China) and fed under the experimental environment for one week. All protocols were supervised and approved by the Institutional Animal Care and Use Committee of the East Hospital Affiliated to Tongji University (No. 2020-12-102). As described previously, the guinea pig model of AC was established by common bile duct ligation (CBDL)[10]. The guinea pigs were anesthetized with isoflurane (concentration: 1.5% to 2.5%, RWD Life Science, Shenzhen, Guangdong Province, China) by mask inhalation. Sterile laparotomy was performed to carefully isolate the tissue surrounding the CBD, and the distal end of the CBD was ligated (6-0 silk, Johnson & Johnson China Ltd.), with minimal manipulation of the CBD and no operation of the gallbladder. After awakening from anesthesia, animals were housed separately and supplied with food and water *ad libitum*. Twenty guinea pigs were randomly divided into four groups: the normal control (NC), AC12h, AC24h, and AC48h groups. Each group had five guinea pigs. The NC, AC12h, AC24h, and AC48h groups were all monitored until sacrificed 12 h to 48 h later (see below).

Tissue preparation

Each guinea pig in the NC, AC12h, AC24h, and AC48h groups was briefly anesthetized with isoflurane (concentration: 1.5% to 2.5%). After cervical dislocation, the gallbladder was precisely removed and then opened with a longitudinal incision at 12 h, 24 h, or 48 h after CBDL, respectively. The full-thickness muscle strips were incised along the longitudinal axis of the gallbladder. For the general preparation of muscle strips, the muscle strips (10.0 mm × 3.0 mm) were placed in iced Krebs-Hensleit's solution (KHS, composition: NaCl 118 mmol/L, KCl 4.7 mmol/L, $CaCl_2$ 2.5 mmol/L, $NaHCO_3$ 25 mmol/L, $MgSO_4 \cdot 7H_2O$ 1.18 mmol/L, KH_2PO_4 1.18 mmol/L, and D-glucose 11.1 mmol/L, pH 7.4) and processed immediately for muscle contractility studies. Especially, for the preparation of muscle strips with impaired ICCs (MB with light groups), the muscle strips removed from normal guinea pig were incubated in KHS containing 50 μM methylene blue (MB, MedChemExpress, Shanghai, China) at 37 °C bubbled with 95% O_2-5% CO_2 for 40 min in the dark and then immediately exposed to the light (532 nm, 50 mW/cm^2) for 5 min, which can selectively inactivate ICCs[11,12]. In addition, each group of the gallbladder tissue samples were either stored at 0-4 °C, which examined by transmission electron microscopy (TEM) and Western blot analysis or fixed in 4% paraformaldehyde (PFA) and then embedded in paraffin for histopathologic and immunohistochemical studies (see below).

Histopathologic analysis

Freshly prepared gallbladder samples were fixed with 4% PFA and then embedded in paraffin (sectioned at 4 μm) for hematoxylin and eosin (H&E) staining and Masson trichrome staining. The sections underwent histopathologic analysis by light microscopy (AX10, Zeiss, Munich, Germany). An inflammation scoring system was used to evaluate the extent of gallbladder inflammation with scores ranging from 0 to 17[10]. Specifically, the degree of inflammatory cell infiltration, hemorrhage, edema, surface ulceration, and fibroblast proliferation were each classified as 0, 1, 2, or 3, respectively. Vascular dilation and Rokitansky-Aschoff (R-A) sinus formation were each counted as 1 if present or 0 if absent.

Slow wave measurement

For *in vivo* study of gallbladder SW recording, after 12 h of fasting, the guinea pigs were anesthetized with continual inhalation of 1.5% to 2.5% isoflurane and immobilized on a constant temperature heating pad in the supine position. After sterilization, a longitudinal mini-incision was performed along the ventrimeson from the xiphoid to expose the gallbladder. Then, two self-made electrodes (1.0 cm interval) were inserted in parallel into the body of the gallbladder. The reference electrode was placed in the subcutaneous tissue near the incision. For *in vitro* study of gallbladder muscle strips SW recording, the normal muscle strips and muscle strips with damaged ICCs were pinned and stretched in Sylgard-coated dish and incubated in KHS. The two self-made electrodes (0.5 cm interval) were inserted in parallel into the muscle layer of strips. The electrical signals were recorded by the 8-channels PowerLab (ADInstruments, New South Wales, Australia). The electromyogram (EMG) was collected and analyzed by the LabChart 8.0 (ADInstruments, New South Wales, Australia), and the frequency of SW was calculated by averaging the frequencies of the stabilization section of the EMG recording (times/min). The recording equipment was calibrated to zero prior to experiment beginning. The EMG of the gallbladder *in vivo* under physiological conditions was recorded for 40 min. The gallbladder strips *in vitro* were recorded for 10 min. The sampling frequency of the recording system was 4000 Hz. The low-pass filter for SW recording was 0.1 Hz.

In vitro gallbladder muscle contractility studies

The gallbladder muscle strips (10 mm × 3 mm) from NC, AC12h, AC24h, AC48h, and MB with light groups were collected and suspended in organ baths filled with KHS (20 mL). The KHS was bubbled continuously with 95% O_2-5% CO_2, and the temperature was maintained at 37 °C. One side of gallbladder muscle strip is tied to a hook at the bottom of the chamber then the other side was attached to the force transducer (ADInstruments, New South Wales, Australia). Each muscle strip sample was applied for preload tension of 1.0 g and allowed to equilibrate for 40 min before starting the experimental procedures. The direct effects of cholecystokinin octapeptide (CCK-8, 5 μmol/L, Aladdin, Shanghai, China) on the gallbladder tone were examined. The mean preload level was recorded as the control value, meanwhile the effects level of CCK-8 as the response value. Statistical analyses were based on CCK-8 induced the change rate (R) of muscle tension, where R = [|(response value-control value)|/control value].

TEM

Selected fresh gallbladder tissue pieces (3 mm × 3 mm) were put into Eppendorf tubes with fresh 2.5% glutaraldehyde (Wuhan Servicebio Technology, Wuhan, Hubei Province, China) for at 4 °C for fixation and preservation. Before examination, wash the tissues with PBS for 3 times, 15 min each. Then, the samples were fixed with 1% OsO_4 under dark conditions (pH 7.4) for 2 h at room temperature (RT). After remove OsO_4 and gradient dehydration, the samples were embedded in resin. The resin blocks were cut to 60-80 nm thin with the ultra-microtome and fished out onto the 150 meshes cuprum grids with formvar film. After staining with 2% uranyl acetate and 2.6% lead citrate, the ultrastructure of gallbladder tissues was observed and photographed under TEM (supported by Wuhan Servicebio Technology, Wuhan, Hubei Province, China).

Detection of c-Kit, α-SMA expression by immunohistochemistry

Immunohistochemistry (IHC) staining was performed on the paraffin-embedded gallbladder samples using the following antibodies: anti-c-Kit (1:200, Novus Biologicals, Abingdon, United Kingdom) to identify ICCs in the muscular layer; anti-α-SMA (1:200, MyBioSource, San Diego, CA, United States) to identify SMCs in the muscular layer. Non-specific binding of antibody was blocked with 3% bovine serum albumin (BSA) before adding primary antibodies. Then samples were then incubated with appropriate horseradish peroxidase (HRP)-conjugated secondary antibodies (Wuhan Servicebio Technology, Wuhan, Hubei Province, China). Antibody localization was performed using a peroxidase reaction with H_2O_2 and 3,3-diaminobenzidine (DAB) tetrahydrochloride (Wuhan Servicebio Technology, Wuhan, China) as the chromogen. The NC gallbladder included in the histological sample was provided an internal control.

Protein extraction and Western blot analysis

Total protein was extracted from gallbladder tissues with RIPA lysis buffer. Protein concentrations were determined by the BCA protein concentration measurement kit (Beyotime Biotech, Shanghai, China). Protein samples were separated in 10% SDS-PAGE gels, then transferred to the PVDF membrane (Millipore, Burlington, MA, United States). According to the prestained protein markers, the membranes were cropped into strips based on the molecular weight of the individual target proteins and then incubated with QuickBlock blocking buffer (Beyotime Biotech, Shanghai, China) for 20 min at RT to block non-specific binding sites. The anti-c-Kit (1:500, GeneTex, Irvine, CA, United States), anti-α-SMA (1:500, MyBioSource, San Diego, CA, United States), anti-CCKAR (1:1000, ABclonal Technology, Wuhan, Hubei Province, China) and anti-CX43 (1:1000, Invitrogen, Carlsbad, CA, United States) and anti-α-Tubulin (1:500, Invitrogen, Carlsbad, CA, United States) primary antibodies were applied overnight at 4 °C. After washing with TBST 3 times, the membranes were incubated with appropriate HRP-conjugated secondary antibodies for 1 h at RT. Immunoblots were then visualized with ECL Plus chemiluminescence reagent kit (Vazyme Biotech, Nanjing, Jiangsu Province, China) and quantified with optical methods with Image J software (Image J 1.53, NIH, Bethesda, MD, United States). The results were normalized using α-Tubulin as an internal control.

Statistical analysis

All data were analyzed with GraphPad Prism 9.0 (GraphPad, San Diego, CA, United States), and each experiment was repeated three times. Results are presented as mean ± TEM. Statistical differences between groups were either analyzed with a two-tailed Student *t*-test or one-way analysis of variance (ANOVA) if the data were normally distributed. Otherwise, the Mann-Whitney or Kruskal-Wallis test was used. $P < 0.05$ was considered statistically significant.

RESULTS

Histology and inflammation score of the AC model

H&E and Masson staining of the gallbladder tissues from the NC, AC12h, AC24h, and AC48h guinea pigs were analyzed. In the NC group, that gallbladder had minimal inflammatory cell infiltration and had no congestion or edema. In contrast, in the AC groups, the gallbladder specimens showed varying degrees of inflammatory cell (mainly neutrophils) infiltration, vascular congestion, edema, and fibroblastic proliferation (Figure 1A). In particular, three of the five guinea pigs in the AC48h group displayed R-A sinus formation. Furthermore, there was a significant increase in the quantitated histologic inflammation score in the AC groups (12 h, 24 h, and 48 h) over time compared with the NC group ($^{a}P < 0.05$ *vs* NC groups, $^{b}P < 0.001$ *vs* NC groups, $^{c}P < 0.0001$ *vs* NC groups, Figure 1B).

ICCs may be the origin of SW in the gallbladder

In order to determine the relationship between gallbladder SW and ICCs, we destroyed the structure of the ICCs by MB with intense light. After incubation with MB, intense illumination partly abolished the activity of SW in the muscle strips (Figure 2A and B). Concurrently, compared to normal muscle strips, the contractions of the impaired ICCs muscle strips were also decreased (Figure 3A). Thus, we suggest that ICCs may be the origin of SW in the gallbladder, and SW could regulate the contractile function of gallbladder.

The SW of gallbladder was damaged in early stage of AC

The SW of guinea pigs exhibited periodic and rhythmic changes after 12 h of fasting (Figure 2C). The mean frequency of the SW in each of the NC and AC groups (12 h, 24 h, and 48 h) was recorded and analyzed. The SW frequencies were 10.66 ± 0.51, 7.13 ± 0.20, 6.46 ± 0.16, and 5.75 ± 0.44, respectively ($^{a}P < 0.0001$ *vs* NC groups, $^{b}P < 0.0001$ *vs* NC groups, $^{c}P < 0.0001$ *vs* NC groups, Figure 2D). Interestingly, the SW frequency of the AC12h group was clearly lower compared with the NC group ($^{a}P < 0.0001$ *vs* NC groups), while there were no significant differences between the AC groups (Figure 2D).

Gallbladder contraction is impaired during AC

In this study, the contractility of gallbladder strips was evaluated using the mean change rate (R) after drug stimulation. Contractility was significantly weakened in all AC groups compared to the NC group with CCK-8 tested (Figure 3B). Notably, the R value of the AC12h group was remarkably reduced in the CCK-8 stimulations compared with the NC group (0.42 ± 0.09 *vs* 0.96 ± 0.21, $^{b}P < 0.05$ *vs* NC groups). Thus, the data suggest that gallbladder contraction has already been impaired in early stage of AC. These results are consistent with the gallbladder SW measurement data.

The number and formation of gallbladder ICCs are damaged during AC

IHC analysis of cross sections of the gallbladder tissues showed that intensely c-Kit- immunopositive ICCs were mostly identified in the muscular layers. In contrast to the NC group, the ICCs density was extremely decreased in the AC groups (Figure 4). There appears to be no significant differences in the thickness or structure of the GBSM. To further investigate the pathological changes of ICCs, TEM was utilized to detect ultrastructural changes in ICCs during AC progression. In the NC group, TEM showed typically elongated, oval-shaped cell bodies and one to three long processes extending from cell poles. The normal ICCs possess large nuclei, a well-developed smooth endoplasmic reticulum, abundant mitochondria, free ribosome and caveolae (Figure 5A). With prolonged CBDL, the ultrastructure of the gallbladder ICCs underwent significant changes. In the AC12h and AC24h groups, the ICCs were swollen, and the nucleolus became smaller, and processes diminished (Figure 5B and C). The gallbladder ICCs from the AC48h group had especially swollen cytoplasm with ruptures in the cytoplasm membrane. The mitochondria and endoplasmic reticulum were significantly reduced, and the processes often disappeared (Figure 5D). These results indicate that the number and function of ICCs were significantly impaired during AC.

Western blot analysis of c-Kit, α-SMA, CCKAR, and CX43

Compared to the NC group, the c-Kit protein expression levels of gallbladder in the AC groups (especially in the AC12h group) were significant decreased, as observed by Western blot analysis ($^{a}P < 0.05$ *vs* NC groups, $^{b}P < 0.05$ *vs* NC groups, $^{c}P < 0.01$ *vs* NC groups, Figure 6). Interestingly, the α-SMA protein expression levels did not decrease with the progression of AC but had a transient increase in the AC12h group ($^{d}P < 0.05$ *vs* NC groups). The CCKAR and CX43 protein expression levels were significantly lower in AC48h ($^{e}P < 0.05$ *vs* NC groups, $^{e}P < 0.05$ *vs* NC groups, respectively).

DISCUSSION

AC is currently a major medical problem. The primary standard treatment for AC is cholecystectomy

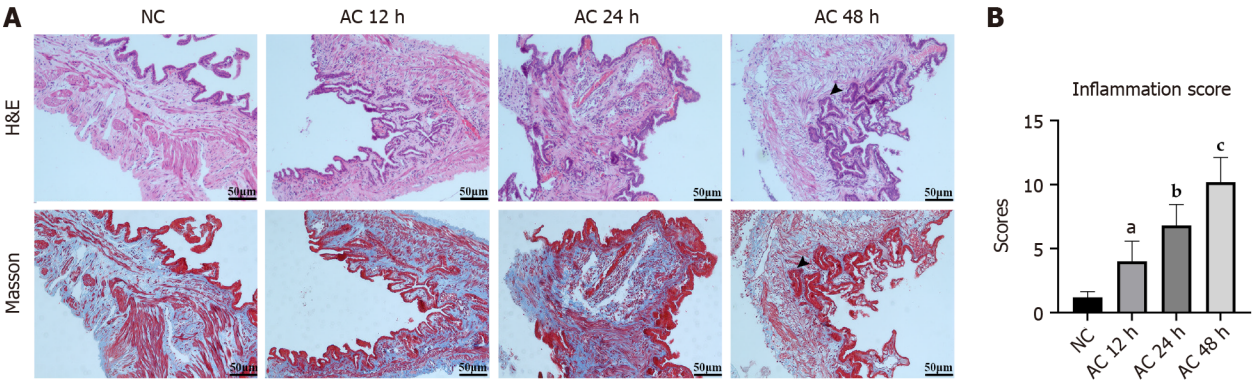

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Figure 1 Histopathological analysis of a guinea pig model of acute cholecystitis (100 ×). A: Gallbladders in the normal control (NC) group were intact and showed no congestion, edema, or obvious inflammatory cell infiltration. The gallbladders in the acute cholecystitis (AC) groups showed edema, fibroplasia, congestion, mucosal necrosis, considerable inflammatory cell infiltration, and were significantly aggravated over time. In addition, the R-A sinus was present in the lamina propria of the gallbladders in the AC48h group (arrowhead); B: The inflammation score of the NC, AC12h, AC24h, and AC48h groups were 1.20 ± 0.20, 4.00 ± 0.71, 6.80 ± 0.73, and 10.20 ± 0.86, respectively ($^{a}P < 0.05$ *vs* NC groups, $^{b}P < 0.001$ *vs* NC groups, $^{c}P < 0.0001$ *vs* NC groups). AC: Acute cholecystitis; NC: Normal control; R-A: Rokitansky-Aschoff; H&E: Hematoxylin and eosin.

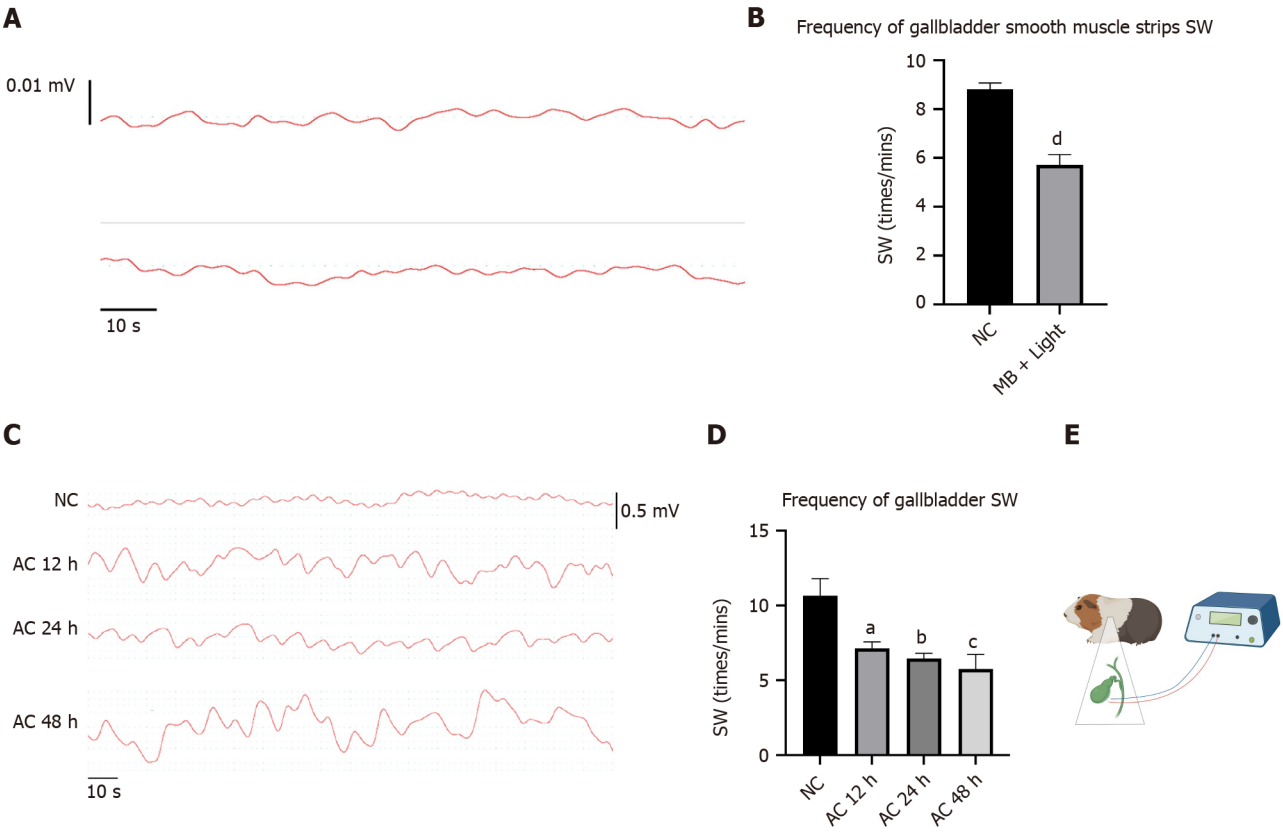

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Figure 2 Recording of the gallbladder slow wave by electromyogram. A and B: The mean slow wave (SW) frequency in the normal control (NC), methylene blue + light groups were 8.81 ± 0.25 *vs* 5.71 ± 0.43 ($^{d}P < 0.001$ *vs* NC groups); C and D: The mean SW frequency in the NC, acute cholecystitis 12 h (AC12h), AC24h, and AC48h groups were 10.66 ± 0.51, 7.13 ± 0.20, 6.46 ± 0.16, and 5.75 ± 0.44, respectively ($^{a}P < 0.0001$ *vs* NC groups, $^{b}P < 0.0001$ *vs* NC groups, $^{c}P < 0.0001$ *vs* NC groups); E: Illustration of a SW recording of the guinea pig gallbladder. SW: Slow wave; EMG: Electromyogram; NC: Normal control; AC: Acute cholecystitis; MB: Methylene blue.

[13]. The pathogenesis of AC is multifactorial. According to widely accepted theories, more than 90% of AC cases are caused by the obstruction at the neck of gallbladder due to gallstones or biliary sludge[14]. Obstruction of the cystic duct rapidly increases the intraluminal pressure within the gallbladder, together with cholesterol supersaturated bile, triggers the acute inflammatory response. The dysmotility of gallbladder results in gallstones as well as persistent biliary sludge, while the sludge itself can cause

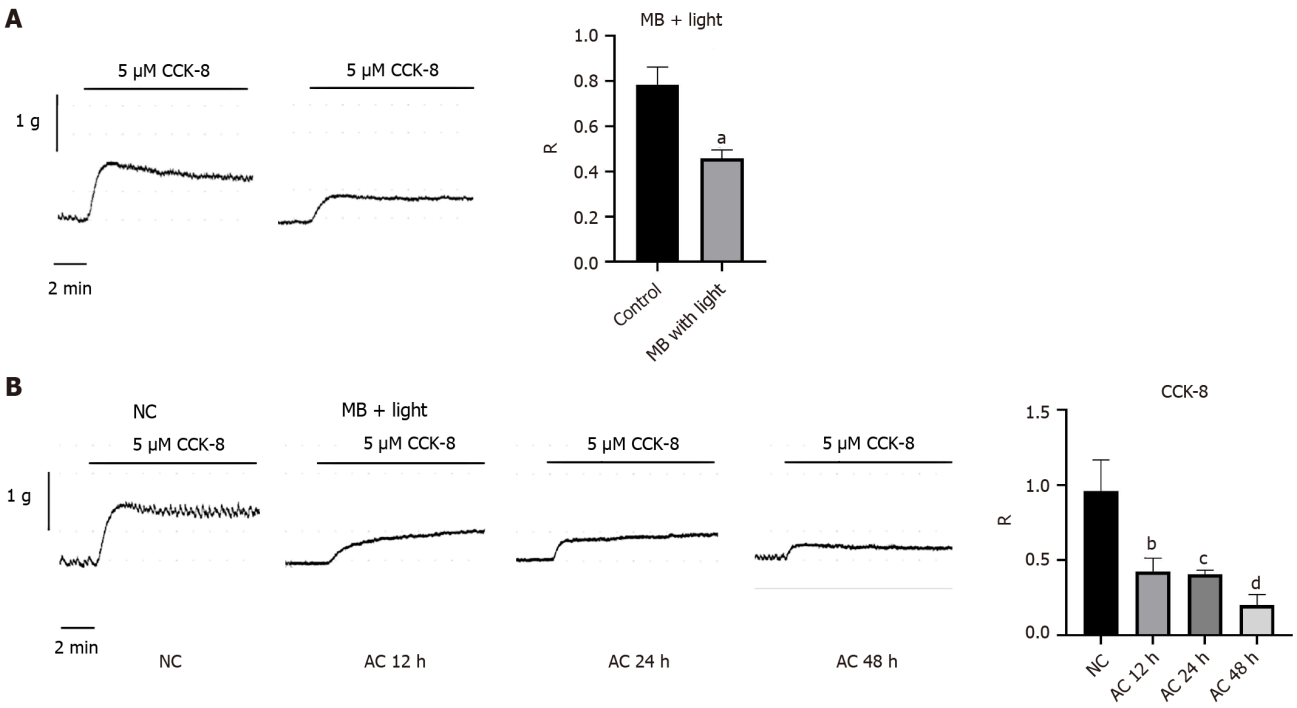

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Figure 3 Effects of cholecystokinin octapeptide-induced contraction of gallbladder muscle strips. A: Destroying interstitial cells of Cajal can induce impairment of gallbladder muscle motility by loading methylene blue with light illumination [0.78 ± 0.08 *vs* 0.46 ± 0.04, $^{a}P < 0.01$ *vs* normal control (NC) groups]; B: The cholecystokinin octapeptide-induced effect of the *R* value in the NC, AC12h, AC24h, and AC48h groups were 0.96 ± 0.21, 0.42 ± 0.09, 0.41 ± 0.03, and 0.20 ± 0.07, respectively ($^{b}P < 0.05$ *vs* NC groups, $^{c}P < 0.05$ *vs* NC groups, $^{d}P < 0.01$ *vs* NC groups). CCK-8: Cholecystokinin octapeptide; ICCs: Interstitial cells of Cajal; MB: Methylene blue; NC: Normal control; AC: Acute cholecystitis.

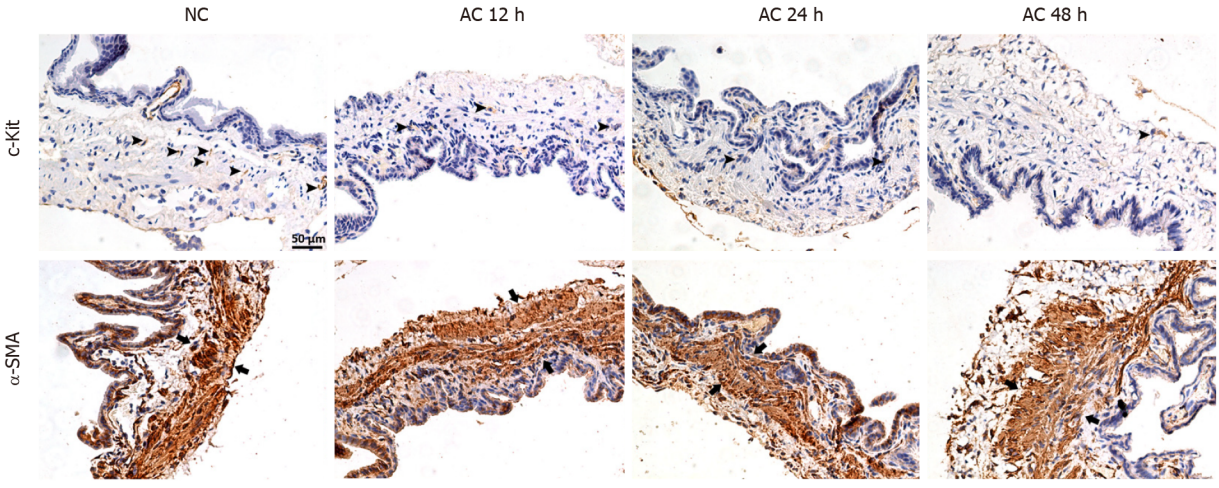

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Figure 4 Sections of guinea pig gallbladder were stained with anti-c-Kit and anti-α-SMA antibodies and visualized with 3,3-diaminobenzidine in the normal control and acute cholecystitis groups (200 ×). Interstitial cells of Cajal (ICCs) (arrowheads) were present in the muscular layer of the gallbladder. The number of ICCs was obviously reduced in each acute cholecystitis (AC) group compared with the normal control (NC) group. Notably, there was no significant difference in gallbladder smooth muscle (arrows) morphology and structure between the NC and AC groups. NC: Normal control; AC: Acute cholecystitis; ICCs: Interstitial cells of Cajal; GBSM: Gallbladder smooth muscle.

AC.

In GI tract, the smooth muscle has two types of potentials: SW and functional action potentials[15]. ICCs are distributed throughout the GI tract in mammalian species, including humans[7,16,17]. ICCs form networks at the borders of the circular and longitudinal muscular layers and electrically couple to each other through gap junctions[18]. These electrical-couple networks extend along and around the organs or tissues of the GI tract to all regions involved in phasic rhythmic contractions. Therefore, SW could be both generated by ICCs and actively propagated to neighboring tissue within ICC-networks.

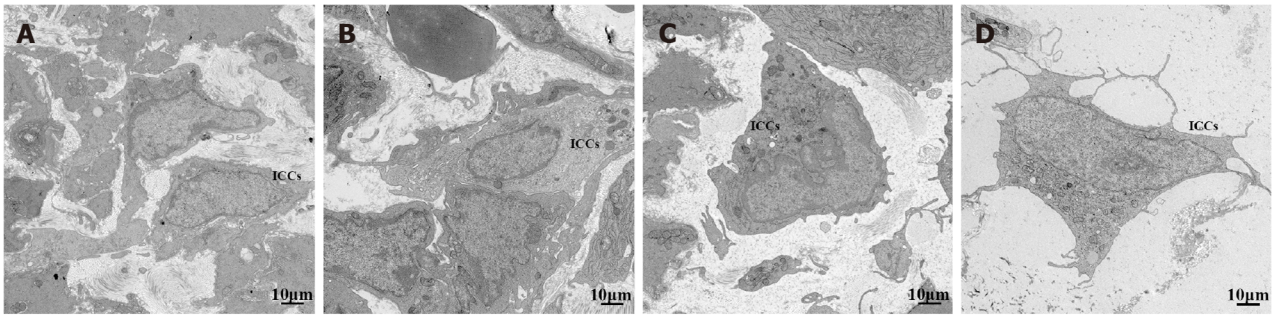

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Figure 5 Transmission electron microscopy results of interstitial cells of Cajal of the guinea pig gallbladder in the normal control and acute cholecystitis groups. A: The normal interstitial cells of Cajal (ICCs) had ovoid or triangular bodies, one to three cytoplasmic processes, large nuclei, abundant mitochondria, endoplasmic reticulum, and caveolae; B: ICCs from the AC12h group presented swollen cell bodies with enlarged mitochondria; C: The impaired ICCs from the AC24h group had more swollen cytoplasm. The distance between ICCs and other cells (mainly smooth muscle cells) was increased; D: The isolated ICCs in loose gallbladder tissue was significant swollen with ruptures in the cytoplasm membrane, and processes diminished. TEM: Transmission electron microscopy; ICCs: Interstitial cells of Cajal; NC: Normal control; AC: Acute cholecystitis; SMCs: Smooth muscle cells; ER: Endoplasmic reticulum. Bar: 10 μm.

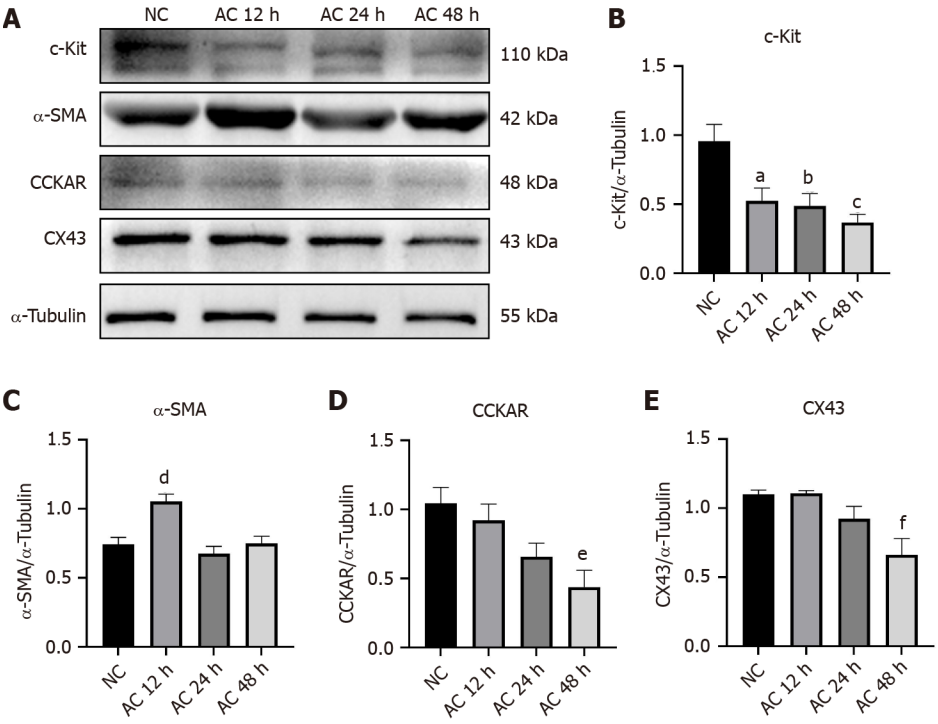

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Figure 6 Western blot analysis of the normal control and acute cholecystitis groups. A: The protein expression level of c-Kit, cholecystokinin A receptor (CCKAR) and connexin 43 (CX43) in guinea pig acute cholecystitis (AC) model of gallbladders was decreased; B: The mean grayscale values of c-Kit protein levels in the normal control (NC), AC12h, AC24h, and AC48h groups were 0.96 ± 0.12, 0.53 ± 0.09, 0.49 ± 0.09, and 0.37 ± 0.06, respectively ($^{a}P < 0.05$ *vs* NC groups, $^{b}P < 0.05$ *vs* NC groups, $^{c}P < 0.01$ *vs* NC groups); C: The mean grayscale values of α-SMA protein levels in the NC, AC12h, AC24h, and AC48h groups were 0.74 ± 0.05, 1.05 ± 0.05, 0.67 ± 0.05, and 0.75 ± 0.05, respectively ($^{d}P < 0.05$ *vs* NC groups); D: The mean grayscale values of CCKAR protein levels in the NC, AC12h, AC24h, and AC48h groups were 1.05 ± 0.11, 0.92 ± 0.12, 0.66 ± 0.10, 0.44 ± 0.12, respectively ($^{e}P < 0.05$ *vs* NC groups); E: The mean grayscale values of CX43 protein levels in the NC, AC12h, AC24h, and AC48h groups were 1.10 ± 0.30, 1.11 ± 0.02, 0.92 ± 0.09, 0.66 ± 0.12, respectively ($^{f}P < 0.01$ *vs* NC groups). NC: Normal control; AC: Acute cholecystitis; CCKAR: Cholecystokinin A receptor; CX43: Connexin 43.

SW could determine the conduction speed and direction of GI motility, as well as the basic electrical rhythm. However, SMCs are deficient in specific ionic mechanisms and therefore cannot generate and actively propagate SW[19]. SW, as a consequences of pacesetter potentials, provides electrophysiological conditions for depolarization of the smooth muscle contraction syncytium, increasing the open probability of L-type Ca^{2+} channels in SMCs to generate phasic contractile activity in many regions of the GI tract. Overall, The SW potential in the GI tract is generated by ICCs and spreads to surrounding SMCs, causing excitation-contraction coupling.

Gallbladder ICCs have been identified in mice in 2006[7], in guinea pigs in 2007[17], and in humans in 2012[20]. Previous studies have indicated that intense illumination of the canine colon after incubation with MB resulted in the selective inactivation of ICCs[11]. Subsequently, Fan *et al*[9] verified that the injury effects of MB with light were specifically limited to gallbladder ICCs and led to the reduction in frequency and amplitude of SW recorded from gallbladder muscle strip *in vitro*. ICCs have been involved in generating and pacemaking spontaneous electrical activity in the gallbladder muscularis propria, because this effect could be eliminated or reduced by exposure to imanitib mesylate, a Kit tyrosine kinase inhibitor[17]. Furthermore, many studies have demonstrated that impairment or loss of ICCs in the biliary system have been associated with various biliary systemic diseases, such as acute inflammation, gallstones, gallbladder cyst, and regional or proximal obstructions[21-24]. However, it remains unclear the relationship between SW and ICCs in gallbladder, and how the ICCs can affect the SW and contraction function of the gallbladder in AC. In the current study, we first recorded the gallbladder SW to determine the relationship between SW and ICCs, then explored the acute inflammation-related alterations in ICCs in a guinea pig model of AC.

As concluded by previous studies, selective lesioning of ICCs by MB and light could result in partly loss of SW[11,12]. Our results also demonstrated that after incubation with MB and light, the frequency of SW of isolated gallbladder muscle strips was remarkably lower than control group (Figure 2A and B). Meanwhile, compared to normal strips, the loss ICCs muscle strips showed lower reactivity to CCK-8 (Figure 3A). These results indicated that ICCs might be the source of SW in the gallbladder, and loss of ICCs reduces gallbladder contractility.

CBDL could produce histological features identical to human AC without chemical or physical manipulation of the gallbladder[10]. In this study, the inflammatory evaluation was consistent with AC according to the pathological score analysis (Figure 1). H&E staining showed that the gallbladder tissues from the NC group were intact and showed no congestion, edema, or obvious inflammatory cell infiltration. The predominant histopathological changes observed in the AC groups included edema, hemorrhage, inflammatory cell infiltration, and blood vessel dilation. R-A sinus was only found in the late stage of AC (AC48h group), which suggests increased intraluminal pressure in the gallbladder and a discontinuous muscle layer associated with AC[25]. Masson staining was used to examine the proliferation of collagen fibers and GBSM in the tissues. There was no significant proliferation of muscle fiber or collagen observed in the gallbladder sample sections between the NC and AC groups.

In recent years, research on the gallbladder SW has only been conducted for isolated muscle strips *in vitro*. Because of the loss of neural, hormonal, and inflammatory factor regulation, isolated gallbladder strips do not fully reflect the electrophysiological characteristics of the SW in normal and pathological states. To record the gallbladder SW *in vivo*, we implanted a self-made dual AgCl-electrode (1.0 cm interval) into the body of the gallbladder (Figure 2E). The results revealed that AC significantly decreased the gallbladder SW frequency (Figure 2C and D, $P < 0.0001$), while a similar trend between the AC groups failed to reach statistical significance. Similarly, the muscle tension of isolated gallbladder muscle strips also showed a significant decrease in AC groups (Figure 3B).

CD117/c-Kit protein expression is a specific marker of ICCs[26]. IHC results showed the density of ICCs (labelled with c-Kit) in each AC group (AC12h, AC24h, and AC48h) was extremely reduced (Figure 4). These pathological changes were most apparent in the AC12h group. Western blot analysis showed the same changing trend about c-Kit protein expression in AC groups (Figure 6). Additionally, Masson staining and IHC assays suggested that GBSM (marked with α-SMA) showed no significant pathological changes in morphology or structure. Interestingly, the protein expression of α-SMA did not decrease with the progression of AC, but rather there was a transient increase in the AC12h group (Figure 6). This may be because in the CBDL model, the increased pressure within the gallbladder leads to a compensatory response of the GBSM. The typical ultrastructural properties of ICCs were obvious, including elongated, fusiform bodies with few processes, discontinuous basal lamina, thin and intermediate filaments, abundant mitochondria and Golgi apparatus, rough and smooth endoplasmic reticulum, intracellular vesicles, free ribosomes and occasional caveolae[27]. With the progression of AC, the impaired ICCs exhibited markedly swollen with impaired or decrease of organelles and showed low contrast for the cytoplasm, and ruptures in the cytoplasm membrane (Figure 5). All these changes might result in the reduction of gallbladder contractile function.

CCK is a kind of gut hormone first identified in extracts from the small intestine, which could vigorously induce gallbladder contraction[28]. This gallbladder contractions effect was once believed to be caused by CCK only through the CCKAR pathway on the SMCs. Recently, CCKAR has been proven be also expressed in ICCs[29]. In this study, loss ICCs muscle strips showed low sensitivity to CCK compared to normal strips (Figure 3A). Therefore, it indicated that CCK acted not only on the CCKAR on the GBSM, but also on the gallbladder ICCs.

CX43 is a member of the gap junction family. Gap junction form transmembrane complexes between adjacent cells that are composed of connexin proteins and allow direct cell-to-cell communication and the transfer of ions and small signaling molecules[30]. In this study, the protein expression of both CCKAR and CX43 showed a significant declining trend in AC48h groups (Figure 6). These changes would cause a further decrease in the electrical conductance of the gallbladder tissue and the responsiveness of the contraction.

CONCLUSION

In conclusion, our study indicates that ICCs may act as pacemaker cells for the SW of the gallbladder. Acute inflammation can cause a reduction in the SW and gallbladder motility deficiency by damaging the density and function of ICCs during early AC stage. At the end stage of AC, the decrease of CCKAR and gap junction leads to the further decrease in gallbladder contractility and electrical conductivity. These changes may further induce functional impairment of gallbladder motility and eventually result in AC. This research strongly suggest that ICCs play a very important role in AC.

ARTICLE HIGHLIGHTS

Research background

Acute cholecystitis (AC) is a common disease with gallbladder dysmotility. Interstitial cells of Cajal (ICCs) damage and loss in the biliary system have been associated with various biliary systemic diseases. However, it remains unclear if or how the pathogenesis affects ICCs morphology, density, distribution, slow waves (SW), and function in gallbladder during AC.

Research motivation

Decreased gallbladder contractile function is an important causative factor in AC. ICCs presented significant pathological changes during AC in various animal and clinical studies. Therefore, ICCs may act as important regulators of gallbladder contractile function.

Research objectives

To investigate the origin of SW in the gallbladder and the effect of ICCs on gallbladder contractions during the process of AC. We hypothesized that ICCs are the origin of SW in the gallbladder, and the impaired leads to the decrease in gallbladder contractile function, which ultimately aggravates the AC.

Research methods

Common bile duct ligation is a common model of AC. Guinea pigs were randomly allocated to four groups: Normal control (NC), AC12h, AC24h, and AC48h. H&E and Masson-stained gallbladder tissues were scored for inflammatory changes. Methylene blue with light was used to establish selective impaired ICCs gallbladder tissue. Gallbladder motility was assessed using the frequency of SW and gallbladder muscle contractility. Then ICCs pathological changes alterations were estimated using immunohistochemistry and TEM. The alterations of c-Kit, α-SMA, cholecystokinin A receptor (CCKAR), and connexin 43 (CX43) were assessed using Western blot.

Research results

Gallbladder strips treated MB with light resulted in the decrease in gallbladder SW frequency and contractility. Compared with the NC group, The frequency of SW, gallbladder contractility, the density and ultrastructure of ICCs were significantly impaired in AC groups. The protein expression levels of c-Kit were significantly decreased in the AC12h group, while CCKAR and CX43 protein expression levels were significantly decreased in the AC48h group.

Research conclusions

This study indicated that ICCs may act as pacemaker cells for the SW of the gallbladder. In acute inflammation stage of AC, impaired ICCs resulted in the reduction of the SW and gallbladder motility deficiency. Then, the decrease of CCKAR and gap junction leads to the further decrease in gallbladder contractility and electrical conductivity, and eventually result in AC.

Research perspectives

This study did not completely destroy ICCs in the gallbladder tissue. The pacing mechanism of ICCs has also not been deeply investigated. These will be examined in the future study.

FOOTNOTES

Author contributions: Ding F and Guo R performed experiments; Hu H, Zhao G, and Wang YX designed the study; Cui ZY performed data analysis; Chen F and Liu LP drafted the manuscript; all authors reviewed the final manuscript.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Fascia- *vs* vessel-oriented lateral lymph node dissection for rectal cancer: Short-term outcomes and prognosis in a single-center experience

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Abstract

BACKGROUND

For the management of lateral lymph node (LLN) metastasis in patients with rectal cancer, selective LLN dissection (LLND) is gradually being accepted by Chinese scholars. Theoretically, fascia-oriented LLND allows radical tumor resection and protects of organ function. However, there is a lack of studies comparing the efficacy of fascia-oriented and traditional vessel-oriented LLND. Through a preliminary study with a small sample size, we found that fascia-oriented LLND was associated with a lower incidence of postoperative urinary and male sexual dysfunction and a higher number of examined LLNs. In this study, we increased the sample size and refined the postoperative functional outcomes.

AIM

To compare the effects of fascia- and vessel-oriented LLND regarding short-term outcomes and prognosis.

METHODS

We conducted a retrospective cohort study on data from 196 patients with rectal cancer who underwent total mesorectal excision and LLND from July 2014 to August 2021. The short-term outcomes included perioperative outcomes and postoperative functional outcomes. The prognosis was measured based on overall survival (OS) and progression-free survival (PFS).

RESULTS

A total of 105 patients were included in the final analysis and were divided into fascia- and vessel-oriented groups that included 41 and 64 patients, respectively. Regarding the short-term outcomes, the median number of examined LLNs was significantly higher in the fascia-oriented group than in the vessel-oriented group. There were no significant differences in the other short-term outcomes. The incidence of postoperative urinary and male sexual dysfunction was significantly lower in the fascia-oriented group than in the vessel-oriented group. In addition, there was no significant difference in the incidence of postoperative lower limb dysfunction between the two groups. In terms of prognosis, there was no significant difference in PFS or OS between the two groups.

CONCLUSION

It is safe and feasible to perform fascia-oriented LLND. Compared with vessel-oriented LLND, fascia-oriented LLND allows the examination of more LLNs and may better protect postoperative urinary function and male sexual function.

Key Words: Rectal cancer; Lateral lymph nodes; Lymph node excision; Fascia anatomy; Treatment outcome; Prognosis

Core Tip: There is a lack of studies comparing the efficacy of fascia-oriented and traditional vessel-oriented lateral lymph node dissection (LLND). To compare the effects of fascia- and vessel-oriented LLND regarding the short-term outcomes and prognosis, we conducted a retrospective cohort study based on seven years of data. We found that it is safe and feasible to perform fascia-oriented LLND. Compared with vessel-oriented LLND, fascia-oriented LLND allows the examination of more lateral lymph nodes and may better protect postoperative urinary and male sexual function.

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INTRODUCTION

Since Gerota first proposed the existence of lateral lymphatic drainage in the rectum in 1895, lateral lymphatic drainage has been proven to be an important lymphatic drainage pathway in the middle and lower rectum. The occurrence of lateral lymph node (LLN) metastasis in newly diagnosed rectal cancer patients ranges from 8.6% to 49%[1-3]. Neoadjuvant chemoradiotherapy (nCRT) and LLN dissection (LLND) are two strategies for the management of LLN metastasis advocated by Western and Japanese scholars, respectively. However, nCRT cannot completely eliminate metastatic tumor cells in LLNs[4]. On the other hand, LLND causes a high incidence of postoperative urinary and sexual dysfunction but has a low postoperative pathological positive LLN rate[3,5]. Therefore, depending on imaging findings in patients with enlarged LLNs, a combination of chemoradiotherapy and selective LLND is gradually being accepted by Chinese scholars[3,4,6,7].

With the expansion of fascial anatomy research, the concept of membrane anatomy-guided surgery has become accepted by surgeons. Theoretically, zoning the lateral space of the rectum and performing LLND guided by the fascia can establish a clear surgical plane and dissection boundary and prevent insufficient and excessive dissection. At the same time, dissociation along the fascial margin can prevent a breach into the lymphoid tissues, preventing the spread of metastatic cancer cells and helping to protect the pelvic autonomic nerves. Therefore, fascia-oriented LLND follows anatomical theory regarding radical tumor resection and protection of organ function and is also conducive to the popularization and quality control of lateral dissection[8]. Although several published studies have demonstrated that fascia-oriented LLND is safe in the perioperative period[9-13], these studies either did not explore the effect of fascia-oriented LLND on postoperative neurological function and prognosis or had relatively small sample sizes. In addition, there is a lack of evidence-based medical studies comparing the efficacy of fascia-oriented and traditional vessel-oriented LLND. Through a preliminary study with a small sample size[14], we found that fascia-oriented LLND was associated with a lower

incidence of postoperative urinary and male sexual dysfunction and a higher number of examined LLNs. In this study, we increased the sample size, refined the postoperative functional outcomes, and further analyzed the clinical data from rectal cancer patients undergoing treatment with two different anatomical approaches for LLND at a high-volume center in China to compare their effects on short-term outcomes and prognosis.

MATERIALS AND METHODS

Patients

In this retrospective cohort study, clinical data from 196 patients with rectal cancer who underwent mesorectal excision with curative intent and simultaneous LLND in the Department of Colorectal Surgery, Cancer Hospital Chinese Academy of Medical Sciences from July 2014 to August 2021 was collected. All patients in this study underwent rectal magnetic resonance imaging (MRI) before neoadjuvant therapy and before surgery. All operations were performed by experienced surgical specialists in colorectal oncology at our center. The surgical approach (fascia-oriented or vessel-oriented LLND) used was determined at the discretion of the individual surgeon.

The patient inclusion criteria were as follows: (1) Pathological diagnosis of rectal cancer; (2) Lower tumor margin below the peritoneal reflection; and (3) Preoperative clinical suspicion or clinical diagnosis of LLN metastasis.

The patient exclusion criteria were as follows: (1) A history of pelvic surgery (including rectal cancer surgery); (2) Preoperative urinary, sexual, lower limb, or anorectal dysfunction; (3) Tumor invasion of adjacent organs or preoperative distant metastasis; (4) Non-R0 resection; and (5) No rectal MRI data or incomplete data collection.

The final analysis comprised 105 patients, divided into two groups: The fascia-oriented group with 41 patients and the vessel-oriented group with 64 patients. Figure 1 shows a flowchart of patient enrollment.

Procedures for LLND

Procedures for fascia-oriented LLND: During fascia-oriented LLND, dissection was performed along the fascia of the three pelvic sidewalls [ureterohypogastric nerve fascia (UNF), vesicohypogastric fascia (VF), and parietal pelvic fascia]. This technique included 4 key steps: First, the lateral side of the UNF was isolated to establish the medial border of No. 263 Lymph node dissection (Supplementary Figures 1 and 2A); second, the fascia covering the muscular surface of the pelvic wall was isolated to establish the lateral border of No. 283 Lymph node dissection (Supplementary Figures 2B and 3); third, the VF was dissociated to reveal the main branches of the internal iliac artery inside the facia according to the orientation of the VF and UNF; fourth, en bloc resection of the No. 263 Lymph node and No. 283 Lymph node was performed. Supplementary Figure 4 shows the intraoperative view after LLND.

Procedures for vessel-oriented LLND: The internal iliac artery and its main branches were exposed through intrathecal dissection. In the obturator region, the lymphatic and fatty tissue around the main internal iliac artery and its main branches were dissected. The obturator nerve was exposed throughout the whole process.

If bilateral LLND was performed, the superior or inferior bladder arteries on one side were preserved as much as possible. To prevent adverse effects from prolonged or improper patient placement in the lithotomy position on the patient's lower limb function to the greatest extent, all surgeries followed the AORN Guidelines for patient positioning[15].

Outcome measures

The short-term outcomes included the following two aspects: (1) Perioperative outcomes, including operation time, intraoperative blood loss, incidence of perioperative surgical complications of grade II or higher[16,17], incidence of perioperative mortality, incidence of reoperation, length of postoperative hospital stay, number of examined LLNs, and LLN metastasis rate; and (2) Postoperative functional outcomes, including urinary function, defecation function, male sexual function, and lower limb motor and sensory function. The prognosis was measured based on overall survival (OS) and progression-free survival (PFS).

Postoperative urinary function, defecation function, and male sexual function were assessed according to the International Prostate Symptom Score (IPSS)[18], the low anterior resection syndrome score[19-21], and the International Index of Eerectile Function (IIEF-5)[22,23], respectively. Patients with one of the following symptoms were considered to have postoperative lower limb dysfunction: Gait disorder caused by thigh adductor weakness or movement disorders of the lower limb; loss of sensation, numbness, or radiating pain in the lower limb that was aggravated by extension and abduction or inward rotation of the thigh[24,25]. OS and PFS were defined as follows: OS referred to the duration from the date of surgery until the date of death from any cause, while PFS referred to the duration from the date of surgery until the occurrence of local or regional recurrence, distant

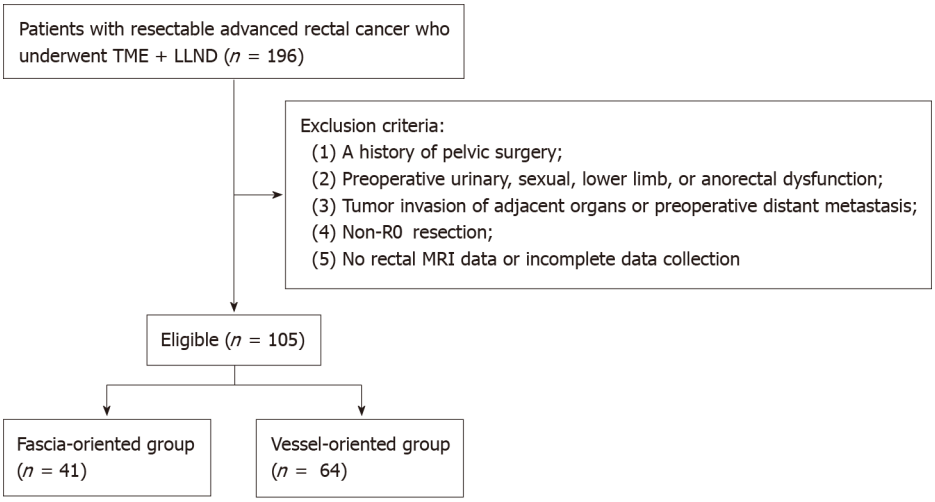

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Figure 1 Flow chart of patient selection. TME: Total mesorectal excision; LLND: Lateral lymph node dissection; MRI: Magnetic resonance imaging.

metastases, or death from any cause.

Follow-up

The follow-up methods included telephone interviews and outpatient examinations. Regarding postoperative functional outcomes, follow-up regarding urinary function was performed by telephone interviews on the 14th day after the operation, follow-up on motor and sensory function of the lower limbs was performed by physical examination or telephone interviews 1 mo after the operation, and follow-up on male sexual function was performed by telephone interviews 1 year after the operation. The last follow-up date was November 31, 2021.

Statistical analyses

The median [interquartile range (IQR)] was used to present continuous variables, while numbers and proportions were used to present categorical variables. The Mann-Whitney U test was used to compare continuous variables, and the χ^2 or Fisher exact test was used to compare categorical variables.

To assess risk factors for postoperative functional outcomes, univariate logistic regression was conducted on the relevant variables. The multivariate logistic regression analyses included the surgical method, potential confounding factors that could impact postoperative functional outcomes, and any baseline factors that were imbalanced between the two groups. Drawing from previous research and our clinical experience, we posited that several factors, aside from the surgical method, could potentially influence postoperative urinary, male sexual, and lower limb function. Specifically, we hypothesized that intraoperative blood loss and single/bilateral LLND may affect postoperative urinary function[5,26], while age, preoperative radiotherapy, and single/bilateral LLND may impact postoperative male sexual function[27,28]. Lastly, we also considered age and single/bilateral LLND as potential factors that could affect postoperative lower limb function, based on our clinical experience and previous studies[24,25,29].

The survival differences among groups were examined using the Kaplan-Meier method and the log-rank test. The reverse Kaplan-Meier method was used to analyze the median follow-up. Cox proportional hazards regression models were employed to select predictive factors for OS and PFS, and the multivariable Cox proportional hazards models included the surgical method, pathological LLN metastasis, and factors with a *P* value lower than 0.05 in the univariate analyses to identify independent risk factors for OS and PFS. IBM SPSS statistics software program, version 23 (IBM, Somers, NY, United States) was used to conduct the statistical analysis.

RESULTS

Clinical and pathological characteristics

Table 1 presents the clinical and pathological characteristics of the patients. The two groups were comparable in terms of age, BMI, neoadjuvant and adjuvant therapy, laparoscopic surgery, bilateral LLND, and each pathological tumor stage. All clinical and pathological characteristics were well balanced between the two groups.

Table 1 Baseline characteristics of the entire cohort (*n* = 105)

Variables	Fascia-oriented group (*n* = 41)	Vessel-oriented group (*n* = 64)	*P* value
Age (yr), median (IQR)	58.0 (48.0, 65.0)	58.5 (47.0, 65.0)	0.908
Sex, *n* (%)			0.728
Male	21 (51.2)	35 (54.7)	
Female	20 (48.8)	29 (45.3)	
BMI (kg/m^2), median (IQR)	24.8 (21.6, 27.8)	24.2 (21.3, 27.5)	0.510
Distance to tumour from AV (cm), median (IQR)	4.0 (3.0, 7.0)	4.0 (3.0, 5.0)	0.358
Pathological type, *n* (%)			0.837
Adenocarcinoma	40 (97.6)	62 (96.9)	
Non-adenocarcinoma	1 (2.4)	2 (3.1)	
Preoperative radiotherapy, *n* (%)			0.356
Yes	10 (24.4)	21 (32.8)	
No	31 (75.6)	43 (67.2)	
Preoperative chemotherapy, *n* (%)			0.698
Yes	17 (41.5)	29 (45.3)	
No	24 (58.5)	35 (54.7)	
Surgical procedure, *n* (%)			0.371
Laparoscopic surgery	40 (97.6)	60 (93.8)	
Conversion to open surgery	1 (2.4)	4 (6.2)	
Surgical approach, *n* (%)			0.571
Dixon	23 (56.1)	31 (48.4)	
Miles	18 (43.9)	32 (50.0)	
Parks	0 (0)	1 (1.6)	
LLND, *n* (%)			0.137
Unilateral dissection	33 (80.5)	43 (67.2)	
Bilateral dissection	8 (19.5)	21 (32.8)	
Pathological tumor stage[a], *n* (%)			0.808
0-I	6 (14.6)	10 (15.6)	
II	7 (17.1)	8 (12.5)	
III	28 (68.3)	46 (71.9)	
Adjuvant therapy, *n* (%)			0.544
Yes	32 (78.0)	53 (82.8)	
No	9 (22.0)	11 (17.2)	

[a]The eighth edition of the American Joint Committee on Cancer TNM staging system.
IQR: Interquartile range; BMI: Body mass index; AV: Anal verge; LLND: Lateral lymph node dissection.

Short-term outcomes

Perioperative outcomes: The lack of a significant difference was found in operation time and length of postoperative hospital stay between the two groups, with respective *P* values of 0.908 and 0.435. The vessel-oriented group had a higher proportion of patients with intraoperative blood loss of ≥ 300 mL compared to the fascia-oriented group (9.4% *vs* 2.4%). Nevertheless, the observed difference was not statistically significant with a *P* value of 0.242. The fascia- and vessel-oriented groups had incidences of perioperative surgical complications of 9.8% and 7.8%, respectively, and the difference between the two groups was not statistically significant (*P* = 0.852). There were no cases of reoperation or perioperative death in either group. Table 2 shows that the fascia-oriented group had a significantly higher median

Table 2 Surgical outcomes of the entire cohort (*n* = 105)

Variables	Fascia-oriented group (*n* = 41)	Vessel-oriented group (*n* = 64)	*P* value
Operation time (min), median (IQR)	245.0 (220.0, 270.0)	269.5 (210.0, 300.0)	0.908
Blood loss (mL), *n* (%)			0.242
≥ 300	1 (2.4)	6 (9.4)	
< 300	40 (97.6)	58 (90.6)	
No. of examined LLN, median (IQR)	9.0 (7.0, 13.0)	6.5 (3.0, 10.3)	0.020
Pathological LLN, *n* (%)			0.720
Positive	9 (22.0)	16 (25.0)	
Negative	32 (78.0)	48 (75.0)	
Surgical complications[a], *n* (%)			0.852
Yes	4 (9.8)	5 (7.8)	
No	37 (90.2)	59 (92.2)	
Urinary dysfunction, *n* (%)			0.015
Yes	9 (22.0)	29 (45.3)	
No	32 (78.0)	35 (54.7)	
Male sexual dysfunction, *n* (%)			0.019
Yes	9 (42.9)	26 (74.3)	
No	12 (57.1)	9 (25.7)	
Lower limb dysfunction, *n* (%)			0.554
Yes	10 (24.4)	19 (29.7)	
No	31 (75.6)	45 (70.3)	
Post-operative hospital stay (d), median (IQR)	7.00 (7.00, 8.00)	8.00 (7.00, 9.00)	0.435
Perioperative mortality, *n* (%)	0 (0)	0 (0)	1.000
Reoperation, *n* (%)	0 (0)	0 (0)	1.000

[a]Specific surgical complications in the fascia-oriented group, *n* (%): Anastomotic bleeding, 1 (2.4); anastomotic leakage, 1 (2.4); lymphorrhagia, 1 (2.4); delayed wound healing, 1 (2.4). Specific surgical complications in the vessel-oriented group, *n* (%): Anastomotic leakage, 3 (4.7); ileus, 1 (1.6); abdominal infection, 1 (1.6).

IQR: Interquartile range; LLN: Lateral lymph nodes.

number of examined LLNs than the vessel-oriented group (9.0 *vs* 6.5, $P = 0.020$). However, there was no significant difference in the positive pathological rate of LLNs between the two groups (22.0% *vs* 25.0%, $P = 0.720$).

Postoperative functional outcomes: (1) Urinary function: Among the 105 patients, the incidence of postoperative urinary dysfunction was 36.2%. The rate of postoperative urinary dysfunction was significantly lower in the fascia-oriented group than in the vessel-oriented group (22.0% *vs* 45.3%, $P = 0.015$), as shown in Table 2. Multivariate logistic regression analysis, after adjustment for intraoperative blood loss and single/bilateral LLND, showed that vessel-oriented LLND increased the risk of postoperative urinary dysfunction (OR = 2.897, 95%CI = 1.163–7.213, $P = 0.022$), as shown in Supplementary Table 1;

(2) Male sexual function: Among the patients included in the final analysis, 56 were male, including 21 in the fascia-oriented group and 35 in the vessel-oriented group. The percentage of patients who received unilateral LLND was significantly higher in the fascia-oriented group than in the vessel-oriented group (85.7% *vs* 65.7%, $P = 0.015$); other clinical and pathological characteristics were well balanced between the two groups, as shown in Supplementary Table 2.

Among male patients, the incidence of postoperative sexual dysfunction was 62.5%. The incidence of postoperative sexual dysfunction was significantly lower in the fascia-oriented group than in the vessel-oriented group (42.9% *vs* 74.3%, $P = 0.019$); additionally, the incidence of sexual dysfunction was significantly lower among patients treated with preoperative radiotherapy than patients not treated

with preoperative radiotherapy (41.2% *vs* 71.8%, P = 0.030). Multivariate logistic regression analyses showed that vessel-oriented LLND increased the risk of postoperative male sexual dysfunction (OR = 5.109, 95%CI = 1.078–24.206, P = 0.040), while preoperative radiotherapy decreased the risk of postoperative male sexual dysfunction (OR = 0.118, 95%CI = 0.024–0.577, P = 0.008), as shown in Supplementary Table 3;

(3) Lower limb function: Among the 105 patients, the incidence of lower limb dysfunction was 27.6%. The incidence of lower limb dysfunction in the fascia- and vessel-oriented groups was 24.4% and 29.7%, respectively. The difference was not statistically significant (P = 0.554), as indicated in Table 2. Multivariate logistic regression analyses showed that vessel-oriented LLND, age ≥ 65 years, and bilateral LLND did not increase the risk of postoperative lower limb dysfunction, as shown in Supplementary Table 4;

And (4) Defecation function: As of the last follow-up, 64 (61.0%) of 105 patients had temporary or permanent enterostomies, including 20 (48.8%) in the fascia-oriented group and 44 (68.7%) in the vessel-oriented group. Since defecation function evaluations were not available for these patients, this study did not compare defecation function between the two groups.

The prognosis

All patients were followed up. The median follow-up time was 32.6 mo. The 2-year OS rate of all 105 patients was 91.6%. The 2-year OS rates in the fascia- and vessel-oriented groups was 89.7% and 92.8%, respectively. Among all 105 patients, the 2-year PFS rate was 81.7%. In the fascia- and vessel-oriented groups, the 2-year PFS rates were 79.8% and 82.9%, respectively.

Kaplan–Meier curves for OS and PFS are shown in Figures 2 and 3. There was no significant difference in OS (log-rank P = 0.918) or PFS (log-rank P = 0.709) on the log-rank test between the fascia- and vessel-oriented groups.

The results of Cox regression analyses for univariate and multivariable are presented in Tables 3 and 4. For OS, univariate Cox regression analysis showed that vessel-oriented LLND, age ≥ 65 years, female sex, pathological LLN metastasis, and postoperative adjuvant therapy did not affect OS; however, pathological stage III disease was a risk factor for poor OS (HR = 9.98, 95%CI = 1.32–75.55, P = 0.026). After adjusting for pathological LLN metastases and pathological tumor stage, the multivariable Cox regression analyses showed that vessel-oriented LLND (HR = 0.94, 95%CI = 0.35–2.48, P = 0.893) and pathological LLN metastases (HR = 1.14, 95%CI = 0.39–3.31, P = 0.807) were not independent risk factors for poor OS, while pathological stage III disease independently increased the risk of poor OS (HR = 9.66, 95%CI = 1.25–74.66, P = 0.030).

For PFS, univariate Cox regression analysis showed that vessel-oriented LLND, age ≥ 65 years, female sex, pathological LLN metastasis, and postoperative adjuvant therapy did not affect PFS; however, pathological stage III disease was a risk factor for poor PFS (HR = 2.99, 95%CI = 1.02–8.76, P = 0.045). After adjusting for pathological LLN metastases and pathological tumor stage, the multivariable Cox regression analyses showed that vessel-oriented LLND (HR = 1.16, 95%CI = 0.51–2.66, P = 0.729) and pathological LLN metastases (HR = 0.83, 95%CI = 0.31–2.22, P = 0.714) were not independent risk factors for poor PFS, while the presence of pathological stage III disease was associated with a significant decline in PFS (HR = 3.16, 95%CI = 1.04–9.60, P = 0.042).

DISCUSSION

In this retrospective cohort study, we compared the impact of fascia-oriented and vessel-oriented LLND on short-term outcomes and prognosis in newly diagnosed rectal cancer patients. Our results indicated that the median number of examined LLNs in the fascia-oriented group was notably higher than that in the vessel-oriented group. Simultaneously, there was no notable discrepancy in the rate of pathological LLN metastasis, operation time, intraoperative blood loss, incidence of perioperative surgical complications, or length of postoperative hospital stay. In terms of postoperative functional indicators, the incidence of postoperative urinary and male sexual dysfunction was significantly lower in the fascia-oriented group than in the vessel-oriented group. In addition, there was no significant difference in the incidence of postoperative lower limb dysfunction between the two groups. In terms of prognosis, no significant difference was observed in either PFS or OS between the two groups.

In this study, we found that compared with traditional vessel-oriented LLND, fascia-oriented LLND did not increase the operative time, length of postoperative hospital stay, or incidence of perioperative surgical complications, and there were no cases of reoperation or perioperative deaths in either group, which is consistent with previous studies[9,10,11-13]. The proportion of patients with intraoperative blood loss ≥ 300 mL was higher in the vessel-oriented group than in the fascia-oriented group (9.4% *vs* 2.4%). Although the observed difference did not reach statistical significance, it likely reflects the inherent advantages of the surgical procedure for fascial-oriented LLND in reducing bleeding events. Using fascia as an anatomical landmark makes it easy to identify anatomical locations and important blood vessels and perform separation on the avascular plane during LLND. The incidence of grade II or higher perioperative surgical complications in the fascia-oriented group was 9.8%, which is consistent

Table 3 Univariable and multivariable Cox regression analyses of overall survival of the entire cohort (*n* = 105)

	Univariable		Multivariable	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
LLND method				
Vessel–oriented LLND	Reference		Reference	
Fascia–oriented LLND	0.95 (0.36–2.50)	0.918	0.94 (0.35–2.48)	0.893
Age				
< 65	Reference		–	
≥ 65	2.56 (0.87–7.51)	0.088	–	
Sex				
Male	Reference		–	
Female	0.78 (0.30–2.06)	0.621	–	
p/yp tumor stage[a]				
0–II	Reference		Reference	
III	9.98 (1.32–75.55)	0.026	9.66 (1.25–74.66)	0.030
Pathological LLN				
Negative	Reference		Reference	
Positive	1.82 (0.64–5.18)	0.264	1.14 (0.39–3.31)	0.807
Adjuvant therapy				
No	Reference		–	
Yes	–	0.202	–	

[a]The pathological tumor stage was based on the eighth edition of the American Joint Committee on Cancer TNM staging system.
LLND: Lateral lymph node dissection; LLN: Lateral lymph nodes; HR: Hazard ratio.

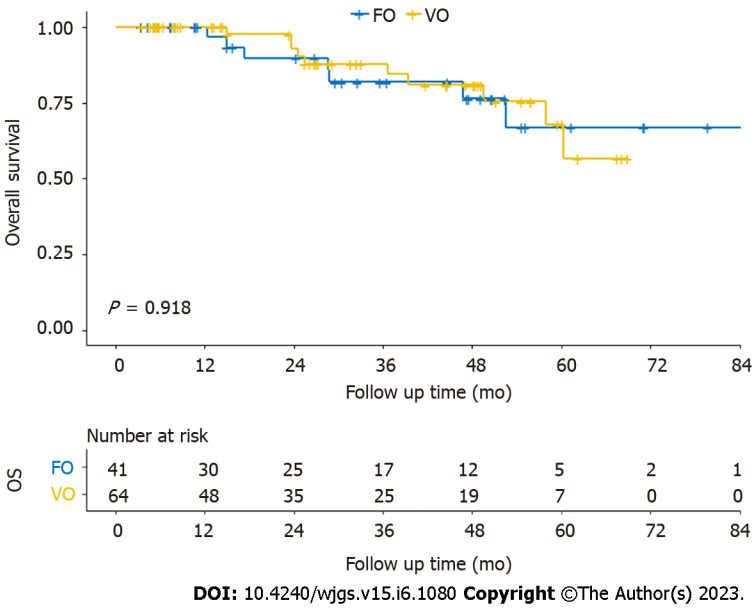

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Figure 2 Kaplan–Meier curves of overall survival for the two groups. OS: Overall survival; FO: Fascia-oriented; VO: Vessel-oriented.

with previous studies[13]; additionally, this rate is lower than that reported for laparoscopic LLND[30]. In this study, the 2-year OS and PFS rates were 91.6% and 81.7%, respectively, consistent with previous reports[31,32]. The above results indicate that fascia-oriented LLND is safe and feasible.

Table 4 Univariable and multivariable Cox regression analyses of progression-free survival of the entire cohort (*n* = 105)

	Univariable		Multivariable	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
LLND method				
Vessel–oriented LLND	Reference		Reference	
Fascia–oriented LLND	1.17 (0.51 - 2.68)	0.709	1.16 (0.51–2.66)	0.729
Age				
< 65	Reference		–	
≥ 65	1.20 (0.47 - 3.07)	0.706	–	
Sex				
Male	Reference		–	
Female	0.7 (0.31-1.55)	0.374	–	
p/yp tumor stage[a]				
0–II	Reference		Reference	
III	2.99 (1.02–8.76)	0.045	3.16 (1.04–9.60)	0.042
Pathological LLN				
Negative	Reference		Reference	
Positive	0.83 (0.33 - 2.12)	0.703	0.83 (0.31–2.22)	0.714
Adjuvant therapy				
No	Reference		–	
Yes	2.08 (0.62-7.02)	0.239	–	

[a]The pathological tumor stage was based on the eighth edition of the American Joint Committee on Cancer TNM staging system.
LLND: Lateral lymph node dissection; LLN: Lateral lymph nodes; HR: Hazard ratio.

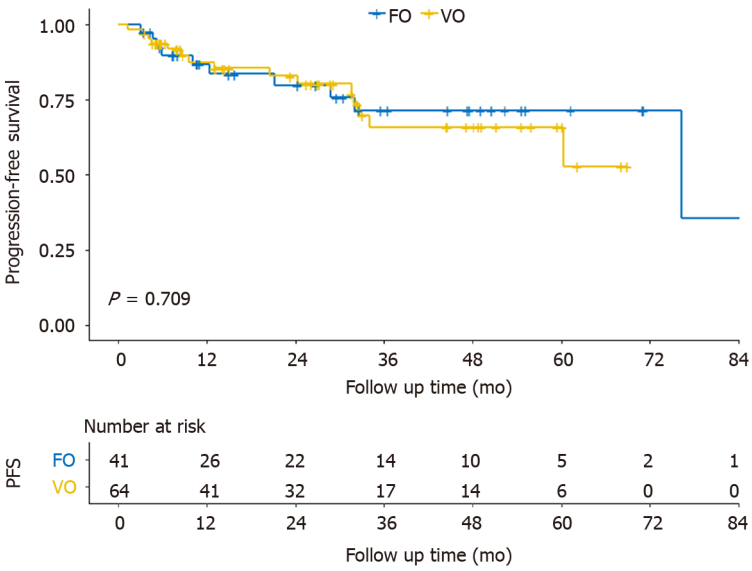

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Figure 3 Kaplan–Meier curves of progression-free survival for the two groups. PFS: Progression-free survival; FO: Fascia-oriented; VO: Vessel-oriented.

The median number of examined LLNs in the fascia-oriented group was 9.0, consistent with previous studies on laparoscopic LLND[30,33]; furthermore, this number was significantly higher than that in the vessel-oriented group (9.0 *vs* 6.5). In terms of the surgical method, this difference may be related to the

thoroughness of lymph node dissection. Vessel-oriented LLND consists of a fragmented and sporadic dissection, which is likely to lead to the omission of lymph nodes and does not conform to the principle of en bloc tumor resection. In fascia-oriented LLND, clear boundaries of medial and lateral dissection are established when dissecting the No. 263 and No. 283 Lymph nodes, which is conducive to guiding the removal of lymphoid tissue in the lateral space and makes it easier to achieve en bloc resection and prevent the omission of lymph nodes. Previous studies have shown that increasing the number of examined lymph nodes may improve the accuracy of tumor staging[34]; therefore, fascia-oriented LLND may be beneficial for assessing of the severity of rectal cancer patients with LLN metastasis.

The incidence of postoperative urinary dysfunction and male sexual dysfunction was much lower in the fascia-oriented group than in the vessel-oriented group. Although the incidence of lower limb dysfunction was comparable between the two groups, the incidence was less than 30% in both groups. Multivariate analyses showed that vessel-oriented LLND was an independent risk factor for postoperative urinary dysfunction and male sexual dysfunction. The above results indicated that compared with vessel-oriented LLND, fascia-oriented LLND effectively prevents intraoperative pelvic nerve damage, which may be attributed to several factors.

First, since the surface of the pelvic autonomic nerve is covered with the UNF, this provides a fascial marker for autonomic nerves protection during surgery. In establishing the medial boundary of LLND, the tissue is separated along the lateral side of the UNF, which protects the integrity of the UNF and prevents injury to the autonomic nerve. Second, the obturator nerve can be exposed after dissociating along the pelvic parietal fascia to the obturator foramen. The surrounding tissue can be dissected from far to near along the obturator nerve so that the obturator nerve can be safely exposed throughout the process of LLND. Similarly, dissociating along the pelvic parietal fascia and the VF can reveal the neurovessel bundle, effectively reducing the probability of nerve damage during surgery.

Limits of the study

This study had several limitations. First, this was a retrospective study with a small sample size. Thus, selection bias may have been a concern and prospective studies including more patients enrolled will be needed in the future to verify the conclusions drawn in this study. Second, regarding the assessment of postoperative urinary dysfunction, although the IPSS is widely used in clinical work because of its simplicity and feasibility, it is more accurate to evaluate urinary dysfunction through the residual bladder volume. Third, there is currently no uniform standard for evaluating female sexual dysfunction; therefore, this study did not perform postoperative sexual function evaluations in female patients.

CONCLUSION

In conclusion, this study demonstrated that it is safe and feasible to perform fascia-oriented LLND at experienced high-volume centers. Compared with vessel-oriented LLND, fascia-oriented LLND allows the examination of more LLNs and may better protect postoperative urinary function and postoperative male sexual function. The conclusions drawn need to be verified in future prospective studies including more patients.

ARTICLE HIGHLIGHTS

Research background

There is a lack of studies comparing the efficacy of fascia-oriented and traditional vessel-oriented lateral lymph node dissection (LLND). Through a preliminary study with a small sample size, we found that fascia-oriented LLND was associated with a lower incidence of postoperative urinary and male sexual dysfunction and a higher number of examined lateral lymph nodes (LLNs). In this study, we increased the sample size and refined the postoperative functional outcomes.

Research motivation

For the management of LLN metastasis in patients with rectal cancer, selective LLND is gradually being accepted by Chinese scholars. Theoretically, fascia-oriented LLND both allows radical tumor resection and protects organ function. However, there is a lack of evidence-based medical studies comparing the efficacy of fascia-oriented and traditional vessel-oriented LLND. The present study will provide information for surgeons regarding the selection of the optimal surgical procedure for LLND.

Research objectives

This study aimed to compare the effects of fascia- and vessel-oriented LLND regarding the short-term outcomes and prognosis.

Research methods

We conducted a retrospective cohort study on data from 196 patients with rectal cancer who underwent total mesorectal excision and LLND from July 2014 to August 2021. The short-term outcomes included perioperative outcomes and postoperative functional outcomes. The prognosis was measured based on overall survival (OS) and progression-free survival (PFS).

Research results

Regarding short-term outcomes, the fascia-oriented group had a higher median number of examined LLNs compared to the vessel-oriented group. However, there were no notable differences in other short-term outcomes. The fascia-oriented group had significantly lower rates of postoperative urinary and male sexual dysfunction compared to the vessel-oriented group, and there were no significant differences in postoperative lower limb dysfunction between the two groups. As for prognosis, there was no significant disparity in PFS or OS between the two groups.

Research conclusions

Our study suggests that fascia-oriented LLND is a safe and feasible option for patients with rectal cancer. Although no significant difference was observed in prognosis compared to vessel-oriented LLND, fascia-oriented LLND may allow for the examination of more LLNs and potentially offer benefits in preserving postoperative urinary and sexual function.

Research perspectives

While our study supports the use of fascia-oriented LLND for rectal cancer, it is important to verify our conclusions with larger prospective studies. Further research is needed to confirm the potential benefits of fascia-oriented LLND, including preserving postoperative urinary and sexual function.

FOOTNOTES

Author contributions: Zhao W and Wang ZJ contributed equally to this work; Liu Q contributed to the study conception and design; material preparation, data collection and analysis were performed by Zhao W, Wang ZJ, Mei SW, Chen JN, Zhou SC, Zhao FQ, Xiao TX, and Huang F; the first draft of the manuscript was written by Zhao W and Wang ZJ, and all authors commented on previous versions of the manuscript; All authors read and approved the final manuscript.

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Institutional review board statement: The study was performed in accordance with the ethical standards of the National Cancer Center ethics committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was reviewed and approved by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College Institutional Review Board, No. 17-116/1439.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Prognostic value of 11-factor modified frailty index in postoperative adverse outcomes of elderly gastric cancer patients in China

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Abstract

BACKGROUND

Preoperative evaluation of frailty is limited to a few surgical procedures. However, the evaluation in Chinese elderly gastric cancer (GC) patients remains blank.

AIM

To validate and estimate the prognostic value of the 11-index modified frailty index (mFI-11) for predicting postoperative anastomotic fistula, intensive care unit (ICU) admission, and long-term survival in elderly patients (over 65 years of age) undergoing radical GC.

METHODS

This study was a retrospective cohort study which included patients who underwent elective gastrectomy with D2 Lymph node dissection between April 1, 2017 and April 1, 2019. The primary outcome was 1-year all-cause mortality. The secondary outcomes were admission to ICU, anastomotic fistula, and 6-mo mortality. Patients were divided into two groups according to the optimal grouping cutoff of 0.27 points from previous studies: High risk of frailty marked as mFI-11^{High} and low risk of frailty marked as mFI-11^{Low}. Survival curves between the two groups were compared, and univariate and multivariate regression analyses were performed to explore the relationship between preoperative frailty and postoperative complications in elderly patients undergoing radical GC. The discrimination ability of the mFI-11, prognostic nutritional index, and tumor-node-metastasis pathological stage to identify adverse postoperative outcomes was assessed by calculating the area under the receiver operating characteristic (ROC) curve.

RESULTS

A total of 1003 patients were included, of which 13.86% (139/1003) were defined as having mFI-11^{High} and 86.14% (864/1003) as having mFI-11^{Low}. By comparing the incidence of postoperative complications in the two groups of patients, it was found that mFI-11^{High} patients had higher rates of 1-year postoperative mortality, admission to ICU, anastomotic fistula, and 6-mo mortality than the mFI-11^{Low} group (18.0% *vs* 8.9%, $P = 0.001$; 31.7% *vs* 14.7%, $P < 0.001$; 7.9% *vs* 2.8%, $P < 0.001$; and 12.2% *vs* 3.6%, $P < 0.001$). Multivariate analysis revealed mFI-11 as an independent predictive indicator for postoperative outcome [1-year postoperative mortality: Adjusted odds ratio (aOR) = 4.432, 95% confidence interval (95%CI): 2.599-6.343, $P = 0.003$; admission to ICU: aOR = 2.058, 95%CI: 1.188-3.563, $P = 0.010$; anastomotic fistula: aOR = 2.852, 95%CI: 1.357-5.994, $P = 0.006$; 6-mo mortality: aOR = 2.438, 95%CI: 1.075-5.484, $P = 0.033$]. mFI-11 showed better prognostic efficacy in predicting 1-year postoperative mortality [area under the ROC curve (AUROC): 0.731], admission to ICU (AUROC: 0.776), anastomotic fistula (AUROC: 0.877), and 6-mo mortality (AUROC: 0.759).

CONCLUSION

Frailty as measured by mFI-11 could provide prognostic information for 1-year postoperative mortality, admission to ICU, anastomotic fistula, and 6-mo mortality in patients over 65 years old undergoing radical GC.

Key Words: Gastric cancer; Frailty; Mortality; Anastomotic fistula; Elderly

Core Tip: Frailty is becoming an increasingly established risk factor for adverse postoperative outcomes. Given the innately high morbidity involved in radical gastric cancer and the propensity for comorbidities among this patient population, we sought to validate and estimate the prognostic value of the 11-index modified frailty index (mFI-11) in the postoperative period and long-term survival of those patients. The mFI-11 has proven to be a potential exponential tool that can easily stratify patients, predict long-term outcomes, and add value to future treatments.

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INTRODUCTION

Globally, gastric cancer (GC) is one of the most common cancers, accounting for more than 1 million cases a year, or 7 percent of all cancer diagnoses[1]. With the development of social aging, there is an increasing trend of patients with GC over the age of 65, and most of them are in the middle or late stages of diagnosis because of the hidden nature of GC[2]. As a general rule, gastrectomy + D2 lymph node dissection is the primary surgical procedure for advanced GC, which has been accepted in many countries[3]. Current perioperative management strategies are maturing; however, serious complications may still occur after radical resection of GC, affecting quality of life, tolerability, and outcome of subsequent management[4]. Thus, preoperative risk assessment and post-cancer symptom management in older patients remains critical.

Numerous studies have shown the predictive role of some indicators regarding postoperative complications, including tumor-node-metastasis (TNM) pathological stage and prognostic nutritional index (PNI)[5-7]. However, these indicators lack the ability to measure the physiological reserve of patients, so this paper introduces the concept of frailty in order to provide references for comprehensive preoperative assessment and risk stratification. Frailty is a complex clinical syndrome characterized by reduced physical strength, reduced metabolic and cognitive function, reduced resistance to adverse events, and reduced ability to deal with surgical blows[8]. Moreover, frailty has been investigated as a valuable predictor of adverse health events and poor postoperative outcomes in patients undergoing surgery. Frailty index (FI) is one of the tools for quantifying the degree of frailty in the clinic, and Velanovich and his colleagues summarized the frailty index with 11 variables, known as the 11-index modified frailty index (mFI-11)[9]. Previous studies have confirmed that frailty is an independent risk factor for perioperative complications in elderly patients. The more frailty the patient, the higher the

incidence of postoperative adverse outcomes[10].

At this stage, preoperative evaluation of weakness is limited to a few surgical procedures such as arthroplasty, colorectal cancer, and urological tumors[11,12]. However, the evaluation of preoperative frailty in Chinese elderly GC patients remains blank. The purpose of this study was to evaluate the efficacy of mFI-11 applications in predicting adverse outcomes after radical GC surgery in elderly patients in China, and compare the efficacy of mFI-11, TNM stage, and PNI in predicting adverse outcomes after surgery.

MATERIALS AND METHODS

Patients

Medical records and clinicopathologic data of patients aged 65 years and older who underwent radical GC surgery were retrospectively studied at the Department of Gastrointestinal Surgery of the First Medical Center of the People's Liberation Army General Hospital (Beijing) between April 1, 2017 and April 1, 2019. Research design and data analysis were approved by the Committee of Medical Research Ethics (Approval No. S2021-342-01). The same committee waived the requirement of written informed consent for participation. The inclusion criteria were: (1) Patients over the age of 65 admitted to the study unit; (2) All patients had histologic confirmation of GC and underwent radical gastrectomy with D2 lymph node dissection; and (3) Patients and their families agreed to provide long-term follow-up information. The exclusion criteria were: (1) Patients had other systemic tumor diseases; (2) Patients who had missing covariate data or follow-up; (3) Patients underwent palliative surgery for distant metastasis and extraregional lymph node metastasis; and (4) Patients received perioperative neoadjuvant chemotherapy. Figure 1 shows the flow chart of this study. The main characteristics of 1003 people included in this study are summarized in Table 1.

Data collection and outcomes

Data were obtained from electronic medical record systems using SQL server (Microsoft, United States). Demographic data were extracted from the Integrated Patient Records Management System (PRIDE 2.1.2.193, Heren Health, China), including age, sex, body mass index, hypertension, diabetes, cardiovascular and lung diseases, cerebrovascular diseases, delirium, independent functional status, and American Society of Anesthesiologists physical score (ASA PS). A non-independent functional state was defined when a patient was unable to perform basic life care alone prior to surgery, such as washing clothes, eating, simply exercising physically, or requiring a full-time escort from a family member, as noted in the care record. Laboratory indicators include serum albumin and lymphocytes. From the anesthesia information management systems (DoCare 3.1.0 build 153, MEDICALSYSTEM, China), intraoperative data were retrieved, including surgical procedures, duration of surgery, ASA PS, TNM stage, and pathologic types of GC. Primary outcome was 1-year of all-cause mortality. Secondary outcomes were 6-mo mortality, anastomotic fistula, and admission to intensive care unit (ICU).

Measurements

We selected mFI-11, TNM stage, and PNI to predict adverse outcomes after radical GC resection in elderly patients, and compared the prognostic value of all three. Initially, because the FI scale contained more than 70 variables, which led to poor clinical outreach, we developed mFI-11 that mapped 70 variables from the original FI to 11 preexisting variables in the National Surgery Quality Improvement Program (NSQIP) database[13]. The 11 variables that were used to calculate the mFI-11 were functional status, history of diabetes, respiratory problems, congestive heart failure, myocardial infarction, cardiac problems, arterial hypertension, delirium, history related to cognitive impairment or loss, cerebrovascular problems, and history of stroke/decreased peripheral pulses[14]. Details of specific variables that match these factors are defined in Supplementary Table 1. mFI-11 score was calculated by dividing the number of positive variables in the patient by the number of total variables (11). Scores range from 0 to 1. High-risk frailty(mFI-11^{High}) was defined when the mFI-11 score was ≥ 0.27 and low-risk frailty (mFI-11^{Low}) was defined when the score was less than 0.27. PNI was calculated as 10 × peripheral serum protein (g/L) + 0.005 × peripheral blood lymphocyte count (mm^3)[15]. PNI is a commonly used indicator to evaluate the nutritional and immune status of patients, which can predict the surgical risk and postoperative complications.

Statistical analysis

If the continuous data are normally distributed, they are shown as the mean ± SD, otherwise they are shown as median and interquartile range (IQR). The categorical data are presented as proportions. Categorical data are reported as frequencies and percentages and compared using the χ^2 test or Fisher's exact test as appropriate. Univariate and multivariate logistic regression analyses were performed to determine independent risk factors for postoperative mortality, anastomotic fistula, and admission to ICU. Receiver operating characteristic (ROC) curve analysis was used to evaluate the efficacy of

Table 1 Intergroup comparison of demographics, intraoperative information, and mFI-11-related variables in 1003 patients

Variable	mFI^{Low} (*n* = 864)	mFI^{High} (*n* = 139)	*P* value
Age (yr)			**0.0392**
65-75	686 (79.4)	102 (73.4)	
≥ 75	178 (20.6)	37 (26.6)	
Gender, male, *n* (%)	656 (75.9)	109 (78.4)	0.522[2]
BMI (kg/m^2)	23.47 ± 3.49	24.65 ± 2.97	0.081[1]
Smokers, *n* (%)	300 (34.7)	54 (38.8)	0.345[2]
Drinkers, *n* (%)	51 (5.9)	18 (12.9)	**0.002**[2]
Serum albumin (g/L)	36.05 ± 4.29	27.85 ± 4.56	**< 0.001**[1]
Lymphocytes (× 10^9/L)	0.20 ± 0.11	0.19 ± 0.11	0.527[1]
PNI	37.03 ± 4.31	28.83 ± 4.58	**< 0.001**[1]
TNM stage, *n* (%)			**< 0.001**[2]
I	159 (18.4)	12 (8.6)	
II	405 (46.9)	30 (21.6)	
II	237 (27.4)	61 (43.9)	
IV	63 (7.3)	36 (25.9)	
ASA physical stage, *n* (%)			**< 0.001**[2]
I + II	706 (81.71)	78 (56.12)	
III + IV	158 (18.29)	61 (43.88)	
Gastrectomy, *n* (%)			0.361[2]
DG	379 (43.9)	52 (37.4)	
PG	117 (13.5)	21 (15.1)	
TG	368 (42.6)	66 (47.5)	
Surgical approach, *n* (%)			**0.035**[2]
Open	85 (9.8)	15 (10.8)	
Robotic surgery	92 (10.6)	25 (18.0)	
Laparoscopy	687 (79.5)	99 (71.2)	
Surgery duration (min)	202.40 ± 63.07	214.02 ± 62.00	**0.041**[1]
Diabetes mellitus	111 (12.8)	78 (56.1)	**< 0.001**[2]
Myocardial infarction	10 (1.2)	18 (12.9)	**< 0.001**[2]
Cardiac problems	52 (6.0)	27 (19.4)	**< 0.001**[2]
Congestive heart failure	1 (0.1)	3 (2.2)	**< 0.001**[2]
Cerebrovascular problems	101 (11.7)	44 (31.7)	**< 0.001**[2]
Stroke	1 (0.1)	6 (4.3)	**< 0.001**[2]
Decreased peripheral pulses	21 (2.4)	29 (20.9)	**< 0.001**[2]
Respiratory problems	12 (1.4)	20 (14.4)	**< 0.001**[2]
Non-independent functional status	38 (4.4)	27 (19.4)	**< 0.001**[2]
Clouding or delirium	43 (5.0)	32 (23.0)	**< 0.001**[2]
Arterial hypertension	235 (27.2)	119 (85.6)	**< 0.001**[2]
Outcomes			
1-year mortality	77 (8.9)	25 (18.0)	**0.001**[2]
Admission to ICU	127 (14.7)	44 (31.7)	**< 0.001**[2]

Anastomotic fistula	24 (2.8)	11 (7.9)	**< 0.001**[2]
6-mo mortality	31 (3.6)	17 (12.2)	**< 0.001**[2]

[1]*t* test;
[2]Pearson χ^2.
P less than 0.05 is marked as bold. BMI: Body mass index; ASA: American Society of Anesthesiologists; TNM: Tumor-node-metastases; DG: Distal partial gastrectomy; TG: Total gastrectomy; PG: Proximal partial gastrectomy; PNI: Prognostic nutritional index; mFI-11: 11-Item modified frailty index; ICU: Intensive care unit.

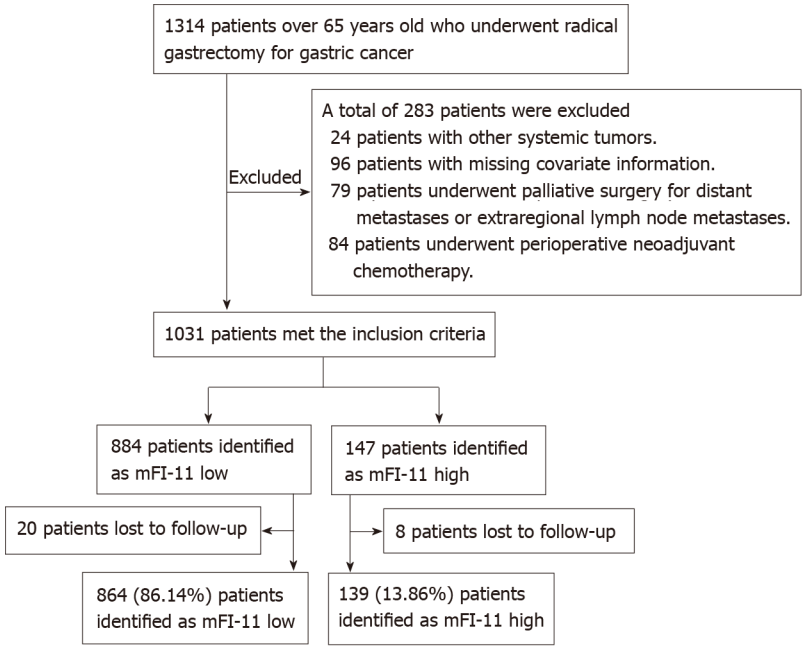

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Figure 1 Flowchart. mFI-11: 11-index modified frailty index.

different variables in predicting postoperative mortality, anastomotic fistula, and admission to ICU. The mFI-11^{High} group and mFI-11^{Low} group were compared using Kaplan-Meier (K-M) survival curves. A *P* value inferior to 0.05 was set to reach significance. Data analyses were performed using the SPSS software (version 26.0, IBM, Armonk, NY, United States).

RESULTS

Complications

A total of 1003 patients were included, of which 13.86% (139/1003) were defined as having mFI-11^{High} and 86.14% (864/1003) as having mFI-11^{Low}. Figure 2 compares the incidence of postoperative ICU admission, anastomotic fistula, death at 6 mo, and death at 1 year in both groups. By comparing the incidence of postoperative complications in the two groups of patients, it was found that mFI-11^{High} patients had higher rates of 1-year postoperative mortality, admission to ICU, anastomotic fistula, and 6-mo mortality than the mFI-11^{Low} group (18.0% *vs* 8.9%, $P = 0.001$; 31.7% *vs* 14.7%, $P < 0.001$; 7.9% *vs* 2.8%, $P < 0.001$; 12.2% *vs* 3.6%, $P < 0.001$).

ROC and K-M survival curve analysis

Figure 3 shows the prognostic value of mFI-11, TNM stage, and PNI for postoperative adverse outcomes. In comparison to the other two measures, the mFI-11 scale showed the best predictive value with regard to the area under the curve. In predicting 1-year mortality after surgery, mFI-11 had the highest area under the curve (0.731), followed by TNM stage (0.643), and the lowest was PNI (0.598). In predicting 6-mo mortality after surgery, mFI-11 had the highest area under the curve (0.759), followed by TNM stage (0.733), and the lowest was PNI (0.668). In terms of admission to ICU after surgery, mFI-11 also had the highest area under the curve (0.776), followed by TNM stage (0.659), and the lowest was PNI (0.559). In predicting anastomotic fistula after surgery, mFI-11 still had the highest area under the

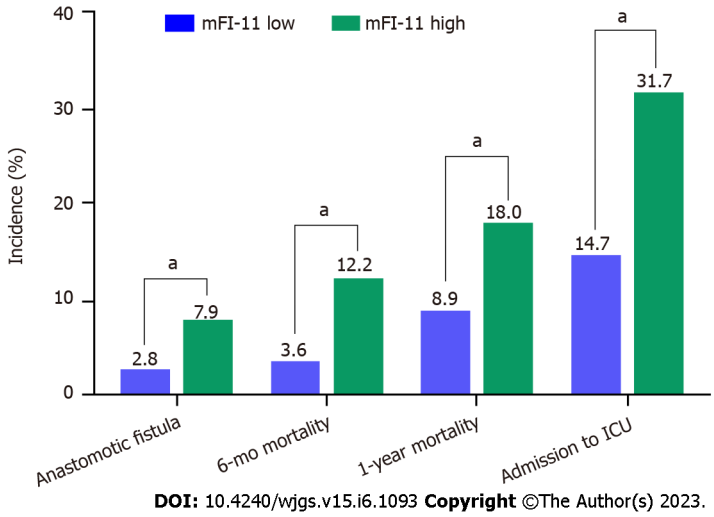

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Figure 2 Incidence of postoperative intensive care unit admission, anastomotic fistula, death at 6 mo, and death at 1 year in both groups. ICU: Intensive care unit; mFI-11: 11-index modified frailty index. [a]*P* < 0.01.

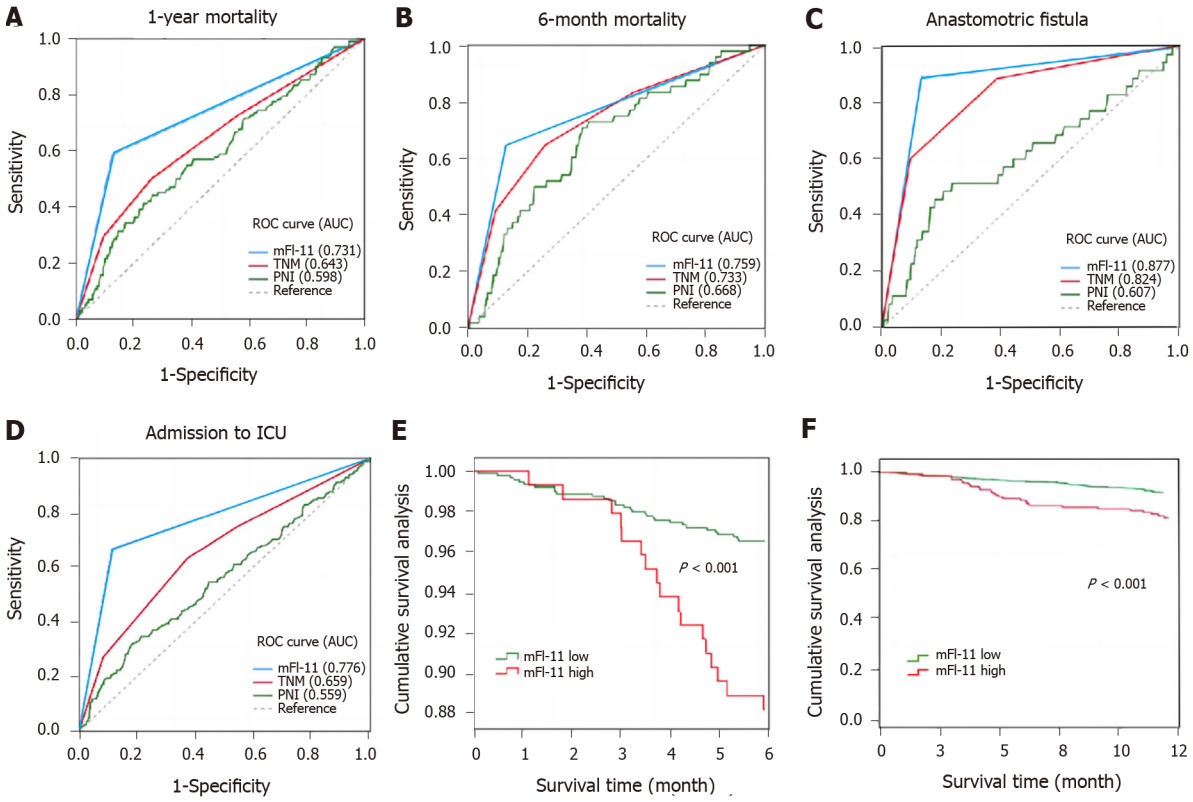

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Figure 3 Prognostic value of 11-index modified frailty index, tumor-node-metastasis stage, and prognostic nutritional index for postoperative adverse outcomes. In comparison to the other two measures, the 11-index modified frailty index scale showed the best predictive value in terms of the area under the curve. A-F: The receiver operating characteristic (ROC) curves of 11-index modified frailty index (mFI-11), tumor-node-metastasis (TNM) stage, and prognostic nutritional index (PNI) in predicting 1-year mortality (A), 6-mo mortality (B), admission to intensive care unit (C), anastomotic fistula (D), survival at mo (E), and survival at 1 year after surgery (F).

curve (0.877), followed by TNM stage (0.824), and the lowest was PNI (0.607). Figure 3 also shows the K-M survival curves at 6 mo and 1 year after surgery between mFI-11^{High} and mFI-11^{Low} patients, and there was a significant difference between them ($P < 0.001$). Supplementary Table 2 shows the area under the curve values of different variables in predicting admission to ICU, anastomotic fistula, 6-mo mortality, and 1-year mortality.

Risk factors for postoperative complications

Table 2 shows multivariate logistic regression analysis of adverse outcomes in elderly patients with GC after radical treatment. Multivariate analysis revealed mFI-11 as an independent predictive indicator for postoperative outcomes (1-year postoperative mortality: Adjusted odds ratio (aOR) = 4.432, 95% confidence interval (95%CI): 2.599-6.343, P = 0.003; admission to ICU: aOR = 2.058, 95%CI: 1.188-3.563, P = 0.010; anastomotic fistula: aOR = 2.852, 95%CI: 1.357-5.994, P = 0.006; 6-mo mortality: aOR = 2.438, 95%CI: 1.075-5.484, P = 0.033. Multivariate analysis also revealed TNM stage and PNI as independent predictive indicators for 1-year postoperative mortality (TNM stage III *vs* I: aOR = 1.423, 95%CI: 1.004-3.453, P = 0.005; TNM stage IV *vs* I: aOR = 2.422, 95%CI: 1.524-5.292, P = 0.032; PNI: aOR = 0.925, 95%CI: 0.902-0.964, P = 0.021).

Supplementary Tables 3-6 show univariate and multivariate logistic regression analyses of 1-year mortality, 6-mo mortality, anastomotic fistula, and admission to ICU, respectively.

DISCUSSION

To the best of our knowledge, this is the first study in China to demonstrate the relationship between preoperative frailty conditions and postoperative adverse outcomes (admission to ICU, anastomotic fistula, and 6-mo mortality) in patients over 65 years of age undergoing radical GC surgery. Similarly, for the first time, we compared the prognostic value of frailty (mFI-11), TNM stage, and PNI in postoperative outcomes in elderly GC patients. After comparing the prognostic value of mFI-11, TNM stage and PNI for the three postoperative adverse outcomes, we found that mFI-11 had the best prognostic value. It was also proved that frailty condition was an independent risk factor for the postoperative adverse outcomes, which provides some reference for clinicians to intervene in frailty condition during the perioperative period.

Radical surgery for GC is one of the best treatment methods for GC patients. However, as a kind of operation which causes great trauma to the body, radical surgery causes many adverse outcomes such as entering ICU, anastomotic fistula, and death[16]. Therefore, preoperative risk assessment is particularly important. In response to interest in accurate risk stratification, the surgical community has largely shifted from assessments based on subjective clinical judgment, such as the ASA classification, to more objective analytical approaches, including mFI-11[17]. Similarly, we sought to investigate the predictive capability of mFI-11 in a cohort of 1003 patients undergoing radical GC surgery. In our study, both the univariate and the multivariate analyses indicated that the mFI-11^{High} was an independent risk factor for postoperative complications. Alternatively, we found that mFI-11 had a better ability to identify high-risk patients and to predict postoperative outcomes when compared to TNM stage and PNI.

In this study, TNM stage was an independent risk factor for postoperative complications of GC. However, cancer is a systemic disease whose prognosis is not only dependent on the tumor itself, but also on the underlying physical condition as well as the physiological reserve. PNI served as a representative parameter of patient nutritional status in this study, and it has been used as a surrogate indicator of nutritional status in various neoplastic diseases. Different from other tumor patients undergoing surgery, GC patients often have loss of appetite and reduced oral food intake, and even some patients need parenteral nutrition support before surgery[18]. In this study, PNI was an independent risk factor for postoperative complications of GC. The deteriorating nutritional status may lead to a poor prognosis, and improving the nutritional status of patients with low preoperative PNI improves outcomes in the perioperative treatment of GC patients[19]. However, the simple use of nutritional status indicators was not included in the physiological reserve, so as expected, this study found that mFI-11 was better and more effective than PNI in terms of predicting 6-mo postoperative mortality, 1-year mortality, postoperative ICU admission, and the incidence of anastomotic fistula.

Frailty is becoming an increasingly established risk factor for adverse postoperative outcomes. Our results are consistent with previous studies in predicting adverse outcomes with perioperative frailty assessment (mFI-11)[20]. Jung *et al*[21] also found that mFI-11 scores in patients with lumbar lateral fusion were associated with urinary complications. The study conducted by Harris *et al*[22] found that frailty risk scores predicted morbidity and mortality in patients following selective endovascular repair of a reduced thoracic aortic aneurysm. In a previous study by Joseph *et al*[23], they also demonstrated that frailty as measured by mFI-11 was an accurate predictor of morbidity and mortality in patients undergoing complex abdominal wall reconstruction. Shi *et al*[24] found that mFI-11 was linked to complications and mortality in hip replacement patients.

The mFI-11 scale might be a useful tool for evidence-based decisions, providing proper patient management, and it is a sensitive tool to stratify and predict patients' long-term outcomes. Additionally, it provides a promising opportunity for more comprehensive and systematic preoperative risk assessment. This study should serve as a stimulus to further research in order to understand the importance and therapeutic value of frailty. Preoperative frailty condition identified by the mFI-11 scale could be used for clinical risk stratification to improve preoperative evaluation in elderly GC population. In contrast, identification of greater risks may lead to management changes, prompt consid-

Table 2 Multivariate logistic regression analysis of adverse outcomes in elderly patients with gastric cancer after radical treatment

Variable	1-year mortality			6-mo mortality			Anastomotic fistula			Admission to ICU		
	B	OR (95%CI)	*P* value	B	OR (95%CI)	*P* value	B	OR (95%CI)	*P* value	B	OR (95%CI)	*P* value
Age, > 75 yr *vs* 65-75 yr							0.883	2.418 (1.202-4.865)	**0.013**	0.914	2.495 (1.723-3.613)	**< 0.001**
Serum albumin, g/L	-0.532	0.923 (0.900-0.954)	**0.023**	0.013	0.936 (0.325-0.999)	**0.002**	-0.881	0.907 (0.484-1.696)	0.759	-0.018	0.718 (0.439-0.909)	**0.012**
PNI	-0.251	0.925 (0.902-0.964)	**0.021**	0.041	0.932 (0.554-0.942)	**0.014**	0.062	0.567 (0.214-1.481)	0.846	-0.019	0.719 (0.438-0.902)	**0.041**
TNM stage, III *vs* I	0.324	1.423 (1.004-3.453)	**0.005**	0.365	1.122 (0.798-2.525)	0.424						
TNM stage, IV *vs* I	0.683	2.422 (1.524-5.292)	**0.032**	0.415	1.041 (0.698-1.464)	0.221				0.345	1.356 (1.008-4.637)	**0.031**
ASA grade, II *vs* I	1.134	1.412 (1.053-2.637)	**0.042**	0.643	1.001 (0.888-2.642)	0.471				0.980	1.643 (0.463-1.976)	0.318
ASA grade, III *vs* I	1.124	2.577 (1.656-3.487)	**0.011**				0.214	1.533 (1.213-4.743)	**0.003**	0.506	2.344 (1.796-4.785)	**0.022**
ASA grade, IV *vs* I	1.412	1.456 (1.077-3.747)	**0.041**							0.602	2.865 (1.092-3.853)	**0.018**
Gastrectomy, PG *vs* TG										0.671	0.312 (0.111-1.764)	0.357
mFI-11^{High} *vs* mFI-11^{Low}	0.931	4.432 (2.599-6.343)	**0.003**	0.887	2.438 (1.075-5.484)	**0.033**	1.048	2.852 (1.357-5.994)	**0.006**	0.722	2.058 (1.188-3.563)	**0.010**

P less than 0.05 is marked as bold. ASA: American Society of Anesthesiologists; BMI: Body mass index; TNM: Tumor- node-metastases; DG: Distal partial gastrectomy; TG: Total gastrectomy; PG: Proximal partial gastrectomy; PNI: Prognostic nutritional index; mFI-11:11-item, modified frailty index; IGA: Intravenous general anesthesia; IIA: Intravenous inhalation anesthesia.

eration of close observation, and/or reducing the threshold for intervention. Radical GC surgery is a complex procedure that requires detailed preoperative risk assessment to reduce patient risk and optimize patient benefit and resource utilization[25].

This study has several important limitations. First, this study was a single-center retrospective study. The study center is conducting a large, multicenter, prospective, frailty-scale evaluation study to validate the value of frailty in predicting adverse postoperative outcomes. Second, the study population was elderly patients with elective radical GC, so the study results cannot be directly generalized to the entire surgical population. Third, despite adjustment for potential confounders, there may be other variables not considered, such as tumor size, so we must acknowledge the effect of unmeasured confounders.

CONCLUSION

In summary, high risk of frailty assessed by mFI-11 based on medical record data has been confirmed to be significantly associated with anastomotic fistula, mortality, and ICU admission after radical GC surgery in elderly patients in China. Preoperative evaluation of frailty may provide useful prognostic information for elderly patients undergoing radical GC surgery. This simple risk score tool may enable

improved risk assessment and patient selection prior to elective radical GC surgery.

ARTICLE HIGHLIGHTS

Research background

Preoperative evaluation of frailty is limited to a few surgical procedures. However, the evaluation in Chinese elderly gastric cancer (GC) patients remains blank.

Research motivation

To validate and estimate the prognostic value of the 11-index modified frailty index (mFI-11) for postoperative anastomotic fistula, intensive care unit (ICU) admission, and long-term survival in elderly patients over 65 years of age undergoing radical GC.

Research objectives

To explore the feasibility of mFI-11 in predicting adverse outcomes after radical GC resection in elderly patients.

Research methods

A retrospective cohort study was conducted on patients over 65 years of age who received curative gastrectomy with D2 Lymph node dissection for GC. The primary outcome was 1-year all-cause mortality. The secondary outcomes were admission to ICU, anastomotic fistula, and 6-mo mortality. Survival curves between the two groups were compared, and univariate and multivariate regression analyses were performed to explore the relationship between preoperative frailty and postoperative complications in elderly patients undergoing radical GC.

Research results

A total of 1003 patients were included, of which 13.86% (139/1003) were defined as having mFI-11^{High} and 86.14% (864/1003) as having mFI-11^{Low}. mFI-11^{High} patients had higher rates of 1-year mortality, 6-mo mortality, anastomotic fistula, and admission to ICU than the mFI-11^{Low} group. Multivariate analysis revealed mFI-11 as an independent predictive indicator for 1-year postoperative mortality, 6-mo mortality, anastomotic fistula, and admission to ICU. mFI-11 showed better prognostic efficacy in predicting 1-year postoperative mortality [area under the ROC curve (AUROC): 0.731], 6-mo mortality (AUROC: 0.759), anastomotic fistula (AUROC: 0.877), and admission to ICU (AUROC: 0.776).

Research conclusions

Frailty as measured by mFI-11 could provide prognostic information for 1-year postoperative mortality, admission to ICU, anastomotic fistula, and 6-mo mortality in patients over 65 years old undergoing radical GC.

Research perspectives

Well-designed multi-center prospective randomized controlled studies are still needed.

FOOTNOTES

Author contributions: Xu ZY and Hao XY contributed equally to this work; Xu ZY, Hao XY, and Wang XX designed the experiments; Wu D performed the experiments; Xu ZY and Hao XY collected the data; Wu D and Song QY analyzed the data; Xu ZY, Hao XY, and Wang XX wrote the initial draft; Wu D and Song QY modified the manuscript.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of Chinese PLA General Hospital (approval No. S2021-342-01).

Conflict-of-interest statement: All authors declare that there is no conflict of interest to disclose.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Retrospective Study

Long-term outcomes and failure patterns after laparoscopic intersphincteric resection in ultralow rectal cancers

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Abstract

BACKGROUND

Intersphincteric resection (ISR), the ultimate anus-preserving technique for ultralow rectal cancers, is an alternative to abdominoperineal resection (APR). The failure patterns and risk factors for local recurrence and distant metastasis remain controversial and require further investigation.

AIM

To investigate the long-term outcomes and failure patterns after laparoscopic ISR in ultralow rectal cancers.

METHODS

Patients who underwent laparoscopic ISR (LsISR) at Peking University First Hospital between January 2012 and December 2020 were retrospectively reviewed. Correlation analysis was performed using the Chi-square or Pearson's correlation test. Prognostic factors for overall survival (OS), local recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS) were analyzed using Cox regression.

RESULTS

We enrolled 368 patients with a median follow-up of 42 mo. Local recurrence and distant metastasis occurred in 13 (3.5%) and 42 (11.4%) cases, respectively. The 3-year OS, LRFS, and DMFS rates were 91.3%, 97.1%, and 90.1%, respectively.

Multivariate analyses revealed that LRFS was associated with positive lymph node status [hazard ratio (HR) = 5.411, 95% confidence interval (CI) = 1.413-20.722, *P* = 0.014] and poor differentiation (HR = 3.739, 95%CI: 1.171-11.937, *P* = 0.026), whereas the independent prognostic factors for DMFS were positive lymph node status (HR = 2.445, 95%CI: 1.272-4.698, *P* = 0.007) and (y)pT3 stage (HR = 2.741, 95%CI: 1.225-6.137, *P* = 0.014).

CONCLUSION

This study confirmed the oncological safety of LsISR for ultralow rectal cancer. Poor differentiation, (y)pT3 stage, and lymph node metastasis are independent risk factors for treatment failure after LsISR, and thus patients with these factors should be carefully managed with optimal neoadjuvant therapy, and for patients with a high risk of local recurrence (N + or poor differentiation), extended radical resection (such as APR instead of ISR) may be more effective.

Key Words: Rectal cancer; Intersphincteric resection; Laparoscopic surgery; Recurrence; Risk factors

Core Tip: We aimed to investigate the failure patterns and risk factors for local recurrence and distant metastasis in 368 patients who underwent iaparoscopic Intersphincteric resection (LsISR). Local recurrence and distant metastasis occurred in 13 (3.5%) and 42 (11.4%) patients, respectively. The 3-year overall survival, local recurrence-free survival, and distant metastasis-free survival rates were 91.3%, 97.1%, and 90.1%, respectively. Multivariate analyses revealed that LRFS was associated with positive lymph node status and poor differentiation, whereas the independent prognostic factors for DMFS were positive lymph node status and (y)pT3 stage. We believe that our study makes a significant contribution to the literature because it confirmed the oncological safety of LsISR for ultralow rectal cancer. This paper will be of interest to the readership of your journal because it demonstrated that poor differentiation, (y)pT3 stage, and lymph node metastasis are independent risk factors for treatment failure after LsISR, and thus patients with these factors should be carefully managed with optimal neoadjuvant therapy and surgical strategy.

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INTRODUCTION

Ultralow rectal cancer refers to cancer located in the lower part of the rectum, < 5 cm from the anal verge (AV)[1]. Intersphincteric resection (ISR), a sphincter-preserving surgical technique, is a better choice for patients with a strong desire to preserve the anus, if the tumor has not invaded the external sphincter or levator muscles[2]. Compared with abdominoperineal resection (APR), ISR can achieve adequate distal resection margins (DRMs), sufficient circumferential resection margins (CRMs), and better anal function without permanent colostomy[3,4].

As an important surgical technique in the treatment of ultralow rectal cancer, laparoscopic ISR (LsISR) surgery has been widely applied in an increasing number of patients; moreover, the failure patterns after ISR, especially local recurrence and distant metastasis, have drawn the attention of surgeons. A study from Japan[5] reported that the mortality and morbidity were relatively low, although the 5-year cumulative local recurrence rate after ISR was 11.5%, which was higher than that after APR (evaluated using propensity score matching); in addition, multivariate analysis revealed that the pT stage, pN stage, and level of ISR were independent risk factors for local recurrence. These factors have also been reported in other studies[6-9]. However, the conclusions drawn by the aforementioned studies on ISR were limited by either a small sample size or selection bias derived from different centers or surgeons. Therefore, it is vital to further identify the risk factors for local recurrence and distal metastasis in patients with ultralow rectal cancers undergoing LsISR, to improve oncological outcomes.

In this cohort study, we investigated the long-term oncological outcomes and failure patterns of LsISR performed by a single surgical team. Furthermore, we investigated the risk factors for local recurrence and distal metastasis to optimize comprehensive treatment such as neoadjuvant therapy and preoperative surgical planning.

MATERIALS AND METHODS

Patients

We collected retrospective data of patients with rectal cancer who underwent LsISR from multicenter between January 2012 and October 2022. We included patients who underwent LsISR surgery with radically local cancer resection and in whom the lower margin of the tumor was 2.0-5.0 cm away from the AV. Exclusion criteria were as follows: (1) Non-adenocarcinoma; and (2) Perioperative death. Multidisciplinary team meetings determined treatment strategies for each patient and the necessity of neoadjuvant chemoradiotherapy (nCRT). The pelvic radiotherapy was administered as a long-course regimen using external beam radiation therapy at a total dose of 45-54 Gy, and 6-12 wk after the radiation therapy underwent surgery. All patients provided informed consent for this study, which was approved by the Ethics Committee of Peking University First Hospital (Approval No. 17-116/1439).

Surgical Procedures

Standard total mesorectal excision (TME) was performed to reach the anorectal junction, while carefully preserving the bilateral hypogastric nerves and neurovascular bundles. The intersphincteric plane between the puborectalis muscle and internal anal sphincter was carefully dissected under direct vision. The distal rectum was transected intracorporeally using a flexible linear stapler. If the distance was ≥ 2.0 cm, the specimen was removed *via* a low midline mini-laparotomy incision, the sigmoid was cut at approximately 10 cm proximal to the tumor, and a circular stapled end-to-end coloanal anastomosis was constructed. If the distal margin was < 2.0 cm, trans-anal dissection was performed. The specimen was then extracted *via* the anus, and proximal resection was performed using a 60 mm linear stapler. Finally, anastomosis was constructed manually[10,11]. Regardless of whether the anastomosis was stapled or hand-sewn, diverting ileostomy was routinely performed[12]. Intraoperative frozen section pathology was normally required to confirm the status of the DRM when the margin was < 1 cm or suspected to be positive.

Data Collection and Follow-up

We collected the basic clinical and pathological characteristics of patients, including sex, age, body mass index, nCRT, diabetes, American Society of Anesthesiologists score, tumor distance from the AV, differentiation status, tumor diameter, (y)pT stage, (y)pN stage, (y)pTNM (tumor node metastasis) stage (American Joint Committee on Cancer, 8th edition), anastomotic leakage, complications, and postoperative chemotherapy. Follow-up was performed every 3 mo for the first 2 years, every 6 mo for the next 3 years, and annually thereafter. At each visit, patients underwent physical examination, serum carcinoembryonic antigen level measurement, and abdominopelvic magnetic resonance imaging or computed tomography. Colonoscopy was routinely performed annually after surgery. Positron emission tomography was performed when required. The primary endpoint of this study was the 3-year local recurrence-free survival (LRFS), whereas the secondary endpoints were the 3-year overall survival (OS) and 3-year distant recurrence-free survival (DMFS). Local recurrence was defined as tumor recurrence in the pelvic cavity, which was confirmed by histopathology or imaging. Distant metastasis was defined as tumor recurrence outside the pelvis.

Statistical Analysis

The Chi-square, Fisher's exact test, or Pearson's correlation test was used to analyze differences between the primary and validation cohorts. Pearson's correlation is a measure of the linear relationship between two continuous random variables, simultaneously, categorical variables were compared with use of χ^2 analysis. Fisher's exact test is applicable to cases where sample size $n < 40$ or theoretical frequency $T < 1$. When one of the expected frequencies is greater than 5, Chi-square test is considered as a statistical method. Variables with a P-value < 0.100 in the univariate analyses were included in the multivariate analyses. Hazard ratios (HRs) and 95% confidence intervals (CIs) of the risk factors were analyzed using multivariate logistic regression. All statistical analyses were two-sided, and statistical significance was set at $P < 0.05$. R software (version 4.0.2) and SPSS software (version 25.0) were used for the statistical analyses.

RESULTS

Patient Characteristics

Data were obtained from a prospectively collected database of 386 consecutive patients who underwent LsISR. We excluded seven patients with distal metastasis and eight patients with non-adenocarcinoma as well as three patients who died perioperatively. Therefore, 368 patients were enrolled in this study (Figure 1). Table 1 shows the baseline characteristics of the whole cohort, local recurrence group, non-local recurrence group, distant metastasis group, and non-distant metastasis group. In the whole cohort, proportions of T stage were: (y)pT1 (43, 11.9%), (y)pT2 (123, 33.7%), and (y)pT3 (202, 54.4%).

Table 1 Patient basic characteristics, *n* (%)

Variables	Total (*n* = 368)	Local recurrence (*n* = 13)	Non-local recurrence (*n* = 355)	*P* value	Distant metastasis (*n* = 42)	Non-distant metastasis (*n* = 327)	*P* value
Age (yr)				0.746			0.325
≤ 60	184 (50)	5 (38.5)	179 (50.3)		18 (42.9)	167 (51.1)	
> 60	184 (50)	8 (61.5)	176 (49.7)		24 (57.1)	160 (48.9)	
Sex				0.855			0.179
Male	228 (62.0)	8 (61.5)	220 (61.9)		30 (71.4)	198 (60.7)	
Female	140 (38.0)	5 (38.5)	135 (38.1)		12 (28.6)	128(39.3)	
BMI (kg/m^2)				0.845			0.503
≤ 25	246 (66.8)	8 (61.5)	238 (66.9)		30 (71.4)	217 (66.4)	
> 25	122 (33.2)	5 (38.5)	117 (33.1)		12 (28.6)	110 (33.6)	
Hb (g/L)				0.204			0.123
Normal	338 (91.8)	12 (92.3)	326 (91.8)		36 (85.7)	303 (92.7)	
Abnormal	30 (8.2)	1 (7.7)	29 (8.2)		6 (14.3)	24 (7.3)	
Alb (g/L)				0.756			0.058
≥ 35	353 (95.9)	12 (92.3)	341 (96.0)		38 (90.5)	316 (96.6)	
< 35	15 (4.1)	1 (7.7)	14 (4.0)		4 (9.5)	11 (3.4)	
CEA (ng/mL)				0.338			0.100
≤ 5	267 (72.6)	8 (61.5)	259 (72.9)		26 (61.9)	242 (74.0)	
> 5	101 (27.4)	5 (38.5)	96 (27.1)		16 (38.1)	85 (26.0)	
CA 19-9 (u/mL)				0.739			0.045
≤ 37	350 (95.1)	11 (84.6)	339 (95.5)		35 (83.3)	316 (96.6)	
> 37	18 (4.9)	2 (15.4)	16 (4.5)		7 (16.7)	11 (3.4)	
Tumor height from anal verge (cm)				0.985			0.053
≤ 4	273 (74.2)	10 (76.9)	243 (68.4)		26 (61.9)	248 (75.8)	
> 4	95 (25.8)	3 (23.1)	112 (31.6)		16 (38.1)	79 (24.2)	
Tumor size (mm)				0.465			0.590
≤ 40	250 (67.9)	7 (53.8)	243 (68.4)		27 (64.3)	224 (68.2)	
> 40	118 (32.1)	6 (46.2)	112 (31.6)		15 (35.7)	103 (31.8)	
(y)pT stage				0.198			< 0.001
1-2	166 (45.1)	4 (30.8)	162 (46.0)		8 (19.0)	158 (48.7)	
3	202 (54.9)	9 (69.2)	193 (54.0)		34 (81.0)	168 (51.3)	
Lymph node metastasis				0.001			< 0.001
No	245 (66.6)	3 (23.1)	242 (68.4)		16 (38.1)	230 (70.6)	
Yes	123 (33.4)	10 (76.9)	113 (31.6)		26 (61.9)	96 (29.4)	
(y)p TNM stage				0.001			< 0.001
0-II	245 (66.6)	3 (23.1)	242 (68.4)		16 (35.6)	231 (70.6)	
III	123 (33.4)	10 (76.9)	113 (31.6)		26 (64.4)	95 (29.4)	
ASA score				0.084			0.467
I-II	357 (97.0)	12 (92.3)	345 (97.5)		40 (95.2)	317 (97.2)	
III	11 (3.0)	1 (7.7)	10 (2.5)		2 (4.8)	9 (2.8)	

Differentiation				0.009			0.070
Well-moderate	328 (89.1)	8 (61.5)	320 (90.1)		34 (81.0)	294 (90.2)	
Poor	40 (10.9)	5 (38.5)	35 (9.9)		8 (19.0)	32 (9.8)	
Lymphovascular invasion				0.054			0.021
No	315 (85.6)	9 (69.2)	306 (86.4)		31 (73.8)	284 (87.2)	
Yes	53 (14.4)	4 (30.8	49 (13.6)		11 (26.2)	42 (12.8)	
Nerve invasion				0.093			0.012
No	327 (88.9)	9 (69.2)	318 (89.5)		32 (76.2)	295 (90.5)	
Yes	41 (11.1)	4 (30.8)	37 (10.5)		10 (23.8)	31 (9.5)	
nCRT				0.324			0.410
No	328 (89.1)	10 (76.9)	318 (89.6)		39 (92.9)	289 (88.7)	
Yes	40 (10.9)	3 (23.1)	37 (10.4)		3 (7.1)	37 (11.3)	
Adjuvant therapy				0.137			0.378
No	190 (51.6)	4 (30.8)	186 (52.5)		19 (45.2)	171 (52.5)	
Yes	178 (48.4)	9 (69.2)	169 (47.5)		23 (54.8)	155 (47.5)	

Alb: Serum albumin; BMI: Body mass index; CA: Cancer antigen; CEA: Carcinoembryonic antigen; Hb: Hemoglobin; nCRT: Neoadjuvant chemoradiotherapy; TNM: Tumor node metastasis; ASA: American Society of Anesthesiologists.

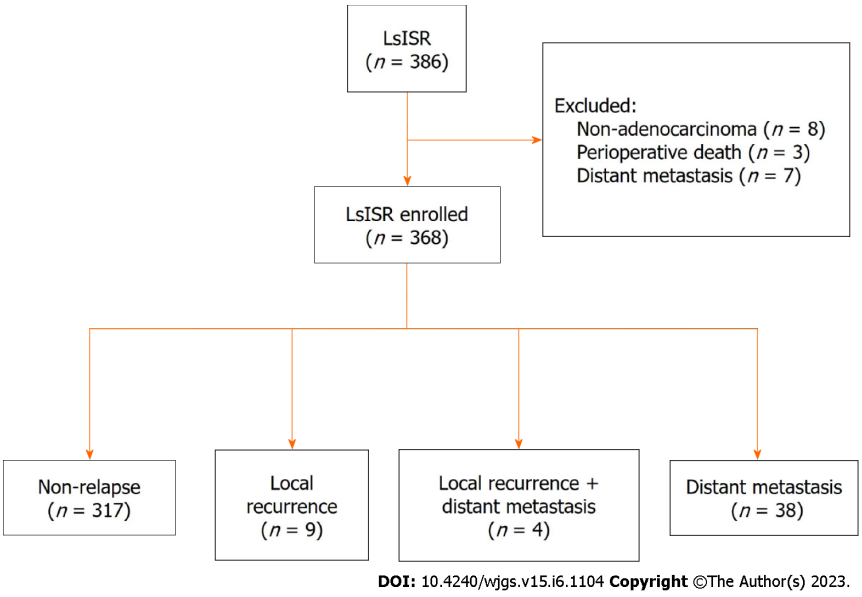

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Figure 1 Patient selection.

Additionally, 121 patients (32.9%) had lymph node metastases. The median distance between the lower edge of the tumor and the AV was 4.0 cm (range, 2.0-5.0 cm), and the median distance between the anastomosis and the AV was 2.2 cm (range, 1.0-4.0 cm).

Local recurrence occurred in 13 patients (3.5%). In the analyses of basic characteristics between the local and non-local recurrence groups, there were significant differences in the distribution of pathological TNM stage (P = 0.001), lymph node status (P = 0.001), and differentiation (P = 0.009). Distant metastasis occurred in 42 (11.4%) patients. Compared with the patients without distant metastasis, the distant metastasis cohorts have higher serum carbohydrate antigen 19-9 level (P = 0.045), more advanced (y)pT stage (P < 0.001), (y)pN stage (P < 0.001), and (y)p TNM stage (P = 0.001), and the distant metastasis cohorts suffered lymphovascular invasion (P = 0.021) and nerve invasion (P = 0.012) tested in the postoperative pathological results.

Failure Pattern after LsISR

The median follow-up times for the whole cohort, local recurrence group, and distant metastasis group were 42, 40, and 43 mo, respectively. The clinical demographics of the 13 (3.5%) patients who developed local recurrence are shown in Table 2, including 9 (69.2%) and 4 (30.8%) patients with anastomotic recurrence and pelvic lymph node metastasis, respectively. Most of the patients with local recurrence had (y)pT3 stage (10/13, 76.9%) and lymph node metastasis (10/13, 76.9%). Three (3/13, 23.1%) patients received preoperative nCRT, and 10 (10/13, 76.9%) patients underwent adjuvant therapy.

Distant metastasis occurred in 42 (11.4%) patients, 4 (1.1%) of whom had both local recurrence and distant metastases. The most common distant metastatic sites were the lungs (20/42, 47.6%), liver (9/42, 21.4%), bones (4/42, 9.5%), and retroperitoneal lymph nodes (4/42, 9.5%).

Univariate and multivariate analyses for OS

The OS rate at 1, 3, and 5 years were 96.5%, 91.3%, and 87.0%, respectively. Univariate analysis revealed that age > 60 years (HR = 2.776, 95%CI: 1.371-5.582, P = 0.004), nerve invasion (HR = 2.596, 95%CI: 1.186-5.683, P = 0.017), (y)pT3 stage (HR = 3.362, 95%CI: 1.541-7.336, P = 0.002), lymph node metastasis (HR = 2.304, 95%CI: 1.218-4.357, P = 0.010) and poor differentiation (HR = 3.117, 95%CI: 1.472-6.600, P = 0.003) were prognostic factors for OS (Table 3). Multivariate analyses demonstrated that age > 60 years (HR = 2.698, 95%CI: 1.329-5.489, P = 0.006), (y)pT3 stage (HR = 2.293, 95%CI: 1.006-5.226, P = 0.048) and poor differentiation (HR = 2.234, 95%CI: 1.021-4.887, P = 0.044) were independent prognostic factors for OS. Figure 2 shows the survival curves for OS according to age, (y)pT stage, and (y)pN stage.

Univariate and multivariate analyses for LRFS

The LRFS rates at 1, 3, and 5 years were 98.4%, 97.1%, and 95.4%, respectively. Table 4 shows the univariate and multivariate analyses findings for LRFS. In the univariate analysis, lymph node metastasis (HR = 6.984, 95%CI: 1.922-25.385, P = 0.003) and poor differentiation (HR = 6.293, 95%CI: 2.048-19.334, P = 0.001) were prognostic factors for LRFS. In the multivariate analysis, lymph node metastasis (HR = 5.358, 95%CI: 1.398-20.532, P = 0.014) and poor differentiation (HR = 3.908, 95%CI: 1.137-13.420, P = 0.030) remained independent prognostic factors for LFRS. The LRFS curves according to (y)pN stage and differentiation are shown in Figure 3.

Univariate and multivariate analyses for DMFS

The DMFS rates at 1, 3, and 5 years were 96.1%, 90.1%, and 82.6%, respectively. Table 5 shows risks factors for distant metastasis after ISR as identified *via* univariate and multivariate analyses. In the univariate analysis, lymphovascular invasion (HR = 2.527, 95%CI: 1.263-5.055, P = 0.009), nerve invasion (HR = 3.061, 95%CI: 1.499-6.252, P = 0.002), (y)pT3 stage (HR = 3.912, 95%CI: 1.810-8.456, P < 0.001), lymph node metastasis (HR = 3.410, 95%CI: 1.829-6.358, P < 0.001), and poor differentiation (HR = 2.451, 95%CI: 1.130-5.314, P = 0.023) were prognostic factors for DMFS. In the Multivariate analysis, pT3 stage (HR = 2.741, 95%CI: 1.225-6.137, P = 0.014) and lymph node metastasis (HR = 2.445, 95%CI: 1.272-4.698, P = 0.007) were independent prognostic factors for DMFS. Survival curves are shown in Figure 4.

DISCUSSION

In recent years, anus-preserving surgery for ultralow rectal cancer and risk factors for postoperative recurrence and metastasis after ISR have been of concern. The failure patterns and predictors of local recurrence and distant metastasis after LsISR require further investigation. In this study, we found that local recurrence and distant metastasis occurred in 3.5% and 11.4% of patients, respectively. The OS/LRFS/DMFS rates at 1, 3, and 5 years were 96.5%/91.3%/87.0%, 98.4%/97.1%/95.4%, and 96.1%/90.1%/82.6%, respectively. LRFS was associated with lymph node metastasis and poor differentiation, whereas the independent prognostic factors for DMFS were lymph node metastasis and (y)pT3 stage. To the best of our knowledge, this study hitherto includes the largest sample of patients who underwent LsISR performed by a single surgical team. Therefore, it can minimize the influence of surgeons on surgical quality and subsequently prognostic outcome, so as to better clarify the prognostic characteristics of this disease itself. In this study, we focused on failure patterns, including local recurrence and distal metastasis.

Previous studies mostly confirmed and compared the oncological safety of ISR and APR. A study from the Japanese Society for Cancer of the Colon and Rectum nationwide registry, including 2125 patients who underwent ISR, reported that the mortality and morbidity were relatively low, and the survivals were relatively better compared with those of patients who underwent APR (5-year OS, 85.4% *vs* 74.8%, P < 0.001; 5-year LRFS, 70.5% *vs* 60.6%, P < 0.001); furthermore, the 5-year cumulative local recurrence rate after ISR was 11.5%[5]. Kim *et al*[13] compared the survival rates between patients who underwent low anterior resection and ISR. In the ISR group, the 5-year cumulative local and systemic recurrence rates were 2.4% and 15.1%, respectively, and no significant differences were observed between the two groups after propensity score matching (n = 166 each). The two groups had similar 5-

Table 2 Clinical demographics of the 13 patients who developed local recurrence

N	Age	Sex	BMI	(y)pT	(y)pN	AV	AT	nCRT	Adjuvant therapy	Recurrence location
1	46	Female	20.2	3	1b	2	4	No	Yes	Lateral and retroperitoneal lymph nodes
2	70	Female	23.6	3	2b	2	4	No	Yes	Axial
3	63	Male	25.5	1	2b	3	4.5	Yes	No	Lateral and retroperitoneal lymph nodes
4	65	Female	23.4	3	2b	2	4	No	Yes	Lateral and retroperitoneal lymph nodes
5	56	Male	18.0	2	0	1.5	3	No	No	Axial
6	69	Male	25.0	3	2a	3	5	No	Yes	Axial
7	35	Male	32.6	3	0	1.5	3	No	No	Axial
8	55	Male	22.8	3	1	2	4	No	No	Axial
9	66	Male	27.4	3	2b	2	4	No	Yes	Axial
10	64	Male	25.1	3	0	2	3	Yes	Yes	Axial
11	51	Female	22.2	3	2b	1.5	3	No	Yes	Lateral and retroperitoneal lymph nodes
12	82	Female	21.5	1	1b	3	5	No	Yes	Axial
13	50	Male	25.6	3	1	2	4	Yes	Yes	Axial

BMI: Body mass index; nCRT: Neoadjuvant chemoradiotherapy; AT: The height of tumor from anal verge; AV: The height of anastomotic stoma from anal verge.

Table 3 Univariate and multivariate analyses through Cox regression for overall survival

	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age (>60/ ≤ 60 yr)	2.766	1.371–5.582	0.004	2.698	1.329–5.489	0.006
Sex (female/male)	0.713	0.359–1.415	0.333			
BMI (> 25/≤ 25 kg/m^2)	0.921	0.465–1.862	0.813			
CEA (> 5/≤ 5 ng/mL)	1.350	0.690–2.639	0.381			
Tumor size (> 40/≤ 40 mm)	1.425	0.742–2.733	0.287			
Tumor height from anal verge (cm)	1.499	0.767–2.931	0.236			
Lymphovascular invasion (yes/no)	1.768	0.808–3.867	0.154			
Nerve invasion (yes/no)	2.596	1.186–5.683	0.017	1.501	0.660–3.414	0.332
(y)p T stage (3/1-2)	3.362	1.541–7.336	0.002	2.293	1.006–5.226	0.048
Lymph node metastasis (yes/no)	2.304	1.218–4.357	0.010	1.713	0.878–3.339	0.114
Differentiation (poor/well-moderate)	3.117	1.472–6.600	0.003	2.234	1.021–4.887	0.044
nCRT (yes/no)	0.525	0.126–2.185	0.376			
Adjuvant therapy (yes/no)	1.176	0.622–2.224	0.617			

BMI: Body mass index; CEA: Carcinoembryonic antigen; nCRT: Neoadjuvant chemoradiotherapy.

year cumulative disease-free survival (78.5% *vs* 81.6%, $P = 0.88$) and OS (83.6% *vs* 90.8%, $P = 0.65$) rates. A meta-analysis including 2438 patients indicated that ISR could be a safe alternative to APR and could achieve oncological results similar to those of APR[14]. We considered that the oncological outcomes of ISR were related to many factors such as surgeon experience and skills, patient condition, malignancy and clinical tumor staging, as well as neoadjuvant chemoradiation. In this study, we enrolled patients operated by a single surgical team, to minimize selection bias. The long-term oncological outcomes and risk factors were analyzed. Although the oncological outcomes were not compared with those of APR, outcomes including the 5-year OS (87.0%), 5-year LRFS (95.4%), and 5-year cumulative local recurrence rate (4.6%) after LsISR in this cohort were similar to those previously reported.

Table 4 Univariate and multivariate analyses through Cox regression for local recurrence-free survival

	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age (> 60/ ≤ 60 yr)	1.318	0.442–3.931	0.620			
Sex (female/male)	0.969	0.317–2.963	0.956			
BMI (> 25/≤ 25 kg/m^2)	1.263	0.413–3.860	0.683			
CEA (> 5/≤ 5 ng/mL)	1.639	0.536–5.010	0.386			
Tumor size (> 40/≤ 40 mm)	1.8332	0.615–5.451	0.277			
Tumor height from anal verge (cm)	0.869	0.239–3.158	0.831			
Lymphovascular invasion (yes/no)	2.897	0.889–9.436	0.077	1.056	0.287–3.884	0.935
Nerve invasion (yes/no)	2.812	0.771–10.258	0.117			
(y)p T stage (3/1-2)	1.982	0.610–6.438	0.255			
Lymph node metastasis (yes/no)	6.984	1.922–25.385	0.003	5.358	1.398–20.532	0.014
Differentiation (poor/well-moderate)	6.293	2.048–19.334	0.001	3.908	1.137–13.420	0.030
nCRT (yes/no)	2.731	0.750–9.940	0.127			
Adjuvant therapy (yes/no)	2.357	0.726–7.653	0.154			

BMI: Body mass index; CEA: Carcinoembryonic antigen; nCRT: Neoadjuvant chemoradiotherapy.

Table 5 Univariate and multivariate analyses through Cox regression for distal metastasis-free survival

	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age (> 60/ ≤ 60 yr)	1.506	0.817–2.779	0.190			
Sex (female/male)	0.597	0.305–1.168	0.132			
BMI (> 25/≤ 25 kg/m^2)	0.783	0.401–1.530	0.474			
CEA (> 5/≤ 5 ng/mL)	1.577	0.846–2.940	0.152			
Tumor size (> 40/≤ 40 mm)	1.685	0.779–3.642	0.185			
Tumor height from anal verge (cm)	1.685	0.779–3.642	0.185			
Lymphovascular invasion (yes/no)	2.527	1.263–5.055	0.009	1.128	0.508–2.506	0.767
Nerve invasion (yes/no)	3.061	1.499–6.252	0.002	1.644	0.745–3.628	0.218
(y)p T stage (3/1-2)	3.912	1.810–8.456	0.001	2.741	1.225–6.137	0.014
Lymph node metastasis (yes/no)	3.410	1.829–6.358	< 0.001	2.445	1.272–4.698	0.007
Differentiation (poor/well-moderate)	2.451	1.130–5.314	0.023	1.446	0.634–3.301	0.381
nCRT (yes/no)	0.718	0.222–2.326	0.581			
Adjuvant therapy (yes/no)	1.299	0.708–2.386	0.398			

BMI: Body mass index; CEA: Carcinoembryonic antigen; nCRT: Neoadjuvant chemoradiotherapy.

Local recurrence, especially anastomotic recurrence, is one of the most important failure patterns of ISR. The 5- year cumulative local recurrence rate could still range from 2.4% to 15.7%, even in the patient with negative DRMs or CRMs in the initial surgery[6,13,15-18]. Previous studies reported that advanced T stage, lymph node metastasis, tumor size, nerve invasion, and lymphovascular invasion are risk factors for local recurrence after ISR[6-8,19,20]. Our study further confirmed that age > 60 years, (y)pT3 stage, and poor differentiation were independent prognostic factors for OS, whereas lymph node metastasis and poor differentiation were prognostic factors for LFRS. In patients with poorly differentiated tumors, submucosal infiltration or adjacent tumor nodules may occur, which would promote

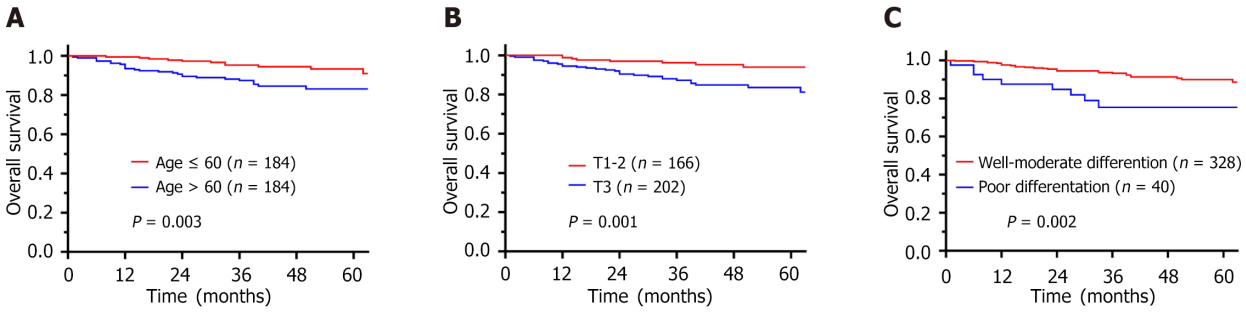

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Figure 2 Kaplan-Meier survival curves for the overall survival of patients with rectal cancer after intersphincteric resection surgery. A: Age; B: (y)pT stage; C: Differentiation.

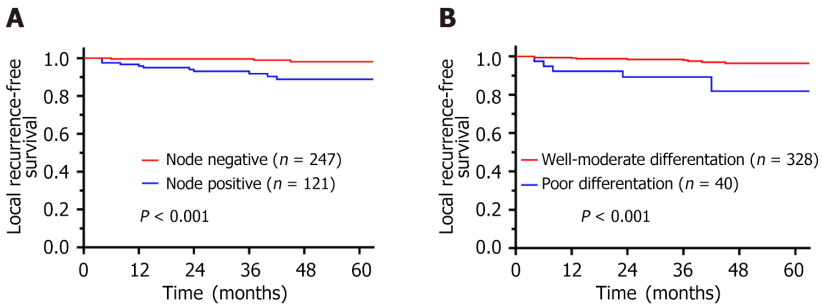

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Figure 3 Kaplan-Meier survival curves for the local recurrence-free survival of patients with rectal cancer after intersphincteric resection surgery. A: (y)pN (3a); B: Differentiation level (3b).

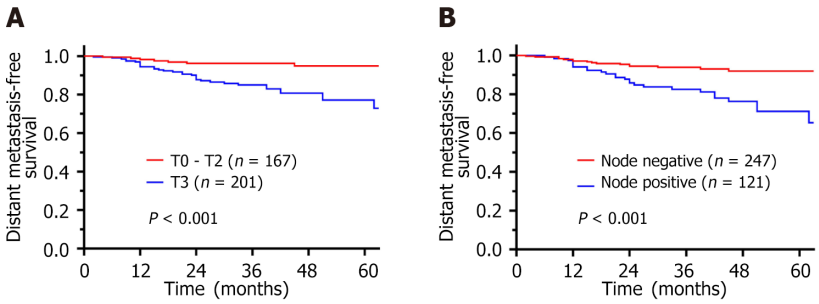

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Figure 4 Kaplan-Meier survival curves for the distant metastasis-free survival of patients with rectal cancer after intersphincteric resection surgery. A: (y)pT (4a); B: (y)pN (4b).

local recurrence of the anastomosis, despite a negative DRM. In patients with positive mesenteric lymph nodes, postoperative lateral lymph node metastasis may occur as another manifestation of pelvic recurrence. All four patients with lateral lymph node metastasis in this study had stage III disease. Prognostic factors for DMFS were further explored, showing that (y)pT3 stage and lymph node metastasis were independent prognostic factors, which were similar to previously reported factors.

The exploration of perioperative strategies aimed at reducing the risk of recurrence and metastasis of rectal cancer has been a hot topic. Preoperative nCRT followed by proctectomy with TME is commonly accepted as the gold standard for treating locally advanced rectal cancer with strong evidence of decreasing local recurrence rate and improving disease-free survival[21-25]; moreover, total neoadjuvant therapy (TNT) may potentially improve local control. However, T-downstaging did not decrease the local recurrence rate in a previous study[26], and data from the RAPIDO trial showed an increased local recurrence rate for patients undergoing TNT, despite having a higher pathologic complete remission rate[27]. In our study, 3 patients with local recurrence were treated with neoadjuvant therapy before surgery, and the recurrence rate of the patients receiving nCRT was higher than that of patients not receiving nCRT (7.5% *vs* 2.7%, $P = 0.324$), although the difference was not significant. The indications for ISR in this study were relatively broad, and eight cases (9.1%) with pT3N

+ locally advanced rectal cancers were finally proven to be locally recurrent. Whether the rule of a 1-cm DRM following nCRT could increase the risk of anastomotic recurrence remains controversial. For patients with a high risk of local recurrence (N + or poor differentiation), extended radical resection (such as APR instead of ISR) may be more effective.

This study had some limitations. First, although only patients operated by a single surgical team were enrolled in this study, selection bias was inevitable due to the retrospective nature of the study. Second, the median follow-up time was relatively short, and the 5-year survival may not reflect the actual results. Furthermore, the proportion of patients who underwent nCRT was relatively small. The effect of nCRT on LRFS and DMFS after ISR remains unelucidated, and a larger cohort with more patients receiving nCRT is needed in future studies. Nonetheless, this study had the largest sample size and a relatively good control of surgical quality; hence, the results can objectively reflect tumor characteristics on the failure patterns of ISR.

CONCLUSION

In conclusion, this study confirmed the oncological safety of LsISR for ultralow rectal cancers. Poor differentiation, (y)pT3 stage, and lymph node metastasis are independent risk factors for treatment failure, and thus patients with these factors should be carefully managed with optimal neoadjuvant therapy, and for patients with a high risk of local recurrence (N + or poor differentiation), extended radical resection (such as APR instead of ISR) may be more effective.

ARTICLE HIGHLIGHTS

Research background

The failure patterns and risk factors for local recurrence and distant metastasis after laparoscopic intersphincteric resection (LsISR) surgery remain controversial and require further investigation.

Research motivation

To investigate the long-term outcomes and failure patterns after LsISR.

Research objectives

Patients with ultralow rectal cancer who underwent LsISR from multicenter between January 2012 and October 2022. We included patients who underwent LsISR surgery.

Research methods

The Chi-square, Fisher's exact test, or Pearson's correlation test was used to analyze differences between the primary and validation cohorts. Variables with a P-value < 0.100 in the univariate analyses were included in the multivariate analyses. Hazard ratios and 95% confidence intervals of the risk factors were analyzed using multivariate logistic regression.

Research results

Local recurrence and distant metastasis occurred in 3.5% and 11.4% of patients, respectively. The overall survival/local recurrence-free survival/distance metastasis-free survival rates at 1, 3, and 5 years were 96.5%/91.3%/87.0%, 98.4%/97.1%/95.4%, and 96.1%/90.1%/82.6%, respectively. LRFS was associated with (y)N + and poor differentiation, whereas the independent prognostic factors for DMFS were lymph node metastasis and (y)pT3 stage.

Research conclusions

We confirmed that poor differentiation, (y)pT3 stage, and (y)Pn + were independent risk factors for treatment failure, and thus patients with these factors should be carefully managed with optimal neoadjuvant therapy and surgical strategies.

Research perspectives

This research will help clarify the high recurrence risk patients and take up most appropriate perioperative treatment strategies.

FOOTNOTES

Author contributions: Qiu WL, Liu JG and Wang XL contributed equally to this work; Protocol/project development:

Qiu WL, Tang JQ; Data collection or management: Qiu QL, Hu G, Mei SW, Liu JG, Wang XL. Data analysis: Qiu WL, Wang XL, Liu JG; Manuscript writing/editing: Qiu WL, Wang XL; All authors reviewed the manuscript.

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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.

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Retrospective Study

Predictors for success of non-operative management of adhesive small bowel obstruction

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Abstract

BACKGROUND

Majority of adhesive small bowel obstruction (SBO) cases can be managed non-operatively. However, a proportion of patients failed non-operative management.

AIM

To evaluate the predictors of successful non-operative management in adhesive SBO.

METHODS

A retrospective study was performed for all consecutive cases of adhesive SBO from November 2015 to May 2018. Data collated included basic demographics, clinical presentation, biochemistry and imaging results and management outcomes. The imaging studies were independently analyzed by a radiologist who was blinded to the clinical outcomes. The patients were divided into group A operative (including those that failed initial non-operative management) and group B non-operative for analysis.

RESULTS

Of 252 patients were included in the final analysis; group A (n = 90) (35.7%) and group B (n = 162) (64.3%). There were no differences in the clinical features between both groups. Laboratory tests of inflammatory markers and lactate levels were similar in both groups. From the imaging findings, the presence of a definitive transition point [odds ratio (OR) = 2.67, 95% confidence interval (CI): 0.98-7.32, P = 0.048], presence of free fluid (OR = 2.11, 95%CI: 1.15-3.89, P = 0.015)

and absence of small bowel faecal signs (OR = 1.70, 95%CI: 1.01-2.88, P = 0.047) were predictive of the need of surgical intervention. In patients that received water soluble contrast medium, the evidence of contrast in colon was 3.83 times predictive of successful non-operative management (95%CI: 1.79-8.21, P = 0.001).

CONCLUSION
The computed tomography findings can assist clinicians in deciding early surgical intervention in adhesive SBO cases that are unlikely to be successful with non-operative management to prevent associated morbidity and mortality.

Key Words: Small bowel obstruction; Adhesive; Conservative; Non-operative

Core Tip: Adhesive small bowel obstruction (SBO) is a common acute surgical presentation. Majority of the cases can be managed successfully with non-operative management. The findings on computed tomography abdomen/pelvis are useful in predicting patients that are unlikely to resolve with conservative management for adhesive SBO and therefore guide decision-making in early surgical intervention to prevent morbidities associated with it.

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INTRODUCTION

Small bowel obstruction (SBO) is one of the most common presentations in acute care surgery, accounting to 15% of cases[1]. Majority of cases are secondary to either adhesions from previous surgeries or incarcerated hernia. There has been a paradigm shift from exploratory laparotomy to non-operative management in patients presenting with adhesive SBO with reasonable success over the past decade[2]. Nevertheless, a small proportion of patient may fail non-operative management. The challenge then lies in early identification of this subset of patients that are unlikely to resolve to prevent development of ischaemic small bowel that carries a significant morbidity[3,4].

A few studies have attempted to investigate the various predictive factors for failures of non-operative management in adhesive SBO including clinical, laboratory tests and imaging findings with mixed sensitivities and specificities[5]. It can be attributed to the subjective clinical findings including components of the history and examination findings and maybe affected by the level of experience of the clinician. The aim of this study was to evaluate the predictors for successful non-operative management of adhesive SBO.

MATERIALS AND METHODS

Ethical approval was obtained from the St John of God Healthcare's ethics committee (Ref: 1358). A retrospective review of all consecutive cases of SBO admitted to St John of God Midland Hospital from November 2015 to May 2018 was performed. The St John of God Midland Hospital is a secondary hospital in Western Australia, staffed with an onsite General Surgery registrar with a dedicated on-call consultant surgeon with 24-h access to anaesthetic care and emergency theatre. Radiological services such as X-ray and computed tomography (CT) scans are available 24 h. The CT scans are reported by a consultant radiologist.

Data collected included basic demographics, co-morbidities, previous history of abdominal surgery, history of presentation (nausea, vomiting, abdominal pain, obstipation, flatus), vitals on presentation (heart rate, blood pressure, respiratory rate, oxygen saturation and temperature), biochemistry tests [white cell count, c-reactive protein (CRP), urea, creatinine and lactate], imaging findings [abdominal X-ray (AXR) and CT] management outcomes (non-operative *vs* surgical intervention) and length of stay.

The inclusion criteria were patients ≥ 16 years of age and SBO secondary to adhesions. Exclusion criteria included: Patients younger than 16 years old, SBO in virgin abdomen, immediate post-operation, secondary to other causes such as stricture, incarceration, inflammatory bowel disease,

volvulus, foreign body, bezoar, small bowel malignancy, peritoneal malignancy, secondary to large bowel obstruction, ileus and patients without a CT scan for analysis.

The patients were divided into two groups for comparison and analysis; group A: Operative (including patients that underwent immediate surgery and patients failed initial non-operative management and underwent surgical intervention) and group B: Non-operative. Non-operative management included nil by mouth, nasogastric tube insertion for decompression of stomach, intravenous fluid resuscitation and/or administration of water-soluble contrast. The nasogastric tube was left to decompress the stomach for four hours prior to administration of water-soluble contrast (Gastrografin - mixture of nonabsorbable sodium diatrizoate and meglumine diatrizoate 100 mL undiluted). The nasogastric tube was clamped for two hours and an AXR was performed at six hours post-administration. If the contrast was not seen in the large bowel at 6-h and patient remains clinically well, a repeat AXR was performed the following day. If there was presence of contrast in the large bowel on AXR, the patients were allowed to have clear liquids and diet was upgraded in a stepwise approach. If there was no contrast in the large bowel (including the repeat AXR), surgical intervention was performed. For patients that underwent immediate surgical intervention on presentation, it was at the discretion of the on-call consultant surgeon.

The standard CT scans were performed with 64-slice and protocoled with intravenous iodinated contrast and taken at the portal venous phase. The only exceptions were allergy to iodine contrast or evidence of acute or chronic renal failure. The CT scans of the abdomen and pelvis performed on presentation were reviewed by an experienced radiologist (William Tee) who was blinded to the clinical history and management outcomes. The CTs were reviewed for: Presence of SBO, the cause of the SBO, small bowel faecal sign, presence of definitive transition point, grade of obstruction, presence of free fluid, distribution of free fluid, presence of mesenteric fat stranding and presence of small bowel thickening/abnormal enhancement. The AXRs were also reviewed for the presence to contrast in the colon (Figure 1A).

The definitions used for the CT findings were as follows: (1) Presence of SBO: Dilatation of small bowel; (2) Adhesive SBO: No other causes of SBO such as incarceration in a hernia, volvulus, foreign body, stricture, inflammatory bowel disease, primary small bowel malignancy, secondary to large bowel obstruction or ileus are found; (3) Definitive transition point (Figure 1B): There is a traceable dilated small bowel loop to another area of collapsed small bowel loop; (4) Grade of obstruction: The largest diameter of the small bowel loop is measured; (5) Presence of mesenteric stranding (Figure 1C): Distinct hazy/wavy stranding at the mesentery; (6) Small bowel thickening/abnormal enhancement (Figure 1C): Near concentric circumferential thickening and/or distinct lower attenuation of the thickened wall; (7) Presence of free fluid: Categorized into nil, trace, small and large; (8) Trace: Barely there only a sliver of fluid; Usually only perceptible by a radiologist; (9) Small: Visually there and easy to be perceived by a non-radiologist clinician; (10) Large: Unequivocal large volume; a striking feature of the scan easily spotted by a non-radiologist clinician; and (11) Distribution of free fluid: Categorized into pelvis, paracolic gutters, peri-small bowel/mesentery/central.

Statistical analysis

SPSS version 16 was used for analysis of the data. Demographics, clinical presentation, imaging variable were compared between two groups using chi square and *t* test depending on if the variable is categorical or numerical. *P* value less than 0.05 is regarded as statistical significance. The categorical data were presented as frequency and percentage and numerical data were presented with mean and standard deviation. Odds ratio was calculated for categorical variable.

RESULTS

Basic demographics

Of 426 patients presented with SBO during the study period. 252 adhesive SBO patients were included in the final analysis (Table 1). Of 252 patients, 90 (male:female = 33:57) were in group A (including 20 patients that underwent immediate surgery) and 162 (male:female = 62:100) were in group B. There was no difference in the mean age in both groups (68.89 years *vs* 68.13 years, $P = 0.72$). There was no difference in patients with comorbidities in both groups (36.2% *vs* 63.8%, $P = 0.57$). Both group of patients had similar average number of previous abdominal surgery (1.92 *vs* 2.12, $P = 0.28$).

Clinical presentation and laboratory tests

There were no differences in the presence of nausea (group A *vs* B: 35.7% *vs* 64.3%, $P = 0.76$) and vomiting (34.2% *vs* 65.8%, $P = 0.42$) in both groups. The symptoms of abdominal pain (35.3% *vs* 64.7%, $P = 0.63$) and abdominal distention (37.0% *vs* 63.0%, $P = 0.22$) were also similar in both groups. The presence of flatus (38.5% *vs* 61.5%, $P = 0.56$) or the absence of obstipation (31.9% *vs* 68.1%, $P = 0.24$) did not differ in both groups (Table 2).

Table 1 Basic demographics in both groups, *n* (%)

	Group A (*n* = 90)	Group B (*n* = 162)	*P* value
Gender			
Female	57 (36.3)	100 (63.7)	
Male	33 (34.7)	62 (65.3)	0.80
Comorbidities	85 (36.2)	150 (63.8)	
No comorbidities	5 (29.4)	12 (70.6)	0.57
No of previous abdominal surgery (mean ± SD)	1.92 ± 1.18	2.12 ± 1.44	0.28
Age (yr), mean ± SD	68.89 ± 17.37	68.13 ± 15.56	0.72

Table 2 Symptoms on presentation in both groups, *n* (%)

	Group A (*n* = 90)	Group B (*n* = 162)	*P* value
Nausea	56 (35.7)	101 (64.3)	
No nausea	9 (37.5)	15 (62.5)	0.76
Vomiting	63 (34.2)	121 (65.8)	
No vomiting	27 (39.7)	41 (60.3)	0.42
Abdominal pain	83 (35.3)	152 (64.7)	
No pain	7 (41.2)	10 (58.8)	0.63
Abdominal distension	37 (37.0)	63 (63.0)	
No distension	50 (33.8)	98 (66.2)	0.22
Flatus	37 (38.5)	59 (61.5)	
No flatus	53 (34.0)	103 (66.0)	0.56
No obstipation	37 (31.9)	79 (68.1)	
Obstipation	53 (39.0)	83 (61.0)	0.24

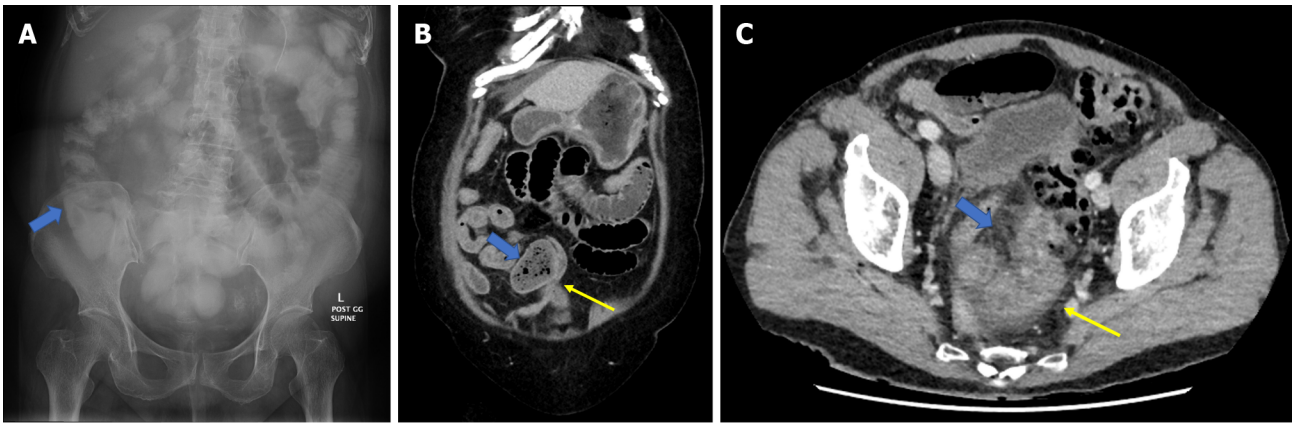

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Figure 1 Images. A: Abdominal X-ray showing the presence of water soluble contrast medium in the large colon; B: Coronal slice of the computed tomography (CT) scan showing small bowel faecal sign (blue arrow) and transition point (yellow arrow) in adhesive small bowel obstruction; C: Axial slice of CT scan showing a segment of small bowel thickening/reduced wall enhancement (yellow arrow) with mesenteric stranding (blue arrow) in the presence of small bowel obstruction.

The physiological parameters on arrival were similar in both groups (Table 3): Heart rate (81.20 beats/min *vs* 82.89 beats/min, $P = 0.474$), systolic blood pressure (142.51 mm/Hg *vs* 146.79 mm/Hg, $P = 0.285$), diastolic blood pressure (69.65 mm/Hg *vs* 69.67 mm/Hg, $P = 0.994$) and respiratory rate (20.15/min *vs* 19.50/min, $P = 0.559$).

Table 3 Physiological and laboratory parameters on arrival in both groups

	Group A (mean ± SD)	Group B (mean ± SD)	*P* value
Heart rate (beat/min)	81.20 ± 15.67	82.89 ± 16.74	0.474
Systolic blood pressure (mmHg)	142.51 ± 26.97	146.79 ± 28.09	0.285
Diastolic blood pressure (mmHg)	69.65 ± 22.08	69.67 ± 20.17	0.994
Respiratory rate (/min)	20.15 ± 10.29	19.50 ± 3.68	0.559
Temperature (°C)	36.56 ± 0.77	36.52 ± 0.72	0.697
White cell count ($\times 10^9$/L)	12.27 ± 3.86	11.89 ± 3.96	0.495
C-reactive protein (mg/L)	24.96 ± 60.88	21.81 ± 45.25	0.691
Urea (mmol/L)	8.77 ± 6.81	9.40 ± 6.59	0.606
Creatinine (umol/L)	103.75 ± 55.35	110.00 ± 131.23	0.660
Lactate (mmol/L)	2.110 ± 0.97	1.942 ± 1.23	0.522

Both the inflammatory markers did not differ in both groups on presentation: White cell count (group A *vs* B: 12.27 × 10^9/L *vs* 11.89 × 10^9/L, P = 0.495) and CRP (24.96 mg/L *vs* 21.81 mg/L, P = 0.691). Urea (8.77 mmol/L *vs* 9.40 mmol/L, P = 0.606) and creatinine (103.75 μmol/L *vs* 110.00 μmol/L, P = 0.660) levels were also similar in both groups. The lactate level was not significantly different (2.110 mmol/L *vs* 1.942 mmol/L, P = 0.522).

Imaging results

From the review of CT scan (Table 4), the findings of a definitive transition point [odds ratio (OR) = 2.67, 95% confidence interval (CI): 0.98-7.32, P = 0.048], presence of free fluid (OR = 2.11, 95%CI: 1.15-3.89, P = 0.015) and absence of small bowel faecal signs (OR = 1.70, 95%CI: 1.01-2.88, P = 0.047) were predictive of the need of surgical intervention. The presence of mesenteric stranding (OR = 1.69, 95%CI: 0.97-2.94, P = 0.061) showed a trend towards prediction of the need of surgical intervention but was not statistically significant. The small bowel thickening/abnormal enhancement (OR = 1.76, 95%CI: 0.77-4.08, P = 0.177) and the grade of obstruction did not predict the need for surgical intervention (36.87 mm *vs* 37.35 mm, P = 0.601).

Outcomes

In patients that received water soluble contrast medium, the evidence of contrast reaching the colon was 3.83 times more successful in non-operative management of adhesive SBO (95%CI: 1.79-8.21, P = 0.001). Length of stay was significantly shorted in group A (4.43 d) that B (6.81 d) (P = 0.002).

DISCUSSION

Adhesive SBO remains a common acute surgical presentation. There has been mixed evidence from systematic review and meta-analysis regarding the outcomes of operative *vs* non-operative management of adhesive SBO due to the heterogeneity of comparison groups[6,7]. Early recognition with appropriate management is key to prevent delay access to theatre in patients that are unlikely to resolve with non-operative management[4]. This study confirms the value of the CT findings in predicting patients that are unlikely to resolve with non-operative management for adhesive SBO.

Some of the studies have proposed models based on clinical and radiological findings to accurately predict the need of surgical intervention in adhesive SBO[8-11]. It is yet to be adopted in routine clinical practice. It is not surprising that the clinical features did not differ between both groups in this study as often these are subjective to the interpretation of the clinicians. In two studies[9,10], absence of flatus has a sensitivity that ranged from 19%-37% and specificity from 94%-95% and positive predictive value 56%-86%. Often, during the early stages of the SBO, these symptoms may mirror other conditions. Schwenter *et al*[12] reported six independent risk factors (pain duration > 4 d, guarding, leucocytosis > 10, CRP > 75 and CT findings) to be useful in predicting strangulation/ischemia of small bowel. Based on the six risk factors, a score of 3 had 90.8% specificity and 67.7% sensitivity for bowel resection and a score of 4 or more was 100% predictive. In real clinical practice, the duration of symptoms is often inaccurate to guide decision making. The inflammatory markers were similar in our study as it could be secondary to other causes and time dependent. One of the CT findings reported in this study of free fluid > 500mL can be largely subjective. In our study, interestingly, the presence of a definitive transition point was a predictor of successful non-operative management of adhesive SBO. This finding is not routinely reported as a predictor in the literature. It is usually a sign used to determine and

Table 4 The findings of computed tomography scan on presentation and abdominal X-ray following administration of water-soluble contrast medium in both groups, *n* (%)

	Group A (*n* = 90)	Group B (*n* = 162)	OR (95%CI)	*P* value
Definitive transition point	85 (94.4)	140 (86.4)	2.67 (0.975-7.318)	0.048
No transition point	5 (5.6)	22 (13.6)		
Mesenteric stranding	64 (71.1)	96 (59.3)	1.69 (0.973-2.942)	0.061
No mesenteric stranding	26 (28.9)	66 (40.7)		
Small bowel thickening	12 (13.3)	13 (8.0)	1.76 (0.768-4.084)	0.177
No small bowel thickening	78 (86.7)	149 (92)		
Water-soluble contrast medium	42 (46.7)	98 (60.5)	0.55 (0.323-0.936)	0.024
Did not receive water-soluble contrast medium	47 (53.3)	60 (39.5)		
Presence of free fluid	72 (80)	106 (65.4)	2.11 (1.149-3.888)	0.015
No free fluid	18 (20)	56 (34.6)		
No small bowel faecal sign	42 (46.7)	55 (34.0)	1.70 (1.005-2.882)	0.047
Small bowel faecal sign present	48 (53.3)	107 (66.0)		
Contrast reaches small bowel only	23 (25.6)	34 (21.0)	3.83 (1.790- 8.209)[1]	0.001
Contrast reach large bowel	19 (74.4)	76 (79.0)		
Grade of obstruction (proximal small bowel diameter in mm), mean ± SD	36.87 ± 7.53	37.35 ± 6.77		0.601

[1]Only patient done repeated abdominal X-ray.
OR: Odds ratio; CI: Confidence interval.

confirm the presence of SBO. In our study, it could be explained that more cases were detected to have transition point on this independent review by the radiologist than first reported. The presence of free fluid and absence of small bowel faecal sign are a predictor of the need of surgical intervention which is concordant with the studies in the literature[5,8-10].

The presence of other two CT findings of mesenteric stranding and small bowel thickening did not achieve statistical significance which could be explained by the duration of symptoms/presentation as it is often a late sign that arose as a result of small bowel ischemia and venous congestion and often subjected to interobserver variability in interpretation. In another study, distal (ileal) obstruction, maximum small bowel diameter over abdominal diameter ratio were associated with failure of non-operative management[13].

The administration of water-soluble contrast medium in adhesive SBO has both diagnostic and therapeutic benefits[14]. Its mechanism of action is postulated to be driven by the gradient that reduces the oedema *via* drawing of water from the bowel wall to the intraluminal space which leads to improve blood flow and enhances smooth muscle contractility. There remains no standardized protocol for the volume of water-soluble contrast medium, timing to administration, time for follow-up AXR and duration following AXR to surgery in cases that failed to progress[14,15]. The Bologna guidelines in 2017 suggested that if the water-soluble contrast medium fails to reach the colon within 24 h, they should be explored surgically[2]. A Cochrane review and a meta-analysis by Koh *et al*[16] showed that it did not reduce the surgery rates. Its role in the setting of adhesive SBO should be interpreted as an effective predictor for the need of operative intervention. There is a small proportion of patients that will still require surgical intervention despite having water-soluble contrast medium within the colon due to incomplete resolution following introduction of oral intake. Most often, the patients will have recurrence of the initial symptoms and a repeat AXR showing persistent dilated small bowel loops. In this setting, the clinician has the option of persisting with non-operative management or for consideration of operative intervention based on the patient's clinical condition. There are no formal guidelines to dictate this scenario.

The combined CT findings and utility of water-soluble contrast medium from this study can assist clinician in early decision making of surgical intervention. There is some evidence which suggest that early laparoscopic surgical adhesiolysis reduces the recurrent SBO rates. This trend was observed in a 10-year population-based analysis from Canada between 2005-2014 which saw an increase in early intervention and use of laparoscopic approach[17]. This could be considered in expert hands who are competent in laparoscopic approach. O'connor and Winter[18] showed that the success rate of laparoscopy was 73.4% if it is secondary to a single-band adhesion. This could be difficult to determine

as shown in the LASSO randomized trial which did not show any significant difference between laparoscopic *vs* open adhesiolysis in morbidity and mortality[19]. Consideration should be given for the likelihood of resolution with non-operative management as the reported recurrence rate has been up to 16%-53% and the expertise available in laparoscopy[20]. In the review by O'connor and Winter[18], there was 29% of conversion to laparotomy due to dense adhesions, bowel resection, unidentified pathology and iatrogenic injury. The enterotomy rate was 6.6% in this study; if unrecognized could have serious implications. With the CT findings and use of water-soluble contrast medium, it will allow frank discussion with frail and co-morbid patients to set the ceiling of care in the event of failure of non-operative management and/or worsening of condition as the one-year mortality following emergency laparotomy remains alarming at 30% despite improvement at early outcomes[21].

The strength of this study was the imaging findings were reviewed by an independent experienced radiologist who was not involved in the initial reporting of the CT or AXR results and was blinded from the clinical indications and outcomes. This study was limited by the retrospective nature where there was an inherent bias in patients that underwent immediate surgical intervention on presentation which was at the discretion of the attending surgeon. This may have led to certain CT findings such as mesenteric stranding and small bowel thickening to be not statistically significant despite being potentially indicative of ischemia[11]. The interpretation of the data on clinical presentation may be subjective as the duration of individual symptoms may not be known and are only recorded as either present or absent. Nevertheless, the findings of this study are not to replace clinical acumen but to assist the clinicians in early decision making in patients that fail to show signs of clinical progress.

CONCLUSION

Majority of adhesive SBO can be managed successfully with non-operative intervention with water-soluble contrast medium as a very effective early predictor. The CT scan features identified in this study are easily detectable and should encourage close monitoring, early planning for surgical intervention if failing non-operative approach to prevent development of bowel ischemia necessitating bowel resection.

ARTICLE HIGHLIGHTS

Research background

Adhesive small bowel obstruction (SBO) is a common presentation in acute care surgery. Majority of cases are managed with non-operative approach successfully. Nevertheless, there is a small proportion of patients will fail non-operative management and require surgical intervention.

Research motivation

The delay surgical intervention in patients that fail non-operative management in adhesive SBO may result in small bowel ischemia requiring resection. This may lead to further morbidity and mortality.

Research objectives

The aim of this study was to identify predictors from clinical presentation, laboratory tests and imaging results that may help identify cases of adhesive SBO that are unlikely to resolve with non-operative management.

Research methods

A retrospective analysis of all cases of SBO in our institute were undertaken. The cases of SBO secondary to causes such as incarceration, tumour, volvulus, inflammatory bowel disease *etc* were excluded. The computed tomography (CT) scans were independently reviewed by a consultant radiologist who was blinded to the outcomes for specific signs that may determine the success of non-operative management of adhesive SBO.

Research results

Clinical presentation and laboratory results were not predictive of the success of non-operative management of SBO. Only the CT findings of a definitive transition point, presence of free fluid and absence of small bowel faecal sign were predictive of the need of surgical intervention in adhesive SBO.

Research conclusions

The CT findings can assist clinicians in deciding early surgical intervention in adhesive SBO cases that are unlikely to be successful with non-operative management to prevent associated morbidity and mortality.

Research perspectives

Future studies should focus on universal definitions of the CT findings and outcomes to allow accurate comparison of the efficacy of the therapeutic options.

FOOTNOTES

Author contributions: Ng ZQ contributed to the data analysis and drafting of manuscript; Hsu V collected the data; Tee WWH collected the radiological data collection, review of manuscript; Tan JH contributed to the statistical data analysis; Hsu V, Tee WWH, and Tan JH involved in the review of the manuscript; Ng ZQ and Wijesuriya R designed the study; Wijesuriya R contributed to critical review of manuscript and supervision of study; and all authors approved the final version of this manuscript for submission and publication.

Institutional review board statement: Ethical approval was obtained from the St John of God Healthcare's ethics committee (Ref: 1358).

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ORIGINAL ARTICLE

Retrospective Study

Preoperative albumin-bilirubin score is a prognostic factor for gastric cancer patients after curative gastrectomy

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Abstract

BACKGROUND

Albumin-bilirubin (ALBI) score is an indicator of liver dysfunction and is useful for predicting prognosis of hepatocellular carcinomas. Currently, this liver function index has been used to predict prognosis in other neoplasms. However, the significance of ALBI score in gastric cancer (GC) after radical resection has not been elucidated.

AIM

To evaluate the prognostic value of the preoperative ALBI status in patients with GC who received curative treatment.

METHODS

Patients with GC who underwent curative intended gastrectomy were retrospectively evaluated from our prospective database. ALBI score was calculated as follows: (log10 bilirubin × 0.660) + (albumin × -0.085). The receiver operating characteristic curve with area under the curve (AUC) was plotted to evaluate the ability of ALBI score in predicting recurrence or death. The optimal cutoff value was determined by maximizing Youden's index, and patients were divided into low and high-ALBI groups. The Kaplan-Meier curve was used to analyze the survival, and the log-rank test was used for comparison between groups.

RESULTS

A total of 361 patients (235 males) were enrolled. The median ALBI value for the entire cohort was -2.89 (IQR -3.13; -2.59). The AUC for ALBI score was 0.617 (95%CI: 0.556-0.673, $P < 0.001$), and the cutoff value was -2.82. Accordingly, 211

(58.4%) patients were classified as low-ALBI group and 150 (41.6%) as high-ALBI group. Older age (P = 0.005), lower hemoglobin level (P < 0.001), American Society of Anesthesiologists classification III/IV (P = 0.001), and D1 lymphadenectomy P = 0.003) were more frequent in the high-ALBI group. There was no difference between both groups in terms of Lauren histological type, depth of tumor invasion (pT), presence of lymph node metastasis (pN), and pathologic (pTNM) stage. Major postoperative complication, and mortality at 30 and 90 days were higher in the high-ALBI patients. In the survival analysis, the high-ALBI group had worse disease-free survival (DFS) and overall survival (OS) compared to those with low-ALBI (P < 0.001). When stratified by pTNM, the difference between ALBI groups was maintained in stage I/II and stage III CG for DFS (P < 0.001 and P = 0.021, respectively); and for OS (P < 0.001 and P = 0.063, respectively). In multivariate analysis, total gastrectomy, advanced pT stage, presence of lymph node metastasis and high-ALBI were independent factors associated with worse survival.

CONCLUSION

The preoperative ALBI score is able to predict the outcomes of patients with GC, where high-ALBI patients have worse prognosis. Also, ALBI score allows risk stratification of patients within the same pTNM stages, and represents an independent risk factor associated with survival.

Key Words: Stomach neoplasms; Adenocarcinoma; Albumin-bilirubin; Biomarker; Prognosis; Survival

Core Tip: The present study evaluates the clinical impact of the preoperative albumin-bilirubin (ALBI) score in patients with gastric cancer who received curative treatment. We found that ALBI score is able to predict short-term and long-term outcomes of patients, and can be applied as a prognostic factor for gastric cancer. The ALBI is a simple and reproducible parameter that allows the risk stratification of patients within the pathologic stage stages, and may be an additional useful tool for decision-making regarding treatment and follow-up individualization.

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INTRODUCTION

Gastric cancer (GC) is a solid gastrointestinal tumor with elevated incidence and mortality, represented by more than 1 million diagnosed cases and 768000 deaths reported worldwide in 2020[1]. Currently, staging is based only on TNM classification, which plays a crucial role in predicting the prognosis. However, it is well known that patients with same stage disease can have different outcomes[2], which indicate that additional parameters can play a role in staging and prognosis.

Thus, the search for alternative parameters that, integrated into staging systems, can provide further information about the prognosis are a constant target of investigation. Due to its potential to allow risk stratification and tailor individual treatment and follow-up, some of the research on additional prognostic variables has focused on inflammatory and nutritional-based biomarkers, based on the fact that tumor development is a complex process dictated by a series of intercellular and its sub product interactions[3]. Over the past years, many articles have been published demonstrating the correlation of inflammatory biomarkers, such as neutrophil-lymphocyte and platelet lymphocyte ratio, with prognosis of patients with GC[4]. The main advantages of these methods are the low cost, the need for simple tests such as a complete blood count, and the reproducibility between different centers.

It is also known that nutritional characteristics and liver function, represented by serum albumin and bilirubin, can interfere with prognosis and cancer survival. The decreased albumin level, which is produced in the liver, could be a sign of malnutrition or liver synthesis dysfunction. In turn, increased serum bilirubin levels usually suggests liver dysfunction[5]. Therefore, the albumin-bilirubin score (ALBI) was created to evaluate both levels together and estimate the extent of liver dysfunction[6,7]. It was first described by Johnson *et al*[6], where were evaluated patients with hepatocarcinoma (HCC) in a way to overcome the limitation of Child-Pugh grade on assessing hepatic function[7]. ALBI was initially developed to assess HCC, and represents a prognostic factor in these patients, irrespective of the degree

of underlying liver fibrosis[8].

However, it has also been extensively investigated in patients who do not have HCC, and some studies demonstrated that ALBI score represents a prognostic factor even in patients without HCC, including patients with non-small cell lung carcinoma, pancreatic, colon, and esophageal cancer[9-12].

Despite the interest in ALBI score, few studies have considered its role in patients with GC. Kanda *et al*[13] were the first to recognize ALBI grade as a predictor of survival after radical gastrectomy. Furthermore, ALBI was also identified as a predictor of postoperative complications (POC) after gastrectomy for GC[14]. However, the clinical impact of the preoperative ALBI score in patients with GC who received curative treatment remains unclear.

Thus, the aim of this study was to investigate the prognostic value of the ALBI score in in patients with GC, and its clinical applicability for risk stratification. We also evaluated the clinicopathological characteristics associated with ALBI score groups.

MATERIALS AND METHODS

Patients and study design

This is a retrospective cohort. All GC treated with curative intent gastrectomy at our Hospital between 2009 and 2021 were evaluated from a prospectively maintained database. Only histologically proven gastric adenocarcinoma and patients who underwent gastrectomy with lymphadenectomy were considered eligible. Emergency gastrectomy or patients who had underlying chronic liver disease were excluded. The study was approved by the ethics committee of the hospital.

Preoperative evaluation and ALBI score

Preoperative staging consisted of upper gastrointestinal endoscopy with biopsy, chest, abdominal and pelvic computed tomography scans, and laboratory tests. The clinical characteristics evaluated included the American Society of Anesthesiologists (ASA) classification and the Charlson-Deyo Comorbidity Index (CCI)[15]. CCI was considered without including age and GC as comorbidity. The neutrophil-lymphocyte ratio was evaluated by the division between serum neutrophil and lymphocytes.

Peripheral blood was obtained after diagnosis and within 1 mo before surgery, at the time the patient had no sign of infection and was not under systemic chemotherapy. The ALBI score was calculated by the formula (log10 bilirubin × 0.660) + (albumin × -0.085), where bilirubin was expressed in μmol/L and albumin in g/L.

Surgery and postoperative

The extent of gastrectomy and lymph node dissection were performed in accordance with Japanese Gastric Cancer Association recommendations[16]. Tumor stage was determined based on the TNM/UICC (8th edition)[17]. Clavien-Dindo's classification was applied to grade POC, when Clavien III-IV was considered as major POC[18].

Follow-up was performed every 3 mo in the first year and every 6 mo after this period, with clinical evaluation. Studies to detect relapse were performed based on the presence of symptoms.

Statistical analysis

Descriptive statistics included frequencies with percent for nominal variables, and mean (with standard deviation, SD) or median (with interquartile range, IQR) for continuous variables. Comparison of clinicopathological characteristics was performed using chi-square tests for categorical variables and *t* test or Mann-Whitney *U* test for continuous variables. The receiver operating characteristic (ROC) curves with area under the ROC curve (AUC) were used to evaluate the ability of ALBI in predicting disease-free survival (DFS) (recurrence/death). The optimal cutoff value was determined by maximizing Youden's index (sensitivity + specificity - 1). Patients were divided into "low-ALBI" and "High-ALBI" groups based on the cutoff value.

Overall survival (OS) and DFS were estimated using the Kaplan-Meier method, and the comparison of curves was obtained through the log-rank test. Multivariate Cox proportional hazard analysis was performed to determine independent risk factors for survival. Only variables that were significant on univariate analysis ($P < 0.05$) were included as co-variable in the multivariate model. Survival time was calculated from the date of diagnosis until the date of death or recurrence for DFS, and until death for OS. The patients alive were censored at the date of the last contact. A P value of < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software, version 20.0 (SPSS Inc, Chicago, IL, United States).

RESULTS

A total of 565 GC patients underwent curative intent gastrectomy in the referenced period. After

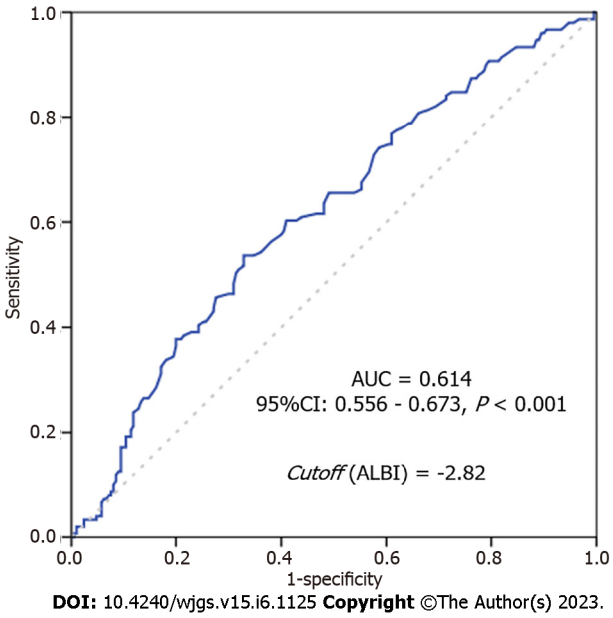

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Figure 1 Receiver operating characteristic for the diagnostic accuracy of albumin-bilirubin score, and the optimal cutoff value. The area under the receiver operating characteristic curve was 0.614. 95%CI: 95% confidence interval; AUC: Area under the curve; ALBI: Albumin-bilirubin.

excluding those with a lack of laboratory tests within one month before surgery, 361 patients met the inclusion criteria and were enrolled in the study. The mean age was 63.5 years-old (± 12.1), and the majority of patients were male (65%).

The mean value of albumin and bilirubin of all cases was 3.9 g/L (SD: 0.6; median of 4, IQR: 3.70-4.30) and 0.43 μmol/L (SD: 0.27; median of 0.37, IQR: 0.26-0.55), respectively. After ALBI calculation, the median ALBI value obtained was -2.89 (IQR: -3.13; -2.59; median of -2.82, SD: -0.48).

The ROC curve with the ALBI metric performance is shown in Figure 1. The AUC for ALBI score was 0.617 (95%CI: 0.556-0.673, $P < 0.00171$), and the optimal cutoff value was - 2.82.

Thus, based on the cutoff value determined by ROC curve, 211 (58.4%) patients were classified as low-ALBI group (ALBI < -2.82); and 150 (41.6%) as high-ALBI group (ALBI ≥ -2.82).

Clinical and surgical characteristics of both groups are presented in Table 1. Older age ($P = 0.005$), lower hemoglobin level ($P < 0.001$), and ASA III/IV ($P = 0.001$) were associated with the High-ALBI group. Also, D1 Lymphadenectomy was more frequent in the High-ALBI group ($P = 0.003$). There was no difference regarding sex, BMI, type of gastrectomy, and preoperative chemotherapy between the groups.

Regarding the pathological characteristics (Table 2), there was no significant difference between the ALBI groups in terms of histological type, depth of tumor invasion (pT), presence of lymph node metastasis (pN), and final pathologic (pTNM) stage.

The postoperative outcomes according to ALBI group are presented in Table 3. The occurrence of major POC ($P = 0.029$) and the mortality rate at 30 d and 90 d were more frequent in the high-ALBI group ($P = 0.023$ and $P = 0.030$, respectively). The frequency of patients undergoing adjuvant chemotherapy was similar between both groups ($P = 0.917$).

Survival analysis

The median follow-up period was 40.1 mo. During this period, 81 patients had recurrence and 142 died. The 5-years DFS and OS rates for the entire cohort were 53.7% and 55.6%, respectively. In the survival analysis (Figure 2), DFS and OS rate was worse for patients with high-ALBI levels compared to the low-ALBI patients ($P < 0.001$ for both). The median DFS and OS for high-ALBI group were of 28.0 mo and 39.5 mo, respectively.

Similarly, when stratified by pTNM stage (Figure 3), pTNM I/II GC with high-ALBI had significantly worse DFS and OS compared to with low-ALBI pTNM I/II patients ($P < 0.001$).

Also, among pTNM III GC, DFS and OS in high-ALBI was shorter compared to low-ALBI group ($P = 0.021$ and $P = 0.063$, respectively).

In multivariate analysis, total gastrectomy, advanced pT stage, presence of lymph node metastasis and high-ALBI were independent factors associated with worse DFS (Table 4). For OS, ASA, type of gastrectomy, pT, pN, and ALBI-groups were factors significantly associated with survival in multivariate model (Table 5).

Table 1 Clinical and surgical characteristics of patients with gastric cancer according albumin-bilirubin risk groups, *n* (%)

Variables	Low-ALBI group (< -2.82), *n* = 211	High-ALBI group (≥ -2.82), *n* = 150	*P* value
Sex			0.712
Female	72 (34.1)	54 (36.0)	
Male	139 (65.9)	96 (64.0)	
Age (yr)			**0.005**
mean (SD)	62.0 (12.0)	65.6 (12.2)	
BMI (kg/cm²)			0.856
mean (SD)	25 (4.5)	25.2 (16.5)	
Hemoglobin (g/dL)			**< 0.001**
mean (SD)	12.7 (2.1)	11.1 (2.1)	
Albumin (g/dL)			**< 0.001**
mean (SD)	4.3 (0.3)	3.5 (0.5)	
Bilirubin (mg/dL)			**0.072**
mean (SD)	0.41 (0.22)	0.47 (0.33)	
Neutrophil to lymphocyte ratio			**0.092**
mean (SD)	2.48 (2.29)	2.91 (2.56)	
American Society of Anesthesiologists			**0.001**
I/II	178 (84.4)	105 (70.0)	
III/IV	33 (15.6)	45 (30.0)	
Charlson–Deyo Comorbidity Index[1]			0.344
0	141 (66.8)	93 (62.0)	
≥ 1	70 (33.2)	57 (38.0)	
Type of gastrectomy			0.562
Subtotal	126 (59.7)	85 (56.7)	
Total	85 (40.3)	65 (43.3)	
Lymphadenectomy			**0.003**
D1	34 (16.1)	44 (29.3)	
D2	177 (83.9)	106 (70.7)	
Preoperative chemotherapy			0.477
No	175 (82.9)	120 (80)	
Yes	36 (17.1)	30 (20)	

[1]Considered without including age and cancer as comorbidity.

P values in bold are statistically significant. BMI: Body mass index; ALBI: Albumin-bilirubin.

DISCUSSION

The aim of the present study was to evaluate the impact of the ALBI status in GC patients who received curative treatment. Accordingly, we found that ALBI score was an independent prognostic factor for patients with GC, and may be useful in predicting patient survival after gastrectomy. Furthermore, ALBI groups were able to stratify survival of patients in the same pTNM stage.

ALBI score has been considered a useful marker for hepatic dysfunction based only the two variables, albumin and bilirubin, which are related to nutrition and liver function[6,19]. Classically, it is a biomarker intended to evaluate prognosis in patients with HCC, and the majority of available studies address this disease[20]. Even so, some articles report results of its application in other diseases[9,10,21]. For instance, Matsukane *et al*[22] reports that ALBI is an independent prognostic factor for patients with non-small cell lung cancer, and Lee *et al*[9] found that ALBI can predicted disease recurrence and

Table 2 Pathological characteristics of patients with gastric cancer according albumin-bilirubin groups, *n* (%)

Variables	Low-ALBI group (< -2.82), *n* = 211	High-ALBI group (≥ -2.82), *n* = 150	*P* value
Lauren type			0.367
Intestinal	124 (58.8)	81 (54.0)	
Diffuse/mixed	87 (41.2)	69 (46.0)	
Histological differentiation			0.993
Well/moderately differentiated	107 (59.7)	76 (50.7)	
Poorly differentiated	104 (49.3)	74 (49.3)	
Lymphatic invasion			0.132
No	121 (57.3)	74 (49.3)	
Yes	90 (42.7)	76 (50.7)	
Venous invasion			0.196
No	150 (71.1)	97 (64.7)	
Yes	61 (28.9)	53 (35.3)	
Perineural invasion			0.743
No	112 (53.1)	77 (51.3)	
Yes	99 (46.9)	73 (48.7)	
T status			0.105
pT1/T2	91 (43.1)	52 (34.7)	
pT3/T4	120 (56.9)	98 (65.3)	
No of dissected lymph nodes			0.543
mean (SD)	40.9 (17.7)	39.8 (17.2)	
pN status			0.239
pN0	99 (46.9)	61 (40.7)	
pN+	112 (53.1)	89 (59.3)	
pTNM			0.222
I/II	122 (57.8)	77 (51.3)	
III	89 (42.2)	73 (48.7)	

ALBI: Albumin-bilirubin; pN: Presence of lymph node metastasis; pTNM: Pathologic.

survival in stage III colon cancer.

Considering the two parameters that comprise the ALBI score, albumin is synthesized in the liver, and its serum level is usually used to assess nutritional status and hepatic function[5]. Nutritional status is something that has already been shown to be related to the immune system and prognosis in GC, where a deficient nutritional condition can suppress the immune response against tumor, accelerating the cancer progression[5,23]. Thus, preoperative serum albumin level and prognostic nutritional index are factors already related to outcomes in GC[23]. But considering the evaluation of bilirubin levels alone, the association between serum levels of bilirubin and GC are poorly described[24].

The present study evaluated the ALBI through the ROC curve based on the DFS for GC, and we set the cut-off value for the ALBI score at -2.82. Our cutoff score was similar to reported by Ju *et al*[21], that include only curative GC patients, where based on OS rates at 3 years and 5 years they determined an ALBI cutoff value of -2.78. Interestingly, a similar value was also found in a study with patients with esophageal cancer, where the cutoff value for the ALBI score was -2.7[10]. This suggests that setting a single cut-off value for esophagogastric tumors may be appropriate.

In our cohort, ALBI groups were different in terms of some clinical characteristics, as age, hemoglobin levels and ASA, indicating a clinically impaired patient who might present a worse prognosis. However, no difference regarding the rate of comorbidity in relation to the ALBI groups were found in this study. Likewise, Kanda *et al*[13] evaluated 283 patients with pT2-4 resected GC and also demonstrated that high-ALBI group patients were older, but without reflecting on the comorbidity rate.

Table 3 Postoperative and surgical outcomes of patients with gastric cancer according albumin-bilirubin groups, *n* (%)

Variables	Low-ALBI group (< -2.82), *n* = 211	High-ALBI group (≥ -2.82), *n* = 150	*P* value
Length of hospital stay (d)			0.673
Median (IQR)	9 (6.0-13.3)	10 (7.0-13.8)	
Postoperative complications (Clavien)			**0.029**
Non/minor POC (I-II)	183 (86.7)	117 (78)	
Major POC (III-IV)	28 (13.3)	33 (22)	
Postoperative chemotherapy			0.917
No	117 (55.5)	84 (56)	
Yes	94 (44.5)	66 (44)	
Chemotherapy-all (pre or postoperative)			0.766
No	99 (46.9)	68 (45.3)	
Yes	112 (53.1)	82 (54.7)	
30-d motality			**0.023**
No	206 (97.6)	138 (92.6)	
Yes	5 (2.4)	11 (7.4)	
90-d motality			**0.030**
No	198 (94.7)	130 (88.4)	
Yes	11 (5.3)	17 (11.6)	

P values in bold are statistically significant. IQR: Interquartile range; ALBI: Albumin-bilirubin; POC: Postoperative complications.

Table 4 Univariate and multivariate analysis for disease-free survival

Disease-free survival	Univariate			Multivariate		
Variables	HR	95%CI	*P* value	HR	95%CI	*P* value
Male (*vs* female)	1.15	0.81-1.61	0.438	-	-	-
Age > 65 yr (*vs* < 65 yr)	1.18	0.86-1.62	0.312	-	-	-
Charlson > 1 (*vs* 0)	1.48	1.07-2.04	**0.019**	1.39	0.94-2.06	0.102
ASA III/IV (*vs* ASA I/II)	1.84	1.29-2.64	**0.001**	1.43	0.93-2.21	0.106
Total gastrectomy (*vs* distal)	1.43	1.04-1.97	**0.030**	1.43	1.03-1.98	**0.031**
Diffuse/mixed (*vs* others)	1.21	0.87-1.67	0.255	-	-	-
pT3/T4 (*vs* pT1/T2)	2.57	1.76-3.76	**< 0.001**	2.03	1.33-3.12	0.001
pN+ (*vs* pN0)	2.26	1.60-3.19	**< 0.001**	1.54	1.04-2.27	**0.030**
non-CMT (*vs* CMT)	1.15	0.83-1.58	0.399	-	-	-
Low-ALBI (*vs* High-ALBI)	2.09	1.51-2.88	**< 0.001**	1.83	1.32-2.53	**< 0.001**

P values in bold are statistically significant. 95%CI: 95% confidence interval; HR: Hazard ratio; ASA: American Society of Anesthesiologists; ALBI: Albumin-bilirubin; pN: Presence of lymph node metastasis; CMT: Chemotherapy.

Considering the pathological characteristics, we expected that the high-ALBI group would have deeper gastric wall invasion and more nodal involvement, suggesting that a more advanced disease could cause impaired liver function and possible hepatic hilar compression due to nodal enlargement. However, similar than Kanda *et al*[13], we did not find this association.

Despite not influencing the pTNM stage, in the preset cohort ALBI score was related to patient survival. Patients with high-ALBI were related to both lower DFS and OS when compared to low-ALBI groups, even in the same TNM stages. Similar results have been reported by Zhu *et al*[14] that

Table 5 Univariate and multivariate analysis for overall survival

Overall survival	Univariate			Multivariate		
Variables	**HR**	**95%CI**	***P* value**	**HR**	**95%CI**	***P* value**
Male (*vs* female)	1.20	0.85-1.71	0.306	-	-	-
Age > 65 yr (*vs* < 65 yr)	1.28	0.94-1.79	0.137	-	-	-
Charlson > 1 (*vs* 0)	1.42	1.02-1.98	**0.041**	1.25	0.83-1.89	0.282
ASA III/IV (*vs* ASA I/II)	1.94	1.35-2.80	**< 0.001**	1.60	1.02-2.52	**0.041**
Total gastrectomy (*vs* distal)	1.50	1.08-2.08	**0.016**	1.56	1.12-2.18	**0.009**
Diffuse/mixed (*vs* others)	1.29	0.93-1.79	0.133	-	-	-
pT3/T4 (*vs* pT1/T2)	2.44	1.65-3.61	**< 0.001**	1.87	1.20-2.91	**0.006**
pN+ (*vs* pN0)	2.24	1.57-3.20	**< 0.001**	1.58	1.06-2.37	**0.026**
non-CMT (*vs* CMT)	1.18	0.85-1.64	0.327	-	-	-
Low-ALBI (*vs* High-ALBI)	1.97	1.41-2.74	**< 0.001**	1.68	1.20-2.35	**0.003**

P values in bold are statistically significant. 95%CI: 95% confidence interval; HR: Hazard ratio; ASA: American Society of Anesthesiologists; ALBI: Albumin-bilirubin; pN: Presence of lymph node metastasis; CMT: Chemotherapy.

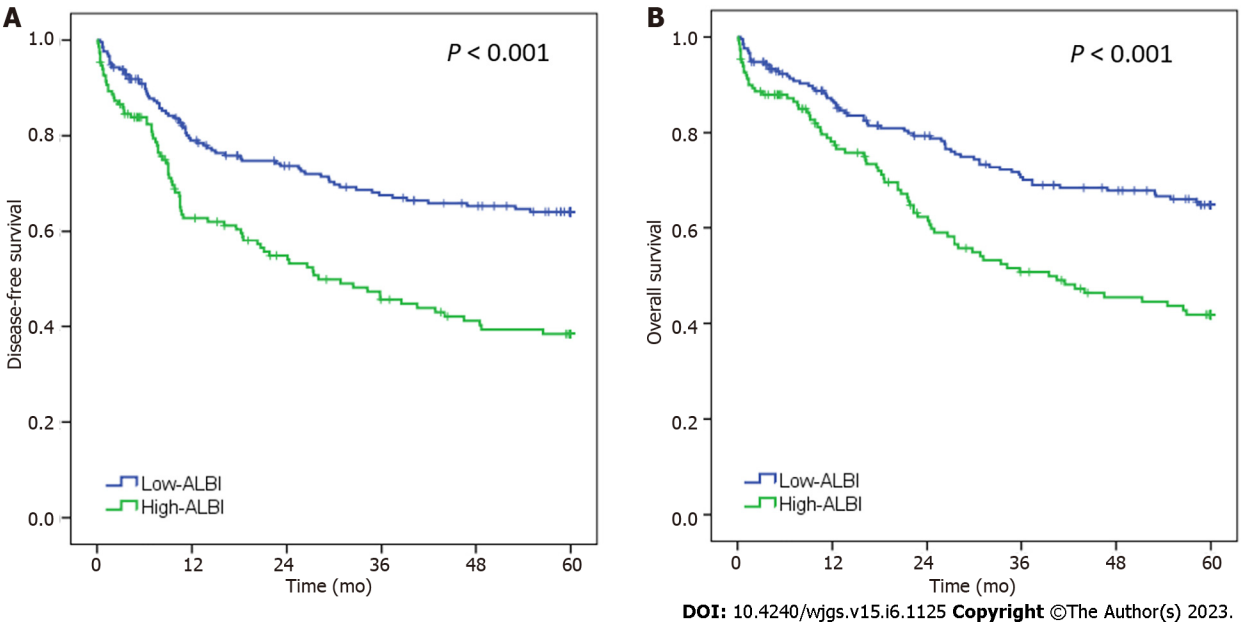

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Figure 2 Disease-free survival and overall survival of patients with gastric cancer according to the albumin-bilirubin groups (low-albumin-bilirubin and high-albumin-bilirubin). A: Disease-free survival; B: Overall survival. ALBI: Albumin-bilirubin.

demonstrated worse OS for patients with GC and high ALBI values, especially those with stage disease II and III. Likewise, Ju *et al*[21] evaluating 244 patients with resected GC showed that increasing in ALBI levels was an independent factor related to OS, with a HR of 2.2. ALBI score was also related to recurrence in advanced GC stage as pT2-T4 after gastrectomy[13]. The association of ALBI with decreased survival can be explained by the prolonged damage caused by a deficient nutritional status, with lower albumin levels and anemia (both seen in our cohort). In addition to debilitating the patient, decreasing adherence to chemotherapy[25,26], malnutrition also affects cell-mediated immunity by T cells, which impairs anti-tumor response and accelerates tumor progression[5,23,27].

Noteworthy, some authors also demonstrated differences in relation to the incidence of POC according to the ALBI score, as described by Aoyama *et al*[10], where the incidence of postoperative anastomotic leakage in patients with esophageal cancer was 46.3% in the ALBI-high group compared with 27.5% in the ALBI-low group (P = 0.038). In patients with GC, some authors reported that there was no significant differences in morbidity and POC rate between ALBI groups[13]; whereas other found that in patients who underwent radical resection, the rate of POC were also higher in patients

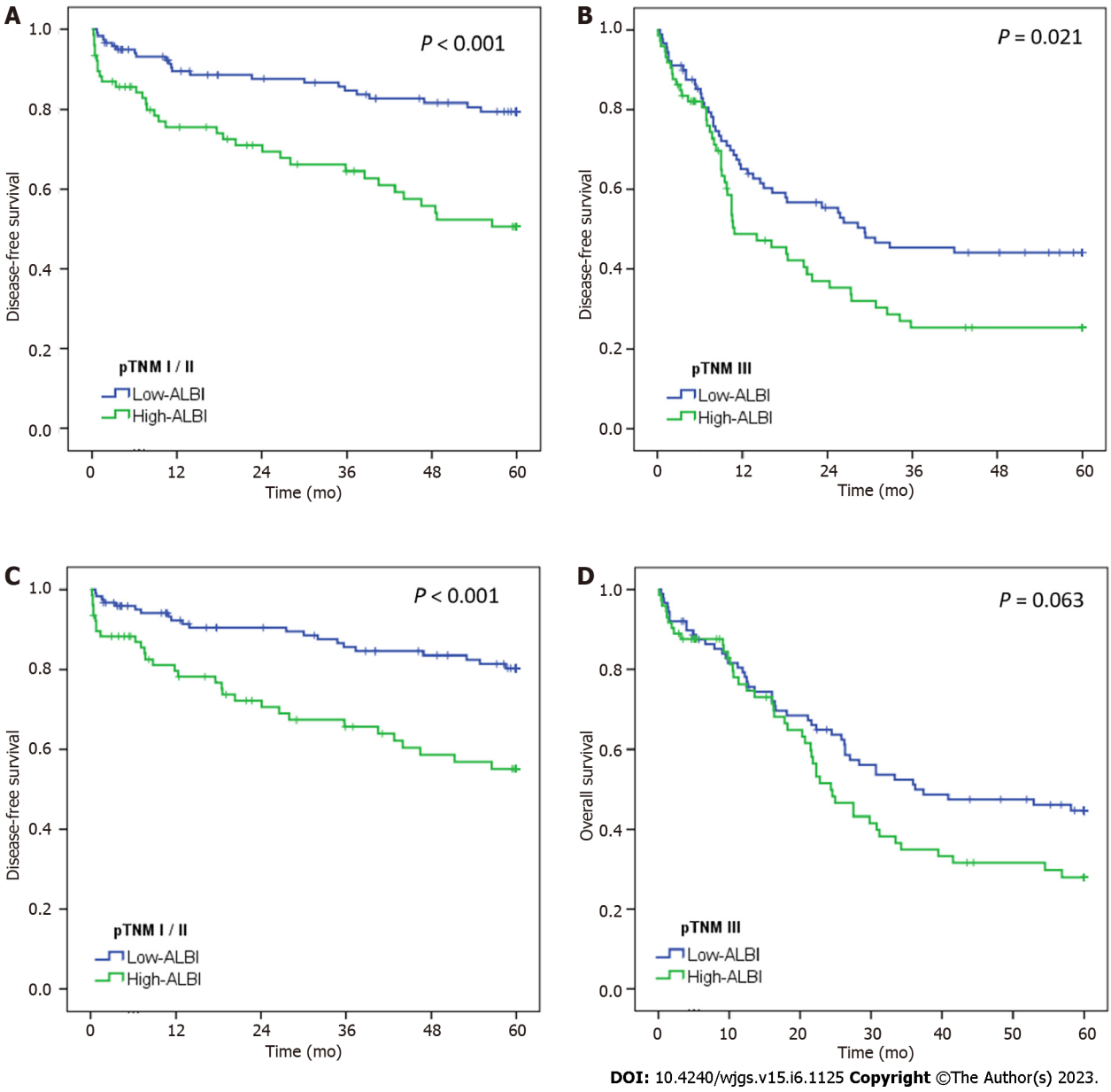

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Figure 3 Disease-free survival and overall survival of patients with gastric cancer according to the albumin-bilirubin groups, stratified by pathologic stage. A and B: Disease-free survival; C and D: Overall survival. pTNM: Pathologic; ALBI: Albumin-bilirubin.

with high-ALBI than low-ALBI levels[14]. Similarly, in our cohort, we also observed that the incidence of major POC was higher in the high-ALBI group, including the mortality at 30 d and 90 d. One of the justifications for this result is probably related to the age of patients, since high-ALBI group are generally older, as seen in our study. So, it may represent a frail group of patients with a higher risk of complications[28]. Still, poor nutritional status can contribute to a higher risk of POC[29], since preoperative hypoproteinemia has already been reported as a risk factor for postoperative infection in gastrointestinal surgery[30]. So, in our study, ALBI had a clinical impact on both short-term and long-term outcomes.

Overall, we proposed a risk stratification in two groups based on ALBI values, which was independently associated with survival and may serve as an additional parameter to predict patient outcomes. Both DFS and OS were clearly separated according to the ALBI status, where those classified as high-ALBI had worse survival outcomes. In addition, the preoperative ALBI was found to be a promising marker for predicting disease relapse and survival even in GC with the same TNM stage. As well as other previously described pretreatment serum-based inflammatory indicators, such as the neutrophil to lymphocyte ratio[31], the ALBI score can be determined using routine tests and has potential to be an useful biomarker for patients with GC.

Some limitations should be mentioned in this study. Firstly, this is a retrospective research; therefore, some confounders and selection bias were not absolutely adjusted. Although ALBI grade has been related to the tolerability and introduction of postoperative adjuvant chemotherapy[21,32], since hepatic

dysfunction are one of the main factors for adverse reactions to chemotherapy, it was not possible to assess the influences of the ALBI score on adherence to regimens and/or duration of chemotherapy. However, we believe that this limitation did not affect the results, since no difference in the frequency of patients treated with chemotherapy between low and high-ALBI groups was seen in our cohort. Also, the lack of a predefined cutoff value limits the comparison between studies. Instead, some studies utilized ALBI cutoff value set for patients with HCC, and maybe this is the reason that some results are different from ours. Nonetheless, as strengths, we included a homogeneous cohort consisted by patients who received curative surgery, minimizing the risk of impaired liver function due to the extension of the disease. To our knowledge, this is the first study to assess the prognostic impact of ALBI score in Western GC patients in the real-world setting, treated at a single referral center. Accordingly, our findings should be validated in other series of cases, and a larger scale multicentric validation study to confirm the relationship between ALBI score in GC is warranted.

CONCLUSION

Preoperative ALBI scores were able to predict short- and long-term outcomes in patients with GC who received curative treatment. High-ALBI patients had poor clinical conditions and worse outcomes compared to those with low-ALBI. Also, the ALBI status allowed the risk stratification of patients within the same pTNM stage, and was an independent risk factor associated with survival. Thus, it is a simple and reproducible parameter, which may serve as an additional prognostic factor for GC.

ARTICLE HIGHLIGHTS

Research background

Albumin-bilirubin (ALBI) score is an indicator of liver dysfunction and is useful for predicting prognosis of hepatocellular carcinomas. Currently, this liver function index has been used to predict prognosis in other neoplasms.

Research motivation

The significance of ALBI score in gastric cancer (GC) after radical resection has not been elucidated.

Research objectives

To analyze the significance of ALBI score in GC after curative gastrectomy.

Research methods

We retrospectively evaluated all GC patients who underwent gastrectomy between 2009 and 2021. ALBI score was calculated as follows: (log10 bilirubin × 0.660) + (albumin × -0.085). The receiver operating characteristic (ROC) curve with area under the curve (AUC) was plotted to evaluate the ability of ALBI score in predicting recurrence or death. Patients were divided into low-ALBI and high-ALBI groups for analysis, based on the optimal cutoff value determined by ROC curve.

Research results

A total of 361 patients were included. The AUC for ALBI score was 0.617, and the cutoff value was -2.82. Accordingly, 211 (58.4%) patients were classified as low-ALBI group and 150 (41.6%) as high-ALBI group. Older age, lower hemoglobin level, American Society of Anesthesiologists classification III/IV, and D1 lymphadenectomy were more frequent in the high-ALBI group. There was no difference between both groups in terms of Lauren histological type, depth of tumor invasion (pT), presence of lymph node metastasis (pN), and pathologic stage (pTNM). Major postoperative complication and 30- and 90-d mortality were higher in high-ALBI patients. In survival analysis, the high-ALBI group had worse disease-free survival and overall survival compared to those with low-ALBI. When stratified by pTNM, the survival difference between ALBI groups was maintained in stage I/II and stage III GC. Multivariate analysis demonstrated that high-ALBI was an independent factor associated to worse survival.

Research conclusions

The preoperative ALBI score is able to predict the outcomes of patients with GC, where high-ALBI patients have worse prognosis. Also, ALBI score allows risk stratification of patients within the same pTNM stages, and represents an independent risk factor associated with survival.

Research perspectives

ALBI score is able to predict short-term and long-term outcomes of patients, and can be applied as a

prognostic factor for GC. The ALBI is a simple and reproducible parameter that allows the risk stratification of patients within the pTNM stages, and may be an additional useful tool for decision-making regarding treatment and follow-up individualization. Thus, our findings can be evaluated in other cohorts, and validated in other series of cases study.

FOOTNOTES

Author contributions: Szor DJ contributed to study design, data retrieval, statistical analysis, critical analysis, and draft of the manuscript; Pereira MA contributed to data retrieval, statistical analysis, critical analysis, and draft of the manuscript; Ramos MFKP, Tustumi F, and Dias AR contributed to data retrieval, critical analysis, and review of the manuscript; Zilberstein B contributed to critical analysis and review of the manuscript; Ribeiro Jr U contributed to implementation of the research, critical analysis, and review of the manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Ability of lactulose breath test results to accurately identify colorectal polyps through the measurement of small intestine bacterial overgrowth

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Abstract

BACKGROUND

While colorectal polyps are not cancerous, some types of polyps, known as adenomas, can develop into colorectal cancer over time. Polyps can often be found and removed by colonoscopy; however, this is an invasive and expensive test. Thus, there is a need for new methods of screening patients at high risk of developing polyps.

AIM

To identify a potential association between colorectal polyps and small intestine bacteria overgrowth (SIBO) or other relevant factors in a patient cohort with lactulose breath test (LBT) results.

METHODS

A total of 382 patients who had received an LBT were classified into polyp and non-polyp groups that were confirmed by colonoscopy and pathology. SIBO was diagnosed by measuring LBT-derived hydrogen (H) and methane (M) levels according to 2017 North American Consensus recommendations. Logistic regression was used to assess the ability of LBT to predict colorectal polyps. Intestinal barrier function damage (IBFD) was determined by blood assays.

RESULTS

H and M levels revealed that the prevalence of SIBO was significantly higher in the polyp group than in the non-polyp group (41% *vs* 23%, $P < 0.01$; 71% *vs* 59%, $P < 0.05$, respectively). Within 90 min of lactulose ingestion, the peak H values in the adenomatous and inflammatory/hyperplastic polyp patients were significantly higher than those in the non-polyp group ($P < 0.01$, and $P = 0.03$, respectively). In 227 patients with SIBO defined by combining H and M values, the rate of IBFD determined by blood lipopolysaccharide levels was significantly higher among patients with polyps than those without (15% *vs* 5%, $P < 0.05$). In regression analysis with age and gender adjustment, colorectal polyps were most accurately predicted with models using M peak values or combined H and M values limited by North American Consensus recommendations for SIBO. These models had a sensitivity of ≥ 0.67, a specificity of ≥ 0.64, and an accuracy of ≥ 0.66.

CONCLUSION

The current study made key associations among colorectal polyps, SIBO, and IBFD and demonstrated that LBT has moderate potential as an alternative noninvasive screening tool for colorectal polyps.

Key Words: Lactulose breath test; Colorectal polyp; Small intestine bacteria overgrowth; Intestinal barrier function; Retrospective study

Core Tip: As the lactulose breath test (LBT) is an indirect method of measuring bacteria in the digestive tract, it is primarily used to support small intestine bacteria overgrowth (SIBO) diagnosis but is implemented as a new method for screening colorectal polyps in this study. A total of 382 patients with LBT results were classified into polyp and non-polyp groups that were confirmed by colonoscopy and pathology. First, it applied the LBT for assessment of its utility as a noninvasive screening tool for colorectal polyps as well as for diagnosis of SIBO. Second, the results revealed certain key associations among colorectal polyps, SIBO and Intestinal barrier function damage (IBFD), such as SIBO was more prevalent in patients with colorectal polyp than those without polyp and IBFD was more susceptible in patients with colorectal polyp than those without polyp only when SIBO was evident. Third, in regression analysis with age and gender adjustment, colorectal polyp was best predicted by models using plain methane peak values or combined hydrogen and methane values limited by the North American Consensus for SIBO. One of the most important result was moderate potential of LBT as an alternative noninvasive screening tool for colorectal polyps.

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INTRODUCTION

Colorectal polyps are caused by colorectal mucosal proliferation that creates pedunculated or sessile outgrowths. They become more common as people age and are prevalent in individuals > 40 years of age[1,2]. While most polyps are benign, some can become cancerous and may even metastasize to other parts of the body[3]. Adenomatous polyps are known precursors of colon cancer but can be difficult to diagnose in their early stages. Moreover, most colorectal cancers develop from focal changes in benign polyps through a multistep process involving genetic, histological, morphological, and intestinal microbiome changes that accumulate over more than 10 years[4,5]. A long precancerous state provides an opportunity to screen for polyps and successfully prevent or treat any cancerous lesions that develop. Thus, new methods that can identify precancerous colorectal lesions can play an important role

in early-stage colorectal cancer treatment and prevention.

Several methods are used to screen for colorectal cancer, including fecal occult blood testing (FOBT), flexible sigmoidoscopy, and colonoscopy, each with its own merits and disadvantages. A pooled meta-analysis of randomized trials found that FOBT and flexible sigmoidoscopy screening reduced colorectal cancer mortality by 16% and 30%, respectively[6]. While colonoscopy is the best method for visualizing focal lesions and taking biopsies for diagnosis[7], it is invasive, costly, and can be uncomfortable, especially for asymptomatic participants with low compliance. Thus, colonoscopy may not suitable for primary screening of colorectal polyps and cancers. Despite the benefits of these modalities, there are overwhelming limitations, which highlight a need for more accurate, noninvasive screening tools for colorectal cancer and precancerous polyps.

The lactulose breath test (LBT) is an indirect method of measuring bacteria in the digestive tract. It uses equipment to determine the concentration in parts per million (ppm) of hydrogen (H) and methane (M) gas in the breath[8]. The LBT can indicate the approximate population size and location of the microbiome, as well as some information about the types of bacteria present. While jejunal aspiration culture remains the gold standard for diagnosing small intestine bacterial overgrowth (SIBO), LBT is widely used as a noninvasive method of diagnosing SIBO due to its safety, accessibility, and affordability. However, there is limited data on the association between SIBO and colorectal polyps.

SIBO is a condition in which the small bowel is colonized by excessive aerobic and anaerobic microbes that are normally present in the colon[9]. SIBO and intestinal microbiota are associated with several conditions, including Crohn's disease[10], irritable bowel syndrome (IBS)[11], functional gastrointestinal disorders (FGID)[12], nonalcoholic fatty liver disease[13], diabetes[14], and hepatic encephalopathy[15]. Recent studies have found a link between the gut microbiome and the pathogenesis of adenomatous polyps and colorectal cancer[16,17], offering a promising avenue for personalized prevention[18]. For example, higher numbers of some bacterial species are found in patients with adenomatous polyps than in those without[17]. The current study analyzed a patient cohort with LBT testing data to characterize potential associations among colorectal polyps, SIBO, and other relevant factors and assessed the use of LBT as a potential screening tool for colorectal polyps.

MATERIALS AND METHODS

Study subjects

Medical records from patients in registry database of The First Affiliated Hospital of Guangdong Pharmaceutical University who received an LBT for gastrointestinal symptoms from July 2017 to February 2019 were reviewed. A total of 382 patients (213 males and 169 females) were included in the study. The subjects ranged in age from 22 to 92 years (mean ± SD, 57 ± 14 years). All patients signed an informed consent prior to inclusion. The study was approved by the Ethics Committee of the First Affiliated Hospital of Guangdong Pharmaceutical University.

The patients were classified into a polyp group (n = 169) and a non-polyp group (n = 213). All colorectal polyps were diagnosed by colonoscopy and pathology. Patients with no polyps or other intestinal lesions identified by colonoscopy were included in the non-polyp group. Individuals with: (1) Acute intestinal infection; (2) antibiotic use within 4 wk before the test; (3) severe heart, lung, brain, and other diseases who are unable to tolerate colonoscopy; (4) susceptibility to hypoglycemia; and (5) age < 18 years were excluded from the study.

Blood assays to evaluate intestinal barrier function damage

Intestinal barrier function damage (IBFD) was assessed using the instruments and assay kits from Beijing Zhongsheng Jinyu Diagnostic Technology Co., Ltd. Blood samples were taken after 8 h of fasting and stored at 4 °C. Within 4 h, the blood samples were tested for diamine oxidase (DAO), D-lactate (D-lac), and lipopolysaccharide (LPS) concentration according to the manufacturer's instructions. Patients whose blood samples had values above the reference for DAO (10 U/L), D-lac (15 mg/L), and LPS (20 U/L) were defined as having IBFD.

Lactulose breath test

The LBT was completed using the Quintron Breath Tracker (SC model) to determine the concentration of H and M. Procedures were performed with common standards[9,19]. In brief, all patients fasted for 12 h and brushed their teeth prior to the test. Lactulose (10 g) in warm water was provided and breath samples were collected every 30 min for 150 min. No drink, food, or exercise was permitted during the test, but subjects were allowed to sleep.

Diagnosis of SIBO and prediction of colorectal polyps by LBT

Diagnosis of SIBO by LBT was made qualitatively according to the following definitions of a positive result recommended by the 2017 North American Consensus[19]: (1) A rise of > 20 ppm H within 90 min of substrate ingestion; and (2) ≥ 10 ppm methane. A patient was determined as having SIBO if either or

both standards were met.

LBT quantitative measurements were also used to predict the presence of colorectal polyps. The performance of prediction models was assessed with logistic regression supported by the R program, pROC. Each model was tested by 100-time repeated re-sampling to ensure its accuracy.

Statistical analyses

All data were tested for statistical differences using IBM SPSS software (v22.0). An ANOVA test was used to assess differences in measurements between groups, and a one-side Fisher Exact test was used to measure differences in frequency between one group and another. $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of patients and colorectal polyps

As shown in Table 1, patients in the polyp group were 9 years older than those in the non-polyp group (mean 62 *vs* 53 years, $P < 0.001$), and were more often male (64% *vs* 49%, $P < 0.01$). Colorectal polyps were least prevalent among patients 19-45 years of age (7%) and most common among those 61-92 years of age (55%). The polyp group also had a higher proportion of patients with constipation than the non-polyp group (22% *vs* 14%, $P < 0.05$), and more often had metabolic disorders, including diabetes (19% *vs* 10%, $P < 0.01$), hyperlipidemia (20% *vs* 13%, $P < 0.05$), and fatty liver/cirrhosis (41% *vs* 27%, $P < 0.01$), in addition to hypertension (38% *vs* 21%, $P < 0.001$). However, patients in the polyp group were less likely to have non-organic disorders, such as FGID (5% *vs* 13%, $P < 0.01$), IBS (8% *vs* 16%, $P < 0.05$) and gastroesophageal reflux disease (11% *vs* 16%, $P = 0.096$), than those in the non-polyp group.

Colonoscopy showed that the colorectal mucosa from 213 patients had a normal appearance, while colorectal polyps were found in 169 patients, including 81 with inflammatory/hyperplastic polyps, and 88 with adenomatous polyps. Polyp size was < 1.0 cm in 136 patients, 1.0-2.0 cm in 25 patients, and > 2.0 cm in eight patients. While 71 patients had single polyps, 98 patients had multiple polyps. In 114 patients, the polyps were found on the left side of the colon, including on the descending colon, sigmoid colon, and rectum, and in 55 patients, polyps were located on other parts of the colon.

Ability of LBT to detect SIBO and predict colorectal polyps

According to H, M measurements, alone or in combination, the prevalence of SIBO by LBT was all significantly higher in the polyp group than in the non-polyp group [H: 41% (70/169) *vs* 23% (49/213), $P < 0.001$; M: 71% (120/169) *vs* 59% (125/213), $P < 0.05$; combined: 80% (136/169) *vs* 67% (143/213), $P < 0.01$] (Table 2). Within 90 min of substrate ingestion, the peak values of hydrogen were significantly higher in patients with adenomatous or inflammatory/hyperplastic polyps than those in the non-polyp group ($P < 0.01$, and $P = 0.03$, respectively; Table 3). The peak values of methane were similar in all three groups ($P = 0.168$), and there was no significant difference in the number of patients with SIBO by polyp type ($P > 0.05$).

Associations between IBFD, SIBO, and colorectal polyps

A total of 311 of the 382 patients were evaluated for IBFD by blood assays, including measurements of DAO, D-lac, and LPS. Of these, 174 (56%) of the patients, including 82 in the polyp group (58%) and 92 in the non-polyp group (54%), were characterized as having potential IBFD using a combination of the three assays ($P > 0.05$) or each assay alone (all $P > 0.05$). Of the 311 patients, 227 were positive for SIBO using combined H and M measurements. Among patients with SIBO, the rate of IBFD using all three blood assays was marginally higher in the polyp group than in the non-polyp group (57% *vs* 48%, $P = 0.13$), but differed significantly when IBFD was defined using LPS alone (polyp = 15% *vs* non-polyp = 5%, $P < 0.05$; Figure 1). Among the remaining 84 patients without SIBO, there was no significant difference in the rate of IBFD between patients in the polyp and non-polyp groups using all three assays together or individually (all $P > 0.05$).

Prediction performance of LBT results for colorectal polyps

LBT was also assessed quantitatively for its prediction performance as a screening tool for colorectal polyps. Using different H and M cutoff values, 17 models were built using different subsets of the patient population (Table 4). Peak values in H and M were obtained during the tests and rise values were got from baseline subtracted peak values. To account for the effects of age and gender on the model performance, 7 of the 17 models with differences in the mean LBT value between the polyp and non-polyp groups ($P < 0.01$) were selected for further assessment (model # 1, 2, 4, 5, 11, 12 and 17; Table 4 and Figure 2A-G). Differences in the area under the receiver operating characteristic curve between age and gender-adjusted and unadjusted models were statistically significant (all $P < 0.01$). These models performed similarly well when age and gender were used as covariates, with almost all of them showing an accuracy of > 65% (Table 5). Models with a methane peak value with or without a ≥ 5

Table 1 Demographics and comorbidity of the study subjects, *n* (%)

	Overall (*N* = 382)	Polyps (*n* = 169)	Non-polyps (*n* = 213)	*P* value
Age, yr	57.0 ± 14.0	62.1 ± 11.7	53.0 ± 14.4	**0**
19-45	70 (18)	11 (7)	59 (28)	**0**
46-60	150 (39)	65 (38)	85 (40)	0.428
61-92	162 (43)	93 (55)	69 (32)	**0**
Male	213 (56)	108 (64)	105 (49)	**0.003**
Bilestone	34 (9)	18 (11)	16 (8)	0.187
Constipation	67 (18)	38 (22)	29 (14)	**0.017**
Diabetes	53 (14)	32 (19)	21 (10)	**0.008**
Fatty liver/cirrhosis	127 (33)	70 (41)	57 (27)	**0.002**
FGID	37 (10)	9 (5)	28 (13)	**0.007**
GERD	54 (14)	19 (11)	35 (16)	0.096
Hyperlipidemia	60 (16)	33 (20)	27 (13)	**0.046**
Hypertension	108 (28)	64 (38)	44 (21)	**0**
Hyperuricemia	42 (11)	20 (12)	22 (10)	0.38
IBS	49 (13)	14 (8)	35 (16)	**0.013**
PU	31 (8)	24 (14)	7 (3)	**0**

Values presented as mean ± SD, or *n* (%) of observations. *P* values were from one-side Fisher exact statistics, with bold font for those less than 0.05. FGID: Functional gastrointestinal disorders; GERD: Gastroesophageal reflux disease; IBS: Irritable bowel syndrome; PU: Peptic ulcer.

Table 2 Small intestine bacteria overgrowth distribution between polyp & non-polyp groups

SIBO (+)	Overall (*N* = 382)	Polyps (*n* = 169)	Non-polyps (*n* = 213)	*P* value
By methane	245 (64)	120 (71)	125 (59)	0.014[a]
By hydrogen 90 min	119 (31)	70 (41)	49 (23)	0.000[a]
By combined M and H	279 (73)	136 (80)	143 (67)	0.004[a]

[a]*P* < 0.05, polyps *vs* non-polyps.
SIBO: Small intestine bacteria overgrowth.

Table 3 The peak values of methane and hydrogen in inflammatory/hyperplastic polyp, adenomatous polyp and non-polyp groups

Peak values	Polyps (*n* = 169)	Non-polyps (*n* = 213)		*P* value
	Inflammatory/hyperplastic polyp	Adenomatous polyp		
Methane	208.2	197.86	182.52	0.168
Hydrogen within 90 min	209.53[b]	220.87[b]	172.51	0.001[a]

[a]*P* < 0.05 was considered to indicate a statistically significant difference between inflammatory/hyperplastic polyp, adenomatous polyp and non-polyp groups.
[b]*P* < 0.05 was considered to indicate a statistically significant difference between inflammatory/hyperplastic polyp and non-polyp groups or between adenomatous polyp and non-polyp groups. Univariate analysis was performed using the nonparametric tests (Kruskal-Wallis independent samples).

ppm cutoff (Figure 2A and D) and the model using the SIBO subpopulation (Figure 2G) performed best.

Table 4 Performance of prediction models for colorectal polyps

Model No.	Value cutoff (ppm) for subset	*N*	*n* (polyp/non-polyp)	Mean ppm (polyp)	Mean ppm (non-polyp)	Mean ppm (*P* value)	Sensitivity	Specificity	Accuracy
1	Methane peak value (not applied)	382	169/213	12.82	12.06	**0.074**[a]	0.427	0.578	0.511
2	Methane peak value (≥ 5)	359	160/199	13.34	12.66	**0.084**[a]	0.417	0.571	0.502
3	Methane peak value (≥ 10)	245	120/125	15.28	15.55	0.905	0.443	0.390	0.416
4	Hydrogen peak value (not applied)	380	169/211	52.34	45.48	**0.091**[a]	0.408	0.604	0.517
5	Hydrogen peak value (≥ 10)	310	140/170	62.05	55.24	**0.090**[a]	0.383	0.590	0.496
6	Hydrogen peak value (≥ 20)	259	125/134	67.85	66.02	0.776	0.400	0.439	0.421
7	Hydrogen rise value (not applied)	372	165/207	41.94	37.40	0.121	0.391	0.582	0.498
8	Hydrogen rise value (≥ 10)	280	130/150	52.12	49.93	0.406	0.380	0.477	0.432
9	Hydrogen rise value (≥ 20)	217	108/109	60.06	63.39	0.479	0.492	0.375	0.433
10	Hydrogen rise value (≥ 20 by 90 min)	119	70/49	47.74	50.10	0.929	0.460	0.323	0.403
11	Combined M peak & H peak (M ≥ 5 &/or H ≥ 10)	373	166/207	66.15	58.48	**0.068**[a]	0.412	0.615	0.525
12	Combined M peak & H peak (M ≥ 5 & H ≥ 10)	294	134/160	76.49	68.28	**0.055**[a]	0.391	0.607	0.508
13	Combined M peak & H risen (M ≥ 5 &/or H ≥ 10)	370	166/204	54.58	50.11	0.166	0.403	0.578	0.499
14	Combined M peak & H rise (M ≥ 5 & H ≥ 10)	267	124/143	66.54	62.50	0.239	0.379	0.530	0.460
15	Combined M peak & H peak (M ≥ 10 &/or H ≥ 20)	177	96/81	86.28	85.49	0.674	0.390	0.395	0.392
16	Combined M peak & H rise (M ≥ 10 & H ≥ 20)	149	84/65	77.32	83.17	0.723	0.522	0.346	0.445
17	Combined M peak & H rise (M ≥ 10 &/or H ≥ 20 by 90 min)	279	136/143	42.29	35.71	**0.008**[a]	0.382	0.702	0.546

[a]$P < 0.1$ for difference in mean value of lactulose breath test between polyp and non-polyp groups for further assessment.
Rise values are baseline-subtracted peak values during the tests. Bold *P* values indicate the 7 best models in further assessment. ppm: Parts per million.

DISCUSSION

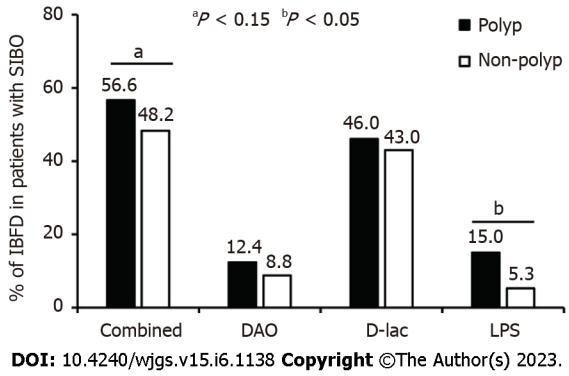
Recent studies have shown that the gut microbiome is associated with certain gastrointestinal symptoms [12], colon polyps, and colorectal cancer[18,20]. However, little is known about the relationship between SIBO and colorectal polyps. The current study analyzed a patient cohort that had recently received LBT for uncertain gastrointestinal symptoms. The findings revealed certain key associations among colorectal polyps, SIBO, and IBFD while demonstrating that LBT had moderate potential as an alternative noninvasive screening tool for colorectal polyps. SIBO was more prevalent in patients with colorectal polyps than those without and IBFD was worse in patients with colorectal polyps than those without only when SIBO was evident.

SIBO is caused by gut microbiota dysregulation and is characterized by the excessive density and/or abnormal composition of bacteria in the small intestine. The current study was the first to demonstrate that patients with colorectal polyps had a higher prevalence of SIBO than those without, defined by methane and hydrogen test results alone or in combination. These findings suggest that SIBO may be a risk factor for colorectal polyps. While this study showed no difference in SIBO by polyp type, further investigation is needed to confirm this finding. The results also showed a higher rate of IBFD among patients with colorectal polyps than those without, however this was only true for patients with SIBO. This suggests that patients with polyps are more susceptible to IBFD when SIBO are present.

Table 5 Model performance with key parameters (area under the receiver operating characteristic curve, accuracy, sensitivity, and specificity)

Panel ID	AUC, % (95%CI)	Accuracy	Sensitivity	Specificity
a	71.6 (66.5-76.7)	0.659	0.666	0.653
b	71.4 (66.3-76.5)	0.642	0.663	0.625
c	72.0 (66.9-77.1)	0.650	0.669	0.634
d	71.7 (66.4-77.0)	0.663	0.679	0.651
e	72.9 (67.3-78.4)	0.651	0.677	0.629
f	72.6 (66.9-78.4)	0.650	0.683	0.622
g	71.7 (65.7-77.7)	0.658	0.673	0.643

AUC: Area under the curve.



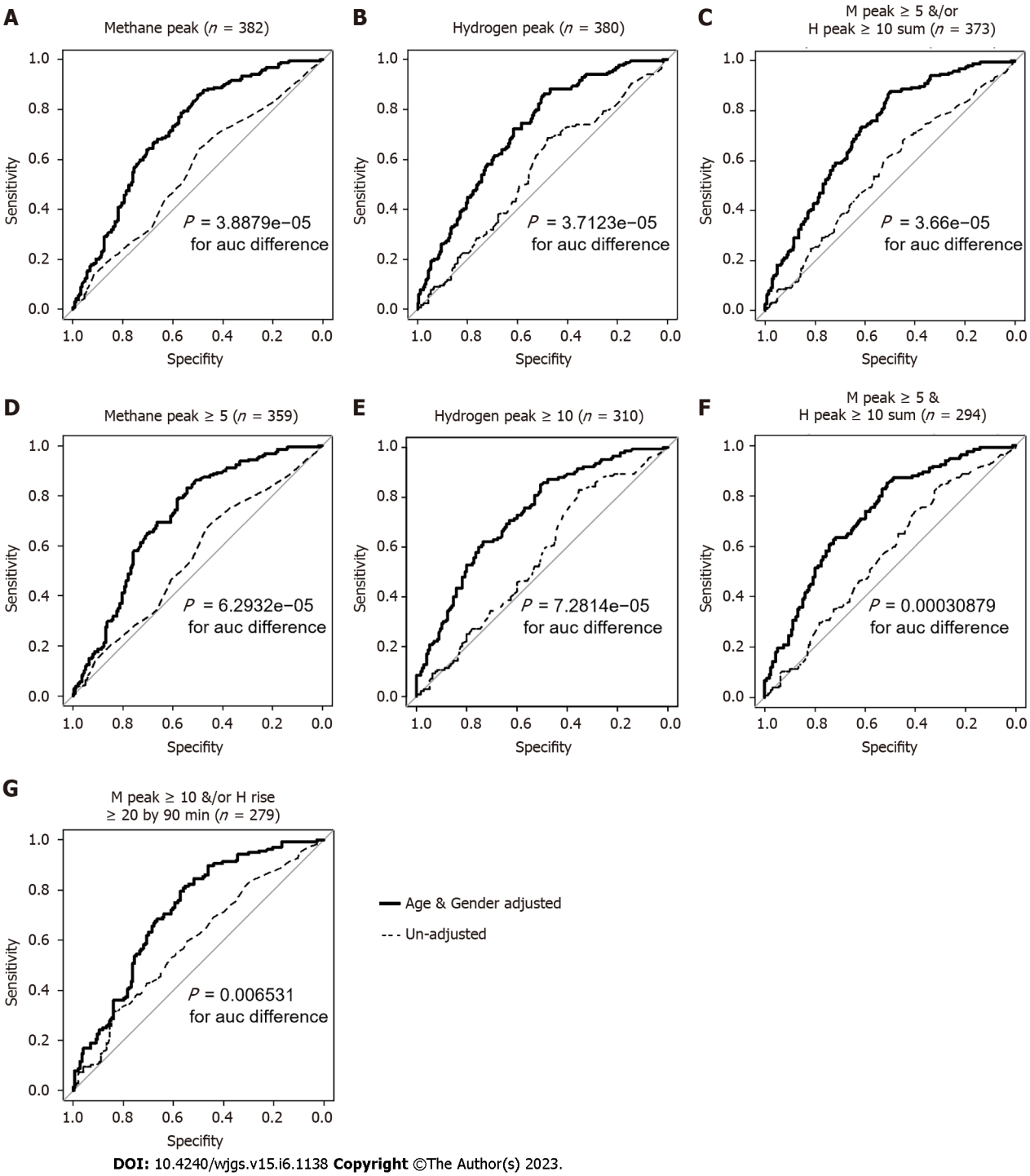
DOI: 10.4240/wjgs.v15.i6.1138

Figure 1 Rate of intestinal barrier function damage in 227 small intestine bacteria overgrowth patients. [a]The rate of intestinal barrier function damage (IBFD) by 3 blood assays altogether was marginally higher in polyp group than that in non-polyp group, but no significance, $P = 0.13$. [b]It was significantly different between polyp group and non-polyp group when IBFD defined by lipopolysaccharide alone, $P < 0.05$. SIBO: Small intestine bacteria overgrowth; DAO: Diamine oxidase; LPS: Lipopolysaccharide.

The culture of small bowel aspirates is the gold standard for SIBO diagnosis, but this is an invasive method and it can be a challenge to culture gut flora[21,22]. As a result, noninvasive testing using LBT results is often used. While the diagnostic criteria for SIBO by LBT are not yet standardized, the 2017 North American Consensus guidelines used in this study can make the results comparable across studies with similar data and analysis. LBT is primarily used to support SIBO diagnosis but is implemented here as a new method for screening colorectal polyps. To our knowledge, this is the first study to use quantitative LBT measurements for prediction analysis. LBT had moderate potential as a screening tool to identify patients with polyps in the large intestine. The best fit models were greatly improved after adjusting for age and gender. It is worth noting that models that only included the peak methane values without filtering by cutoff values performed as well as the model with combined H and M values limited by North American Consensus guidelines (Figure 2H). This suggests that methane peak values were as useful as combined hydrogen and methane values in patients with SIBO when using LBT as a screening tool for colorectal polyps.

In this retrospective study, patients with colorectal polyps were about 9 years older and more often male than those without polyps. These findings are consistent with the characteristics of polyp development and support the results of prior studies. Most studies report that men have almost twice the prevalence of polyps as women[23,24], and this tends to increase with age[3]. In addition, comorbidity analysis showed that patients with colorectal polyps were more often complicated with metabolic disorders and less likely with non-organic abnormalities. This is consistent with recent studies indicating that metabolic syndrome is a high-risk factor for colorectal adenomatous polyps and cancer and should be included in colorectal cancer screening programs[25,26]. These findings suggest that metabolic disorders can be an inherent characteristic among certain patients with colorectal polyps.

The incidence of constipation was significantly higher in the polyp than non-polyp groups. Patients with constipation have prolonged oro-cecal transit time[27] and constipation can significantly increase the incidence of colorectal polyps[28]. However, colonoscopy for patients with constipation as the sole indication had fewer neoplastic lesions than for those undergoing routine screening colonoscopy[29].



DOI: 10.4240/wjgs.v15.i6.1138

Figure 2 The receiver operation characteristic curves for age and gender adjusted performance of prediction models. A-G: Each model is for a subset of patient population defined by the cutoffs and the size of the subpopulation showing at the top of each box.

Additional randomized controlled double-blind studies with a larger sample size are needed to confirm the findings of the present study.

CONCLUSION

The current study identified key associations among colorectal polyps, SIBO and IBFD while demonstrating the moderate potential of LBT as an alternative noninvasive screening tool for colorectal polyps. SIBO was more prevalent in patients with colorectal polyps than those without and IBFD was more severe in patients with colorectal polyp than those without only when SIBO has present. This study also found that colorectal polyps were more common in older individuals and men. Moreover,

patients with polyps tended to have metabolic disorders such as diabetes and hyperlipidemia and were less likely to have non-organic abnormalities such as functional gastrointestinal disease and IBS.

ARTICLE HIGHLIGHTS

Research background

Polyps can often be found and removed by colonoscopy; however, this is an invasive and expensive test. Due to its safety, accessibility, and affordability, the lactulose breath test (LBT) is widely used as a noninvasive method of diagnosing small intestine bacterial overgrowth (SIBO). SIBO suggests dysbiosis of the intestinal flora, which is associated with the pathogenesis of adenomatous polyps and colorectal cancer.

Research motivation

New methods that can identify precancerous colorectal lesions can play an important role in early-stage colorectal cancer treatment and prevention.

Research objectives

To identify a potential association between colorectal polyps and SIBO or other relevant factors in a patient cohort with LBT results.

Research methods

This retrospective analysis of data from a total of 382 patients who had received an LBT were collected. SIBO was diagnosed by measuring LBT-derived hydrogen (H) and methane (M) levels according to 2017 North American Consensus recommendations. Logistic regression was used to assess the ability of LBT to predict colorectal polyps. Intestinal barrier function damage (IBFD) was determined by blood assays.

Research results

H and M levels revealed that the prevalence of SIBO was significantly higher in the polyp group than in the non-polyp group (41% *vs* 23%; 71% *vs* 59%, respectively). Within 90 min of lactulose ingestion, the peak H values in the adenomatous and inflammatory/hyperplastic polyp patients were significantly higher than those in the non-polyp group. In regression analysis with age and gender adjustment, colorectal polyps were most accurately predicted with models using M peak values or combined H and M values limited by North American Consensus recommendations for SIBO. These models had a sensitivity of ≥ 0.67, a specificity of ≥ 0.64, and an accuracy of ≥ 0.66.

Research conclusions

The current study made key associations among colorectal polyps and SIBO and demonstrated that LBT has moderate potential as an alternative noninvasive screening tool for colorectal polyps.

Research perspectives

Due to its safety, accessibility, and affordability, the LBT has the potential to become one of the routine non-invasive screening methods for polyps and precancerous lesions. Furthermore, non-invasive tests such as fecal occult blood testing and LBT will help to improve the detection rate of precancerous lesions during colonoscopy screening.

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FOOTNOTES

Author contributions: Lan Li and Zhang XY have contributed equally to this work. Lan Li participated the study design and wrote the manuscript draft; Zhang XY conducted clinical data collections and participated the writing of the draft; Zhou HM and Qin Y performed lactulose breath test tests; Xie WR participated statistical analysis of the data; Ding WJ interpreted the lactulose breath test results; Yu JS participated the study design, performed the statistical analysis of the data, and edited the final version of the manuscript; He XX conceived the study concept and design, supervised all the work, provided the study funding, and reviewed the final version of the manuscript. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrollment.

Conflict-of-interest statement: The authors have no conflicts of interest to declare. There are no ethical or legal conflicts involved in the article.

Data sharing statement: Statistical code, and dataset available from the corresponding author at hexingxiang@gdpu.edu.cn. Participants gave informed consent for data sharing.

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ORIGINAL ARTICLE

Retrospective Study

Treatment outcome analysis of bevacizumab combined with cyclophosphamide and oxaliplatin in advanced pseudomyxoma peritonei

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Abstract

BACKGROUND

Pseudomyxoma peritonei (PMP) is a rare peritoneal malignant tumor syndrome. Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy is its standard treatment. However, there are few studies and insufficient evidence regarding systemic chemotherapy of advanced PMP. Regimens for colorectal cancer are often used clinically, but there is no uniform standard for late-stage treatment.

AIM

To determine if bevacizumab combined with cyclophosphamide and oxaliplatin (Bev+CTX+OXA) is effective for treatment of advanced PMP. The primary study endpoint was progression-free survival (PFS).

METHODS

Retrospective analysis was conducted on the clinical data of patients with advanced PMP who received Bev+CTX+OXA regimen (bevacizumab 7.5 mg/kg ivgtt d1, oxaliplatin 130 mg/m^2 ivgtt d1 and cyclophosphamide 500 mg/m^2 ivgtt d1, q3w) in our center from December 2015 to December 2020. Objective response rate (ORR), disease control rate (DCR) and incidence of adverse events were evaluated. PFS was followed up. Kaplan-Meier method was used to draw survival curve, and log-rank test was used for comparison between groups. Multivariate Cox proportional hazards regression model was used to analyze the independent influencing factors of PFS.

RESULTS

A total of 32 patients were enrolled. After 2 cycles, the ORR and DCR were 3.1% and 93.7%, respectively. The median follow-up time was 7.5 mo. During the

follow-up period, 14 patients (43.8%) had disease progression, and the median PFS was 8.9 mo. Stratified analysis showed that the PFS of patients with a preoperative increase in CA125 (8.9 *vs* 2.1, P = 0.022) and a completeness of cytoreduction score of 2-3 (8.9 *vs* 5.0, P = 0.043) was significantly longer than that of the control group. Multivariate analysis showed that a preoperative increase in CA125 was an independent prognostic factor for PFS (HR = 0.245, 95%CI: 0.066-0.904, P = 0.035).

CONCLUSION

Our retrospective assessment confirmed that the Bev+CTX+OXA regimen is effective in second- or posterior-line treatment of advanced PMP and that adverse reactions can be tolerated. A preoperative increase in CA125 is an independent prognostic factor of PFS.

Key Words: Pseudomyxoma peritonei; Bevacizumab; Oxaliplatin; Cyclophosphamide

Core Tip: For systemic chemotherapy of advanced pseudomyxoma peritonei (PMP), there are currently few studies and insufficient evidence. In this study, the bevacizumab combined with cyclophosphamide and oxaliplatin regimen was used for advanced PMP for the first time. The scheme used in this study was based on clinical experience and had achieved good results.

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INTRODUCTION

Pseudomyxoma peritonei (PMP) is a rare peritoneal malignant tumor syndrome with an incidence of approximately 2 to 4 per 1 million[1]. It is characterized by accumulation and redistribution of mucus produced by mucinous tumor cells in the abdominal cavity, mainly from appendiceal mucinous tumors. Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is the standard treatment for PMP[2,3]. Our previous work showed obvious clinical benefits after standardized CRS + HIPEC treatment, with a median survival time after surgery of 55.4 mo[4], but the postoperative recurrence and metastasis rate is still high. For patients with advanced PMP who have no chance of surgery, systemic chemotherapy regimens for colorectal cancer are often used clinically, such as FOLFOX, FOLFIRI, or FOLFOX combined with bevacizumab[5]. The disease control rate (DCR) is 65.0% to 88.0%, with a median progression-free survival (PFS) of 8 to 13 mo[6-8]. However, there is no uniform standard for second- or posterior-line treatment. Therefore, exploring feasible treatment options is still a clinical problem that needs to be solved.

Cyclophosphamide (CTX) is a nitrogen mustard alkylating agent that has been used in the treatment of a variety of solid tumors. Application of CTX for treating PMP can be traced back to the 1950s[9]. Recent studies have reported that the DCR of CTX combined with capecitabine for PMP is 87.0%[10]. To date, there has been no report on the use of bevacizumab combined with CTX and oxaliplatin (hereinafter referred to as the Bev+CTX+OXA regimen) to treat PMP. This single-center, retrospective study aimed to evaluate the efficacy, safety, and prognosis of the Bev+CTX+OXA regimen for patients with unresectable PMP.

MATERIALS AND METHODS

Patients

This was a retrospective study involving clinical data of patients with advanced PMP who received the Bev+CTX+OXA regimen in the Department of Peritoneal Cancer Surgery in Beijing Shijitan Hospital affiliated with Capital Medical University from December 2015 to December 2020.

The inclusion criteria were as follows: (1) Pathologic confirmation of PMP; (2) Incomplete CRS + HIPEC treatment or recurrence and metastasis after complete CRS + HIPEC treatment that could not be operated on again; (3) Received at least first-line or above chemotherapy; (4) Karnofsky performance

status > 60 points; (5) Measurable target lesions; (6) Received at least 2 cycles of treatment with the Bev+CTX+OXA regimen; and (7) Complete clinical pathology and follow-up data.

Exclusion criteria were: (1) Concomitant other malignant tumors; (2) Unable to complete the efficacy evaluation; (3) PMP from a noncolorectal origin; and (4) Follow-up time < 3 mo. In this study, application of chemotherapy regimens was carried out with the informed consent of patients and their families.

Treatment plan

The following drugs were used: Bevacizumab (bevacizumab, Bev, Avastin, Germany/Roche Diagnostics GmbH, 400 mg (16 mL)/bottle), 7.5 mg/kg, d1, ivgtt (60-90 min), q3w; oxaliplatin (oxaliplatin, L-OHP, Jiangsu Hengrui Pharmaceuticals Co., Ltd., National Medicine Standard H20000337, 50 mg/bottle), 130 mg/m^2, d1, ivgtt (120 min), q3w; and CTX [CTX (endoxan), CTX, Baxter Oncology GmbH, 200 mg/bottle], 500 mg/m^2, ivgtt (approximately 30 min), q3w. Patients received this regimen until the disease progressed or an intolerable adverse reaction occurred or the patient withdrew informed consent. When patients had drug-related grade III or above adverse reactions during treatment, the dose was reduced by 25%; if it was still not tolerated, we adjusted to single-agent maintenance therapy or changed the chemotherapy regimen. Such cases were censored.

The primary study endpoint was PFS, as defined as the time from when a patient started receiving treatment to disease progression, death, or the follow-up deadline. The last follow-up date was July 4, 2021.

Efficacy and safety evaluation

All patients received baseline examinations before treatment, including routine blood, liver and kidney function, tumor marker, electrocardiogram, and CT scans of measurable target lesions. Imaging evaluation was carried out before and every 2 cycles of treatment, and we identified the most defined and clearly assessable lesions that we chose as target lesions. Efficacy was evaluated according to "Response Evaluation Criteria in Solid Tumors" (RECIST) version 1.1 criteria by a radiologist with special expertise to define complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). We calculated the objective response rate (ORR) by (CR + PR)/total number of cases × 100% and the DCR by (CR + PR + SD)/total number of cases × 100%. Short-term efficacy in all patients was determined at the end of the second cycle. Serum tumor markers were evaluated once a month. The level of serum tumor markers at the beginning of treatment and the lowest level of serum tumor markers during treatment were used to evaluate chemotherapy response. The safety evaluation adopted National Cancer Institute Common Terminology Criteria.

Statistical analysis

SPSS 19.0 software (SPSS Inc., Chicago, IL, United States) and R studio 4.1.0 software (http://www.rstudio.com/) were used for statistical analysis. Measurement data are expressed as the median (range) or x ± s, and enumeration data are expressed as the rate. The Kaplan-Meier method was used to draw survival curves, and the log-rank test was used for comparisons between groups. The Cox proportional hazard regression model was employed to perform univariate analysis, and factors with $P < 0.1$ were included in multivariate analysis. The Wilcoxon paired signed rank test was used to compare changes in tumor markers before and after treatment. Bilateral $P < 0.05$ was considered statistically significant.

RESULTS

Clinicopathological characteristics

A total of 41 patients with advanced unresectable PMP received the Bev+CTX+OXA regimen, and 9 cases were excluded according to the inclusion and exclusion criteria. Finally, 32 patients were enrolled in the study (Figure 1A), and the swimmer plot of the 32 patients was shown in Figure 1B. Among them, 24 (75%) were males and 8 (25%) females, with a median age of 57.5 (34-74) years. The main clinicopathological characteristics are shown in Table 1.

Short-term efficacy and PFS

The median chemotherapy cycle of 32 patients was 4 (2-11) cycles. After 2 cycles, 1 (3.1%) case of PR, 29 (90.6%) cases of SD, and 2 (6.3%) cases of PD were observed; the ORR and DCR were 3.1% and 93.7%, respectively. The median follow-up time was 7.5 mo. During the follow-up period, 14 (43.8%) patients experienced disease progression, and the median PFS was 8.9 mo (95%CI: 6.53-11.18), as shown in Figure 2A. By the end of follow-up, no deaths had occurred. The stratified analysis showed that patients with a preoperative increase in CA125 (8.9 *vs* 2.1, $P = 0.022$, Figure 2B) and a completeness of cytoreduction (CC) score of 2-3 (8.9 *vs* 5.0, $P = 0.043$, Figure 2C) had prolonged PFS, which was significantly different from the control group.

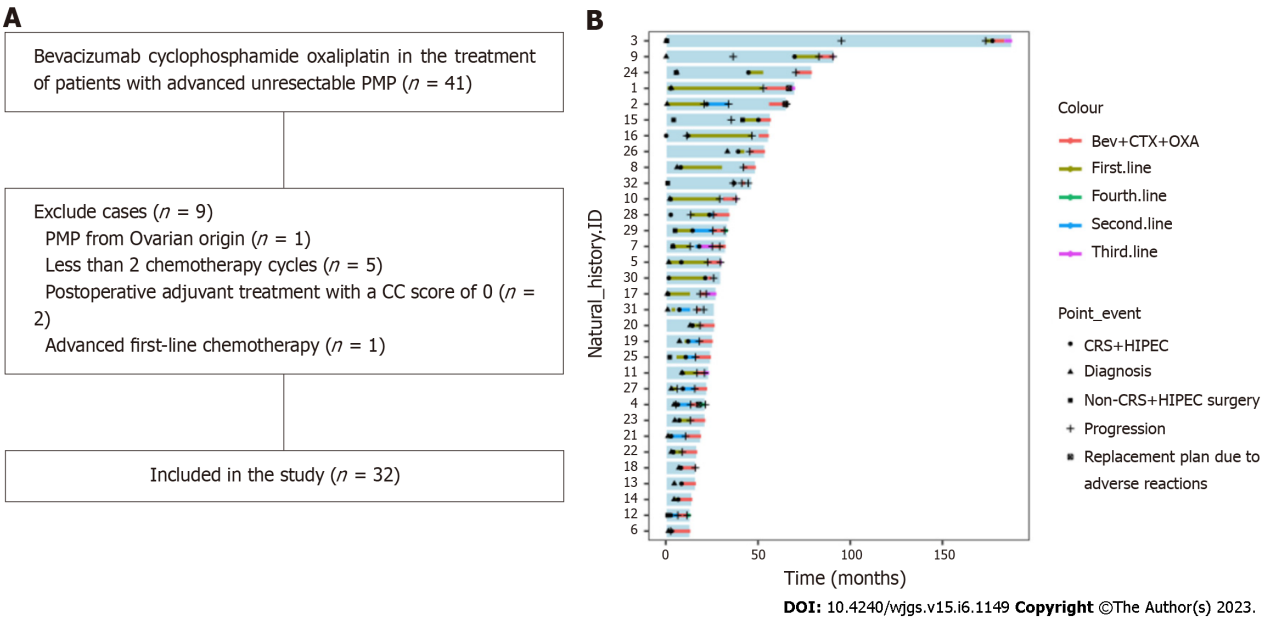

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Figure 1 Study design. A: Flow chart; B: Swimmer plot of the 32 patients. PMP: Pseudomyxoma peritonei; CC: Completeness of cytoreduction; Bev+CTX+OXA: Bevacizumab combined with cyclophosphamide and oxaliplatin; CRS: Cytoreductive surgery; HIPEC: Hyperthermic intraperitoneal chemotherapy.

Adverse events

Adverse events occurred in 24 (75.0%) patients. The most common adverse events were neutropenia, anemia, and nausea and vomiting. One (3.1%) patient was allergic to oxaliplatin, and we replaced oxaliplatin with irinotecan. Five (15.6%) patients had grade 3 adverse events that were improved through dose reduction and symptomatic treatment, including 2 (6.3%) cases of neutropenia, 4 (12.5%) cases of anemia, 1 (3.1%) case of nausea and vomiting, and 1 (3.1%) case of proteinuria. In 2 (2.3%) patients, we replaced oxaliplatin with carboplatin due to grade 3 peripheral neurotoxicity (Table 2).

Changes in tumor markers

The mean values of serum CA199, carcinoembryonic antigen (CEA) and CA125 levels of 32 patients before chemotherapy were 844.17 ± 462.33 U/mL, 72.95 ± 25.22 ng/mL and 39.51 ± 6.15 U/mL, respectively. The mean minimum values during the treatment were 668.54 ± 384.65 U/mL, 71.65 ± 25.12 ng/mL and 27.41 ± 5.29 U/mL respectively. Both had a downward trend compared with that before treatment, but the difference was not statistically significant (Figure 3).

Analysis of influencing factors for PFS

Univariate analysis showed that the following two factors were related to PFS ($P < 0.1$): Preoperative increase of CA125 ($P = 0.035$), CC score was 2-3 points ($P = 0.054$). Multivariate analysis showed that preoperative increase of CA125 was an independent prognostic factor of PFS (HR = 0.245, 95%CI: 0.066-0.904, $P = 0.035$) (Table 3).

DISCUSSION

For systemic chemotherapy of advanced PMP, there are currently few studies and insufficient evidence. In this study, the Bev+CTX+OXA regimen was used for advanced PMP for the first time. The results showed that although the ORR was only 3.1%, the DCR reached 93.7%. This result is higher than the DCR with Pietrantonio *et al*'s FOLFOX4 and Hiraide *et al*'s mFOLFOX6 regimens, suggesting that this regimen has a certain effect on patients with advanced PMP[6,7]. We consider the following reasons. First, CTX was added to this regimen for the first time. Some studies have shown that CTX has a certain immunomodulatory effect[11]. Research suggests that low-dose CTX can induce secretion of interferon-γ, thereby enhancing the antitumor immune response in mice, which may be one of the underlying mechanisms[12,13]. Second, studies have shown that screening for gene mutations related to vascular endothelial growth factor (VEGF) signal transduction and administering anti-VEGF therapy may provide new options for treatment of patients with refractory/relapsed advanced PMP[14-16]. In this study, 59.4% of tumors were positive for VEGF expression. The higher DCR may be related to inhibition of VEGF and its downstream pathways by addition of bevacizumab. It is worth noting that 59.4% of the patients in this study had previously used bevacizumab; considering the clear evidence for

Table 1 Clinicopathological characteristics of 32 pseudomyxoma peritonei patients

Characteristic	No. of patients (%)
Sex	
Male	24 (75)
Female	8 (25)
Age (years), median (rang)	57.5 (34-74)
BSA (m^2), median (rang)	1.69 (1.27-2.07)
KPS score, median (rang)	90 (60-100)
PCI score, median (rang)	31 (16-39)
Ca199 before chemotherapy, median (rang), U/mL	46.09 (4.68-10707.5)
CEA before chemotherapy, median (rang), ng/mL	16.63 (1.08-632.27)
Ca125 before chemotherapy, median (rang), U/mL	26.25 (5.3-146.7)
CC score	
0-1	8 (25)
2-3	24 (75)
Histological diagnosis	
Low-grade	12 (37.5)
High-grade	18 (56.2)
High-grade with signet ring cells	2 (6.3)
Lymph node metastasis	
Yes	2 (6.3)
No	30 (93.7)
Vascular tumor thrombus	
Yes	2 (6.3)
No	30 (93.7)
Nerve invasion	
Yes	2 (6.3)
No	30 (93.7)
VEGF expression	
Positive	19 (59.4)
Negative	3 (9.4)
Unknown	10 (31.2)
Microsatellite status	
MSS	14 (43.8)
MSI-L	1 (3.1)
Unknown	17 (53.1)
Past use of bevacizumab	
Yes	13 (40.6)
No	19 (59.4)
First-line chemotherapy (months), median (rang)	4.72 (0.01-34.73)

BSA: Body surface area; KPS: Karnofsky performance status; PCI: Peritoneal cancer index; CC: Completeness of cytoreduction; VEGF: Vascular endothelial growth factor; MSS: Microsatellite stability; MSI-L: Low microsatellite instability; CEA: Carcinoembryonic antigen.

Table 2 Adverse events, *n* (%)

Adverse events	Total	Grade 1-2	Grade 3-5
Total	24 (75.0)	20 (62.5)	5 (15.6)
Neutropenia	14 (43.8)	12 (37.5)	2 (6.3)
Thrombocytopenia	1 (3.1)	1 (3.1)	0 (0)
Anemia	16 (50.0)	12 (37.5)	4 (12.5)
Peripheral neurotoxicity	8 (25.0)	6 (18.8)	2 (6.3)
Fatigue	9 (28.1)	9 (28.1)	0 (0)
Nausea and vomiting	15 (46.9)	14 (43.8)	1 (3.1)
Liver damage	7 (21.9)	7 (21.9)	0 (0)
Renal impairment	9 (28.1)	9 (28.1)	0 (0)
Proteinuria	5 (15.6)	4 (12.5)	1 (3.1)
Hypertension	5 (15.6)	5 (15.6)	0 (0)
Allergy	1 (3.1)	1 (3.1)	0 (0)

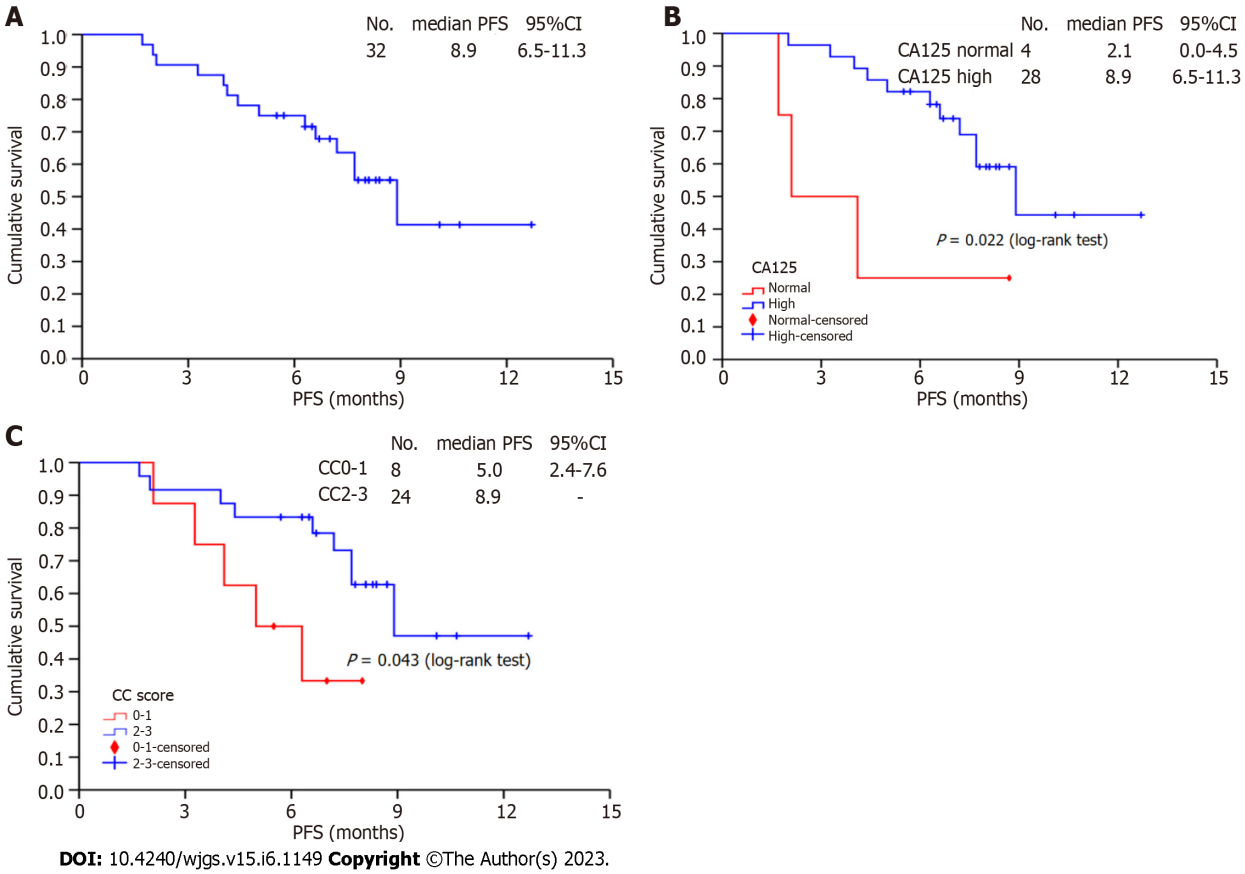

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Figure 2 Progression-free survival for 32 patients. A: Total progression-free survival; B: Stratified analysis of preoperative CA125; C: Stratified analysis of completeness of cytoreduction score. PFS: Progression-free survival; CC: Completeness of cytoreduction.

bevacizumab in cross-line treatment of a variety of solid tumors, we did not remove it. The results of the study also showed that whether bevacizumab has been used in the past did not affect PFS, suggesting that in second- or posterior-line treatment of patients with advanced PMP, cross-line application of bevacizumab may still bring survival benefits.

In terms of adverse events, 24 (75.0%) patients had adverse events, 2 (6.3%) patients had grade 3 neutropenia, and 4 (12.5%) patients had grade 3 anemia. These rates are slightly higher than those of Pietrantonio *et al*[7] and Hiraide *et al*[6], but lower than that of Raimondi[10]. This may be related to the fact that our enrolled population had received at least first-line chemotherapy in the past, which may

Table 3 Analysis of influencing factors for progression-free survival

Prognostic factors	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Sex (female *vs* male)	0.522	0.143-1.906	0.325		-	-
Age (< 60 *vs* ≥ 60)	0.630	0.208-1.910	0.414		-	-
Preoperative CEA (increased *vs* normal)	1.383	0.309-6.193	0.671	-	-	-
Preoperative CA199 (increased *vs* normal)	1.289	0.446-3.725	0.639			
Preoperative CA125 (increased *vs* normal)	0.245	0.066-0.904	0.035	0.245	0.066-0.904	0.035
KPS (≥ 80 *vs* < 80)	0.946	0.119-7.493	0.958			
CC (2-3 *vs* 0-1)	0.319	0.100-1.012	0.054	0.351	0.106-1.164	0.087
Pathology (high-grade with signet ring cells *vs* high-grade *vs* low-grade)	1.247	0.463-3.357	0.662			
Lymph node metastasis (yes *vs* no)	0.044	0.000-435.823	0.506			
Vascular tumor thrombus (yes *vs* no)	0.044	0.000-435.823	0.506			
Nerve invasion (yes *vs* no)	0.043	0.000-196.970	0.464			
VEGF expression (+ *vs* -)	0.764	0.157-3.712	0.739			
CA199 before chemotherapy (increased *vs* normal)	0.764	0.266-2.197	0.618			
CEA before chemotherapy (increased *vs* normal)	0.743	0.232-2.379	0.616			
CA125 before chemotherapy (increased *vs* normal)	1.401	0.489-4.014	0.530			

CEA: Carcinoembryonic antigen; KPS: Karnofsky performance status; CC: Completeness of cytoreduction.

have caused a decline in bone marrow hematopoietic function. In terms of proteinuria and peripheral neurotoxicity, the rate of grade 3 adverse events in this study was not high, and the grade 1-2 adverse events were all alleviated by symptomatic treatment, suggesting that the regimen can be tolerated.

During the treatment period of this study, serum CEA, CA125, and CA199 levels exhibited a downward trend. Although the difference was not statistically significant, this trend is still worth noting. The research of Randall *et al*[17] showed that in patients with epithelial ovarian cancer and peritoneal cancer continuously treated with bevacizumab, RECIST and CA125 are related in disease evaluation. Approximately 10% of patients may be found disease progression earlier through CA125. Hiraide *et al*[6] and others also used tumor markers as a method to monitor the efficacy. This provides a certain basis for monitoring efficacy in patients with no measurable lesions in the future. The median PFS in this study was 8.9 mo, which was lower than that with the FOLFOX4[6] and mFOLFOX6[7] regimens. However, considering that the mediean follow-up time of this study was only 7.5 mo, the median chemotherapy cycle was 4 cycles; thus, further follow-up is still needed to assess the PFS with this program. At the same time, 62.5% of patients with high-grade pathological types were included in this study, and patients with CC scores 2-3 accounted for 75%. These poor baseline data may limit the improvement in PFS. Stratified analysis and multivariate analysis showed that a preoperative increase in serum CA125 is an independent prognostic factor of prolonged PFS in this study. However, this trend was not observed in patients with elevated CA125 at the beginning of this regimen, which may be related to the surgical cytoreduction and previous chemotherapy that caused a significant decrease in serum CA125 before this regimen. The patients in this study had symptoms of abdominal and pelvic effusion during initial treatment. Previous studies have shown that an increase in CA125 is related to the degree of ascites. Anti-VEGF treatment can inhibit neovascularization and has obvious benefits for ascites control. This may be one of the reasons for the prolonged PFS of these patients. On the other hand, stratified analysis showed that the PFS of the patients with CC scores of 2-3 was prolonged, but the CC score in multivariate analysis was not an independent prognostic factor. This may be related to the large proportion of patients with CC scores of 2-3, and further research is needed for verification.

This study has certain limitations. First, this study was a single-center retrospective study. The previous treatment plan, clinical pathological data and biological characteristics of the enrolled patients were heterogeneous, which will lead to patient selection bias in the results. Second, the sample size was small, and the follow-up time was short, leading to some results that may be contrary to theory. In general, selection of beneficial regimens needs to be verified by expanding the sample and extending the follow-up time. Third, this study did not establish a control group.

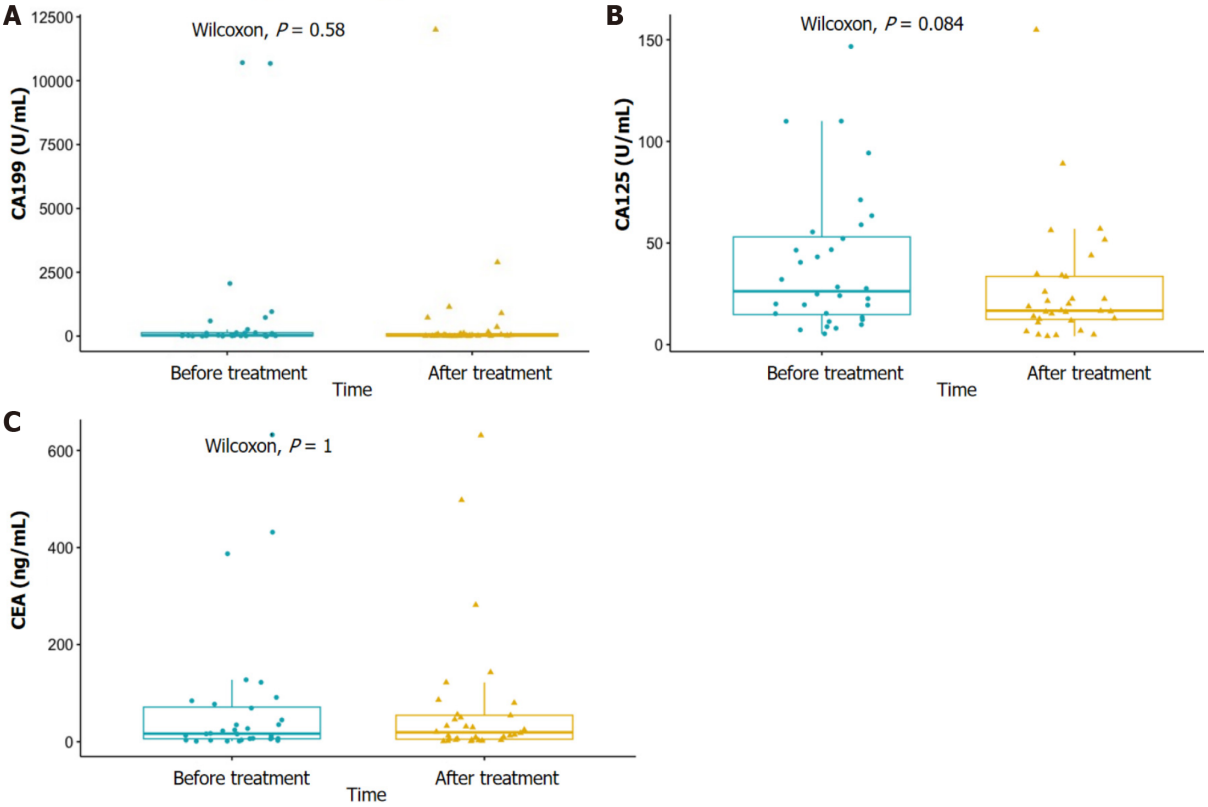

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Figure 3 Changes in serum tumor markers in 32 patients before and after treatment. A: Changes in CA199 before and after treatment; B: Changes in CA125 before and after treatment; C: Changes in carcinoembryonic antigen before and after treatment. CEA: Carcinoembryonic antigen.

CONCLUSION

In summary, the Bev+CTX+OXA regimen is effective in second- or posterior-line treatment of advanced PMP, and adverse reactions can be tolerated. A preoperative increase in CA125 is an independent prognostic factor of PFS.

ARTICLE HIGHLIGHTS

Research background

Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy is its standard treatment. But for systemic chemotherapy of advanced pseudomyxoma peritonei (PMP), there are currently few studies and insufficient evidence.

Research motivation

Regimens for colorectal cancer are often used clinically, but there is no uniform standard for late-stage treatment.

Research objectives

The purpose of this single-center, retrospective study was to determine if bevacizumab combined with cyclophosphamide and oxaliplatin (Bev+CTX+OXA) is effective for treatment of advanced PMP.

Research methods

Retrospective analysis was conducted on the clinical data of patients with advanced PMP who received Bev+CTX+OXA regimen from December 2015 to December 2020. Objective response rate (ORR), disease control rate (DCR) and incidence of adverse events were evaluated. Progression-free survival (PFS) was followed up.

Research results

A total of 32 patients were enrolled, after 2 cycles, ORR and DCR were 3.1% and 93.7% respectively. The

median follow-up time was 7.5 mo. During the follow-up period, 14 patients (43.8%) had disease progression, and the median progression-free survival (PFS) was 8.9 mo. Stratified analysis showed that the PFS of patients with preoperative increase of CA125 (8.9 *vs* 2.1, P = 0.022) and completeness of cytoreduction score of 2-3 (8.9 *vs* 5.0, P = 0.043) were significantly longer than those of the control group. Multivariate analysis showed that preoperative increase of CA125 was an independent prognostic factor for PFS (HR = 0.245, 95%CI: 0.066-0.904, P = 0.035).

Research conclusions

Bev+CTX+OXA regimen is certain effective in the posterior-line treatment of advanced PMP, and the adverse reactions can be tolerated. The preoperative increase of CA125 is an independent prognostic factor of PFS.

Research perspectives

More sample size should be conduct in the future to validate the conclusion of our study.

FOOTNOTES

Author contributions: Zhao X and Gao C collected the data; Zhang Y and Lin LY performed the data analysis; Zhang Y wrote the original draft preparation; Zhang Y and Li Y wrote the review and editing; Li Y contributed to the supervision.

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Institutional review board statement: This study was reviewed and approved by the ethics committee of Beijing Shijitan Hospital, Capital Medical University, No. sjtkyll-lx-2022(066).

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ORIGINAL ARTICLE

Retrospective Study

Surgical management of duodenal Crohn's disease

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Abstract

BACKGROUND

The case of Crohn's disease involving the duodenum is rare, and its surgical management requires a thorough understanding.

AIM

To investigate the surgical management of duodenal Crohn's disease.

METHODS

We systematically reviewed patients diagnosed with duodenal Crohn's disease who underwent surgery in the Department of Geriatrics Surgery of the Second Xiangya Hospital of Central South University from January 1, 2004, to August 31, 2022. The general information, surgical procedures, prognosis, and other information of these patients were collected and summarized.

RESULTS

A total of 16 patients were diagnosed with duodenal Crohn's disease, where 6 cases had primary duodenal Crohn's disease, and 10 had secondary duodenal Crohn's disease. Among patients with primary disease, 5 underwent duodenal bypass and gastrojejunostomy, and 1 received pancreaticoduodenectomy. Among those with a secondary disease, 6 underwent closure of duodenal defect and colectomy, 3 received duodenal lesion exclusion and right hemicolectomy, and 1 underwent duodenal lesion exclusion and double-lumen ileostomy.

CONCLUSION
Crohn's disease involving the duodenum is a rare condition. Different surgical management should be applied for patients with Crohn's disease presenting with different clinical manifestations.

Key Words: Duodenum; Crohn's disease; Surgical treatment; Inflammatory bowel disease

Core Tip: Crohn's disease is a chronic, incurable inflammatory disease that affects the gastrointestinal tract function and causes extraintestinal complications. Crohn's disease involving the duodenum is a rare condition and different surgical management should be applied for patients with Crohn's disease presenting with different clinical manifestations. This study mainly summarized the surgical approaches and prognosis of 16 patients with duodenal Crohn's disease, thus providing some reference for the surgical management of the disease.

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INTRODUCTION

Crohn's disease is a chronic, incurable inflammatory disease that affects the gastrointestinal tract function and causes extraintestinal complications. Its prevalence is rising in adults and children with confirmed genetic susceptibility and is associated with specific environmental factors. Common symptoms include diarrhea, abdominal pain, rectal bleeding, fever, weight loss, and fatigue[1]. More than 50% of the patients have strictures or penetrating complications in the first 10 years after diagnosis. Surgery, followed by biotherapy, immunomodulators, and leukocyte isolation therapy, is the most common treatment method[2]. The stricture-induced intestinal obstruction is one of the common surgical indications, followed by intestinal obstruction, fistula, and abscess formation[3,4]. Chronic inflammation may involve any portion of the gastrointestinal tract; however, it is more common in the terminal ileum and proximal colon while it is rarely observed in the stomach and duodenum. Most cases of duodenal Crohn's disease present as a secondary disease, accounting for about 2% of all Crohn's disease cases[5]. The most common manifestation of gastroduodenal Crohn's disease is stricture, leading to obstructive symptoms. Its diagnostic criteria include typical lesions involving the whole stomach, mucosal abscesses, and sinuses connected with fissures; loose tuberculous-like lesions; no tuberculosis, fungi, foreign bodies, or parasites in the lesions; typical regional enteritis in the small intestine[6]. Treatment of the duodenal Crohn's disease includes proton pump inhibitors and biotherapy. Endoscopic and surgical treatment may be needed to resolve the obstruction-like symptoms of the strictures [7]. The most common surgical procedures for duodenal Crohn's disease include resection, bypass, and angioplasty, which are chosen based on the affected portion of the duodenum, the number and length of strictures, and other portions lesions of the gastrointestinal tract[7]. No unified standard operation has been developed so far.

This study mainly summarized the surgical approaches and prognosis of 16 patients with duodenal Crohn's disease who underwent surgeries in the Department of Geriatric Surgery of the Second Xiangya Hospital of Central South University between January 1, 2004, and August 31, 2022, thus providing some reference for the surgical treatment of the disease.

MATERIALS AND METHODS

Data collection

Data from patients with duodenal Crohn's disease undergoing surgeries in the Department of Geriatric Surgery, the Second Xiangya Hospital of Central South University between January 1, 2004, and August 31, 2022, were reviewed.

Inclusion criteria

Crohn's disease diagnosed according to the Consensus Opinions on the Diagnosis and Treatment of Inflammatory Bowel Disease from the Inflammatory Bowel Disease Group of Gastroenterology Society of Chinese Medical Association in 2018); duodenal lesions have been confirmed by gastroscopy, colonoscopy, computed tomography (CT) and gastrointestinal radiography combined with intraoperative observation.

Exclusion criteria

Non-Crohn's disease; patients diagnosed with Crohn's disease that was not confirmed by pathology.

Ethic statements

Patients' clinical information, including name, gender, age, type of disease, personal history, clinical manifestations, disease behavior, location of disease, surgical approach, and prognosis was collected and analyzed. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of The Second Xiangya Hospital of Central South University, Approval No. 2022-155 (Approval date: September 28, 2022). Informed consent and consent for publication were obtained from all subjects involved in the study.

RESULTS

Finally, 16 patients (11 males and 5 females) were included in the study, with an average age of 30.25 years and a median age of 30 years (Table 1). All patients had a chronic relapse, and one had a history of smoking. There were 6 cases with diarrhea, 4 cases with nausea and vomiting, and 9 cases with intestinal obstruction. According to Montreal classification, 16 patients were A2 type; lesion location (L): 1 case of L1 + L4 type, 2 cases of L2 + L4 type, 7 cases of L3 + L4 type, 6 cases of L4 type; disease behavior (B): 9 cases of B2 type, 7 cases of B2 + B3 type (Table 2). Almost all the patients were transferred to our department for surgery after treatment in the Department of Gastroenterology and had received one or more treatments, including mesalamine, azathioprine, steroid, anti-tumor necrosis factor (anti-TNF), nutritional support, or anti-inflammatory treatment preoperatively.

Preoperative treatment and imaging examination

Before the hospitalization, 16 patients had received medical treatment for clinical symptoms: six patients received 5-ASA, two patients received steroid plus azathioprine, three patients received 5-ASA plus steroid plus azathioprine, and five patients received biological agents. All patients had different degrees of incomplete intestinal obstruction before the operation. Partial parenteral nutrition and dietary management were given to most patients with mild obstruction to improve their nutritional status and enhance their ability to withstand surgery. For the five patients with severe duodenal obstruction, balloon dilation and jejunal nutrient tube insertion were attempted in the stenosis segment under the endoscope before surgery. Among the 5 patients, one patient received complete parenteral nutrition due to the severe duodenal stenosis, which made the jejunal nutrition tube unable to cross the stenosis segment. The other four patients were successfully implanted with jejunal nutrition tubes (Figure 1) and received adequate enteral nutrition for 2-3 wk before surgery. All patients were transferred to our department for surgery when they were in good nutritional status, and the disease was in state of remission. Gastroscopy, colonoscopy, CT, and gastrointestinal radiography were performed in our hospital before the operation. The abdominal CT images (Figure 1A) and gastrointestinal radiography (Figure 1B) in 6 patients confirmed the existence of an internal fistula between the duodenum and colon. The internal fistula between the duodenum and colon could be seen under gastroscopy (Figure 1C) and colonoscopy (Figure 1D) in six patients.

Surgery

Duodenal Crohn's disease included primary and secondary duodenal Crohn's disease. Among 16 patients, there were 6 cases with primary duodenal Crohn's disease (5 cases had duodenal strictures and 1 case had tumor-like lesions) and 10 cases of secondary duodenal Crohn's disease (6 cases had an internal fistula and 4 cases had no internal fistula). All the 16 cases had indications for surgery, without obvious contraindications. Of the 6 patients with primary duodenal Crohn's disease, 5 underwent duodenal bypass and gastrojejunostomy, and 1 underwent pancreatoduodenectomy. Of the 10 patients with secondary duodenal Crohn's disease, 6 underwent duodenal defect closure and diseased intestinal segment resection, 3 underwent duodenal lesion exclusion and right hemicolectomy, and 1 underwent duodenal lesion exclusion and double-lumen ileostomy (Table 1).

Postoperative treatment and prognosis

To timely manage postoperative complications, all patients need to be hospitalized in the surgical ward for a while after surgery before being transferred to the department of gastroenterology. The duration of

Table 1 Basic information, the primary site of lesion, and detailed information of surgical approaches of 16 patients with duodenal Crohn's disease

Classification	Sex	Age	Primary site	Manifestation	Surgical approach	Postoperative surgical recurrence
Primary	Female	29	Duodenum	Stricture	Duodenal bypass and gastrojejunostomy	No
	Female	35	Duodenum	Stricture	Duodenal bypass and gastrojejunostomy	No
	Female	30	Duodenum	Stricture	Duodenal bypass and gastrojejunostomy	No
	Male	20	Duodenum	Stricture	Duodenal bypass and gastrojejunostomy	No
	Male	25	Duodenum	Stricture	Duodenal bypass and gastrojejunostomy	No
	Male	29	Duodenum	Tumor-like	Pancreaticoduodenectomy	No
Secondary	Male	26	Ileocolon	Internal fistula (d = 0.3 cm)	Direct closure of the duodenal defect and right hemicolectomy	No
	Male	30	Ascending colon	Internal fistula (d = 1 cm)	Direct closure of the duodenal defect and subtotal colectomy	No
	Female	20	Right hemicolon	Internal fistula (d = 1 cm)	Direct closure of the duodenal defect and right hemicolectomy	No
	Male	37	Right hemicolon	Internal fistula (d = 5.0 cm)	Closure of duodenal defect with pedicled terminal ileum flap, right hemicolectomy	No
	Male	41	Right hemicolon	Internal fistula (d = 3.5 cm)	Closure of duodenal defect with pedicled terminal ileum flap, right hemicolectomy	No
	Male	32	Ascending colon	Internal fistula (d = 3.5 cm)	Closure of duodenal defect with pedicled terminal ileum flap and ascending colectomy	No
	Female	23	Right hemicolon	Without internal fistula	Duodenal lesion exclusion and right hemicolectomy	No
	Male	39	Ileocolon	Without internal fistula	Duodenal lesion exclusion and right hemicolectomy	No
	Male	32	Right hemicolon	Without internal fistula	Duodenal lesion exclusion and right hemicolectomy	No
	Male	36	Ileum	Without internal fistula	Duodenal lesion exclusion and double lumen ileostomy	No

"d" is the size of duodenal defect (cm).

Table 2 Montreal classification of patients with Crohn's disease (*n* = 16)

Item	Group	Frequency	Constituent ratio (%)
Diseased location (L)	L4: Upper gastrointestinal tract	6	38
	L1 + L4: Ileum + upper gastrointestinal tract	1	6
	L2 + L4: Colon + upper gastrointestinal tract	2	12
	L3 + L4: Ileocolon + upper gastrointestinal tract	7	44
Disease behavior (B)	B2: Stenotic type	9	56
	B2 + B3: Stenotic penetration type	7	44

this period mainly depends on whether there is an anastomosis in the duodenum and the healing of the anastomosis. In addition, the jejunal nutrition tube across the duodenal anastomosis could enable patients to receive enteral nutrition as early as possible after surgery, which helps to maintain the physiological homeostasis of the intestinal tract and accelerate the postoperative recovery of the body. Furthermore, if obstruction occurred, the customarily secreted gastric juice can be drawn out of the body through the gastrostomy tube to prevent fluid accumulation at the anastomotic site and reduce the risk of duodenal anastomotic leakage as much as possible. All patients had no severe complications and were successfully transferred to the department of gastroenterology for follow-up treatment. Eight patients continued to receive anti-TNF four weeks after the operation, seven patients received 5-ASA maintenance therapy, and one patient who underwent pancreaticoduodenectomy did not receive

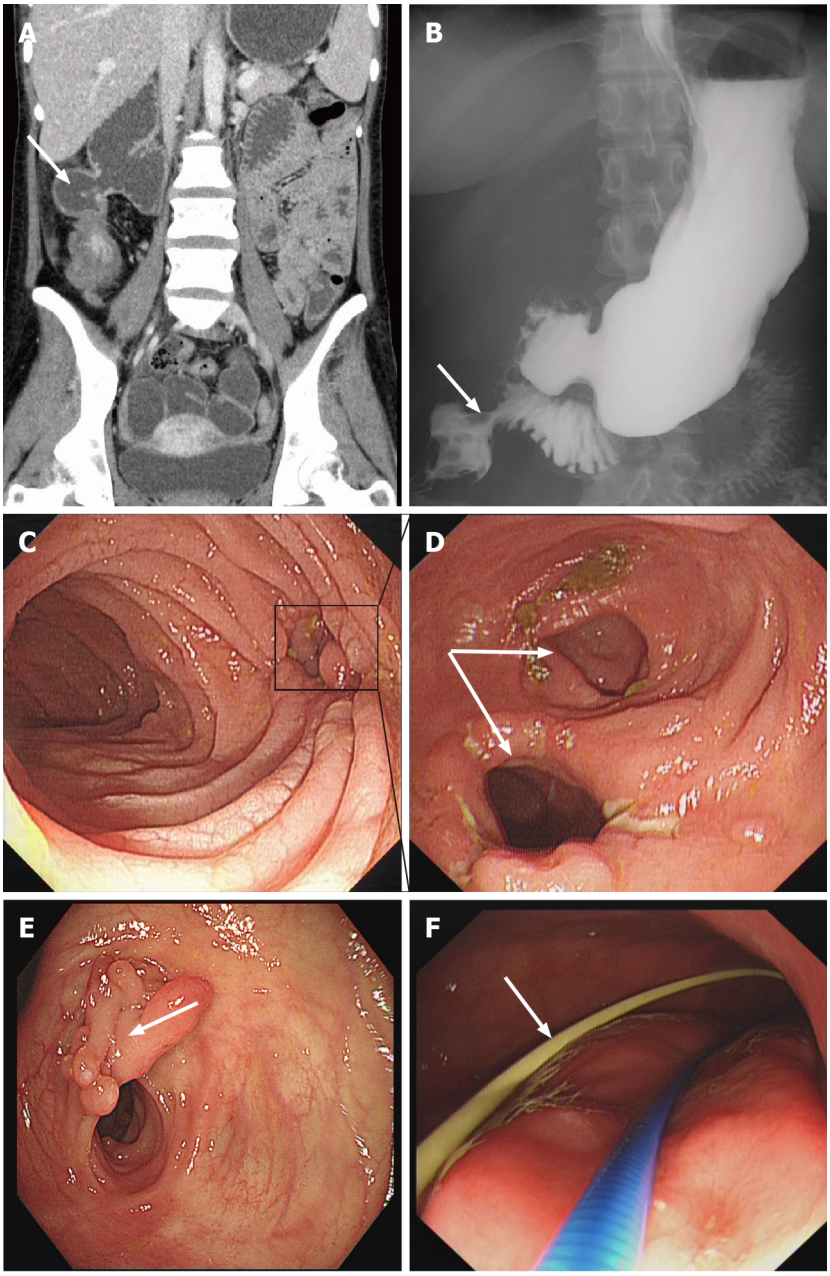

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Figure 1 The imaging examinations of patients with an internal fistula between the duodenum and colon. A: The abdominal computed tomography image showed the existence of an internal fistula between the duodenum and colon; B: The gastrointestinal radiography showed the existence of an internal fistula between the duodenum and colon; C: The ileocecus can be accessed through the internal duodenal fistula under gastroscopy; D: The internal fistula between the duodenum and colon under colonoscopy; E: The placement of jejunal nutrition tube under gastroscope.

appropriate medical treatment. Due to the high postoperative recurrence rate of Crohn's disease, active follow-up was carried out for all the patients. All patients received a follow-up period of at least 6 mo, and the most extended follow-up period was about 18 years. All patients received the serological examination (Table 3) and abdominal CT examination three months after the operation, and digestive tract endoscopy six months after the procedure, and no sign of clinical recurrence was found. The patient who underwent pancreaticoduodenectomy developed severe fatty diarrhea two years after the operation and received pancreaticojejunostomy that year. Still, the effect of the process was poor, which seriously affected the patient's quality of life.

DISCUSSION

Surgical treatment for primary duodenal Crohn's disease

Duodenal strictureplasty: Resection anastomosis of duodenal stricture is suitable for horizontal or

Table 3 Results of laboratory examination and body mass index in patients with duodenal Crohn's disease before and after surgery

mean ± SD	Pre-operation	Post-operation			
		Day 1	Day 3	Day 7	The 3rd month
WBC (× 10^9/L)	7.38 ± 4.44	16.36 ± 7.47	7.06 ± 2.36	5.56 ± 3.10	5.38 ± 1.09
NEUT%	67.32 ± 21.31	88.62 ± 4.06	74.11 ± 10.83	67.27 ± 12.37	67.44 ± 7.79
PLT (× 10^9/L)	394 ± 191.73	335 ± 181.17	273 ± 95.04	294 ± 96.90	253 ± 55.52
HGB (g/L)	107 ± 23.30	108 ± 27.61	100 ± 25.27	101 ± 21.16	128 ± 18.84
ESR (mm/h)	41.60 ± 30.59	20.50 ± 14.85	72.67 ± 27.15	22.00 ± 16.97	6.61 ± 4.22
CRP (mg/L)	34.56 ± 42.57	39.58 ± 23.74	85.47 ± 87.36	39.75 ± 38.52	1.91 ± 1.18
PCT (ng/mL)	0.07 ± 0.05	0.24 ± 0.24	1.52 ± 2.05	0.26 ± 0.14	0.02 ± 0.01
ALB (g/L)	31.31 ± 10.45	30.77 ± 6.48	32.11 ± 4.17	34.12 ± 4.53	41.71 ± 3.12
BMI (kg/m^2)	15.90 ± 2.31	NA	NA	NA	20.83 ± 1.69

WBC: White blood count; CRP: C-reactive protein; BMI: Body mass index; NEUT: Neutrophil; PLT: Platelet count; HGB: Hemoglobin; ESR: Erythrocyte sedimentation rate; PCT: Procalcitonin; ALB: Albumin; NA: Not available.

ascending duodenal strictures. End-to-end, end-to-side, or side-to-side anastomosis and early drug treatment should be used to prevent recurrence and secondary strictures. Strictureplasty, which was first performed by Lee and Papiaoannu in the 1970s, is a safe and effective surgical approach for treating duodenal Crohn's disease[8]. Strictureplasty may be suitable when the second or third portion of the duodenum is stenotic in less than two sites. For multiple strictures located in the first or distal duodenum, resection should be used as the first option[9]. There are various types of strictureplasty; the most commonly used duodenal CD strictureplasty is Heineke Mikulicz strictureplasty for strictures less than 10 cm in length and Finney strictureplasty for a longer segment of 15 to 25 cm in length[10]. In jejunoileal CD, strictureplasty is a recognized surgical technique that can relieve symptoms of obstruction, maintain intestinal length, and avoid the occurrence of short bowel syndrome[4]. Strictureplasty can treat the strictures caused by CD involving the duodenum and may be an option for the treatment of Oddi sphincter incontinence in primary duodenal Crohn's disease[11].

Duodenal stricture bypass surgery: Loop gastrojejunostomy and Roux-en-Y gastrojejunostomy are widely used to treat duodenal Crohn's disease. Racz *et al*[11] reported a case of duodenal Crohn's disease and found that descending, horizontal and ascending segments of the duodenum were significantly stenotic intraoperatively. Duodenojejunostomy and gastrojejunostomy were then performed, and the patients recovered well after surgery. Based on surgical treatment of duodenal Crohn's disease at our department, 5 patients underwent the bypass procedure and gastrojejunostomy; all patients recovered well after surgery. The advantage of the duodenal bypass procedure is that it excludes the duodenal strictures and reconstructs the patency and continuity of the gastrointestinal tract. Yet, duodenal bypass is also associated with complications and risks such as gastric emptying disorder, disease progression of duodenal bypass location, non-biopsy of bypass site, ulcer formation, anastomotic restructure, and so on.

Currently, the best surgical approach for duodenal Crohn's disease is still a matter of debate. Yamamoto *et al*[12] suggested that duodenal bypass is better than duodenal strictureplasty when treating patients with duodenal Crohn's disease, while Worsey *et al*[8] reported different results. Some studies suggested a combination of surgical resection, bypass, and strictureplasty, which maximizes the protection of the intestinal tract and allows complete remission of symptoms[11]. We believe that the surgical approach should be based on the location and degree of Crohn's disease in combination with the operation level and clinical experience of the surgeon.

Pancreaticoduodenectomy: Gastroduodenoplasty, strictureplasty, and Roux-en-Y bypass are considered effective surgical treatments for duodenal Crohn's disease. If technically feasible, it can be used to treat the strictures of the second and third portions of the duodenum with strictureplasty. Duodenectomy or pancreatoduodenectomy should be regarded as the final surgical treatment option for the disease[13]. For primary duodenal stricture with tumor-like manifestations, the surgical approach should be selected based on the location and degree of the lesion. The surgical approach can include segmental duodenectomy, partial duodenectomy, or pancreatoduodenectomy. Among patients with primary duodenal Crohn's disease receiving surgical treatment in our department, one case presented with a tumor-like lesion, which was difficult to diagnose intraoperatively. Rapid pathological examination showed a small number of heterogeneous cells; consequently, pancreatoduodenectomy was performed. The postoperative pathological report was Crohn's disease, involving a portion of the

pancreas. Later, the patient developed fat diarrhea and underwent pancreaticojejunostomy, but the effect of postoperative treatment was poor. This case indicated that surgery can only solve the surgical complications of Crohn's disease, and the patients still needed standardized medical treatment. We also suggest caution in choosing pancreatoduodenectomy for primary duodenal Crohn's disease.

Other surgical approaches: In addition to duodenal strictureplasty and duodenal bypass, other procedures for the primary duodenal Crohn's disease include duodenal balloon dilatation, endoscopic stricture incision, and self-expanding metal stent[14]. Previous studies have shown that the short-term technical and clinical success rate of balloon dilatation for upper gastrointestinal Crohn's disease-related stricture is high, the long-term curative effect is relatively good, and the incidence of postoperative complications is acceptable. Although continuous balloon dilatation does not change the curative effect, it may be a feasible option to delay or prevent surgery[15].

Surgical treatment for secondary duodenal Crohn's disease

In addition to primary duodenal Crohn's disease, Crohn's disease in other organs, such as the colon, and small intestine, can also involve the duodenum, leading to duodenal lesions, which is named secondary duodenal Crohn's disease in the clinic. In this study, 10 cases had secondary duodenal Crohn's disease, including 6 cases with and 4 cases without internal fistula. The formation of the internal fistula is one of the important factors in determining the surgical approach.

Surgical approach of secondary duodenal Crohn's disease with internal fistula: Gong *et al*[16] suggested that one-stage duodenal closure is safe for Crohn's disease as long as there is no duodenal stricture, and that it may even be used for large duodenal defects. Our data suggest that pathological segmental resection and internal fistula resection should be used for cases with intestinal penetration that eventually involve the duodenum and form internal fistula, while duodenal closure should be applied according to the circumstances. For patients with Crohn's disease complicated with duodenal fistula, the treatment should be based on surgery, while special attention should be paid to perioperative management, induction of remission through drug and nutrition treatment, and selection of the appropriate time to intervene by surgery. Once the duodenum is seriously involved and forms an internal fistula with other intestines, it is often necessary to close the duodenal defects. According to the size of duodenal defects, different closure techniques are used. Among 10 cases of secondary duodenal Crohn's disease in our department, 6 cases (3/5) had internal fistula formation. We summarized the basic information, including primary lesion location, duodenal defect size, and the surgical approach in Table 1. Three cases underwent direct duodenal closure and 3 duodenal closures with pedicled terminal ileal flap. Direct closure of duodenal defects was performed when the duodenal defect was ≤ 3 cm in diameter (Figure 2). When the duodenal defect was larger than 3cm in diameter, duodenal stricture could easily occur after simple closure of the defect or suture, after which pedicled flap closure of the duodenal defect was performed (Figure 2A-D)[17-19].

The main surgical approaches for duodenal defect closure include direct closure, pedicled intestinal flap closure, and sometimes additional gastrostomy and jejunal nutrition tube implantation, depending on the situation. Among 6 patients with duodenal defect closure, 4 patients had additional gastrostomy, 4 patients had an additional ileostomy, 4 patients had additional jejunal nutrition tube implantation, and 1 patient received additional ileal nutrition tube implantation.

Surgical approach of secondary duodenal Crohn's disease without internal fistula: Secondary duodenal Crohn's disease usually appears secondary to the colon, ileum, and other primary lesions. Although the duodenum is involved, there is no internal fistula or duodenal stricture. For patients with duodenal involvement but no obvious clinical manifestations, individualized surgical treatment should be performed according to the lesion location, lesion degree, duodenal fistula formation, and duodenal strictures.

Among 16 cases, there were 4 cases of secondary duodenal Crohn's disease without internal fistula, including 3 cases of duodenal lesion exclusion and right hemicolectomy. When other diseases involve the duodenum without the formation of an internal fistula, and when the ascending colon or hepatic flexure of the colon is found to involve the duodenum intraoperatively, the primary diseased intestinal segment can be resected based on our experience, and with the exclusion of duodenal lesion, which is to retain the seromuscular layer of the colon adhering to the duodenum, while removing the mucosa and submucosa of the colon. In addition, we also completed one case of duodenal lesion exclusion and double lumen ileostomy. We believe that the surgical treatment of Crohn's disease is different from that of gastrointestinal cancer. Gastrointestinal malignancies are performed over a limited period of time and require radical resection of diseased tissue, whereas Crohn's disease is benign. For patients with secondary duodenal Crohn's disease without fistula, who usually had poor nutritional status, combined with hypoproteinemia, ascites, bloody exudation, and other conditions, transitional surgery, namely double-lumen ileostomy, was considered first. Deterministic surgery was performed after nutritional support and standardized medical treatment to improve the patient's general condition.

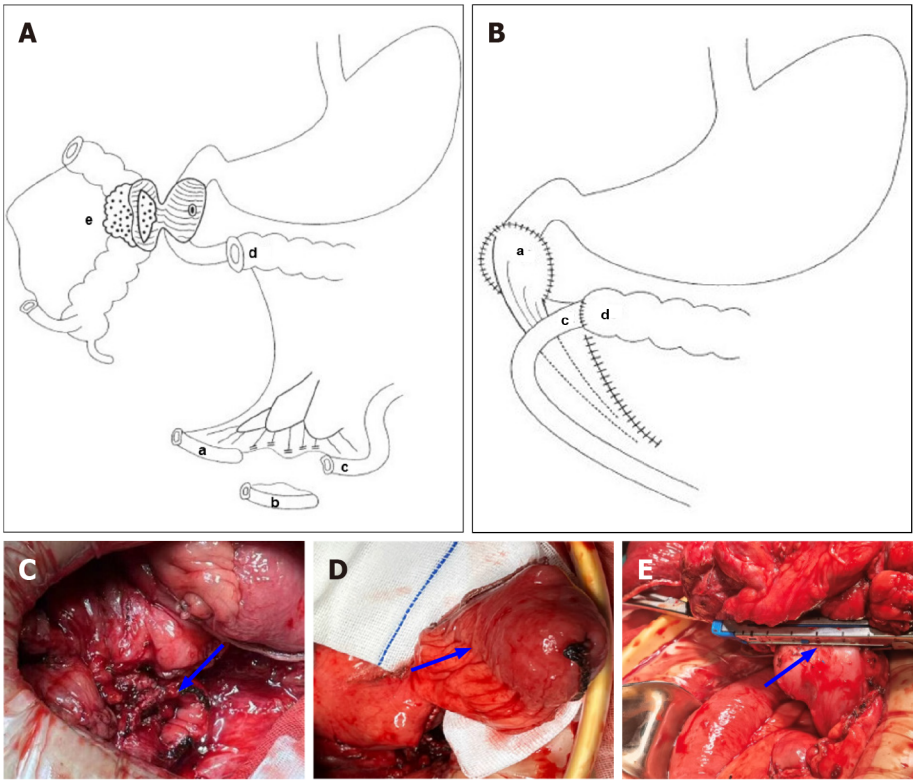

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Figure 2 Schematic diagram of pedicled terminal ileum flap closure of the duodenal defect. A: Pedicled terminal ileum (a), ileum (b), proximal ileum (c), transverse colon (d), Crohn's disease lesions (e); B: Duodenal defect repaired with a pedicled terminal ileal flap (a), terminal ileum (c), transverse colon (d); C: The duodenal defect was larger than 3 cm in diameter; D: Pedicled terminal ileum; E: Direct closure by mechanical stapling of duodenal defects was performed when the duodenal defect was ≤ 3 cm in diameter.

CONCLUSION

Duodenal Crohn's disease is a rare event that can be classified into primary and secondary duodenal Crohn's disease. Surgical treatment for duodenal Crohn's disease should be performed based on the patient's condition and the surgeon's experience. However, surgery can only solve the surgical complications. Thus, patients should receive standard medical treatment preoperatively and postoperatively to obtain an ideal therapeutic effect. In addition, it is often necessary for various departments such as gastroenterology, gastrointestinal surgery, radiology, pathology, and nutrition to cooperate to fully achieve the unique advantages of comprehensive multidisciplinary treatment[20].

ARTICLE HIGHLIGHTS

Research background

Treating Crohn's disease that affects the duodenum requires a personalized surgical approach that takes into account the patient's individual health status.

Research motivation

The involvement of the duodenum in Crohn's disease is relatively rare, so it is necessary to summarize the surgical management.

Research objectives

Provide surgical treatment recommendations for duodenal Crohn's disease as a reference for surgeons.

Research methods

We systematically reviewed patients diagnosed with duodenal Crohn's disease who underwent surgery in the Department of Geriatrics Surgery of the Second Xiangya Hospital of Central South University from January 1, 2004, to August 31, 2022.

Research results

All patients had a chronic relapse, and one had a history of smoking. There were 6 cases with diarrhea, 4 cases with nausea and vomiting, and 9 cases with intestinal obstruction. Among 16 patients, there were 6 cases with primary duodenal Crohn's disease (5 cases had duodenal strictures and 1 case had tumor-like lesions) and 10 cases of secondary duodenal Crohn's disease (6 cases had an internal fistula and 4 cases had no internal fistula).

Research conclusions

Surgical treatment for duodenal Crohn's disease should be performed based on the patient's condition and the surgeon's experience.

Research perspectives

The incidence of Crohn's disease has been increasing year by year. This study explores surgical management for duodenal Crohn's disease from the perspective of surgeons.

FOOTNOTES

Author contributions: Yang LC analyzed the data, prepared the figures and wrote the manuscript; Wu GT, Wu Q, Peng LX, Zhang YW and Yao BJ collected some data and contributed to manuscript preparation; Liu GL and Yuan LW contributed to the revision of the article; all authors have read the paper and approved the final submission.

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ORIGINAL ARTICLE

Retrospective Study

Influences of dexmedetomidine on stress responses and postoperative cognitive and coagulation functions in patients undergoing radical gastrectomy under general anesthesia

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Abstract

BACKGROUND

Radical gastrectomy (RG) is commonly used in the treatment of patients with gastric cancer (GC), but this procedure may lead to stress responses, postoperative cognitive dysfunction, and blood coagulation abnormalities in patients.

AIM

To investigate the influences of dexmedetomidine (DEX) on stress responses and postoperative cognitive and coagulation functions in patients undergoing RG under general anesthesia (GA).

METHODS

One hundred and two patients undergoing RG for GC under GA from February 2020 to February 2022 were retrospectively reviewed. Of these, 50 patients had received conventional anesthesia intervention [control group (CG)] and 52 patients had received DEX in addition to routine anesthesia intervention [observation group (OG)]. Inflammatory factor (IFs; tumor necrosis factor-α, TNF-α; interleukin-6, IL-6), stress responses (cortisol, Cor; adrenocorticotropic hormone, ACTH), cognitive function (CF; Mini-Mental State Examination, MMSE), neurological function (neuron-specific enolase, NSE; S100 calcium-binding protein B, S100B), and coagulation function (prothrombin time, PT; thromboxane B2, TXB2; fibrinogen, FIB) were compared between the two groups before surgery (T0), as well as at 6 h (T1) and 24 h (T2) after surgery.

RESULTS

Compared with T0, TNF-α, IL-6, Cor, ACTH, NSE, S100B, PT, TXB2, and FIB

showed a significant increase in both groups at T1 and T2, but with even lower levels in OG *vs* CG. Both groups showed a significant reduction in the MMSE score at T1 and T2 compared with T0, but the MMSE score was notably higher in OG compared with CG.

CONCLUSION

In addition to a potent inhibitory effect on postoperative IFs and stress responses in GC patients undergoing RG under GA, DEX may also alleviate the coagulation dysfunction and improve the postoperative CF of these patients.

Key Words: Dexmedetomidine; Radical gastrectomy; General anesthesia; Inflammatory factors; Stress responses

Core Tip: Radical gastrectomy (RG), a minimally invasive procedure, is reported to be the optimal cure for gastric cancer (GC) with the advantages of lesser pain and faster recovery. Dexmedetomidine (DEX) is used in a wide range of clinical scenarios. Available evidence suggests that DEX can reduce perioperative inflammation and stress and exert a certain protective effect on cognitive function (CF) in elderly patients after laparoscopic cholecystectomy. In this study, we aimed to assess the influence of DEX on stress responses, CF, and coagulation function of GC patients undergoing RG under general anesthesia, with a view to contributing to the improvement of prognosis in these patients.

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INTRODUCTION

Despite the advances in the diagnosis and treatment of gastric cancer (GC), the postoperative prognosis of patients remains unsatisfactory[1]. Radical gastrectomy (RG), a minimally invasive procedure, is reported to be the optimal cure for GC with the advantages of lesser pain and faster recovery[2,3]. However, this procedure may induce physiological abnormalities such as excessive release of inflammatory factors (IFs), stress responses, and blood hypercoagulability[4]. The excessive release of IFs is known to adversely affect the central nervous system, resulting in neurological impairment and increased risk of postoperative cognitive dysfunction[5,6]. Studies have shown that cognitive dysfunction is a common adverse event after cardiac surgery, with approximately one-third of patients suffering from cognitive decline at 6 wk after surgery[7]. Thus, it is incumbent on researchers to search for effective measures to improve the postoperative cognitive function (CF) of GC patients undergoing RG under general anesthesia (GA) from the perspectives of IFs, stress responses, CF, and coagulation function.

Optimization of anesthesia strategy can help reduce postoperative adverse events in patients undergoing RG for GC, with a certain protective effect on vital organ functions and postoperative CF[8,9]. Dexmedetomidine (DEX) is a multipotent central α-2 adrenergic agonist with sedative, analgesic, and anti-sympathetic functions, which is often used as an anesthetic adjuvant[10]. It is used in a wide range of clinical scenarios. Besides RG, it can also be used in colorectal cancer surgery, joint replacement, cardiac surgery, and other clinical scenarios, helping to reduce the risk of delirium in elderly patients [11]. Available evidence suggests that DEX can reduce perioperative inflammation and stress and exert a certain protective effect on CF in elderly patients after laparoscopic cholecystectomy[12,13].

In this study, we aimed to assess the influence of DEX on stress responses, CF, and coagulation function of GC patients undergoing RG under GA, with a view to contributing to the improvement of prognosis in these patients.

MATERIALS AND METHODS

General data

This was a retrospective study approved by the Ethics Committee of The Second Affiliated Hospital of Guangxi Medical University. The study population comprised of 102 patients with GC who underwent RG under GA at our hospital between February 2020 and February 2022. Patients who received routine anesthesia intervention were included in the control group (CG; n = 50) while those who received DEX in combination with conventional anesthesia intervention were included in the observation group (OG; n = 52). The two groups were comparable with respect to baseline clinical characteristics (P > 0.05).

Criteria for patient enrollment and exclusion

All the included patients met the surgical indications for GC and underwent GA, with the America Society of Anesthesiologist (ASA) classification II or III[14], intact case data, no mental illness or mental disorders, and active cooperation with the research.

The exclusion criteria for this study were as follows: Severe arrhythmia as confirmed by electrocardiograph (ECG); diseases such as severe malnutrition, anemia and abnormal liver function; diabetes, hypertension or coronary heart disease; infectious diseases.

Intervention methods

CG group received routine anesthesia intervention. OG group received was DEX in addition to routine anesthesia intervention.

For all the patients, blood pressure, ECG, and pulse oxygen saturation were routinely monitored after entering the operating room, and venous access was established. DEX infusion was initiated before conventional induction and discontinued before the heart resumed beating. In OG, DEX was injected intravenously at a loading dose of 0.5 μg/kg followed by a continuous infusion at a rate of 0.2–0.6 μg/kg/h; patients in the CG were administered normal saline at the same dose. After the above procedure, both groups of patients underwent routine anesthesia induction in the same manner, namely, administration of intravenous midazolam, fentanyl, atracurium, and propofol. Endotracheal intubation and mechanical ventilation were then performed with a tidal volume of 8–10 mL/kg and a ventilation frequency of 12–20 times/min; the $P_{ET}CO_2$ was maintained at 35–40 mmHg. Propofol, remifentanil, and atracurium were injected intravenously for anesthesia maintenance.

Evaluation indices

After anesthesia, five milliliters of peripheral elbow venous blood was collected before surgery (T0), as well as at 6 h (T1) and 24 h (T2) after surgery. Serum was separated *via* centrifugation after 2 h of standing, and refrigerated at -20°C for later use.

IFs: Serum levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were determined by enzyme-linked immunosorbent assay (ELISA).

Stress responses: ELISA was performed to quantify blood cortisol (Cor) and adrenocorticotropic hormone (ACTH) levels.

CF: According to the Mini-Mental State Examination (MMSE), the CF of patients at T0, T1, and T2 was evaluated from seven aspects: Time orientation, place orientation, registration, attention and calculation, recall, language, and copying. The lower the score, the more significant the cognitive dysfunction.

Neurological function: ELISA was employed to measure neuron-specific enolase (NSE) and S100 calcium-binding protein B (S100B) levels.

Coagulation function: An automatic hemagglutination analyzer was used to quantify coagulation function indicators prothrombin time (PT), thromboxane B2 (TXB2), and fibrinogen (FIB).

Statistical analysis

Continuous variables were presented as mean ± SD and between-group differences were assessed using the independent sample t test. Multi-group and within-group differences were assessed using one-way ANOVA. Categorical variables were presented as frequency (percentage) and between-group differences were assessed using the χ^2 test. Statistical analysis was performed using SPSS 19.0. P values < 0.05 were considered indicative of statistical significance.

RESULTS

Comparison of baseline data between the two groups

There was no significant difference between the two groups with respect to sex, age, disease course,

body weight, tumor staging, ASA grade, or history of hypertension and diabetes ($P > 0.05$) (Table 1).

Influence of DEX on IFs

Serum levels of TNF-α and IL-6 were not significantly different between the two groups at T0 ($P > 0.05$). The levels showed a marked increase in both groups at T1 and T2 ($P < 0.05$), with significantly lower levels in OG as compared to CG ($P < 0.05$) (Figure 1).

Influence of DEX on stress responses

The stress responses of both groups were evaluated by measuring Cor and ACTH (Figure 2). There were no significant between-group differences with respect to Cor and ACTH at T0 ($P > 0.05$). Compared with T0, Cor and ACTH in both groups showed a significant increase at T1 and T2 ($P < 0.05$), especially in OG ($P < 0.05$).

Impact of DEX on CF

There was no significant between-group difference in the MMSE score at T0 ($P > 0.05$). MMSE scores at T1 and T2 were significantly lower than that at T0 in both groups ($P < 0.05$), but the scores of OG were still higher than those of CG ($P < 0.05$) (Figure 3).

Effect of DEX on neurological function

The effects of two anesthesia methods on neurological function were evaluated by detecting NSE and S100B (Figure 4). There were no significant between-group differences with respect to NSE and S100B at T0 ($P > 0.05$). Significant increase in NSE and S100B was observed in both groups at T1 and T2 ($P < 0.05$), with lower levels in OG as compared to CG ($P < 0.05$).

Influence of DEX on coagulation function

There were no significant between-group differences with respect to PT, XB2, or FIB at T0 ($P > 0.05$). At T1 and T2, both groups showed a significant increase in PT, TXB2 and FIB compared with the respective levels at T0 ($P < 0.05$), with lower levels in OG *vs* CG ($P < 0.05$) (Figure 5).

DISCUSSION

RG is the main treatment modality for GC, but the inflammation, stress responses, and neurological dysfunction induced by surgical trauma have a negative impact on patient postoperative recovery and survival[2]. The influence of DEX on postoperative stress responses, CF, and coagulation function of GC patients undergoing RG under GA remains poorly elucidated in the contemporary literature.

Several studies have investigated the application value of DEX in RG for GC. In the study by Guo *et al*[15], DEX outperformed epidural anesthesia in terms of sedative and analgesic effects in elderly adults undergoing RG for GC and accelerated their recovery. Liu *et al*[16] focused on the influence of DEX combined with propofol on postoperative analgesia and cellular immune function during RG. The combination of the two was found to suppress postoperative stress responses, improve analgesia effects, enhance immune function, and reduce the occurrence of postoperative adverse events. In the present study, we investigated the clinical effects of DEX in GC patients undergoing RG under GA from five aspects: inflammation, stress, CF, neurological function, and coagulation function. In terms of inflammation, postoperative TNF-α and IL-6 levels were significantly lower in OG, suggesting the anti-inflammatory effect of DEX in these patients. TNF-α and IL-6 are known inflammatory indices of RG, both of which mediate the inflammatory process and participate in organ involvement and can be inhibited to some extent postoperatively under the intervention of DEX, consistent with our observations[17,18]. The anti-inflammatory mechanism of DEX may be related to the activation of cholinergic anti-inflammatory pathway to suppress systemic inflammatory responses[19]. In the stress response evaluation, Cor and ACTH in OG were found to be significantly elevated after surgery but were still lower than those in CG, suggesting that DEX used in RG has a more prominent inhibitory effect on stress responses. Consistently, Yang *et al*[20] also reported that DEX can alleviate stress responses in patients undergoing laparoscopic cholecystectomy, which was reflected in significant reductions in Cor and ACTH levels. Further, CF evaluation results showed that although the postoperative MMSE score of OG reduced notably just like CG, it was still significantly higher than CG, indicating a significant protective effect of DEX on the CF of patients undergoing RG under GA, which is in line with the findings of Yang *et al*[21]. When evaluating neurological function, NSE and S100B in OG were also found to be significantly increased as those in CG, but were still markedly lower in OG *vs* CG, indicating that DEX intervention can inhibit NSE and S100B in patients. NSE and S100B are known to be neurological function indices related to brain injury; the former can reflect neuronal abnormalities, while the latter is a marker of glial cell damage[22]. Zhao *et al*[23] also reported a neuroprotective effect of DEX in patients with hypertensive cerebral hemorrhage in the perioperative period by inhibiting NSE and S100B levels, which is consistent with our results. Finally, we verified the effect of DEX on coagulation function, and

Table 1 Comparison of baseline data of two groups of gastric cancer patients undergoing radical gastrectomy under general anesthesia

Classification	Control group (n = 50)	Observation group (n = 52)	χ^2 value	P value
Gender (male/female)	32/18	29/23	0.718	0.397
Age (yr)	50.82 ± 6.65	49.85 ± 7.63	0.683	0.496
Course of disease (yr)	2.32 ± 0.55	2.25 ± 0.56	0.637	0.526
Weight (kg)	63.76 ± 8.02	64.38 ± 8.43	0.380	0.705
Tumor staging (I/II)	28/22	27/25	0.171	0.680
ASA classification (II/III)	26/24	30/22	0.334	0.564
History of hypertension (yes/no)	10/40	15/37	1.078	0.299
Medical history of diabetes (yes/no)	7/43	12/40	1.386	0.239

ASA: America Society of Anesthesiologist.

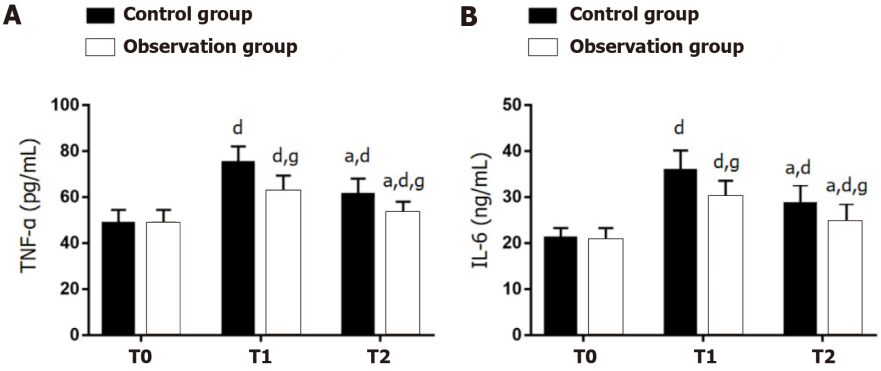

Figure 1 Influence of dexmedetomidine on inflammatory factors in gastric cancer patients undergoing radical gastrectomy under general anesthesia. A: Tumor necrosis factor-α at different time points in two groups of gastric cancer (GC) patients undergoing radical gastrectomy (RG) under general anesthesia (GA); B: Interleukin-6 at different time points in two groups of GC patients undergoing RG under GA. $^{a}P < 0.05$ *vs* T1; $^{d}P < 0.05$ *vs* T0; $^{g}P < 0.05$ *vs* control group. T0: Before surgery; T1: 6 h after surgery; T2: 24 h after surgery; TNF-α: Tumor necrosis factor-α; IL-6: Interleukin-6.

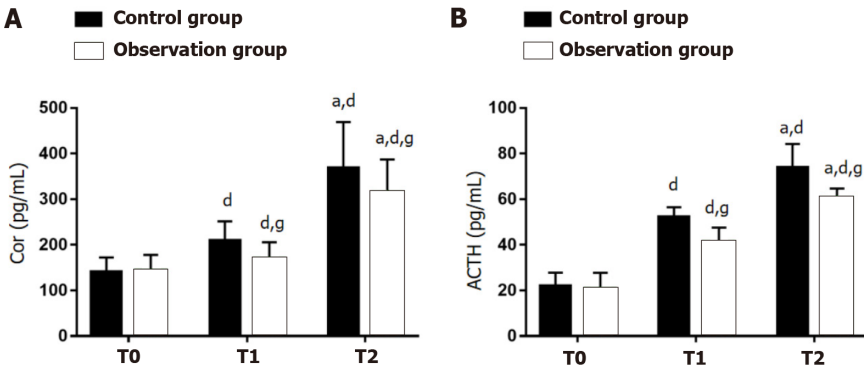

Figure 2 Influence of dexmedetomidine on stress responses of gastric cancer patients undergoing radical gastrectomy under general anesthesia. A: Cortisol at different time points in two groups of gastric cancer (GC) patients undergoing radical gastrectomy (RG) under general anesthesia (GA); B: Adrenocorticotropic hormone at different time points in two groups of GC patients undergoing RG under GA. $^{a}P < 0.05$ *vs* T1; $^{d}P < 0.05$ *vs* T0; $^{g}P < 0.05$ *vs* control group. T0: Before surgery; T1: 6 h after surgery; T2: 24 h after surgery; Cor: Cortisol; ACTH: Adrenocorticotropic hormone.

found that PT, TXB2, and FIB in OG after the intervention of DEX were significantly increased but significantly lower than those in CG, indicating that DEX can significantly improve coagulation function in patients undergoing RG under GA. Chen *et al*[24] also found that the application of DEX in patients

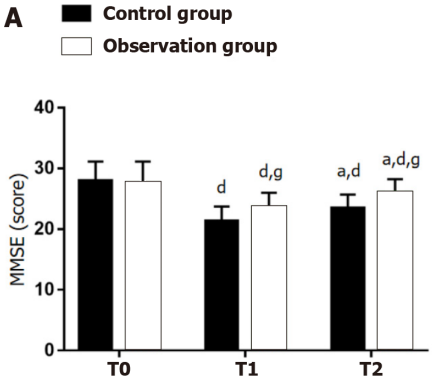

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Figure 3 Effect of dexmedetomidine on cognitive function (Mini-Mental State Examination) of gastric cancer patients undergoing radical gastrectomy under general anesthesia. $^{a}P < 0.05$ *vs* T1; $^{d}P < 0.05$ *vs* T0; $^{g}P < 0.05$ *vs* control group. T0: Before surgery; T1: 6 h after surgery; T2: 24 h after surgery; MMSE: Mini-Mental State Examination.

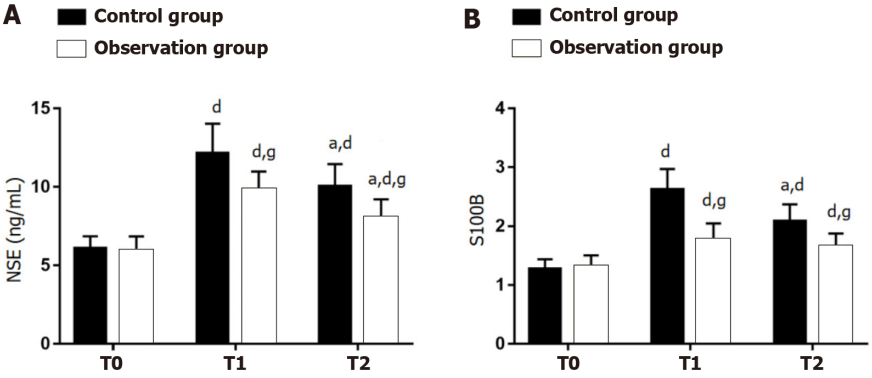

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Figure 4 Effect of dexmedetomidine on neurological function of gastric cancer patients undergoing radical gastrectomy under general anesthesia. A: Neuron-specific enolase at different time points in two groups of gastric cancer (GC) patients undergoing radical gastrectomy (RG) under general anesthesia (GA); B: S100 calcium-binding protein B at different time points in two groups of GC patients undergoing RG under GA. $^{a}P < 0.05$ *vs* T1; $^{d}P < 0.05$ *vs* T0; $^{g}P < 0.05$ *vs* control group. T0: Before surgery; T1: 6 h after surgery; T2: 24 h after surgery; NSE: Neuron-specific enolase; S100B: S100 calcium-binding protein B.

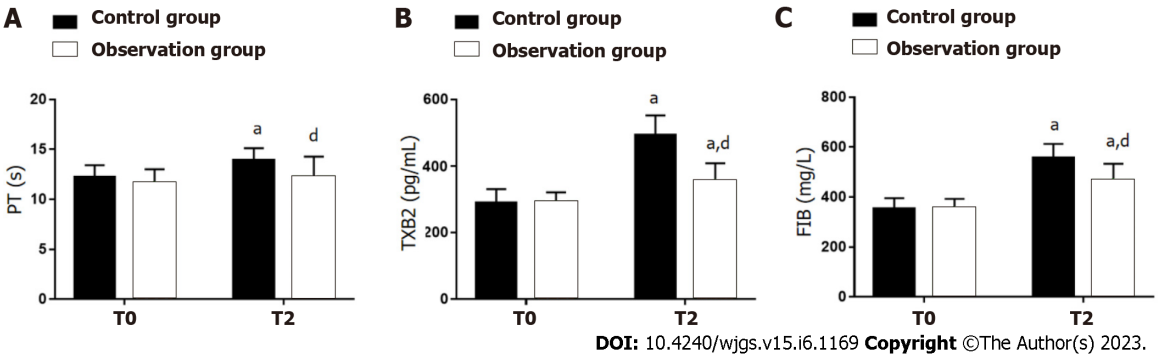

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Figure 5 Influence of dexmedetomidine on neurological function of gastric cancer patients undergoing radical gastrectomy under general anesthesia. A: Prothrombin time at different time points in two groups of gastric cancer (GC) patients undergoing radical gastrectomy (RG) under general anesthesia (GA); B: Thromboxane B2 at different time points in two groups of GC patients undergoing RG under GA; C: Fibrinogen at different time points in two groups of GC patients undergoing RG under GA. $^{a}P < 0.05$ *vs* T0; $^{d}P < 0.05$ *vs* control group. T0: Before surgery; T1: 6 h after surgery; T2: 24 h after surgery; PT: Prothrombin time; TXB2: Thromboxane B2; FIB: Fibrinogen.

undergoing RG under GA inhibited postoperative blood hypercoagulability by weakening the activation of coagulation function, which is related to the direct or indirect regulation of platelet function by DEX.

Some limitations of our study should be considered. This was a single-center retrospective study with a relatively small sample size, which may have introduced an element of bias. A larger multi-center study is required to obtain more definitive evidence.

CONCLUSION

In this study, the use of DEX demonstrated a significant clinical benefit in patients undergoing RG under GA. DEX was found to inhibit inflammation and stress reactions, as well as improve the postoperative cognitive, neurological, and coagulation functions in these patients. Our findings may provide a new reference for anesthesia management optimization and prognosis improvement of such patients.

ARTICLE HIGHLIGHTS

Research background

Radical gastrectomy (RG) is often used to treat patients with gastric cancer (GC), but it may cause stress responses, postoperative cognitive dysfunction and abnormal coagulation function.

Research motivation

The effects of dexmedetomidine (DEX) on stress responses, postoperative cognitive function and coagulation function of GC patients undergoing RG under general anesthesia were analyzed retrospectively.

Research objectives

This study aimed to optimize anesthesia strategy to help reduce the perioperative risk of GC patients receiving RG.

Research methods

One hundred and two patients undergoing RG for GC under general anesthesia were included. Of them, 50 cases receiving routine anesthesia were set as a control group (CG) and 52 cases receiving routine anesthesia plus DEX were set as an observation group (OG). Then inflammatory factors, stress responses, cognitive function, neurological function, and coagulation function of the two groups were comparatively analyzed at various time points [before (T0), and 6 h (T1) and 24 h (T2) after surgery].

Research results

Compared with T0, tumor necrosis factor-α, interleukin-6, cortisol, adrenocorticotropic hormone, neuron-specific enolase, S100 calcium-binding protein B, prothrombin time, thromboxane B2, and fibrinogen were markedly elevated at T1 and T2 in both groups, with even lower levels of these parameters in OG compared with CG. In addition, a marked reduction in the Mini-Mental State Examination (MMSE) score was observed at T1 and T2 compared with T0 in both groups, with a significantly higher MMSE score in OG *vs* CG at each postoperative time point.

Research conclusions

In addition to effective inhibition of inflammatory factors and stress responses in GC patients undergoing RG under general anesthesia, DEX can also alleviate coagulation dysfunction and improve postoperative cognitive function in these patients.

Research perspectives

Our findings may provide a novel reference for optimizing anesthesia management and improving outcomes in patients undergoing RG for GC.

FOOTNOTES

Author contributions: Ma XF proposed the overall research goal and designed the research plan and model design; Ma XF, Lv SJ, Wei SQ and Mao BR conducted feasibility analysis, review and supervision of the experiment; Du XK, Zhao XX, and Jiang XQ collected clinical data; Ma XF, Zhao XX, and Zeng F conducted statistical processing and analysis of the data; Ma XF and Du XK are responsible for writing the first draft of the paper; Ma XF is responsible for the review, revision and quality control of the paper; all authors determined the final draft of the paper.

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ORIGINAL ARTICLE

Retrospective Study

Dissimilar survival and clinicopathological characteristics of mucinous adenocarcinoma located in pancreatic head and body/tail

Zheng Li, Xiao-Jie Zhang, Chong-Yuan Sun, Ze-Feng Li, He Fei, Dong-Bing Zhao

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Abstract

BACKGROUND

Growing evidence shows that pancreatic tumors in different anatomical locations have different characteristics, which have a significant impact on prognosis. However, no study has reported the differences between pancreatic mucinous adenocarcinoma (PMAC) in the head *vs* the body/tail of the pancreas.

AIM

To investigate the differences in survival and clinicopathological characteristics between PMAC in the head and body/tail of pancreas.

METHODS

A total of 2058 PMAC patients from the Surveillance, Epidemiology, and End Results database diagnosed between 1992 and 2017 were retrospectively reviewed. We divided the patients who met the inclusion criteria into pancreatic head group (PHG) and pancreatic body/tail group (PBTG). The relationship between two groups and risk of invasive factors was identified using logistic regression analysis. Kaplan-Meier analysis and Cox regression analysis were conducted to compare the overall survival (OS) and cancer-specific survival (CSS) of two patient groups.

RESULTS

In total, 271 PMAC patients were included in the study. The 1-year, 3-year, and 5-year OS rates of these patients were 51.6%, 23.5%, and 13.6%, respectively. The 1-year, 3-year, and 5-year CSS rates were 53.2%, 26.2%, and 17.4%, respectively. The median OS of PHG patients was longer than that of PBTG patients (18 *vs* 7.5 mo, $P < 0.001$). Compared to PHG patients, PBTG patients had a greater risk of metastases [odds ratio (OR) = 2.747, 95% confidence interval (CI): 1.628-4.636, $P <$

0.001] and higher staging (OR = 3.204, 95% CI: 1.895-5.415, $P < 0.001$). Survival analysis revealed that age < 65 years, male sex, low grade (G1-G2), low stage, systemic therapy, and PMAC located at the pancreatic head led to longer OS and CSS (all $P < 0.05$). The location of PMAC was an independent prognostic factor for CSS [hazard ratio (HR) = 0.7, 95%CI: 0.52-0.94, $P = 0.017$]. Further analysis demonstrated that OS and CSS of PHG were significantly better than PBTG in advanced stage (stage III-IV).

CONCLUSION

Compared to the pancreatic body/tail, PMAC located in the pancreatic head has better survival and favorable clinicopathological characteristics.

Key Words: Pancreatic mucinous adenocarcinoma; Anatomical location; Pancreatic head; Pancreatic body/tail; Survival

Core Tip: Pancreatic tumors had different clinicopathological characteristics by anatomic location in the pancreas. We first investigated the different outcomes and characteristics between mucinous adenocarcinoma in the pancreatic head and body/tail using a variety of analytical methods. In conclusion, adenocarcinoma located at the pancreatic head tended to be characterized by longer survival and more favorable characteristics.

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INTRODUCTION

Pancreatic cancer (PC) is a common malignancy with a poor prognosis. The incidence and mortality of PC have dramatically increased in recent decades. It has been estimated that PC will be the third leading cause of cancer-related mortality in the future[1,2]. In the subtype classification of PC, pancreatic mucinous adenocarcinoma (PMAC) is a rare type, a malignancy lined by tall, columnar mucinous epithelium[3]. With main symptoms of abdominal pain, weight loss and diarrhea, PMAC can be detected by endoscopy, computed tomography, and other imaging methods. The diagnosis of PMAC can be confirmed by histopathology, and surgical resection remains the primary treatment strategy[4].

Recently, studies have suggested that there is diversity in the genetic and biological characteristics of pancreatic cancer depending on the localization of the tumor[5,6], which indicates that we can classify pancreatic cancer by anatomical location and develop targeted treatment strategies to achieve better outcomes. There is a burgeoning discussion on how the anatomical location of pancreatic cancer impacts its clinical outcomes and pathological characteristics, such as pancreatic ductal adenocarcinoma[7-10] and pancreatic neuroendocrine tumors[11]. However, no study has reported the differences in pancreatic mucinous adenocarcinoma (PMAC) in different pancreatic locations.

Given these considerations, we conducted the present study to compare the survival and clinicopathological features of PMAC in the head vs. the body/tail of the pancreas. A total of 271 PMAC patients from the Surveillance, Epidemiology, and End Results database (1992-2017) were reviewed.

MATERIALS AND METHODS

Data collection and study design

Patients' data in this population-based retrospective study were investigated from the Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov/), which is supported by National Cancer Institute. We screened the data "Incidence-SEER Research Plus Data, 13 Registries, Nov 2019 Sub (1992-2017)" using SEER*Stat 8.4.0.1. Furthermore, "8.6.4 Carcinoma of pancreas", "8480/3: Mucinous adenocarcinoma", and "Positive histology" were selected, and a total of 2058 pathologically confirmed patients with information of age, race, sex, grade, TNM, stage, primary malignancy, systemic therapy, and survival were collected. The exclusion criteria of this study were as follows: (1) Patients

without TNM data (n = 1710); (2) Patients with incomplete information of cancer-specific survival (n = 2); (3) Patients with carcinoma located at 'OthPancreas' (n = 74); and (4) Patients with unknown race (n = 1). Then, we divided the eligible patients into pancreatic head group (PHG) and pancreatic body/tail group (PBTG) according to the location of PMAC. Additionally, we have to declare that the patients included in this study were not including those with cystic mucinous adenocarcinoma and intraductal papillary mucinous tumor, which could lead to a contaminated result.

Statistical analysis

Student's t test, Mann–Whitney U test, chi-square test, and X^2 test were properly utilized to compare the clinicopathological data and survival of the two groups of patients. Logistic regression analysis was applied to identify the relationship between tumor locations and pathological characteristics. The survival analyses were conducted using Kaplan-Meier analysis (log-rank test) and Cox regression analysis. Significance was considered as $P < 0.05$. All statistical analyses in the study were conducted using R software (version 4.2.0).

RESULTS

Baseline characteristics

Finally, 271 patients met the inclusion criteria and were included in the study. According to the locations of tumor, these patients were divided into pancreatic head group (PHG) (n = 159) and PBTG (n = 112) (Table 1). In general, the median OS of 271 patients was 13 mo. Patients over 65 years old (61.3%) and white (74.5%) accounted the majority. Concerning the clinical characteristics, males in PHG were more than that in PBTG (P = 0.009), and the ratios of male to female of PHG and PBTG were 1.45 *vs* 0.67, while there was no significant difference of age and race between the two groups. Compared to PHG, PBTG patients were observed to have more metastatic tumors ($P < 0.001$) staged in advanced stage ($P < 0.001$). The differences in T, N, and primary malignancy of the two groups were not statistically significant. Moreover, patients in PHG were likely to have a longer OS than PBTG (median OS 18 *vs* 7.5 mo, $P < 0.001$).

The correlation between clinicopathological features and risk of aggressive factors

By comparing the basic characteristics of the two groups, we identified that locations of the tumor were related to the metastasis and higher staging. After eliminating confounding factors, we included sex, age, race, location, and primary malignancy into the logistic regression models (Figure 1). It was shown that patients in PBTG have higher risk of metastasis [OR = 2.747, 95% confidence interval (CI): 1.628-4.636, $P < 0.001$] and high staging (III-IV) (OR=3.204, 95%CI: 1.895-5.415, $P < 0.001$) compared with PHG. Additionally, there was a higher risk of metastasis in patients over 65 years old (OR = 1.877, 95%CI: 1.079-3.264, P=0.026) with PMAC as the primary malignancy (OR = 2.317, 95%CI: 1.196-4.488, P = 0.013).

General survival analysis of the two groups

The 1-year, 3-year, and 5-year OS rates of all patients were 51.6%, 23.5%, and 13.6%, respectively. While the 1-year, 3-year, and 5-year CSS rates were 53.2%, 26.2%, and 17.4%, respectively. Univariate and multivariate Cox regression models of OS and CSS were further constructed (Table 2; Table 3), and the results could be drawn that age, grade, stage, and systemic therapy were independent factors for predicting both OS and CSS of these patients (all $P < 0.05$). Besides, tumor located at pancreatic head was considered as a favorable independent prognostic factor for CSS (HR = 0.7, 95%CI: 0.52-0.94, P = 0.017). Then, we depicted survival curves of the two groups using Kaplan-Meier analysis, which suggested that patients in PHG had longer OS and CSS than those in PBTG (all $P < 0.05$) (Figure 2A and B). Nevertheless, it is known that cancers of the body and especially of the tail are diagnosed at a more advanced stage or even metastatic than cancers of the head, which manifest themselves by jaundice at an earlier stage, probably being one of the contributors of "better prognosis" of pancreatic head cancer. Additionally, the rate of R1 surgery will be higher in PHG during cephalic resections because of the closer vascular relationships. Given these, we made a selection of PMAC without surgical resection treatment and compared the long-term survival of PHG (n = 81) and PBTG (n = 80), which avoided the imbalance in surgery thoroughness (non-surgery, R0 and R1 resection) of the two groups. The Kaplan-Meier curves elucidated that the long-term outcomes of PHG without surgery were better than PBTG without surgery (all $P < 0.05$) (Figure 3A and B).

Survival analysis of systemic therapy

In this retrospective study, 86 patients (31.7%) received systemic therapy, while the remaining 185 (68.3%) patients did not. Patients who received systemic therapy had longer OS and CSS (all $P < 0.05$) (Figure 4A and B). Then, we conducted the analysis in PHG and PBTG, respectively. It demonstrated that regardless of which group the patients were in, patients who had received systemic therapy had better prognosis (all $P < 0.05$) (Figure 4C-F). Furthermore, we divided the patients into systemic therapy

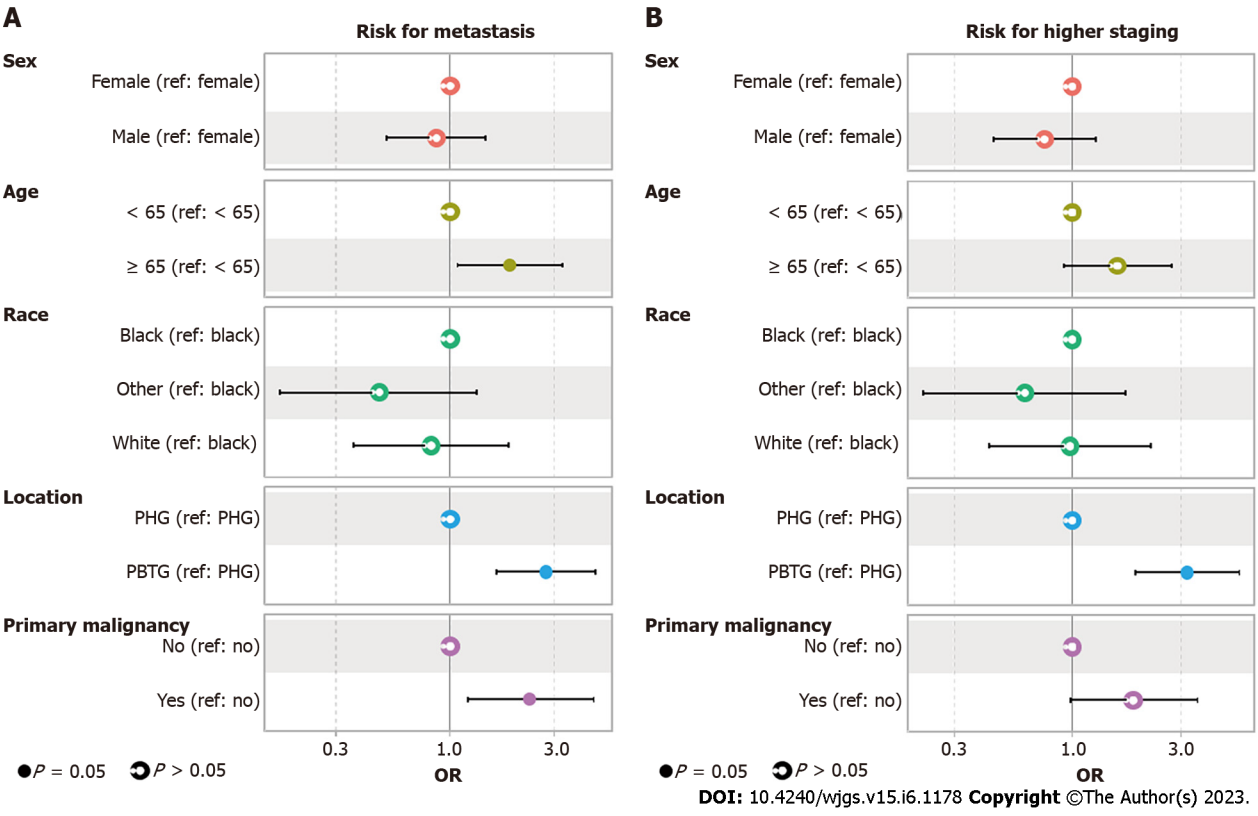

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Figure 1 Logistic regression analysis of aggressive factors. A: Risk analysis of metastasis; B: Risk analysis of higher staging. PHG: Pancreatic head group; PBTG: Pancreatic body/tail group; OR: Odds ratio.

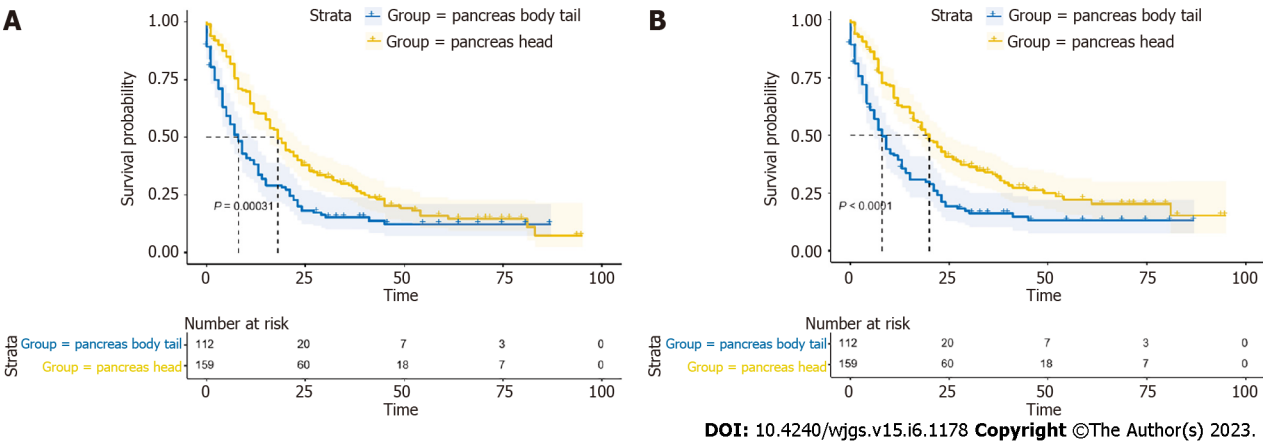

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Figure 2 Kaplan-Meier survival analysis of the two groups. A: Analysis for overall survival; B: Analysis for cancer-specific survival.

group and non-systemic therapy group and compared the survival of PHG and PBTG in each group. It showed that patients in PHG had a better survival in non-systemic therapy group (all $P < 0.05$) (Figure 5A and B), while there were no significant differences of survival in systemic therapy group (Figure 5C and D).

Subgroup analysis of stages

The significant differences of survival curves for all patients in stage I-IV were identified ($P < 0.05$) (Figure 6A and B). In early stage (stage I-II), there were no statistically significant differences between the survival of PHG and PBTG (Figure 6C and D). However, OS and CSS of PHG were significantly better than PBTG in advanced stage (stage III-IV) (Figure 6E and F). Moreover, surgical resection was considered as the best potential curative treatment for PMAC. The ratio of patients with advanced stage who received a surgery of two groups were calculated and depicted to avoid the impact of surgery on the results (Figure 7). From the ratio, we can see that more patients in PBTG received a surgery than PHG (6.8% *vs* 5.1%).

Table 1 Baseline characteristics of two patient groups, *n* (%)

	PBTG (*n* = 112)	PHG (*n* = 159)	Overall (*n* = 271)	*P* value
Age, yr				
< 65	39 (34.8)	66 (41.5)	105 (38.7)	0.538
≥ 65	73 (65.2)	93 (58.5)	166 (61.3)	
Race				
Black	15 (13.4)	17 (10.7)	32 (11.8)	0.443
Other	20 (17.9)	17 (10.7)	37 (13.7)	
White	77 (68.8)	125 (78.6)	202 (74.5)	
Sex				
Female	67 (59.8)	65 (40.9)	132 (48.7)	0.009
Male	45 (40.2)	94 (59.1)	139 (51.3)	
Grade				
G1 + G2	35 (31.3)	70 (44.0)	105 (38.7)	0.041
G3 + G4	11 (9.8)	26 (16.4)	37 (13.7)	
Unknown	66 (58.9)	63 (39.6)	129 (47.6)	
Stage				
I	10 (8.9)	18 (11.3)	28 (10.3)	< 0.001
II	28 (25.0)	82 (51.6)	110 (40.6)	
III	9 (8.0)	6 (3.8)	15 (5.5)	
IV	65 (58.0)	53 (33.3)	118 (43.5)	
T				
T1	11 (9.8)	15 (9.4)	26 (9.6)	0.209
T2	26 (23.2)	34 (21.4)	60 (22.1)	
T3	49 (43.8)	93 (58.5)	142 (52.4)	
T4	26 (23.2)	16 (10.1)	42 (15.5)	
T0	0 (0)	1 (0.6)	1 (0.4)	
N				
N0	67 (59.8)	83 (52.2)	150 (55.4)	0.462
N1	45 (40.2)	76 (47.8)	121 (44.6)	
M				
M0	47 (42.0)	106 (66.7)	153 (56.5)	< 0.001
M1	65 (58.0)	53 (33.3)	118 (43.5)	
Primary malignancy				
No	23 (20.5)	36 (22.6)	59 (21.8)	0.918
Yes	89 (79.5)	123 (77.4)	212 (78.2)	
OS, mo				
mean (SD)	14.6 (18.5)	24.1 (21.2)	20.2 (20.6)	< 0.001
Median [Min, Max]	7.50 [0, 87.0]	18.0 [0, 95.0]	13.0 [0, 95.0]	

PBTG: Pancreatic body/tail group; PHG: Pancreatic head group.

DISCUSSION

For pancreatic cancer (PC), there are various studies focusing on the characteristics of tumors occurring

Table 2 Cox regression analysis of overall survival in patients with pancreatic mucinous adenocarcinoma

Characteristics	Univariate			Multivariate		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age, yr						
< 65	Reference			Reference		
≥ 65	1.62	1.23-2.14	0.001	1.42	1.06-1.89	0.017
Race						
Black	Reference					
Other	0.91	0.54-1.53	0.725			
White	0.94	0.62-1.41	0.751			
Sex						
Female	Reference			Reference		
Male	0.68	0.52-0.89	0.004	0.81	0.61-1.07	0.134
Location						
Pancreas body/tail	Reference			Reference		
Pancreas head	0.61	0.47-0.8	< 0.001	0.76	0.57-1.01	0.057
Grade						
G1 + G2	Reference			Reference		
G3 + G4	1.82	1.21-2.73	0.004	2.17	1.43-3.31	< 0.001
Unknown	2.21	1.64-2.97	< 0.001	1.23	0.89-1.69	0.216
Stage						
I	Reference			Reference		
II	2.39	1.3-4.37	0.005	3.2	1.73-5.92	< 0.001
III	6.2	2.81-13.68	< 0.001	6.5	2.89-14.61	< 0.001
IV	6.73	3.67-12.37	< 0.001	6.2	3.34-11.5	< 0.001
Systemic therapy						
No	Reference			Reference		
Yes	0.32	0.24-0.44	< 0.001	0.39	0.27-0.56	< 0.001

HR: Hazard ratio; CI: Confidence interval.

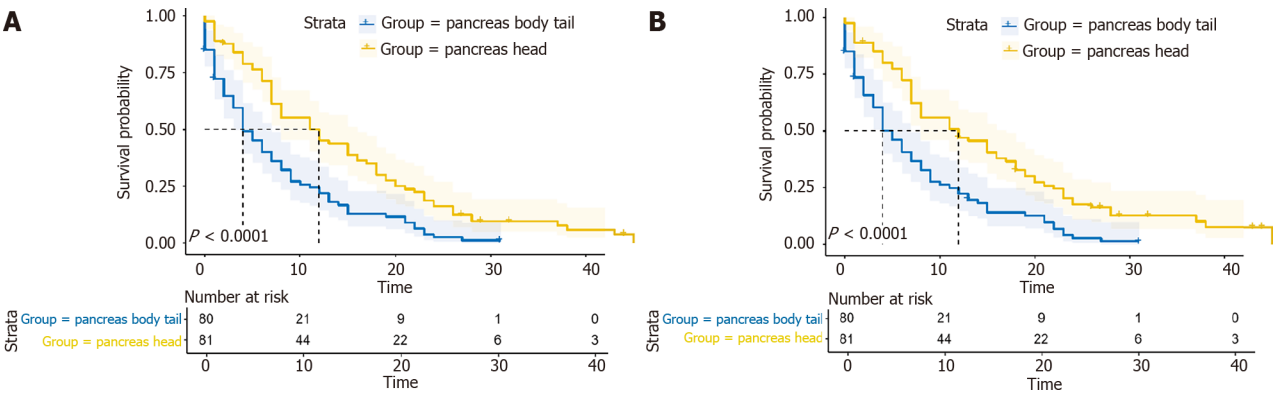

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Figure 3 Kaplan-Meier survival analysis of the two groups without surgical resection. A: Analysis for overall survival; B: Analysis for cancer-specific survival.

Table 3 Cox regression analysis of cancer-specific survival in patients with pancreatic mucinous adenocarcinoma

Characteristics	Univariate			Multivariate		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age, yr						
< 65	Reference			Reference		
≥ 65	1.56	1.17-2.08	0.002	1.37	1.02-1.84	0.038
Race						
Black	Reference					
Other	0.91	0.54-1.55	0.739			
White	0.89	0.58-1.34	0.568			
Sex						
Female	Reference			Reference		
Male	0.64	0.48-0.84	0.001	0.77	0.58-1.03	0.082
Location						
Pancreas body/tail	Reference			Reference		
Pancreas head	0.56	0.43-0.74	< 0.001	0.7	0.52-0.94	0.017
Grade						
G1 + G2	Reference			Reference		
G3 + G4	1.75	1.14-2.67	0.01	2.2	1.42-3.4	< 0.001
Unknown	2.12	1.56-2.88	< 0.001	1.1	0.79-1.54	0.559
Stage						
I	Reference			Reference		
II	3.7	1.71-8.03	0.001	5.02	2.29-11	< 0.001
III	10.3	4.09-25.95	< 0.001	10.75	4.19-27.61	< 0.001
IV	10.47	4.83-22.73	< 0.001	9.81	4.47-21.51	< 0.001
Systemic therapy						
No	Reference			Reference		
Yes	0.3	0.22-0.42	< 0.001	0.35	0.24-0.51	< 0.001

HR: Hazard ratio; CI: Confidence interval.

in different anatomical locations[6,8]. However, pancreatic mucinous adenocarcinoma (PMAC) is a rare type of PC. To the best of our knowledge, there is no study reported to discuss the characteristics of PMAC in different locations. Based on these viewpoints, this retrospective study was conducted to compare the survival and clinicopathological features of PMAC in pancreatic head and that in pancreatic body/tail. The new findings may provide novel insights for clinical workers to select appropriate strategies for pancreatic ductal adenocarcinoma (PDAC) management in the future.

Several previous studies had revealed that compared to pancreatic body/tail, patients with PC occurring in pancreatic head owned a better survival, especially for PDAC and pancreatic neuroendocrine tumors (PNETs)[6-8,12,13]. Not only that, anatomical locations of multiple cancer types produced a significant impact on cancer prognosis, such as gastric cancer[14-16], breast cancer[17], lung cancer[18], colorectal cancer[19-22]. These previous evidences provided support for our study through a broader cancer spectrum. However, there was also a study revealed that PDAC of pancreatic head had similar oncological outcomes with PDAC of pancreatic body/tail[10]. The divergence may be caused by different inclusion criteria of patients and various types of biases. In the present study, we firstly identified the better survival of PMAC located at pancreatic head compared to pancreatic body/tail, which was consistent with previous studies. Concerning the potential mechanisms underlying this situation, we believe that it is related to genetics and tumor biological diversity[5]. Pancreatic cancer cells in different anatomical positions have various embryonic origins and biological progresses[6], thereby leading to different clinical and pathological characteristics.

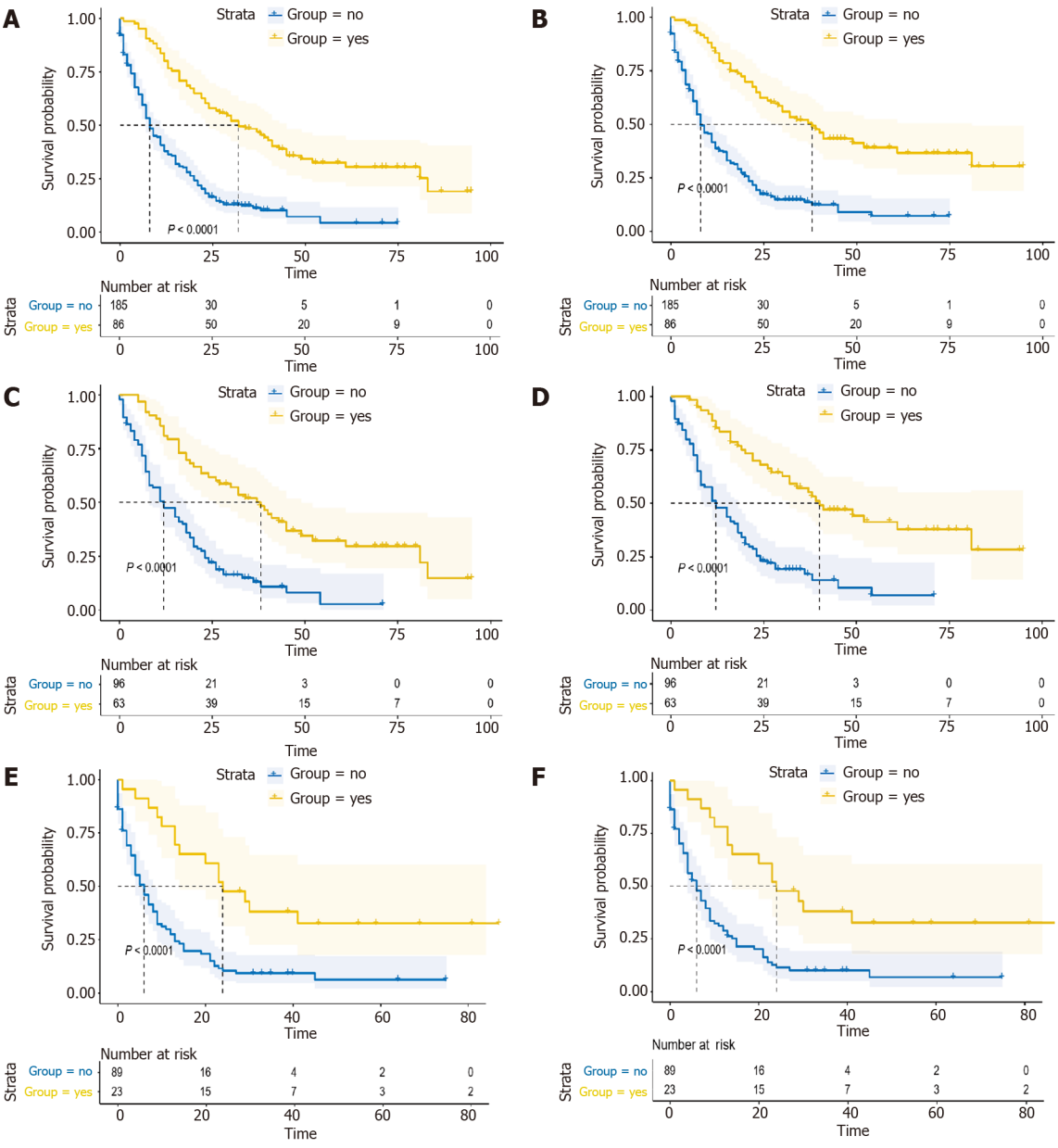

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Figure 4 Analysis of systemic therapy. Survival of patients receiving and not receiving systemic therapy (A: Overall survival; B: Cancer-specific survival). Survival of pancreatic head group patients with and without systemic therapy (C: Overall survival; D: Cancer-specific survival). Survival of pancreatic body/tail group patients with and without systemic therapy (E: Overall survival; F: Cancer-specific survival).

In the risk analysis for aggressive pathological factors, it was also shown that patients with PMAC of pancreatic body/tail had a greater risk for metastasis and higher staging compared to PMAC of pancreatic head. Such results were not contradictory to previous studies, which demonstrated that the pancreatic body/tail PDAC was larger, more frequently metastasized, and less likely to be resected compared to pancreatic head PDAC[8]. We thought the possible mechanisms were as follows: Firstly, the stemness of pancreatic tumor stem cells varies widely according to various embryonic origins and is related to the resistance to radiotherapy, chemotherapy, and tumor metastasis[23]. In this study, pancreatic body/tail PMAC was easy to metastasize, which may be caused by the high stemness of tumor cells in the body/tail of the pancreas. Secondly, the tumor microenvironment (TME) of different tumor sites is variable. TME is considered to play an important role in the process of pancreatic tumor metastasis, which can promote metastasis by stimulating angiogenesis/Lymphangiogenesis, epithelial-mesenchymal transition and so on[24]. Among these, pancreatic stellate cells (PSCs) were found to regulate angiogenesis and immune evasion, thereby promoting the resistance of therapy and tumor metastasis[25]. Thirdly, due to genetic and biological diversity, different tumor sites are characterized by variable gene communities. Alterations in these genes and characteristic signaling pathways are associated with tumor invasion and metastasis[26-29].

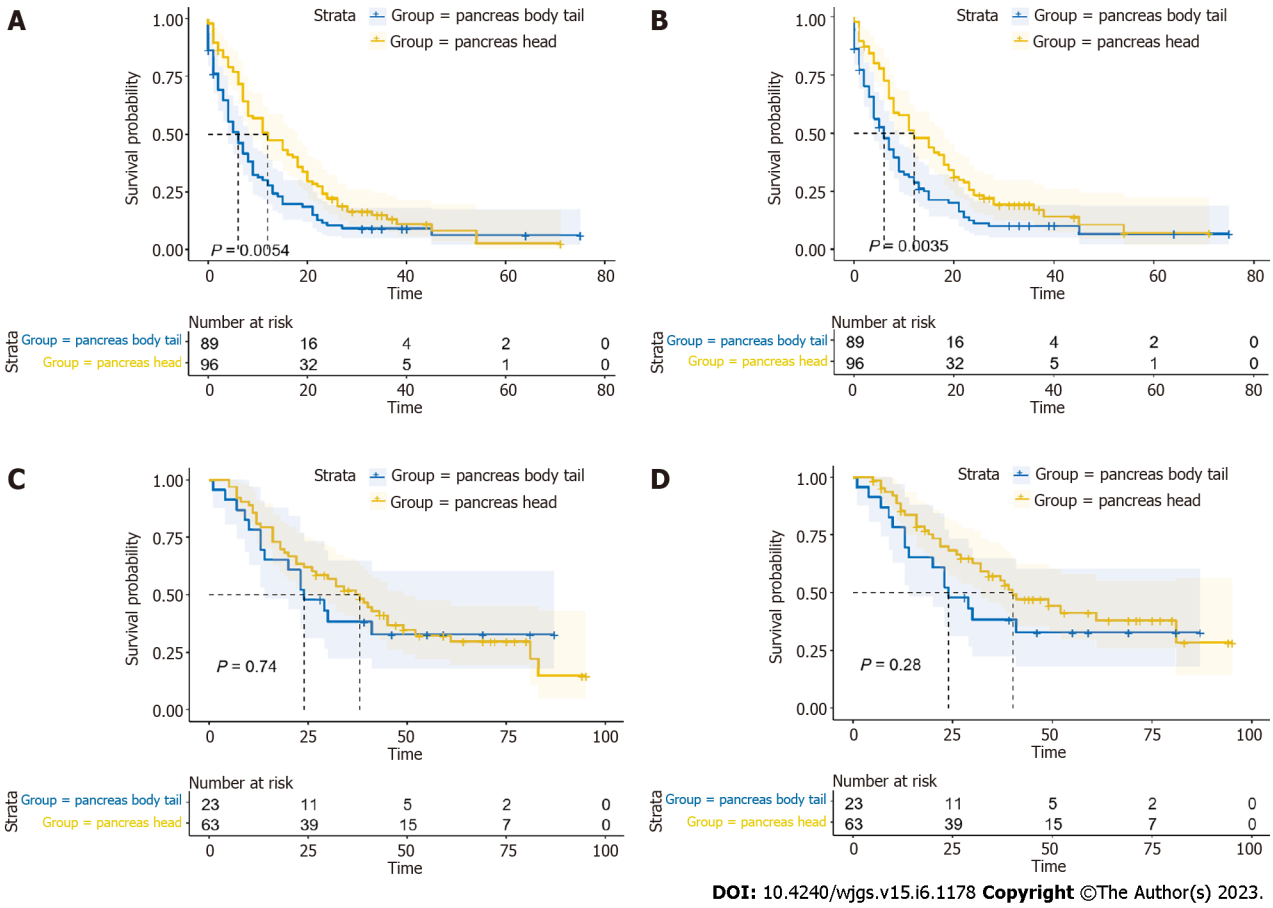

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Figure 5 Survival analysis of pancreatic head group and pancreatic body/tail group patients without systemic therapy. (A: Overall survival; B: Cancer-specific survival). Survival analysis of pancreatic head group and pancreatic body/tail group patients with systemic therapy (C: Overall survival; D: Cancer-specific survival).

Systemic therapy is a combination of chemotherapy, radiotherapy, immunotherapy, targeted therapy and so on. Cancer patients rarely receive radical treatment, and more patients are treated with systemic therapy to control disease progression and prolong survival time[30]. In the survival analysis of this study, we revealed that patients treated with systemic therapy were prone to longer OS and CSS, regardless of the PMAC locations. In further investigation, non-systemic therapy patients with pancreatic head PMAC were observed to have a significant better survival compared to those with pancreatic body/tail PMAC. However, the survival of the two groups had no statistically significant difference after treated with systemic therapy. Although this was an observational analysis, without intervention experiments. Such results can also suggest that systemic therapy played an important role in prolonging the prognosis of patients. Meanwhile, systemic therapy has been paid attention to and applied to various cancer types, including cervical cancer[31], breast cancer[32], lung cancer[33], and even genitourinary malignancies of patients infected with COVID-19[34]. These consistent evidences from previous studies make our results easier to understand and more reliable.

There were also several limitations in this study that should be taken into account. Firstly, this was a retrospective study containing a relatively small simple size. Therefore, various biases existed in the study that may affect the results. Secondly, this study was unable to determine the exact mechanisms underlying the results, and further experiments are preferred to confirm our results. Thirdly, due to the limitations of SEER database, data of aggressive factors were incomplete including tumor size, tumor metastasis site and so on. In addition, typically pancreatic head cancer shows symptom in earlier stage than pancreatic body/tail ones and receives a surgical resection. That may be one of the contributors of "better prognosis" of pancreatic head cancer. Furthermore, in the group of patients who received curative surgery, the rate of R1 surgery will be higher during cephalic resections because of the closer vascular relationships, and such imbalance in surgery (R0 and R1) will lead to a compromised result. To solve there problems, we selected the PMAC located in pancreatic head (PHG) and body/tail (PBTG) without surgical resection treatment and compared the long-term outcomes of PHG and PBTG, which made the two groups comparable and drew more rigorous conclusions.

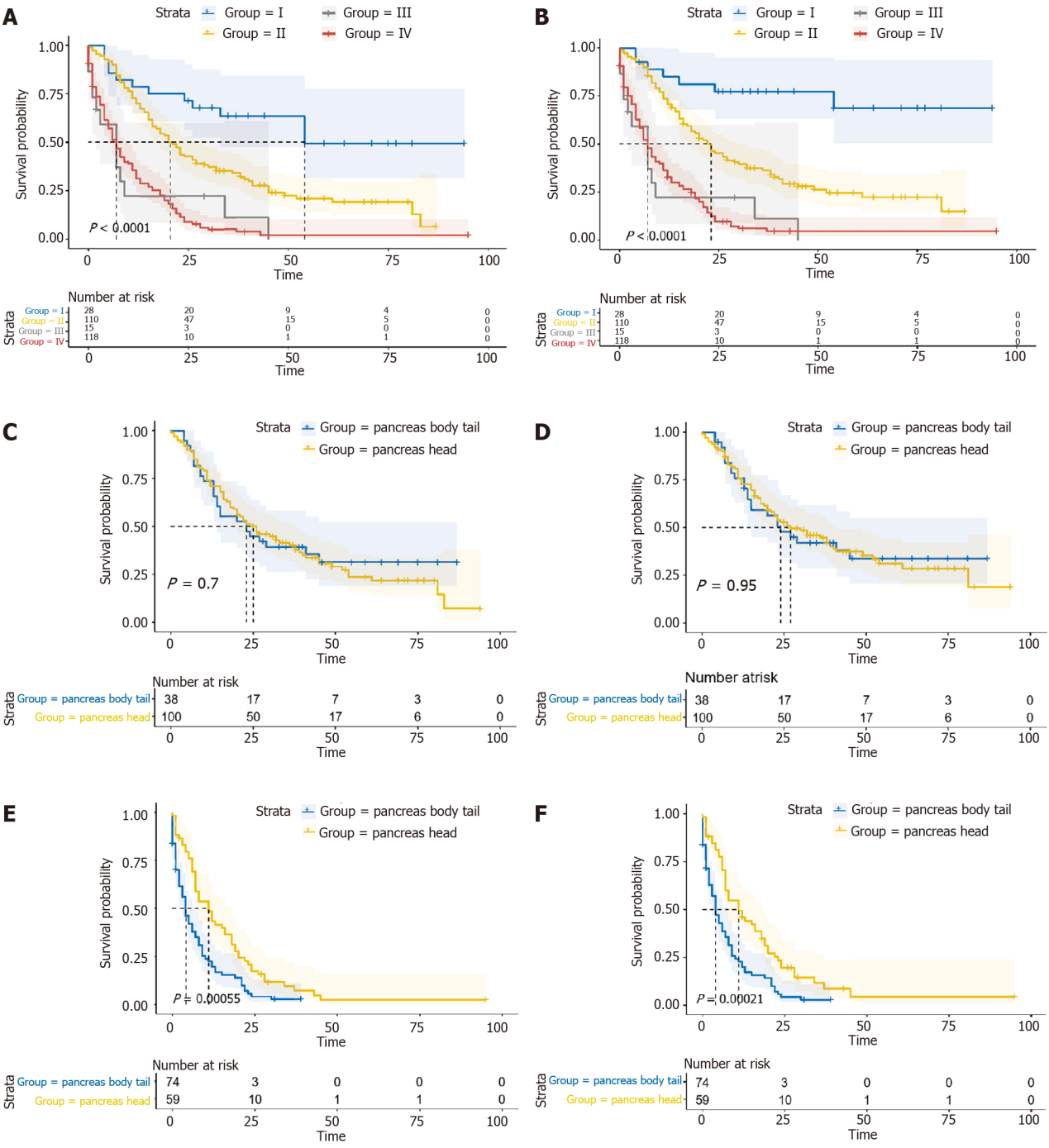

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Figure 6 Survival analysis of stages between the two groups. Survival curves of all patients in stage I-IV (A: Overall survival; B: Cancer-specific survival). Different survival of pancreatic head group (PHG) and pancreatic body/tail group (PBTG) patients in early stage (stage I-II) (C: Overall survival; D: Cancer-specific survival). Different survival of PHG and PBTG patients in advanced stage (stage III-IV) (E: Overall survival; F: Cancer-specific survival).

CONCLUSION

In summary, mucinous adenocarcinoma of pancreatic head has better survival and favorable clinicopathological characteristics compared to that of pancreatic body/tail. Moreover, systemic therapy was observed to effectively prolong the long-term survival of patients including OS and CSS.

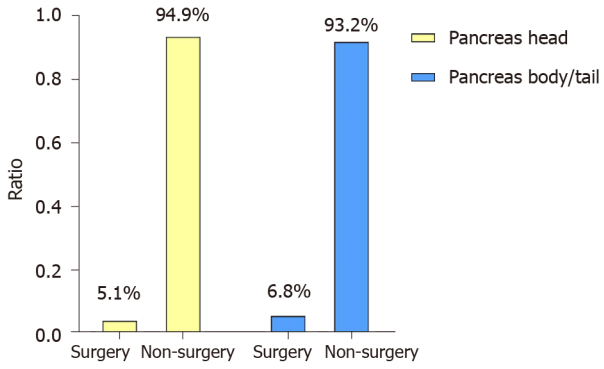

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Figure 7 Ratio of surgery in pancreatic head group and pancreatic body/tail group.

ARTICLE HIGHLIGHTS

Research background

Growing evidence shows that pancreatic tumors varied according to different anatomical locations, which produce a significant impact on the prognosis. However, there was no study reported to determine the differences between pancreatic mucinous adenocarcinoma (PMAC) in the head and body/tail of pancreas.

Research motivation

We aimed to investigate the differences in long-term outcomes (overall survival and cancer-specific survival) and clinicopathological characteristics between PMAC in the head and body/tail of pancreas.

Research objectives

A total of 2058 PMAC patients from the Surveillance, Epidemiology, and End Results database diagnosed between 1992 and 2017 were retrospectively reviewed.

Research methods

We divided the patients who met the inclusion criteria into pancreatic head group (PHG) and pancreatic body/tail group (PBTG). The relationship between two groups and risk of invasive factors was identified using logistic regression analysis. Kaplan-Meier analysis and Cox regression analysis were conducted to compare the overall survival (OS) and cancer-specific survival (CSS) of two patient groups.

Research results

After selection, 271 PMAC patients were included in the study. The 1-year, 3-year, and 5-year OS rates of these patients were 51.6%, 23.5%, and 13.6%, respectively. While the 1-year, 3-year, and 5-year CSS rates were 53.2%, 26.2%, and 17.4%, respectively. The median OS of PHG was longer than that of PBTG (18 *vs* 7.5 mo, $P < 0.001$). Compared to PHG, patients in PBTG had a greater risk of metastases [odds ratio (OR) = 2.747, 95% confidence interval (CI): 1.628-4.636, $P < 0.001$] and higher staging (OR = 3.204, 95%CI: 1.895-5.415, $P < 0.001$). Survival analysis revealed that age < 65 years, male, low-grade (G1-G2), low-stage, systemic therapy, and PMAC located at pancreatic head led to longer OS and CSS (all $P < 0.05$). The location of PMAC was an independent prognostic factor for CSS [hazard ratio (HR)=0.7, 95%CI: 0.52-0.94, $P = 0.017$]. Further analysis demonstrated that OS and CSS of PHG were significantly better than PBTG in advanced stage (stage III-IV).

Research conclusions

Compared to pancreatic body/tail, the PMAC located in pancreatic head have a better long-term outcomes and favorable clinicopathological characteristics.

Research perspectives

The new findings may provide novel insights for clinical workers to select appropriate strategies for pancreatic ductal adenocarcinoma management in the future.

FOOTNOTES

Author contributions: Li Z, Zhang XJ and Zhao DB designed research; Sun CY, Fei H and Li Z collected data; Li Z analyzed data; Li Z, Zhang XJ, Fei H, Li Z and Zhao DB wrote the paper; Zhao DB guaranteed integrity of study.

Institutional review board statement: This study was reviewed and approved by the institutional review board of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

Informed consent statement: This was a retrospective, observational cohort study based on publicly accessible database-SEER, therefore informed consent was waived.

Conflict-of-interest statement: The authors have declared that no competing interest exists.

Data sharing statement: The data used is from a publicly accessible database-SEER (www.seer.cancer.gov).

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SYSTEMATIC REVIEWS

Gallbladder perforation with fistulous communication

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Abstract

BACKGROUND

The management of gallbladder perforation (GBP) with fistulous communication (Neimeier type I) is controversial.

AIM

To recommend management options for GBP with fistulous communication.

METHODS

A systematic review of studies describing the management of Neimeier type I GBP was performed according to the PRISMA guidelines. The search strategy was conducted in Scopus, Web of Science, MEDLINE, and EMBASE (May 2022). Data extraction was obtained for patient characteristics, type of intervention, days of hospitalization (DoH), complications, and site of fistulous communication.

RESULTS
A total of 54 patients (61% female) from case reports, series, and cohorts were included. The most frequent fistulous communication occurred in the abdominal wall. Patients from case reports/series had a similar proportion of complications between open cholecystectomy (OC) and laparoscopic cholecystectomy (LC) (28.6 *vs* 12.5; $P = 0.569$). Mortality was higher in OC (14.3 *vs* 0.0; $P = 0.467$) but this proportion was given by only one patient. DoH were higher in OC (mean 26.3 d *vs* 6.6 d). There was no clear association between higher rates of complications of a given intervention in cohorts, and no mortality was observed.

CONCLUSION
Surgeons must evaluate the advantages and disadvantages of the therapeutic options. OC and LC are adequate options for the surgical management of GBP, with no significant differences.

Key Words: Gallbladder perforation; Open cholecystectomy; Laparoscopic cholecystectomy; Fistulous communication

Core Tip: Gallbladder perforations are rare. Management guidelines are non-specific. Although a clear benefit of laparoscopic cholecystectomy over open cholecystectomy is lacking, with the increase in laparoscopic training and availability, this approach may demonstrate superiority in time.

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INTRODUCTION

Gallbladder disease is a common pathology, frequently aggravated by gallstones, with a risk of complications. Such complications include the rare spontaneous (non-traumatic) gallbladder perforation (GBP), with an incidence ranging from 0.8% to 15.0% and a mortality of 12% to 16%[1-3]. It is caused by an obstruction of the cystic duct, which results in bile stasis with bacterial proliferation, distension, increased pressure, and vascular and lymphatic collapse and thereby leads to ischemia, necrosis, and finally perforation[3,4]. The most common site of perforation is the fundus, as it has the lowest vascular supply[5].

Acute cholecystitis may be classified into different grades of severity using the Tokyo guidelines or the Parkland classification[6,7]. However, GBP itself can be classified into three types according to Neimeier: Chronic perforation with fistulous communication (type I); subacute perforation with a surrounding abscess contained by adhesions (type II); and acute perforation and spillage to the cavity with generalized biliary peritonitis (type III)[8]. Due to a historically erroneous cite, authors frequently switch types I and III, a reason why it is important to specify the characteristics of the perforation[1-3,8-12].

Management protocols are well established in acute cholecystitis, but GBP management remains controversial. Preoperative diagnosis is difficult, usually only identified in half the cases[13]. Abdominal computed tomography (CT) provides the most sensitive and specific imaging tool allowing the evaluation of surrounding structures[1-3,14]. A recent systematic review of localized GBP established that open cholecystectomy (OC) has a lower incidence of requiring added procedures and a lower rate of postoperative complications[13]; however, recent cohorts support laparoscopic management[10,12,15]. Recommendations need to be reviewed as more current studies are added to the available literature. Fistulous communication has not been studied in detail and may vary depending on the organ/cavity of communication[16-19]. This systematic review aims to gather and revise the available evidence regarding chronic GBP with fistulous communication, focusing on management, specifically the type of surgical intervention, timing, and complications.

MATERIALS AND METHODS

Design and registration

This study adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement[20]. It was successfully registered in the International Prospective Register of Systematic Reviews (PROSPERO, NIHR) under the ID: CRD42021275733. It was also reviewed and approved by the University's Ethics and Research Committees with the registration number RV21-0019.

Eligibility criteria

Studies meeting the following criteria were included in this review: (1) Randomized controlled trials (RCTs), quasi-RCTs, and observational studies (cohorts, case studies, and case series) that compared/reported OC and/or laparoscopic cholecystectomy (LC) for Neimeier type I GBP in adult patients (> 18 years old). The intervention must have been OC or LC and patients could have received another intervention either before or after the interventions of interest; (2) Studies that reported mean DoH (set as primary outcome), complications related to the surgical intervention, need of another intervention after OC/LC (the interventions did not resolve the GBP), mortality, fistulation organ, and need of intensive care unit (ICU) admission and (3) Studies reported in English or Spanish. Studies in which GBP Neimeier type I diagnosis was unclear were excluded. No restrictions were applied in terms of study setting or time frame.

Data sources and search strategy

An experienced librarian designed and conducted the search strategy in the following databases in May 2022: Scopus, Web of Science, MEDLINE, and EMBASE. An additional search was performed on Google Scholar. Reference lists from studies selected by the authors were added to identify any potential studies that may have been missed. This included clinical trial registries, and contacting experts in the field to identify any unpublished or in-progress eligible studies.

Data management

EndNote X8 was used to upload results and process de-duplication. The resulting studies were uploaded to Distiller Systematic Review (DSR) software to continue with title/abstract and full-text screening.

Study selection process

A two-phase study selection was performed (title/abstract and full-text screening). In each, two reviewers worked independently and in duplicate to assess the eligibility of the studies. Kappa statistic was used to calculate chance-adjusted inter-rater agreement[21]. A pilot test was performed before each screening phase, using a random sample of studies from the search strategy results to standardize the reviewers' criteria. In case of disagreements, these were discussed to adjust criteria, if necessary. The pilot tests were repeated until reaching a Kappa index of > 0.70. The title and abstract were screened during the first phase, and reviewers selected the eligible articles based on the established inclusion criteria. Studies with discordant decisions were passed to the full-text phase to achieve a highly sensitive selection. Eligibility was then assessed through a full-text screening. In the second phase, any disagreements between the reviewers were resolved by consensus and if it was not achieved, a third reviewer arbitrated the evaluation. The number of included and excluded articles, as well as the reasons for the exclusion were documented.

Data collection process

Data from eligible articles were collected using a web-based data extraction form by two independent reviewers working in duplicate. The information obtained included: The type of study, author information, follow-up, year of publication, baseline characteristics of patients, type of intervention, DoH, days from diagnosis to intervention, complications, mortality, ICU admission, site of perforation, and fistulous communication. Disagreements were resolved by consensus, with the final decision made by a third reviewer in case that an agreement was not reached.

Missing data

Missing or unclear data considered important for the outcomes were sought out. The corresponding author was contacted *via* e-mail with specific questions regarding their study. In case of non-response in a lapse of 10 d, a second email was sent. If no response was obtained, other authors were contacted. If contact failed, the data or study was excluded.

Risk of bias and quality assessment

Two reviewers working independently and in duplicate evaluated the risk of bias from the studies using the Cochrane's ROBINS-I tool for the quasi-RCTs and observational studies[22], and the tool for

assessing the methodological quality of case reports/series proposed by Murad *et al*[23] for case reports/series. Any disagreement during this process was resolved by consensus, with the final decision made by a third reviewer in case that an agreement was not achieved.

Data synthesis

The studies included are described in a table detailing study design and setting, sample size, target population characteristics, description of the intervention, study groups, type of outcomes, and the level of risk of bias.

SPSS version 25[24] and RevMan5[25] were used for statistical analyses. Variables are summarized and presented as the mean with standard deviation for the primary outcome. Dichotomous outcomes are presented as the number of events and proportions. Categorical variables were analyzed using the Chi-squared test, and Student's *t*-test for independent groups for continuous numerical variables. If two or more studies were homogeneous enough, a cumulative meta-analysis was performed. A random-effects model was used with χ^2 test and I^2 statistic to assess heterogeneity between studies. The χ^2 cut-off value of $P < 0.10$ and an I^2 value > 50% were considered indicative of considerable heterogeneity. For all statistical analyses, a P value of < 0.05 was considered statistically significant. If this was not achieved, clinical outcomes are summarized narratively.

RESULTS

Study characteristics

There was a sustainable level of agreement between reviewers in the title and abstract screening phase (k = 0.72) and full-text phase (k = 0.86). A total of 1443 studies were identified and screened, with 210 included for full-text screening. After both screening phases, 18 studies were included for the qualitative and quantitative synthesis of fifteen case reports/series and two cohort studies (Figure 1). Across all studies, no conflict of interest was observed. Most studies were published in 2016 or later (n = 47 patients *vs* 8 from studies published in 2015 or before), with 26 of the 55 total patients managed by LC (Table 1).

Patient characteristics

A total of 20 patients were included from case reports/series, with a mean age of 66.6 ± 17.6, of which 65% were female (Table 2). Nine patients denied comorbidities. The most common comorbidity was diabetes mellitus followed by cardiovascular diseases (Supplementary Table 1)[26-41]. Preoperative diagnosis was identified as a cholecystic fistula in 16 patients (4 not reported). The most utilized diagnostic imaging tool was abdominal ultrasound (US) and CT. The most common site of GBP was the fundus (n = 5) with communication to the abdominal wall (n = 11). Eight patients were treated by LC, but three were converted to OC, making it the most common (n = 12) approach. Four patients were managed conservatively, while three required added endoscopic retrograde cholangiopancreatography (ERCP). One patient with a pleural fistula required a chest tube. Patients treated conservatively had a shorter evolution time of symptoms to their admission to the emergency room (ER) with (141.5 d; range, 13-270), compared to those treated by OC (265 d; range, 10-730) and LC (174.2 d; range, 2-730). Patients undergoing OC had a shorter range of 7-18 d from their ER admission to the operating room (OR) compared to those undergoing LC with a range of 16-34 d. No patient was admitted to the ICU. OC had longer mean DoH than LC (26.3 *vs* 7.0, P = 0.277) (Table 3).

A total of 35 patients were included from two cohort studies, with a mean age of 62.45 years, of which 60% were female (Table 4). Similar to case reports/series, the most common comorbidities were cardiovascular diseases (n = 7) and diabetes mellitus (n = 7). The most frequent site of perforation was the gallbladder's body (n = 16) followed by the fundus (n = 14). Less than half (n = 13) were diagnosed pre-operatively. One study favored OC (n = 17/20) with a higher mean of DoH (10.60 d), while the other study favored LC (n = 14/15) with a shorter mean of DoH (1.69 d), although this was from a larger sample, and not only fistulous GBP.

Risk of bias and quality assessment

Both cohort studies included had a moderate risk of bias. This was due to concerns in the domains of bias due to confounding, and bias in the measurement of outcomes due to the lack of blinding (Supplementary Table 2)[10,42]. Except for two case reports and one case series which had an overall low risk of bias, the rest presented a moderate risk of bias. This was most commonly due to the patient(s) selection, as it did not represent the whole experience of the investigator's center (Supplementary Table 3)[26-41].

Surgical intervention outcomes

In patients from case reports/series (Table 3), there was a similar proportion of patients presenting any complication post-OC and post-LC (28.6% *vs* 12.5%; P = 0.569). LC had a higher proportion of need for another intervention compared to OC, although this outcome was not statistically significant. The

Table 1 Surgical treatment from case report/series studies and cohorts

Year	Patients with type I GBP	Men	Women	Lap Chol			Open Chol			Conservative treatment
				n	Qx pre	Qx post	*n*	Qx pre	Qx post	
≤ 2005	2	1	1	1	1	0	0	0	0	1
2006-2010	3	1	2	0	0	0	2	0	0	1
2011-2015	3	0	3	1	0	0	1	0	0	1
2016-2020	25	11	14	19	0	0	5	0	1	1
≥ 2021	22	5	17	5	4	0	17	4	0	0

GBP: Gallbladder perforation; Lap Chol: Laparoscopic cholecystectomy; Open Chol: Open cholecystectomy; Qx: Surgery or procedure; pre: Previous to the cholecystectomy; post: After the cholecystectomy.

Table 2 Patient characteristics of case reports/series

Fistulous communication	N (fem)	Site of perforation			Preoperative diagnosis	Laparoscopic cholecystectomy (converted)	Open cholecystectomy	Conservative	Added procedures
		Fundus	Body	Neck					
Abdominal wall	11 (8)	3	3	3	9	3 (1)	7	1	1 ERCP
Gastric	4 (4)	-	-	1	2	2	1	1	
Duodenum	3 (1)	-	-	-	3	2 (2)	2	1	1 ERCP
Colon	2 (1)	2	-	-	2	0	2	0	1 ERCP
Pleura	1 (0)	-	-	-	1	1	0	0	1 pleural tube
Total	20 (13)[1]	5	3	3[1]	16[1]	8 (3)	12	3	4

[1]One patient had both abdominal wall and gastric fistula.
N: Sample size; fem: Female; converted: Laparoscopic cholecystectomy converted to open; ERCP: Endoscopic retrograde cholangiopancreatography.

Table 3 Surgical outcomes in case report/series patients

Surgical approach	*n*	Cx	*P* value	Convertion	*P* value	Mortality	*P* value	DoH	*P* value
Open Chol	7	2	0.550	NA	0.213	1	0.438	26.3 (± 22.7[1])	0.277
Lap Chol	9	1		3		0		7.0 (± 5.1[1])	

[1]Four patients were not included in this analysis due to their conservative management.
It is reported as the mean ± SD. *P* value was calculated using Chi-square test, with statistical significance set at < 0.05. DoH: Days of hospitalization; Lap Chol: Laparoscopic cholecystectomy; Open Chol: Open cholecystectomy.

mortality proportion was higher in OC than in LC (14.3% *vs* 0.0%; $P = 0.467$), but this was given by only one patient. DoH were higher in patients undergoing OC than LC (mean 26.3 d *vs* 6.6 d), although this outcome was not statistically significant ($P = 0.277$). Patients receiving conservative treatment did not present any morbidity or mortality.

In patients from included cohort studies, no mortality was observed in either intervention. Two patients in the LC group and seven in the OC group presented a complication after the intervention. However, there was no clear association between higher rates of complications of a given intervention (odds ratio = 0.33, 95% confidence interval: 0.03-3.31; $I^2 = 0\%$, $P = 0.64$). Three LC were converted to OC and none of the OC needed another intervention (Figure 2).

DISCUSSION

This systematic review summarizes the management of patients with Niemeir type I GBP (perforation

Table 4 Patient characteristics of cohort studies

Ref.	N (fem)	Mean age	Site of perforation			Preoperative diagnosis	Laparoscopic cholecystectomy (converted)	Open cholecystectomy	Conservative	Added procedures	DoH post chol
			Fundus	Body	Neck						
Gupta *et al* [10], 2022	20 (16)	53.1	7	11	2	2	3 (0)	17	0	8	10.64 ± 6.39
Sahbaz *et al* [42], 2017	15 (5)	71.8	7	5	2	11	14 (0)	1	0	0	1.69[1]

[1]Not specific to gallbladder perforation (GBP) type 3 (data from 133 patients with GBP).

N: Sample size; fem: Female; converted: Laparoscopic cholecystectomy converted to open; added procedures included 5 common bile duct explorations and 3 choledochoduodenostomies; DoH post-chol: Days of hospitalization post-cholecystectomy.

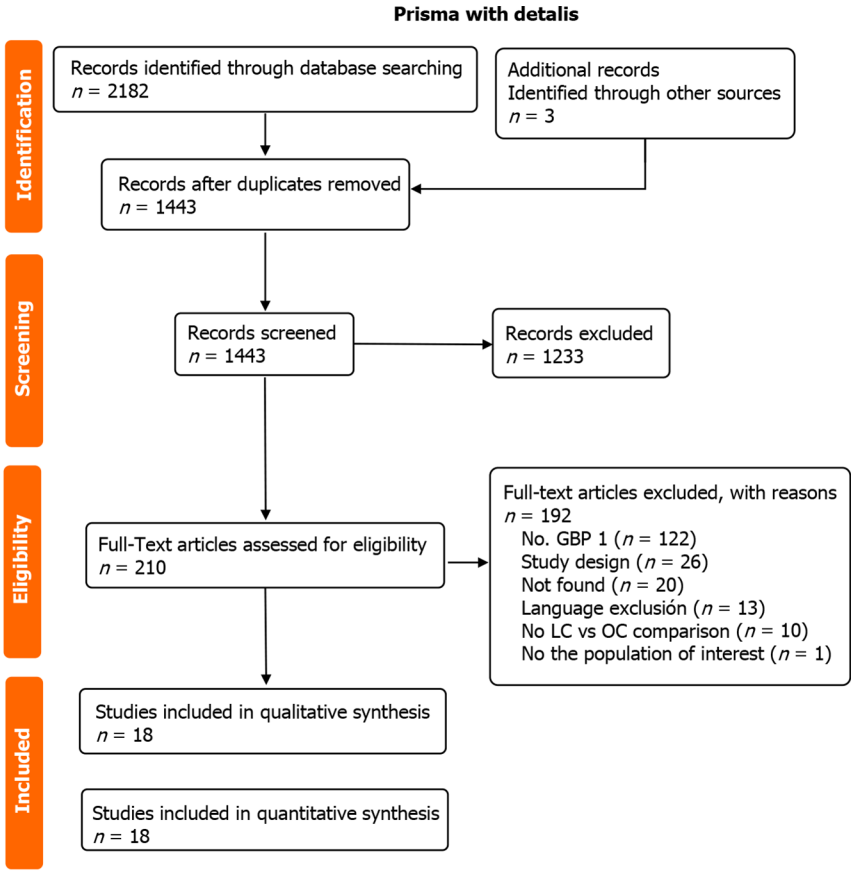

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Figure 1 CONSORT diagram. GBP 1: Gallbladder perforation Neiemier type 1; LC: Laparoscopic cholecystectomy; OC: Open cholecystectomy.

with a fistulous tract). A fistulous communication may be formed as a result of chronic GBP with various structures. There is a higher prevalence in women, and the abdominal wall is the most common site, followed by hollow viscera (stomach, duodenum, and colon), and the pleural cavity in one case[36,42-44]. There was no statistically significant difference between OC and LC; however, LC tended to have fewer DoH, in both case reports/series and cohorts.

The first report of this rare complication was described in 1670 by Thilesus[42]. In 1890, Courvoisier reported 169 cases of spontaneous cholecystocutaneous fistulae[45]. The most commonly reported cutaneous communication occurred in the right upper quadrant; however, the left upper quadrant, right iliac fossa, periumbilical, anterior chest wall, and gluteal region have also been described[32,40,42,46-48]. The ideal imagining modalities for the diagnosis are ultrasonography followed by CT with a fistulography. Clinical management includes analgesic therapy, antimicrobials, and individualized surgical treatment. OC and LC are both described as ideal surgical options for scheduled interventions.

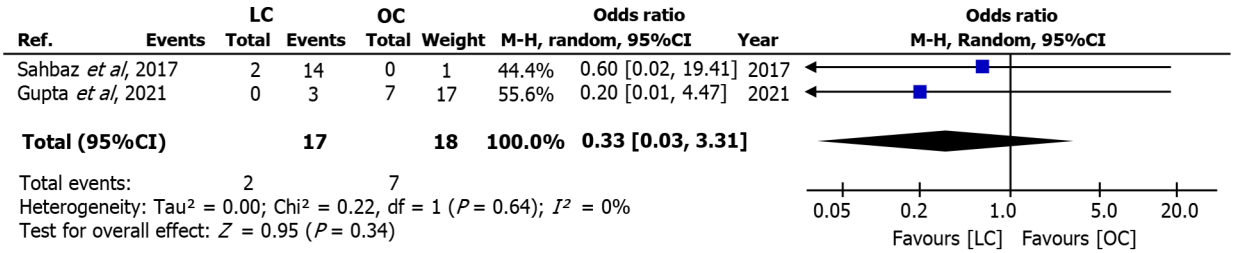

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Figure 2 Post-intervention complications after cholecystectomy. LC: Laparoscopic cholecystectomy; OC: Open cholecystectomy; CI: Confidence interval.

Complete excision of the fistulous tract is the recommended surgical treatment. Conservative approaches such as percutaneous cholecystectomy with drain insertion may be considered for high-risk patients or in palliative care settings[13,49].

Gastric and duodenum fistulae were the most common internal communications. This is due to their anatomical proximity to the gallbladder. US and CT are helpful in diagnosis, most of these being identified preoperatively; however, 22% of hollow visceral communications were transoperative findings[50]. OC was the preferred approach, with a conversion rate of 37.5% in LC (n = 3/8).

The cholecystocolic fistulae were also reported. These have been associated with other pathologies such as a history of gastric surgery, diverticular disease, trauma, or gallbladder carcinoma. Most of the patients are asymptomatic; however, diarrhea, right upper abdominal pain, fever, and jaundice can be present, and rarely hemorrhage, sepsis, or extraperitoneal abscess[44,46]. Savvidou *et al*[38] proposed a triad of pneumobilia, chronic diarrhea, and vitamin K malabsorption to be pathognomonic of a chlolecystocolic fistula. The clinical presentation of both reported cases had watery diarrhea and weight loss in common. Cholecystectomy with resection of the fistulous tract is the standard treatment, although in difficult cases a partial colonic resection may be required[30,46].

The reported cholecystopleural fistula was diagnosed by US and CT. The patient presented with malaise, vomiting, and dyspnea. The presence of *Escherichia coli* in the thoracentesis confirmed the imaging diagnosis. A laparoscopic approach with fistulous communication resection was decided to avoid negative pressure drainage with a chest tube[17]. A thoracic *vs* abdominal approach for the resection is still controversial[26].

The predominant site of GBP for fistulous communication was equal between the fundus (n = 19) and body (n = 19). The healing of the gallbladder due to the chronicity of the pathology may influence this, as the fundus has been described as the most common site of perforation due to the lowest vascular supply[5].

A chronic GBP with fistulous communication with the bile duct may be classified as Niemeier type I, but is more commonly known as the Mirizzi syndrome. A chronic inflammation is caused by a calculus stuck in the Hartmann or neck of the gallbladder, creating a fistula with the biliary tract. Mirizzi syndrome should be considered separately and recommendations made independently, as it requires urgent surgical intervention due to the obstruction of the biliary tract and its implications[51-53]. Niemeier type I can be scheduled when the patient's clinical state allows it, and even be managed conservatively in unstable patients.

More studies detailing GBP characteristics and management are needed to update current guidelines. No difference was established between OC and LC, with half the cases in recent years managed conventionally. To choose the optimal surgical technique, the surgeon must evaluate the advantages and disadvantages of the therapeutic options, the resources available in their environment, and their expertise. In patients with multiple co-morbidities and a high risk of trans- and post-operative complications, conservative medical treatment should be considered.

Limitations

More cohort studies are needed to ascertain the effect estimates of the outcomes. Cohorts need to include subgroup analysis to delve across specific groups with GBP. The current cohorts do not specify the organ/structure of fistulous communication, limiting a proposal of management options based on organ/structure. Many of the corresponding authors did not respond to emails, or could not provide the specific data needed. A strength of this systematic review and meta-analysis is the rigorous methodology performed across all the steps of the review (search strategy-data analysis).

CONCLUSION

Open and LC are adequate options for surgical management of Neimeier type I GBP, with no significant

differences in complications, DoH, or need for other interventions.

ARTICLE HIGHLIGHTS

Research background

Gallbladder perforation (GBP) is rare and its management remains controversial.

Research motivation

Authors are experts in the field, and have a high interest in GBP management.

Research objectives

To determine the best management options for GBP.

Research methods

A systematic review with rigorous search strategies.

Research results

Open cholecystectomy was associated with higher mortality and days of hospital stay.

Research conclusions

Although each case needs to be individually analyzed and considered according to the surgeons expertise, laparoscopic cholecystectomy (LC) is a viable option.

Research perspectives

Open cholecystectomy and LC are both adequate surgical management options for GBP.

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FOOTNOTES

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META-ANALYSIS

Efficacy of transanal drainage tube in preventing anastomotic leakage after surgery for rectal cancer: A meta-analysis

Shiki Fujino, Masayoshi Yasui, Masayuki Ohue, Norikatsu Miyoshi

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Abstract

BACKGROUND

Anastomotic leakage (AL) following rectal cancer surgery is an important cause of mortality and recurrence. Although transanal drainage tubes (TDTs) are expected to reduce the rate of AL, their preventive effects are controversial.

AIM

To reveal the effect of TDT in patients with symptomatic AL after rectal cancer surgery.

METHODS

A systematic literature search was performed using the PubMed, Embase, and Cochrane Library databases. We included randomized controlled trials (RCTs) and prospective cohort studies (PCSs) in which patients were assigned to two groups depending on the use or non-use of TDT and in which AL was evaluated. The results of the studies were synthesized using the Mantel-Haenszel random-effects model, and a two-tailed *P* value > 0.05 was considered statistically significant.

RESULTS

Three RCTs and two PCSs were included in this study. Symptomatic AL was examined in all 1417 patients (712 with TDT), and TDTs did not reduce the symptomatic AL rate. In a subgroup analysis of 955 patients without a diverting stoma, TDT reduced the symptomatic AL rate (odds ratio = 0.50, 95% confidence interval: 0.29–0.86, *P* = 0.012).

CONCLUSION

TDT may not reduce AL overall among patients undergoing rectal cancer surgery.

However, patients without a diverting stoma may benefit from TDT placement.

Key Words: Meta-analysis; Drainage; Transanal; Anastomotic leakage; Surgical stomas; Rectal cancer

Core Tip: Anastomotic leakage (AL) following rectal cancer surgery is a serious problem, and a transanal drainage tube (TDT) is expected to reduce AL. However, the preventive effects of TDT placement are controversial. Thus, we performed a meta-analysis of three randomized controlled trials and two prospective cohort studies. A systematic literature search was performed, and the results of the meta-analysis were synthesized using the Mantel-Haenszel random-effects model. Overall, TDT did not significantly reduce the symptomatic AL rate, but it did among patients without a diverting stoma.

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INTRODUCTION

Colorectal cancer (CRC) is a major cause of death in many countries and regions[1], and surgical resection of primary tumors is an important treatment for CRC[2]. With the development of surgical devices and procedures, from open to laparoscopic to robot-assisted surgeries, surgical outcomes have improved[3,4]. However, anastomotic leakage (AL) following surgery remains a serious complication related to mortality and recurrence, and the rate of AL is higher for rectal cancer surgery than that for colon cancer surgery[5,6].

To avoid AL, a combination of prophylactic procedures has been used, such as bowel preparation before surgery, anastomosis blood flow evaluation[7,8], and especially transanal drainage tubes (TDTs) and diverting stomas[8,9]. In recent years, preoperative therapies, such as chemoradiotherapy (CRT) or radiotherapy followed by chemotherapy, have been aggressively performed for advanced rectal cancer, and higher-risk patients are undergoing surgery after radiotherapy[10,11]. A diverting stoma is recommended for patients at high risk for AL[12], but stoma-related complications, such as high-output syndrome, skin irritation, stoma necrosis, and parastomal hernia, decrease the patient's quality of life and may lead to rehospitalization[13]. Therefore, many clinical studies have been performed to determine whether TDT can prevent AL; however, the results are controversial and most studies were retrospective[14-17]. Recently, the two most randomized controlled trials (RCTs) on the role of TDT in the prevention of AL were reported by Zhao *et al*[18] and Tamura *et al*[19]. The only related RCT published before these studies was reported by Bülow *et al*[20], but surgical procedures and pre-operative treatments have changed since then, as did the shape of the most commonly used TDT and the placement location. Thus, we performed an updated meta-analysis to incorporate the two new RCTs and new prospective cohort studies (PCSs), aiming to reveal the role of TDTs in preventing AL after rectal cancer surgery.

MATERIALS AND METHODS

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines[21]. The inclusion criteria were as follows: (1) An RCT or PCS for patients with a TDT; (2) Patients assigned to two groups depending on the use or non-use of TDT; and (3) The primary endpoint was the AL rate. Studies were excluded if one of the following occurred: (1) It was retrospective; (2) It was a review or case report; (3) Data were duplicated; (4) No comparisons were performed with a non-TDT group; (5) Full text could not be obtained; or (6) The TDT was not located at least several centimeters above the anastomosis. This study was not registered to public database.

Patients and study outcomes

We targeted patients with rectal cancer who underwent surgery for resection of the primary tumor with anastomosis. This is because the outcome is difficult to understand if the patient population is expanded, for instance, including those with inflammatory bowel disease. The outcome was the incidence of symptomatic AL after TDT.

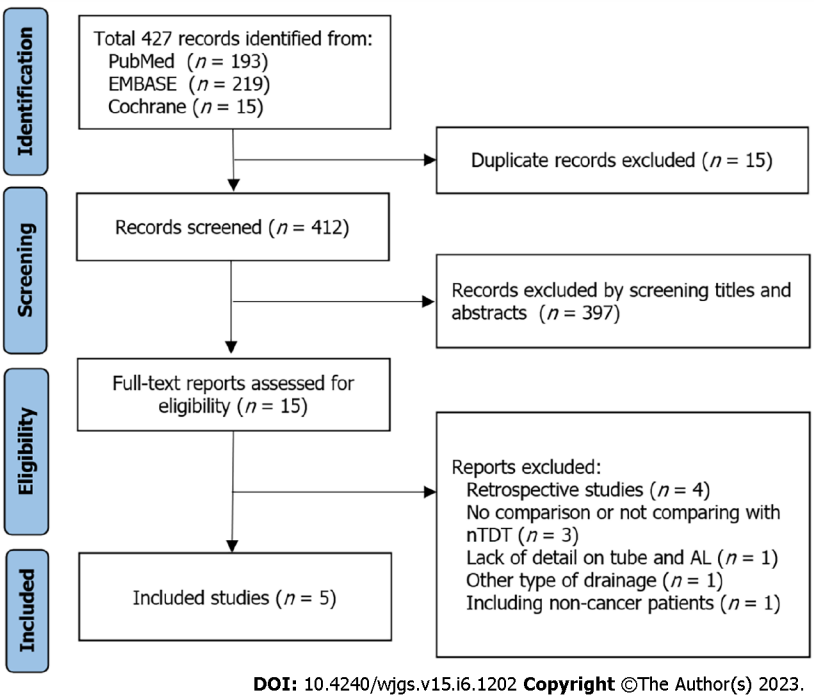

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Figure 1 Identification of studies *via* databases and registers. nTDT: Non-transanal drainage; AL: Anastomotic leakage.

Data sources and extraction

A systematic literature search for this study was performed using the advanced search of MEDLINE/PubMed, Embase, and Cochrane Library databases from inception until December 12, 2022, without language restrictions. The following search terms were used in all database searches: "transanal OR trans anal" AND "drainage OR tube OR stent" AND "rectal cancer". The titles and abstracts of all the retrieved records were reviewed independently by two investigators (Fujino S and Miyoshi N). All disagreements were resolved by consensus with a third investigator (Yasui M). The information extracted included the name of the first authors, year of publication, study design, study setting, types of operation, randomization procedure, TDT-related information (material, diameter, placement, duration), number of cases of AL, and grades of AL.

Meta-analysis

The results were synthesized using the Mantel-Haenszel random-effects model. Data were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). A funnel plot was used to evaluate potential publication bias and other possible biases. A two-tailed P value > 0.05 was considered statistically significant. A sensitivity analysis detected the influence of individual studies on the pooled OR by omitting one study at a time and recalculating the pooled OR. Subgroup analyses determined the effect of TDT in patients without a diverting stoma. Data were analyzed using R software (CRAN, R 3.6.2; cran.r-project.org) and the meta package (v4.17-0)[22]. The statistical methods of this study were reviewed by Miyoshi N.

RESULTS

Overall, 412 records were identified from the selected databases. We carefully evaluated each of them according to the inclusion and exclusion criteria. Finally, three RCTs[18,19,23] and two PCSs[24,25] were included in this study (Figure 1). The characteristics of the study population are summarized in Table 1. None of the studies revealed differences between the TDT and non-TDT groups in terms of sex, age, diverting stoma, or preoperative CRT. Patients undergoing preoperative CRT were excluded from three studies, and patients undergoing diverting stoma were excluded from two studies.

Symptomatic AL

Symptomatic AL was examined in all 1417 patients: 712 with TDT and 705 without TDT. Funnel plots based on AL grades are shown in Figure 2. Symptomatic AL was observed in 47 patients (6.6%) with TDT and 60 (8.5%) without TDT. TDT did not reduce the symptomatic AL rate (OR = 0.74, 95%CI: 0.39-1.40, P = 0.355) (Figure 3A). AL that required re-operation, *i.e.*, grade C, was observed in 13 patients (1.8%) with TDT and 34 (4.8%) without TDT. TDT did not reduce the grade C AL rate (OR = 0.43,

Table 1 Characteristics of the studies

		Zhao *et al* [18]	Tamura *et al* [19]	Xiao *et al*[23]	Challine *et al*[24]	Zhao *et al* [25]
Country		China	Japan	China	France	China
Published year		2021	2021	2011	2020	2013
Study design		RCT	RCT	RCT	PCS	PCS
Study setting		Multicenter	Multicenter	Single center	Single center	Singlecenter
Age	TDT	62 (54-69)[1]	69 (40-90)[1]	59 ± 11[2]	64 ± 12[2]	≥ 60/< 60, 30/51
	Non-TDT	62 (52-69)[1]	69 (39-91)[1]	58 ± 12[2]	60 ± 12[2]	≥ 60/< 60, 36/41
Sex (male/female)	TDT	177/103	51/28	115/85	51/21	47/34
	Non-TDT	169/111	50/28	121/77	51 / 21	43/34
Preoperative treatment (radiochemotherapy)	TDT	Excluded	10 (12.7%)	Excluded	41 (56.9%)	Excluded
	Non-TDT	Excluded	19 (24.3%)	Excluded	47 (65.3%)	Excluded
DS	TDT	72 (25.7%)	34 (43.0%)	Excluded	Unknown but equal rate by matching	Excluded
	Non-TDT	89 (31.8%)	37 (47.4%)	Excluded	Unknown but equal rate by matching	Excluded
Type of tube		Silicone tube, 28 Fr	Latex tube, 20-24 Fr	Silicone tube commonly used for abdominal drainage	Foley catheter, Ch 22	Rubber tube, 26 Fr
Duration		3-7 d	At least 5 d	5-7 d	At least 4 d	5-6 d
Significant side effects relating to anal tube		Anal pain	None	Perianastomotic bleeding	None	None
AL (A/B/C)	TDT	NA/14/4	2/5/1	NA/6/2	12/9/4	NA/0/2
	Non-TDT	NA/11/8	3/7/1	NA/3/16	9/5/2	NA/0/7
AL in the patients wihout a DS (A/B/C)	TDT	NA/8/4	NA	NA/6/2	NA	NA/0/2
	Non-TDT	NA/7/8	NA	NA/3/16	NA	NA/0/7

[1]Median (range).
[2]mean ± SD.
NA: Not available; TDT: Transanal drainage tube; RCT: Randomized controlled trial; PCS: Prospective cohort study; AL: Anastomotic leakage; DS: Diverting stoma.

95%CI: 0.16-1.17, P = 0.099) (Figure 3B). Sensitivity analysis showed that the pooled estimate of the effect of TDT for AL in all patients did not vary substantially (Figure 4).

Subgroup analysis of patients without a diverting stoma

In two studies, incidence of AL in patients without a diverting stoma was not mentioned. Therefore, a total of 955 patients without a diverting stoma were identified in three studies[18,23,25]: 489 with TDT and 466 without TDT. Symptomatic AL was observed in 22 patients (4.5%) with TDT and 41 (8.8%) without TDT. TDT reduced the symptomatic AL rate (OR = 0.50, 95%CI: 0.29-0.86, P = 0.012) (Figure 5A). Grade C AL was observed in eight patients (1.6%) with TDT and 31 (6.7%) without TDT. TDT also reduced the grade C AL rate (OR = 0.26, 95%CI: 0.11-0.59, P = 0.001) (Figure 5B). Sensitivity analysis revealed that the pooled estimate of the effect of TDT for AL in patients without a diverting stoma did not vary substantially (Figure 6).

DISCUSSION

The development of surgical methods and the intensification of combination therapies with radiation

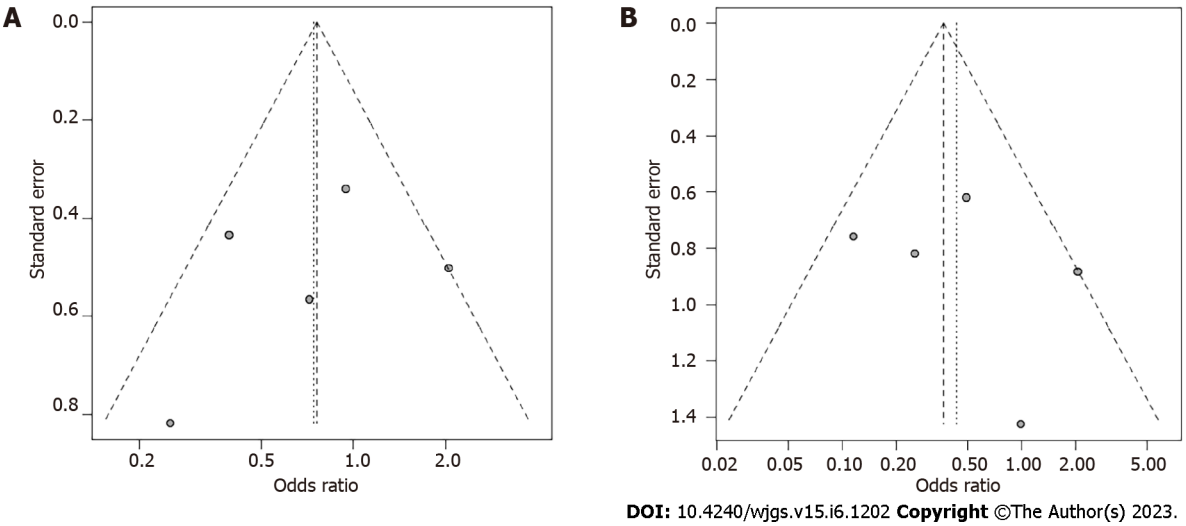

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Figure 2 Funnel plots based on symptomatic anastomotic leakage grades. A: Symptomatic leakage of grades; B: Leakage that required re-operation (grade C).

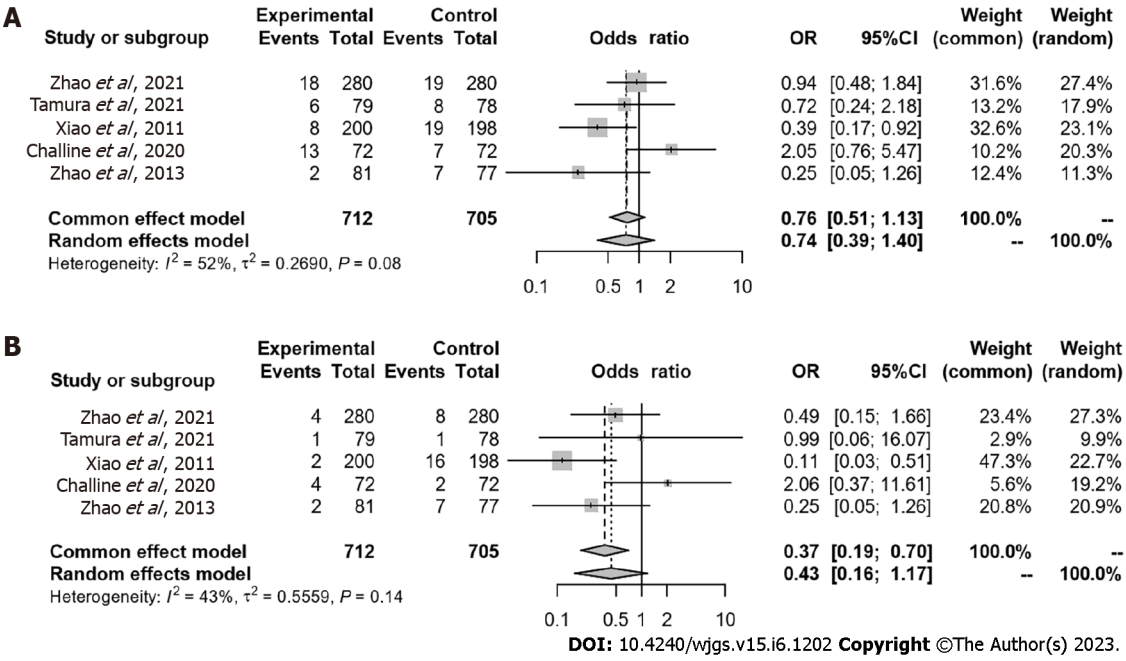

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Figure 3 Comparison of anastomotic leakage rates between transanal drainage tube group and non-transanal drainage tube group in all patients. A: Analysis based on symptomatic leakage (grades B and C); B: Analysis based on leakage that required re-operation (grade C). OR: Odds ratio; CI: Confidence interval.

therapy, chemotherapy, *etc*., constantly changes the background of the patients that physicians encounter. However, we must continue efforts to improve surgical outcomes because they are directly related to patient outcomes[5,6]. Regarding the background of the five trials included in this meta-analysis, patients who had received preoperative treatment were excluded in three. as the stated reason was that radiotherapy is a risk factor for AL[18]. In addition, patients with diverting stomas were excluded from two studies and allowed in three studies. The decision to use a diverting stoma depended on the surgeon, that is, diverting stomas were used in patients whom surgeons considered at a high risk for AL. Thus, the results of these studies should be interpreted carefully, recognizing the limitations inherent in the patient samples. In this meta-analysis, TDT did not reduce the rate of AL in any of the patients. Therefore, we attempted to clarify the role of TDT by subgroup analysis. Accordingly, we revealed that TDT significantly reduced the incidence of AL among patients without a diverting stoma.

Thus, based on patients' background and the analysis results, a diverting stoma should be used in high-risk patients, but TDT is sufficient in patients who are not at a high risk of AL, without the use of a

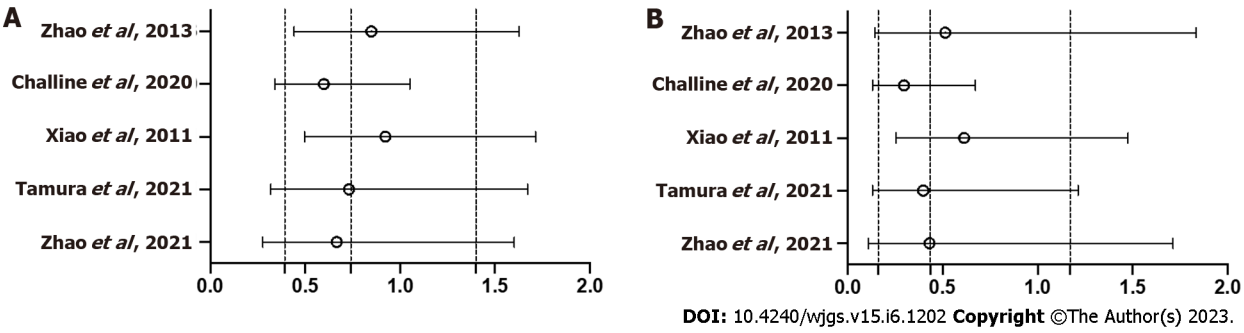

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Figure 4 Sensitivity analysis of anastomotic leakage rates between transanal drainage tube group and non-transanal drainage tube group in the meta-analysis. A: Analysis based on symptomatic leakage (grades B and C); B: Analysis based on leakage that required re-operation (grade C). Odds ratios (ORs) and 95% confidence intervals (CIs) are shown as circles and bars when each noted study is omitted. The dash lines show the pooled ORs and 95%CIs for all included studies.

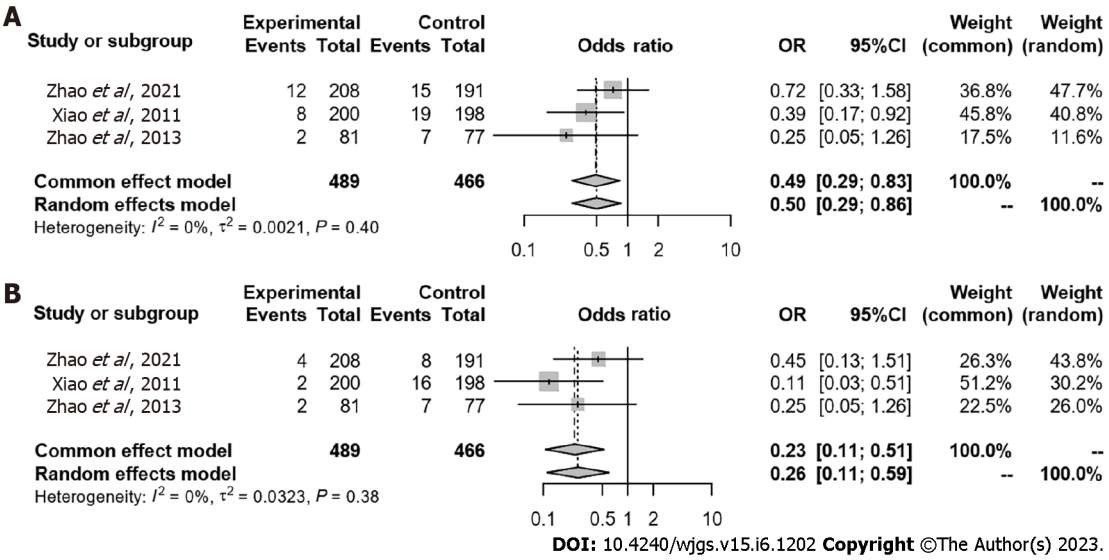

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Figure 5 Comparison of anastomotic leakage rates between transanal drainage tube group and non-transanal drainage tube group among patients without diverting stoma. A: Analysis based on symptomatic leakage (grades B and C); B: Analysis based on leakage that required re-operation (grade C). OR: Odds ratio; CI: Confidence interval.

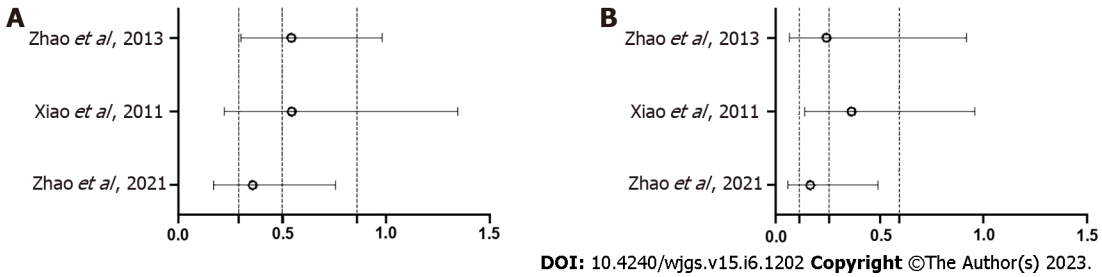

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Figure 6 Sensitivity analysis of anastomotic leakage rates between transanal drainage tube group and non-transanal drainage tube group in the sub-group meta-analysis. A: Analysis based on symptomatic leakage (grades B and C); B: Analysis based on leakage that required re-operation (grade C). Odds ratios (ORs) and 95% confidence intervals (CIs) are shown as circles and bars when each noted study is omitted. The dash lines show the pooled ORs and 95%CIs for all included studies.

diverting stoma. We expect that further research will be conducted to determine which patients are at a high risk and are eligible for diverting stoma augmentation. The time from preoperative radiation therapy to surgery varies among patients[10], and other risk factors for AL, such as sex, age, tumor size, and tumor location have been reported[26,27]. The role of TDT may be to steadily reduce AL in patients for whom a stoma may be avoided, rather than to place a stoma in such high-risk patients.

Besides, there are also some meta-analyses including tow RCTs[18,19] reported in 2021. Zhao *et al*[18] analyzed only 3 RCTs[18,19,23] and concluded that TDTs do not reduce the incidence of AL, but may reduce the grade C AL[28]. Deng *et al*[29] analyzed 7 studies, including retrospective studies, and concluded that TDTs do not reduce the incidence of AL in all patients. They also performed subgroup analyses and the AL rate was significantly low in patients without neoadjuvant therapy and diverting stoma but mentioned that TDT may be useless for those in high-risk situations. Zhang *et al*[30] analyzed 13 studies including retrospective studies and concluded that TDT reduced the incidence of AL in the patients without diverting stoma. Although each study was conducted in a different, separately selected group, we can conclude, as we did, that the benefit of TDT for all patients is low, but the benefit of TDT for a limited number of patients is high. Therefore, we would like to reiterate that the role of TDT would not be to avoid diverting stoma, but to steadily decrease AL in low-risk patients who were thought to be able to avoid diverting stoma.

Finally, in the five included studies, complications of TDT were anal pain and anal bleeding, whereas no intestinal injuries due to the tube were observed. However, such injuries were previously reported [31], and patients should be carefully monitored to determine when and where to place a TDT and to confirm its position using radiography.

As the limitations of this study, the patients' background was different in studies, and the criteria for high-risk patients with a diverting stoma was not standardized. Additionally, the number of studies included in our review was small, and there may have been some bias. However, rather than viewing TDTs as substitutes for diverting stomas, one may need to identify high-risk patients, in whom a stoma should be used, and non-high-risk patients, in whom a TDT should be placed to prevent AL and improve surgical outcomes for patients with rectal cancer.

CONCLUSION

TDTs did not reduce AL in any of the patients with rectal cancer who underwent primary tumor resection with anastomosis. However, patients who do not undergo diverting stoma augmentation based on the surgeon's decision may benefit from TDT placement.

ARTICLE HIGHLIGHTS

Research background

Anastomotic leakage (AL) following rectal cancer surgery remains a serious problem, and transanal drainage tubes (TDTs) and diverting stomas have been performed to avoid AL. However, the efficiency of TDTs results is controversial.

Research motivation

Recently, the two randomized controlled trials (RCTs) on the role of TDT were reported. Therefore, we performed an updated meta-analysis to incorporate them.

Research objectives

We aimed to reveal the role of TDTs in preventing AL after rectal cancer surgery.

Research methods

A systematic literature search was performed using databases and meta-analyses were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

Research results

TDT did not reduce the symptomatic AL rate in all patients, but TDT reduced the symptomatic AL rate in patients without a diverting stoma.

Research conclusions

TDT may not reduce AL in all patients undergoing rectal cancer surgery. However, patients without a diverting stoma may benefit from TDT placement.

Research perspectives

Rather than viewing TDTs as substitutes for diverting stomas, we must identify high-risk patients, in whom a stoma should be used, and non-high-risk patients, in whom a TDT should be placed to prevent AL.

FOOTNOTES

Author contributions: Fujino S, Yasui M, Ohue M, and Miyoshi N designed the research study; Fujino S, Yasui M, and Miyoshi N performed the research; Fujino S and Miyoshi N analyzed the data; Fujino S wrote the manuscript; and all authors have read and approve the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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CASE REPORT

Percutaneous transhepatic cholangial drainage-guided methylene blue for fistulotomy using dual-knife for bile duct intubation: A case report

Bing-Xi Tang, Xin-Li Li, Ning Wei, Tao Tao

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Tsutsumi K, Japan; Yildiz K, Turkey

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Abstract

BACKGROUND

Difficult bile duct intubation is a big challenge for endoscopists during endoscopic retrograde cholangiopancreatography (ERCP) procedure. We report a case of percutaneous transhepatic cholangial drainage (PTCD)-guided methylene blue for fistulotomy using dual-knife for bile duct intubation.

CASE SUMMARY

A 50-year-old male patient had developed obstructive jaundice, and ERCP procedure need to be performed to treat the obstructive jaundice. But intubation cannot be performed if the duodenal papilla cannot be identified because of previous surgery for a perforated descending duodenal diverticulum. We used PTCD-guided methylene blue to identify the intramural common bile duct before dual-knife fistulotomy, and bile duct intubation was successfully completed.

CONCLUSION

The method that combing methylene blue and dual-knife fistulotomy to achieve bile duct intubation during difficult ERCP is safe and effective.

Key Words: Percutaneous transhepatic cholangial drainage; Bile duct intubation; Endoscopic retrograde cholangiopancreatography; Methylene blue; Case report

Core Tip: We report a case of difficult bile duct intubation during endoscopic retrograde cholangiopancreatography (ERCP) procedure. We introduce the clinical features, findings of ERCP, and response to treatment in this male patient.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) has currently become an essential diagnostic and treatment method for pancreatobiliary diseases. However, the failure rate of routine bile duct intubation during ERCP is 10%[1,2]. Methylene blue can be used to identify the duodenal papilla for bile duct intubation[3], and dual-knife fistulotomy is an effective and safe method for accessing the bile duct [4]. We combined these two methods in a patient undergoing surgery for a perforated descending duodenal diverticulum.

CASE PRESENTATION

Chief complaints

A 50-year-old male patient with developed jaundice was transferred to our outpatient service in October 2022.

History of present illness

The patient underwent surgery for a perforated descending duodenal diverticulum. He had duodenal diverticulum resection, partial small bowel resection, cholecystostomy, and jejunostomy. After the cholecystostomy tube was removed, obstructive jaundice appeared to develop.

History of past illness

In medical history the patient alleged healthy and denied a history of heart illness and inspiratory illness.

Personal and family history

From the patient's medical history, we precluded a history of allergies, asthma, and alcoholism. His father and mother had no hereditary diseases and were all healthy.

Physical examination

On admission we performed a physical examination on the patient, and the result revealed yellow staining of the skin and sclera, but there were no enlarged superficial lymph nodes. There were no abnormal cardiopulmonary and abdominal examinations.

Laboratory examinations

Laboratory results revealed that the blood count of the patient was normal, the patinet's renal function, carcinoembryonic antigen, cancer antigen 125, cancer antigen 19-9, carcinoembryonic antigen, and alpha-fetoprotein values were also normal. Liver fibrosis test of the patient was normal, and the levels of immunoglobulins immunoglobulin (Ig) A, IgM, and IgG were also normal. As for the levels of serum type III procollagen, type IV collagen, laminin, and hyaluronic acid, all normal. But the liver function was abnormal and total bilirubin was 130.8 μmol/L, direct bilirubin was 98.5 μmol/L, and indirect bilirubin was 32.3 μmol/L.

Imaging examinations

Postoperative cholecystostomy tube imaging (Figure 1) revealed slight dilation of the common bile duct and a small amount of contrast agent flowing into the duodenum.

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Figure 1 Transcholecystostomy imaging showing slight common bile duct dilation.

FINAL DIAGNOSIS

The patient was diagnosed as obstructive jaundice.

TREATMENT

The patient was discharged after PTCD drainage. The daily drainage volume was 2500-2800 mL but the PTCD drainage tube could not be clamped outside of the hospital. ERCP was performed for internal drainage in the bile duct. During ERCP procedure, descending duodenal scarring was observed and the papilla could not be identified after repeated attempts (Figure 2A). Similarly, no ectopic papilla was observed. Insertion of a PTCD tube into the duodenum *via* a guidewire was attempted but we could not insert the guidewire into the common bile duct after repeated adjustments (Figures 2B and C). After injecting a combination of ioversol and methylene blue (Jichuan Pharmaceutical Group Co. LTD, Jiangsu Province, China) *via* the PTCD tube, pale blue-colored duodenal scar protrusions were observed, which were identified as the intramural common bile duct (Figure 2D). We used a dual-knife (KD-650 L; Olympus Medical Systems) to perform layer-by-layer resection. As a result, large amount of ioversol and methylene blue could be seen flowing out (Figure 2E and F). After routine intubation of the stoma was successful, an 8.5 Fr × 5.0 cm plastic stent was inserted and patent ioversol and methylene blue flow was observed (Figure 2G-I).

OUTCOME AND FOLLOW-UP

After the endoscopic procedure, the patient's jaundice and liver function was relieved after 3 wk. Laboratory tests performed in December 2022 revealed that total bilirubin, direct bilirubin and indirect bilirubin was 31.8 μmol/L, 18.9 μmol/L, and 12.9 μmol/L respectively. Until November 2022, the patient was still undergoing follow-up.

DISCUSSION

A possible explanation for the increasing success rate of ERCP procedures is attributed to the excellent ERCP supporting facilities concerning ultrasonography and duodenoscopic viewing, and the application of adjunctive intubation methods to increase intubation success, reduce complications, and alleviate patient pain[5]. However, questions such as how the native papilla or biliopancreatoenteric anastomosis can be identified and cannulated were still challenging for endoscopists. The position of the native papilla in surgically altered anatomy differs greatly from that in the normal anatomy[5].

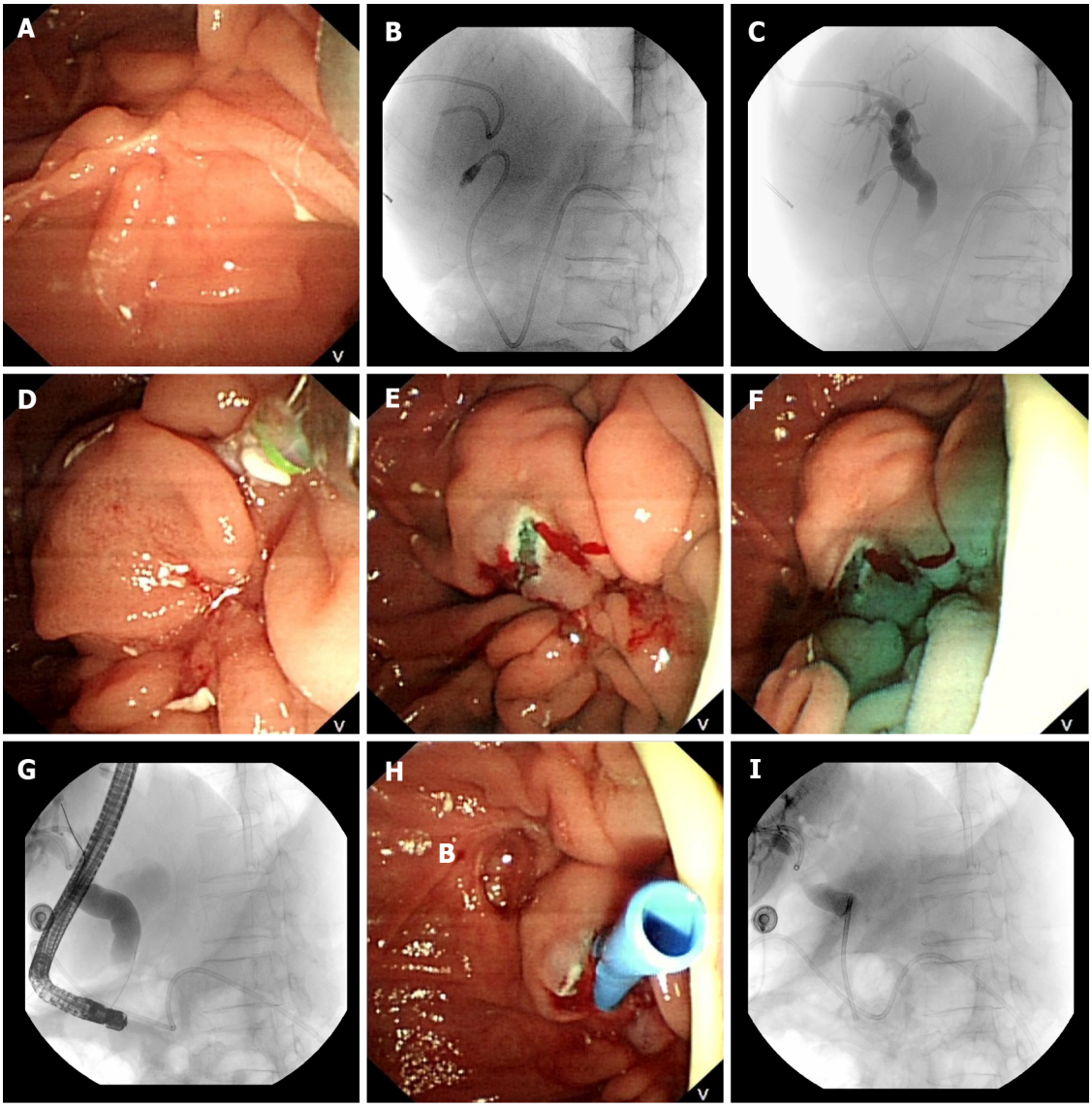

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Figure 2 Treatment. A: Repeated failed attempts to identify the duodenal papilla, a small amount of contrast agent entered the duodenum; B and C: Repeated attempts at guidewire insertion through the percutaneous transhepatic cholangial drainage (PTCD) tube failed; D: mixture of ioversol and methylene blue was injected *via* the PTCD tube; E: Dual-knife was used for layer-by-layer resection. Pale blue-colored protrusions, which were considered to be the intramural common bile duct, can be seen at the duodenal scar; F: A large amount of methylene blue flowed out after dual-knife resection; G: Common bile duct dilation was observed on endoscopic retrograde cholangiopancreatography imaging; H: Insertion of an 8.5 Fr × 5.0 cm plastic stent; I: A large amount of ioversol and methylene can be seen flowing out.

From the disease history we concluded that surgery was the cause of the obstructive jaundice in this case. As for the treatment of obstructive jaundice, ERCP has a lower incidence of complications and shorter hospital stays and a lower cost than other methods such as PTCD.

During ERCP, the duodenal papilla is usually identified using endoscope landmarks, such as an oral protrusion, duodenal folds, and a small belt formed by the anal columns. Occasionally, the duodenal papilla cannot be identified. Since our patient had undergone perforated descending duodenal diverticulum surgery, the duodenal papilla could not be located. After PTCD guidewire insertion failed, methylene blue was injected into the PTCD tube and visible protrusions in the intramural common bile duct were visualized as blue surfaces. This technique improved visualization of the intramural common bile duct and reduced the risk of complications due to inaccurate intramural common bile duct identification. After visualizing the position of common bile duct, we selected a dual-knife for fistulotomy because the front end of the dual-knife's sheath was as short as 2 mm. The short knife tip of the dual knife can be directly applied to the mucosal surface to improve control of the incision depth and prevent injury to the posterior sphincter wall of the common bile duct. Therefore, dual-knife is safer than needle knife in our experience. Due to the unique design of the expansive tip, dual-knife can also be used to hook the bile duct to the intestinal cavity for incision, which cannot be achieved with needle knife[7]. We combined methylene blue tracer and dual-knife fistulotomy to successfully complete bile duct

intubation and insert a plastic stent in the patient's bile duct. This enabled internal bile drainage.

CONCLUSION

The combined use of methylene blue tracer and dual-knife incurs a lower risk and is effective method to achieve bile duct intubation during difficult ERCP.

FOOTNOTES

Author contributions: Tang BX performed the endoscopic retrograde cholangiopancreatography procedure and wrote the manuscript; Tao T designed the research study; Li XL and Wei N helped collecting medical data; all authors have read and approve the final manuscript.

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CASE REPORT

Optimal resection of gastric bronchogenic cysts based on anatomical continuity with adherent gastric muscular layer: A case report

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Abstract

BACKGROUND

Bronchogenic cysts are congenital lesions requiring radical resection because of malignant potential. However, a method for the optimal resection of these cysts has not been completely elucidated.

CASE SUMMARY

Herein, we presented three patients with bronchogenic cysts that were located adjacent to the gastric wall and resected laparoscopically. The cysts were detected incidentally with no symptoms and the preoperative diagnosis was challenging to obtain *via* radiological examinations. Based on laparoscopic findings, the cyst was attached firmly to the gastric wall and the boundary between the gastric and cyst walls was difficult to identify. Consequently, resection of cysts alone caused cystic wall injury in Patient 1. Meanwhile, the cyst was resected completely along with a part of the gastric wall in Patient 2. Histopathological examination revealed the final diagnosis of bronchogenic cyst and revealed that the cyst wall shared the muscular layer with the gastric wall in Patients 1 and 2. In Patient 3, the cyst was located adjacent to the gastric wall but histopathologically originated from diaphragm rather than stomach. All the patients were free from recurrence.

CONCLUSION

The findings of this study state that a safe and complete resection of bronchogenic

cysts required the adherent gastric muscular layer or full-thickness dissection, if bronchogenic cysts are suspected *via* pre- and/or intraoperative findings.

Key Words: Bronchogenic cysts; Laparoscopic resection; Gastric wall; Muscular layer; Case report

Core Tip: Bronchogenic cysts are rare congenital lesions, which require radical resection as they might turn malignant. We presented three patients with bronchogenic cysts that were located adjacent to the gastric wall and resected laparoscopically. Based on the findings, we hypothesized that it was advisable to proceed to the stomach wall to remove the cyst completely, preventing rupture of it. This was supported by histopathological assessment which revealed bronchogenic cysts of the stomach generally shared the muscular layer with the gastric wall. Resection of cysts with the adherent gastric muscular layer or full-thickness dissection should be considered for a safe and complete resection.

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INTRODUCTION

Bronchogenic cysts are congenital lesions that develop during embryogenesis, with a prevalence rate of 1 in 68000[1]. Most of them are found in the mediastinum because they arise from the primitive tracheobronchial trees. Therefore, bronchogenic cysts located adjacent to the stomach are extremely rare[2,3].

Surgical resection is considered a radical treatment for bronchogenic cysts because they have a malignant potential[4-6]. However, the sole resection of the cyst has a possible risk of rupture because the boundary between the gastric and cyst walls is sometimes difficult to recognize grossly[7,8]. Meanwhile, the partial or conventional gastrectomy seems to be an excessive treatment in terms of the balance between postoperative decreased quality of life and the low incidence of malignant transformation. Thus, the optimal way of resection for bronchogenic cyst has not been completely established, coupled with the rarity of the disease.

We have recently encountered three patients with bronchogenic cysts. During the surgical treatment, it was challenging to identify the proper dissection line between the gastric and cyst walls. Based on these experiences, we hypothesized that it is advisable to proceed to the stomach wall to remove the cyst completely, preventing rupture of it. To elucidate our hypothesis, we aimed to histopathologically assess the three patients with bronchogenic cyst that were located adjacent to the gastric wall, mainly focusing on the continuity of the gastric muscular layers. This case report and pathological assessments will really help surgeons remove gastric bronchial cysts with minimum invasion, safely and completely because gastric bronchial cyst is extremely rare, and few surgeons can effectively tackle the disease.

CASE PRESENTATION

Chief complaints

All three patients had no chief complaints.

History of present illness

Patient 1: A 37-year-old female patient was referred to our hospital due to a mass that was incidentally detected on perioperative examination for palate tonsillectomy.

Patient 2: A 47-year-old male patient underwent physical assessment, and a cystic mass with a diameter of 3 cm was detected in the abdomen for which he had been undergoing follow-up examinations from 4 years at a local hospital. However, the mass size increased to 5 cm and referred to our hospital thereafter.

Patient 3: A 37-year-old male patient was referred to our hospital due to a mass that was incidentally detected.

History of past illness

Patient 1: The patient had a previous history of immunoglobulin A nephropathy.

Patients 2 and 3: The patients had no previous history of illness.

Personal and family history

All three patients had no personal and family history.

Physical examination

All three patients had neither symptoms nor abnormal physical findings.

Laboratory examinations

Patient 1: Routine blood examination results and the levels of tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 were normal.

Patient 2: Routine blood examination results were normal, but there was an increase in the serum CA 19-9 levels of the patient.

Patient 3: The routine laboratory tests results and serum levels of tumor markers, such as CEA and CA 19-9, were normal.

Imaging examinations

Patient 1: Computed tomography (CT) scan revealed a cystic mass with a diameter of 3 cm. There was no contrast enhancement, and the mass was located adjacent to the gastric cardia with regular outlines (Figure 1A). No calcification or septation was observed. Upper endoscopic examination showed no communication between the lesion and gastric lumen.

Patient 2: CT scan revealed a homogeneous low-density lesion with a diameter of 5 cm, and the mass was located adjacent to the cardia of the stomach (Figure 2A and B). Upper endoscopic examination showed no malignant findings in the stomach.

Patient 3: CT scan revealed a cystic mass with a diameter of 35 mm. The lesion was located adjacent to the posterior wall of the proximal stomach (Figure 3A). Magnetic resonance imaging showed a smooth and quasi-circular lesion with a high intensity on T2-weighted images and iso-intensity on T1-weighted images.

FURTHER DIAGNOSTIC WORK-UP

Patient 1

Endoscopic ultrasonography (EUS) detected an extramural cystic mass in the cardia (Figure 1B). However, there was no continuity with the gastric wall. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) was not performed. The preoperative differential diagnoses were gastric duplication, foregut cyst, and bronchogenic cyst.

Patient 2

EUS revealed an extramural mass in the cardia (Figure 2C). Pseudostratified ciliated columnar epithelium and seromucous glands were observed on EUS-FNA. Thus, gastric bronchogenic cyst was suspected.

Patient 3

EUS showed a hyperechoic cystic mass (Figure 3B), which might be connected to the gastric wall. However, its continuity could not be detected. A yellow-brownish liquid was aspirated *via* subsequent needle biopsy.

FINAL DIAGNOSIS

Patient 1

Histopathologically, the cystic wall was lined with the ciliated columnar epithelia and mucous glandular cells without cytological atypia and was surrounded by smooth muscle fibers (Figure 1E). A diagnosis of bronchogenic cyst was made. The smooth muscle fibers of the cyst wall were continuous with the gastric muscular layer (Figure 1F). Based on these findings, the bronchogenic cyst arose from the gastric wall.

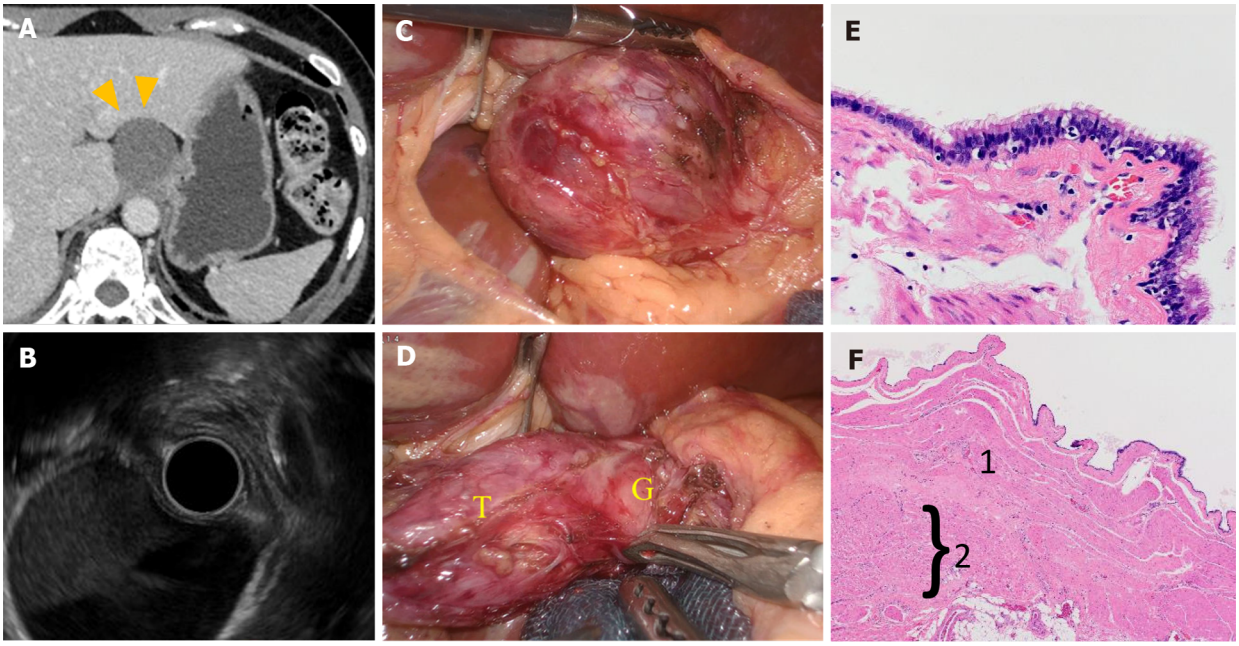

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Figure 1 The findings of Patient 1. A: Computed tomography scan of the abdomen revealed a cystic mass with a diameter of 3 cm. The lesion was attached to the gastric cardia with regular outlines (arrows); B: Endoscopic ultrasonography findings: A cystic mass was found in the submucosal layer of the cardia; C and D: Laparoscopic findings: (C) A smooth cystic mass arose from the gastric cardia and (D) part of the cyst (T) adhered firmly to the gastric wall (G); E: Histopathological findings: The cystic wall was lined with ciliated columnar epithelia and mucous glandular cells without cytological atypia; high-power magnification; F: the smooth muscle fibers surrounded the cystic wall (1) and they were continuous with the gastric muscular layer (2); low-power magnification. G: The gastric wall; T: The tumor.

Patient 2

As in Patient 1, histopathological examination showed the typical findings of bronchogenic cyst, which include the presence of smooth muscle fibers, focal mucous glands, and ciliated columnar epithelia (Figure 2F). The cyst shared the muscular layer with the stomach, which indicated that the smooth muscle of the bronchogenic cyst was continuous with that of the gastric wall (Figure 2G).

Patient 3

Bronchogenic cyst was diagnosed on account of the microscopic examination, which revealed that the cystic wall was lined with ciliated columnar epithelia. However, it had no evident connection with the gastric wall (Figure 3E and F).

TREATMENT

Patient 1

A smooth cystic mass was identified on laparoscopic exploration of the gastric cardia (Figure 1C). A part of the cyst adhered firmly to the gastric wall and might have shared the muscular layer with the stomach (Figure 1D). Hence, it was difficult to detach from the gastric wall, and there was a bright yellow fluid discharge from the cyst during resection. Thus, the gastric muscular layer was incised, and the tumor was extracted. Thereafter, the gastric wall was sutured and reinforced by hand-sewing. Subsequently, intraoperative endoscopy was performed to validate gastric integrity.

Patient 2

Laparoscopy was performed, and the cyst was found in the lesser gastric curvature (Figure 2D). The lesser omentum was opened, and the tissue surrounding the lesion was resected. The feeding artery was found around the lesion and was transected using a vessel sealing system. The cyst wall was firmly connected to a part of the gastric wall (Figure 2E). Therefore, the muscular layer of the cyst seemed to be continuous with the gastric wall. The muscle between the cyst and gastric wall was divided. The tumor was completely excised along with a part of the gastric muscle layer. After extracting the specimen, the gastric wall was reapproximated, and the suture line was secured *via* intraoperative endoscopy.

Patient 3

Laparoscopy was performed, and the cyst was found in the lesser gastric curvature (Figure 3C). The

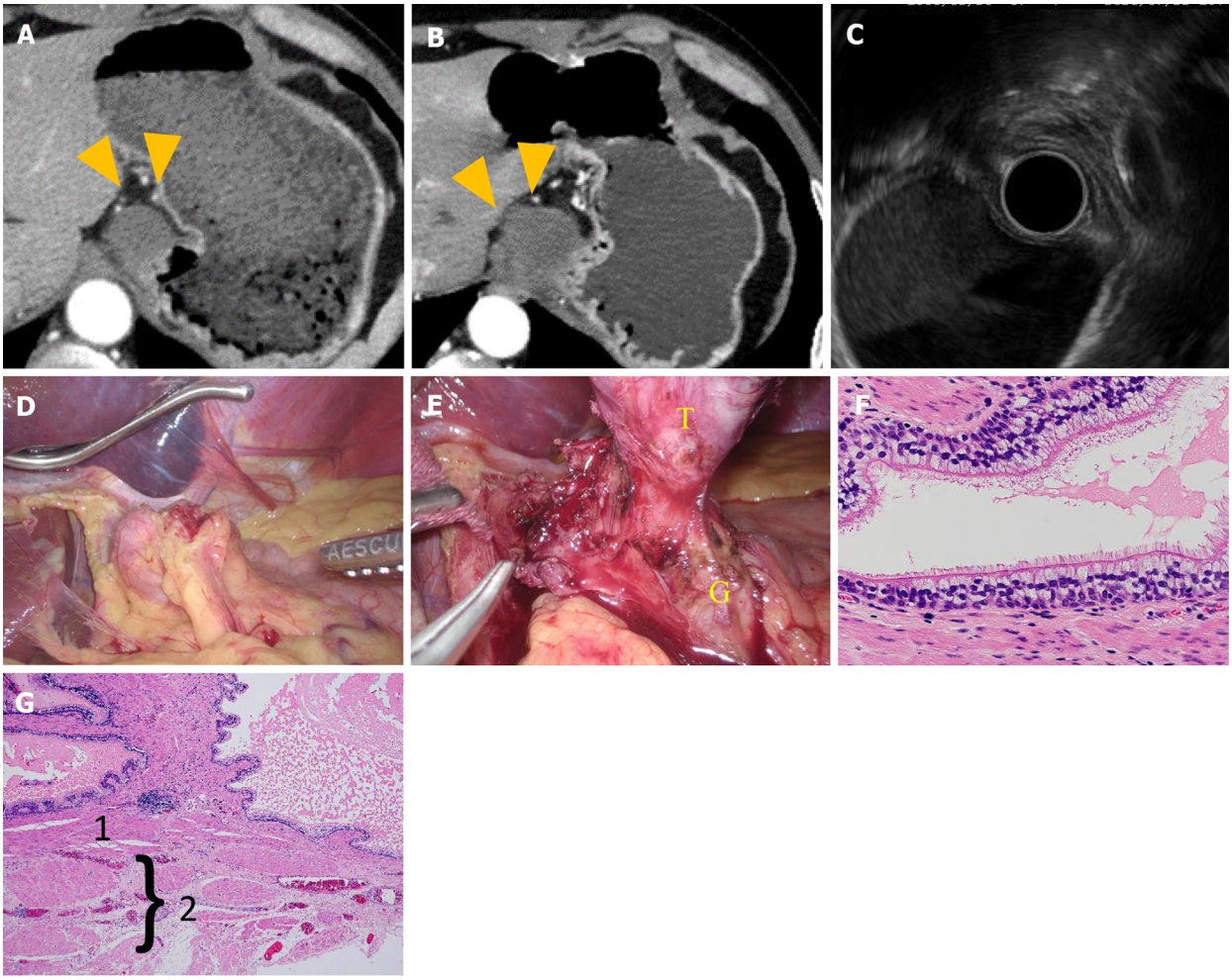

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Figure 2 The findings of Patient 2. A: Computed tomography scan showed a homogeneous lesion with a diameter of 3 cm. The lesion was connected to the gastric cardia (arrows); B: The mass size increased to 5 cm after 4 years. C: Endoscopic ultrasonography findings: A cystic mass was found in the submucosal layer of the cardia; D and E: Laparoscopic findings: (D) A mass was observed in the lesser gastric curvature, and (E) it was strongly connected with a part of the gastric wall; F: Histopathological findings: The cystic wall was lined with ciliated columnar epithelia and mucous glandular cells without cytological atypia; high-power magnification; G: The smooth muscle fibers surrounded the cystic wall (1) and they were continuous with the gastric muscular layer (2); low-power magnification. G: The gastric wall; T: The tumor.

lesser omentum was opened, and the tissue surrounding the lesion was resected. The feeding artery was found around the lesion and was transected using a vessel sealing system. The cyst wall was firmly connected to a part of the gastric wall (Figure 3D). Therefore, the muscular layer of the cyst seemed to be continuous with the gastric wall. The muscle between the cyst and gastric wall was divided. The tumor was completely excised along with a part of the gastric muscle layer. After extracting the specimen, the gastric wall was reapproximated, and the suture line was secured *via* intraoperative endoscopy.

OUTCOME AND FOLLOW-UP

Patient 1

The postoperative course was uneventful, and the patient was discharged on postoperative day 7. No recurrence was observed within the follow-up period of postoperative 9 mo.

Patient 2

The postoperative course was satisfactory, and no recurrence was observed within the follow-up period of postoperative 6 mo.

Patient 3

The postoperative course was uneventful, and no recurrence was observed within the follow-up period

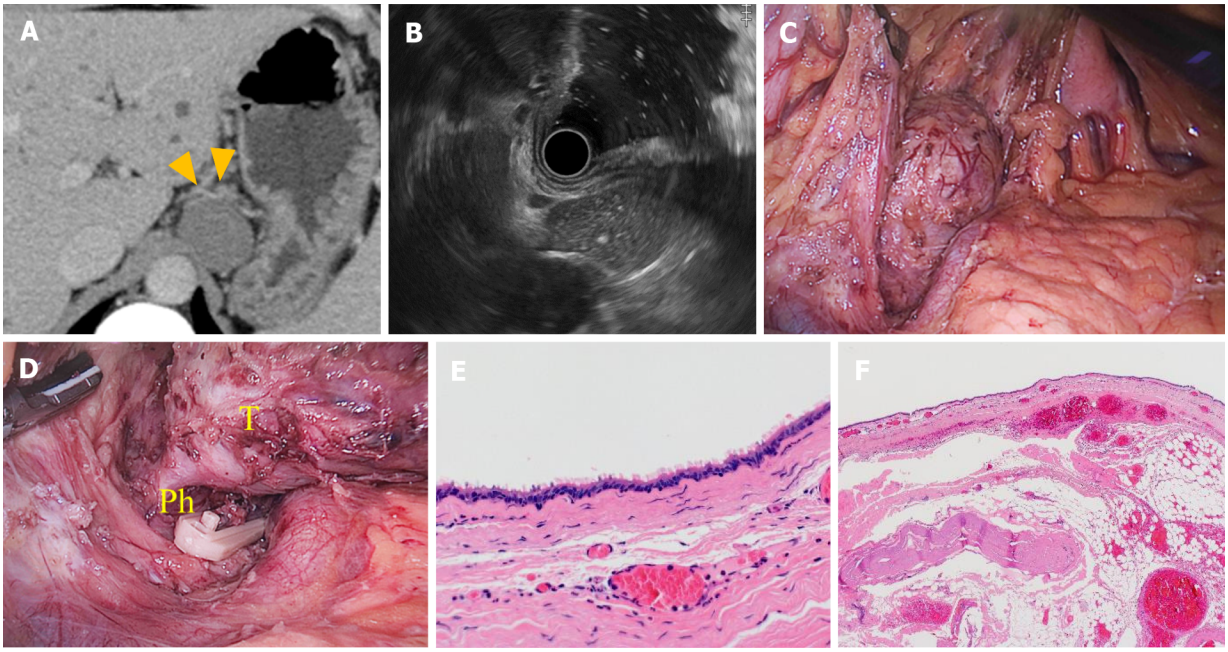

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Figure 3 The findings of Patient 3. A: Computed tomography scan revealed a cystic mass with a diameter of 3.5 cm in diameter adjacent to the posterior wall of the proximal stomach; B: Endoscopic ultrasonography findings: A hyperechoic cystic mass was connected to the gastric wall; C and D: Laparoscopic findings: (C) A cyst was located adjacent to the gastric wall, and (D) it was attached firmly to the diaphragm muscle (Ph); E: Histopathological findings: The cystic wall was lined with ciliated columnar epithelia and mucous glandular cells without cytological atypia; high-power magnification; F: The cystic wall contained few smooth muscle fibers, and it had no evident connection with the gastric wall; low-power magnification. Ph: The diaphragm muscle; T: The tumor.

of postoperative 3 mo.

DISCUSSION

Bronchogenic cysts of the stomach are extremely rare[9]. Their histogenesis comprises abnormal buds of the tracheobronchial tree that are pinched off and migrate into the abdomen. Surgical resection is recommended as these cysts can be malignant. However, the current knowledge on the methods used for the optimal resection of bronchogenic cysts is limited due to the small number of cases. Herein, we report three patients with bronchogenic cysts that were located adjacent to the stomach and resected laparoscopically. Based on our surgical experiences and detailed histopathological examination results, knowledge on the pathological features of bronchogenic cyst is essential in facilitating a safe, complete, and less invasive resection.

Bronchogenic cysts should be considered when a cystic mass is found in the stomach, especially near the cardia and esophagogastric junction. Embryologically, they arise in the mesogastrium. A typical differential diagnosis of gastric cysts are gastric duplication cysts; however, they are usually located along the greater gastric curvature and endoscopically presented with ulcer formations or overlying dimple at the top of the protruding mass[10]. Therefore, these anatomical differences might be beneficial in diagnosing bronchogenic cysts. Meanwhile, a preoperative definitive diagnosis is still challenging *via* radiological examinations. CT scan could detect a solitary, low density, homogeneous uniocular mass, and magnetic resonance imaging revealed iso-intensity on T1-weighted images and high intensity on T2-weighted images[11,12]. However, these radiological findings are not specific to bronchogenic cysts. EUS can be performed to evaluate anatomical relationship and echoic characteristics, and subsequent FNA cytology can be useful[13]. No studies have discussed the diagnostic rate of bronchogenic cysts, and several reports have shown the feasibility of EUS-FNA for establishing a preoperative histological diagnosis of gastric bronchogenic cysts, as in Patient 2[13,14]. Some reports have shown that the diagnostic yield of cytology is limited because of the low number of cells that disperse in the cystic fluid [15], as in Patient 3. Thus, further research is required to evaluate the usefulness of EUS-FNA. However, to date, it is the only tool that can be used to obtain a preoperative diagnosis of bronchogenic cysts.

Surgical resection is recommended for radical treatment if bronchogenic cysts of the stomach are suspected due to the risk of malignant transformation. The carcinoma arising from the epithelial cells of bronchogenic cyst was reported[16]. Also, the patient with bronchogenic cyst of the stomach involved with gastric adenocarcinoma was reported[17]. Therefore, the risk of recurrence was high with incomplete resection, and complete resection was required[18,19]. Previous report showed that patients

who underwent complete resection showed no recurrence[20]. The laparoscopic approach may be less invasive[21]. However, no optimal strategies for the complete resection of bronchogenic cysts of the stomach have been established. Previous reports showed that incomplete resection of bronchogenic cysts could lead to local recurrence or dissemination[4]. In the cases in which bronchogenic cysts are firmly attached to and invading the surrounding organs, combined resection is required to completely excise the lesions. As the lesions are commonly found in the lesser curvature of the stomach near the gastroesophageal junction or gastric cardia[1], partial or conventional gastrectomy is occasionally unavoidable[8,22]. However, most lesions had no communication with the gastric lumen, as in our case. Gastrectomy might be extensive with consideration of the facts that the incidence of malignant transformation is low and the procedure is associated with a decreased quality of life.

However, resection of cysts alone is associated with a risk of rupture because bronchogenic cysts have thin walls with regular borders[1]. Knowledge on pathological features is essential for the complete and less invasive resection of cysts because radiological examinations could not detect the positional associations between the cysts and surrounding organs. In previous cases of gastric bronchogenic cysts, the lesion was continuous with the stomach wall or was surrounded with the smooth muscle, which is continuous with the gastric muscular layer[23]. In Patients 1 and 2, the cysts also shared their muscular layer with that of the gastric wall histopathologically. However, the cyst had no communication with the muscular layer of the gastric wall, and it originated from the retroperitoneum rather than the stomach in Patient 3. In Patient 1, based on the preoperative radiological findings, the cyst was located outside the gastric wall, and resection of cysts alone was performed, which caused cystic wall injury. By contrast, in Patient 2, the cyst was successfully resected along with a part of the gastric wall. Based on these findings, combined resection of cysts with a part of the gastric wall or full-thickness dissection is required to facilitate a safe and complete resection in cases wherein the cyst shared the muscular layer with the stomach. This notion was confirmed by our pathological findings. To the best of our knowledge, this is the first report that discussed the optimal resection of bronchogenic cysts of the stomach based on its histopathological feature. Our patients were free from recurrence, and this type of resection was less invasive than conventional gastrectomy.

CONCLUSION

In conclusion, bronchogenic cyst of the stomach shares the muscular layer with the gastric wall. Resection of cysts with the adherent gastric muscular layer or full-thickness dissection should be considered for a safe and complete resection, if bronchogenic cysts are suspected *via* pre- and/or intraoperative findings.

FOOTNOTES

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CASE REPORT

Intrahepatic cholangiocarcinoma in patients with primary sclerosing cholangitis and ulcerative colitis: Two case reports

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Abstract

BACKGROUND

Primary sclerosing cholangitis (PSC) is an extraintestinal manifestation of ulcerative colitis (UC). PSC is a well-known risk factor for intrahepatic cholangiocarcinoma (ICC), and ICC is known to have a poor prognosis.

CASE SUMMARY

We present two cases of ICC in patients with PSC associated with UC. In the first case, a tumor was found by magnetic resonance imaging (MRI) in the liver of a patient with PSC and UC who presented to our hospital with right-sided rib pain. The second patient was asymptomatic, but we unexpectedly detected two liver tumors in an MRI performed to evaluate bile duct stenosis associated with PSC. ICC was strongly suspected by computed tomography and MRI in both cases, and surgery was performed, but unfortunately, the first patient died of ICC recurrence 16 mo postoperatively, and the second patient died of liver failure 14 mo postoperatively.

CONCLUSION

Careful follow-up of patients with UC and PSC with imaging and blood tests is necessary for early detection of ICC.

Key Words: Ulcerative colitis; Primary sclerosing cholangitis; Intrahepatic cholangiocarcinoma; Hepatic lobectomy; Inflammatory bowel disease; Case report

Core Tip: Intrahepatic cholangiocarcinoma (ICC) commonly develops on top of primary sclerosing cholangitis (PSC) associated with ulcerative colitis (UC). Both of our patients died, although they were asymptomatic or mildly symptomatic at the time the ICC was discovered. Patients with long-term PSC coexisting with UC require regular follow-up with imaging such as magnetic resonance imaging even if they are asymptomatic.

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INTRODUCTION

In the treatment of ulcerative colitis (UC), attention should be paid not only to intestinal lesions but also to extraintestinal complications, especially primary sclerosing cholangitis (PSC)[1]. The incidence of UC associated with PSC varies widely; it is reported to be 23% in Japan and 80% in Sweden[2]. In addition, UC associated with PSC often causes mild symptoms, and many cases show a good treatment response [3]. PSC is a chronic liver disease that causes cholestasis due to diffuse and multiple sites of inflammation and narrowing of the intrahepatic and extrahepatic bile duct[4]. Gastrointestinal cancer is reported to be complicated in patients with PSC, and cancer of the bile duct such as intrahepatic cholangiocarcinoma (ICC) in particular, is a poor prognostic factor for PSC[5]. ICC is known to have a poor prognosis, and it was reported that patients with multiple lymph node metastases did not survive more than 2 years after surgery[6].

We managed two cases of ICC resulting from PSC associated with long-standing UC. In both cases, the ICC was surgically resected, but the patients died relatively shortly after the operation. ICC, which develops in cases of long-term UC associated with PSC, is often asymptomatic early in its onset.

CASE PRESENTATION

Chief complaints

Case 1: A 34-year-old male patient with PSC presented to our hospital with right lower abdominal pain.

Case 2: A 47-year-old male patient presented to our hospital for follow-up of PSC.

History of present illness

Case 1: The patient's symptoms started 2 mo prior.

Case 2: The patient was followed up regularly with abdominal ultrasound examination and magnetic resonance imaging (MRI). A liver mass was noted on a routine MRI and had increased in 4 mo, so additional close examination was performed and cancer was strongly suspected.

History of past illness

Case 1: He was diagnosed with UC (right-side significant pancolitis type) and PSC at the age of 20, and developed interstitial pneumonia caused by 5-aminosalicylate (5-ASA) one year later. His condition was maintained on steroids and 6-mercaptopurine. At the age of 32, the patient complained of right lower abdominal pain.

Case 2: At the age of 19, he was diagnosed with UC (pancolitis type) and PSC, and was administered oral 5-ASA to maintain mucosal healing. At the age of 31, he developed pancreatitis, which was diagnosed as UC-related autoimmune pancreatitis based on the diffuse parenchymal enlargement giving a sausage-like appearance on abdominal contrast enhanced (CE)-computed tomography (CT) examination. For the treatment of pancreatitis, he was given steroids, which were gradually reduced;

however, they could not be stopped due to the appearance of signs of liver failure caused by the progression of PSC.

Physical examination

Case 1: The patient's appetite was normal, and he had no weight loss. There was no increase in stool frequency, and jaundice was not observed.

Case 2: The patient had no subjective symptoms, no loss of appetite, and no weight loss. There was no increase in stool frequency and no jaundice.

Laboratory examinations

Case 1: Laboratory results showed elevated alanine aminotransferase (ALT), alkaline phosphatase (ALP), and γ-glutamyl transferase (γ-GT), but no change from previous data. Bilirubin levels were also normal, but carbohydrate antigen 19-9 (CA19-9) was abnormally high at 1121 U/mL.

Case 2: Laboratory results showed elevations in aspartate aminotransferase, ALT, ALP, γ-GT, and elevated bilirubin with an indirect predominance, but no change from previous data. CA19-9 was below detection sensitivity.

Imaging examinations

Case 1: Abdominal CE-MRI/CT examination revealed a huge mass (10 cm in size) in the right lobe of the liver, raising the suspicion of ICC (Figure 1).

Case 2: At the age of 45, an abdominal CE-MRI examination was performed for PSC follow-up and showed a nodular lesion in the left lobe of the liver (Figure 2A). Reexamination 4 mo later showed that the lesion had increased in size (Figure 2B). Abdominal CE-CT examination was performed and ICC was strongly suspected.

FINAL DIAGNOSIS

Case 1

ICC (low to moderately differentiated adenocarcinoma, pT3N1M0 Stage IVB) was pathologically confirmed (Figure 3).

Case 2

ICC was pathologically confirmed (highly to moderately differentiated adenocarcinoma, pT3N1M0 Stage IVB) (Figure 4). Immunohistochemical examination of tumor cells was performed. The tumor cells showed CK7 (+), Ck19 (+), MUC1 (partly+), CD10 (-), HepPar-1 (-), alpha-fetoprotein (-), Arginase-1 (-), Glypican-3 (-), CD117 (-), and CD56 (-).

TREATMENT

Case 1

Right hepatic lobectomy was performed, and the patient received S-1 therapy (120 mg) as postoperative adjuvant chemotherapy, but discontinued it in the middle of the second course due to liver damage.

Case 2

Left hepatic lobectomy was performed, and the patient was administered Inchinkato (Chinese herbal medicine), ursodeoxycholic acid, and phenobarbital for postoperative jaundice, but the total bilirubin value did not fall below 10 mg/dL. As a result, postoperative adjuvant chemotherapy was not administered.

OUTCOME AND FOLLOW-UP

Case 1

Abdominal CE-CT examination performed 3 mo postoperatively showed recurrence of bone metastasis in the left ilium (Figure 5A). Gemcitabine and cisplatin (GC) therapy (gemcitabine 1400 mg/cisplatin 35 mg; both 80% of their dose) was started 4 mo postoperatively with irradiation of the same site, and partial remission was sustained for over 10 mo. However, local recurrence was suspected on the dorsal

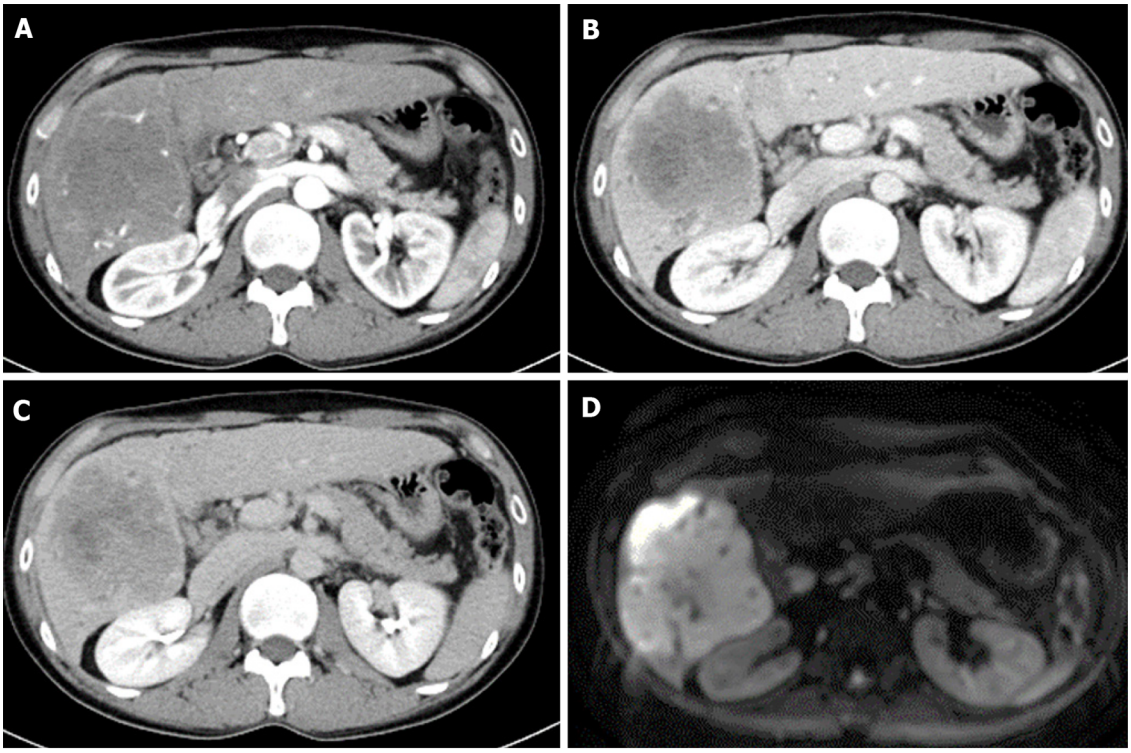

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Figure 1 Abdominal contrast-enhanced computed tomography images and magnetic resonance image of case 1. A: Early arterial phase of computed tomography (CT); B: Portal vein phase of CT; C: Late phase of CT. A massive mass with a major axis of about 10 cm almost occupies the right lobe of the liver S5-6. The mass is gradually stained in a non-uniform ring shape. D: Diffusion weighted image of magnetic resonance image.

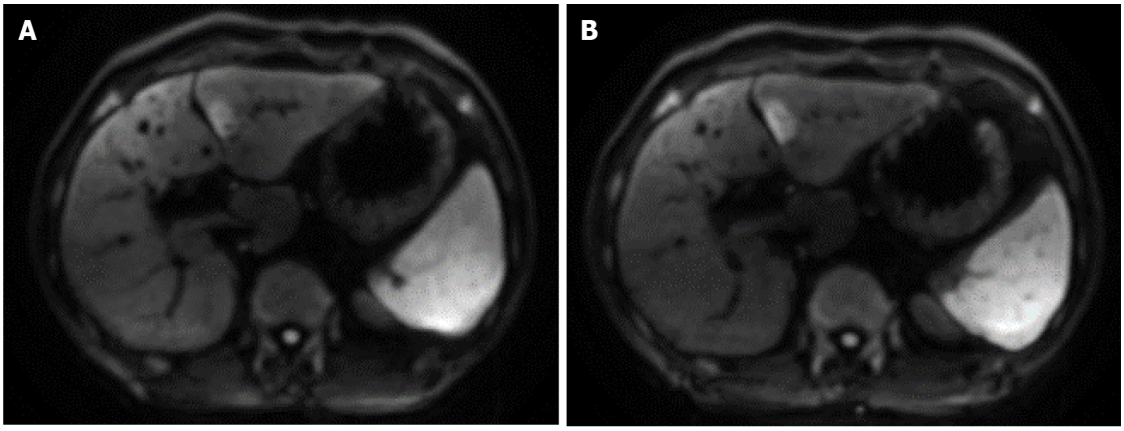

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Figure 2 Contrast enhanced magnetic resonance image of case 2. A: Abdominal contrast-enhanced magnetic resonance image (MRI) diffusion-weighted images show a hyperintensity nodule of about 20 mm in the lateral segment of the left lobe of the liver; B: MRI 4 mo after A. The mass in the lateral section of the left lobe of the liver is 23 mm, which is slightly larger than in the previous image, and the possibility of malignancy could not be ruled out.

side of the portal vein by abdominal CE-CT examination performed 13 mo postoperatively (at the end of 11 courses of GC therapy) (Figure 5B). The patient developed obstructive jaundice due to the appearance of recurrent lesions, and percutaneous transhepatic biliary drainage was performed. Irradiation and gemcitabine monotherapy were started after waiting for the improvement of jaundice, but systemic weakness progressed due to biliary tract infection. It became difficult to continue chemotherapy due to the deterioration of performance status, and the patient received palliative care. He died 16 mo postoperatively. The progress is shown in Figure 6.

Case 2

Jaundice with a total serum bilirubin level of around 20 mg/dL persisted postoperatively, and although oral treatment for jaundice was continued, jaundice persisted and liver failure progressed. Hepatic

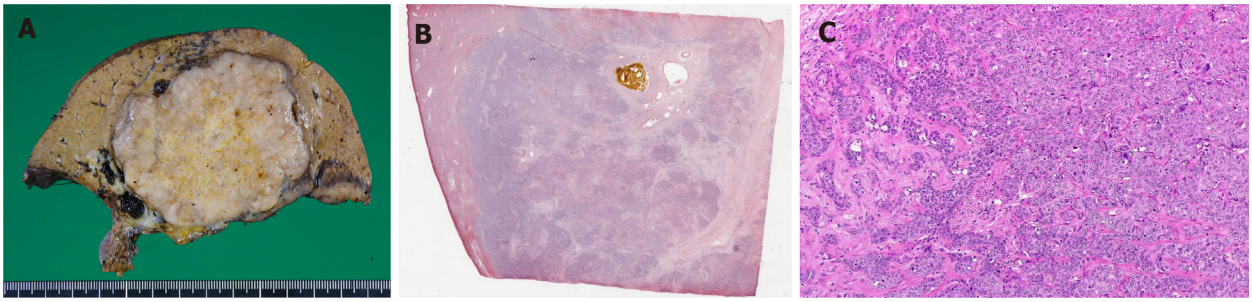

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Figure 3 Pathological findings of case 1. A: Macro image shows a large white phyllodes tumor (12.0 cm × 11.8 cm × 10.5 cm); B: Loupe image; C: Micro image shows that the adenocarcinoma is mainly cord-like and has a "partially irregular tubular" to an "obscure tubular" structure. Some areas are accompanied by abundant fibrous stroma.

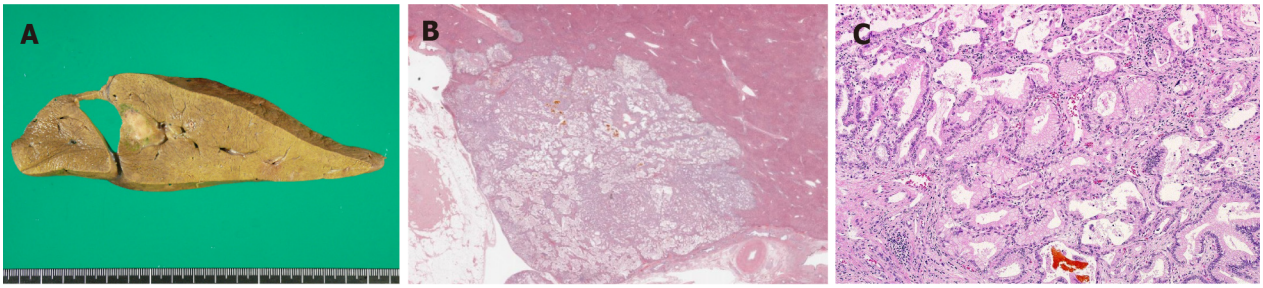

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Figure 4 Pathological findings of case 2. A: Macro image shows a white to greenish solid mass (17 mm × 16 mm) close to the hepatic sickle mesentery; B: Loupe image; C: Micro image shows arrangement of tubular to papillary, small tubular, and indistinct tubular swelling/infiltration of columnar to rectified atypical cells with mucus. Mucus is found in the glandular cavity with abundant fibrous stroma.

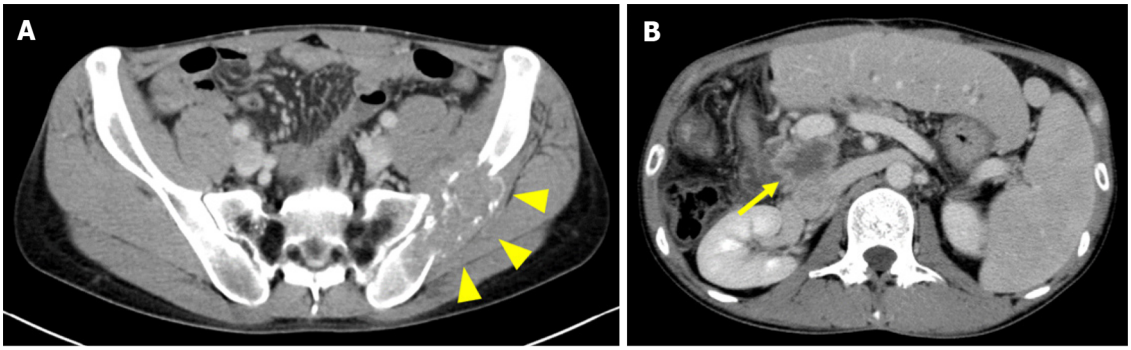

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Figure 5 Postoperative contrast enhanced computed tomography of case 1. A: Left iliac metastasis (arrowhead) is visible 3 mo postoperatively; B: Local recurrence (arrow) is visible on the posterior surface of the portal vein 13 mo postoperatively.

transplantation was also considered, but it was not indicated because the patient was in a cancer-bearing state. He was followed up while receiving symptomatic treatment for liver failure and jaundice, but died 14 mo postoperatively. The progress is shown in Figure 7.

DISCUSSION

PSC is characterized by the inflammation and destruction of intrahepatic and extrahepatic bile ducts, leading to progressive hepatic fibrosis, and its etiology remains unknown[7]. Inflammatory bowel diseases (IBD) such as Crohn's disease (CD) and UC are frequently complicated (66%-80% of cases), commonly by PSC[8,9]. Moreover, it is reported that 83% of IBDs associated with PSC are UC and 5% are CD[10]. However, the PSC complication rate in IBD patients is not high, and it has been reported

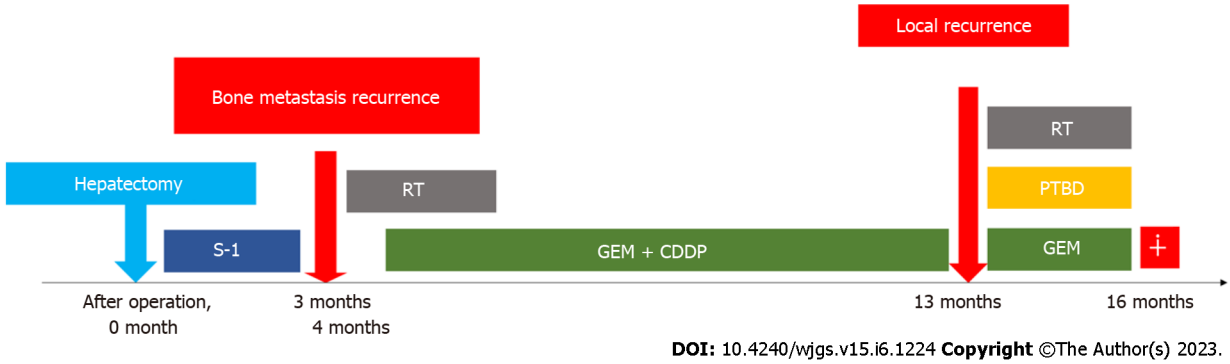

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Figure 6 Clinical course of case 1. RT: Radiation therapy; GEM: Gemcitabine hydrochloride; CDDP: Cisplatin; PTBD: Percutaneous transhepatic biliary drainage.

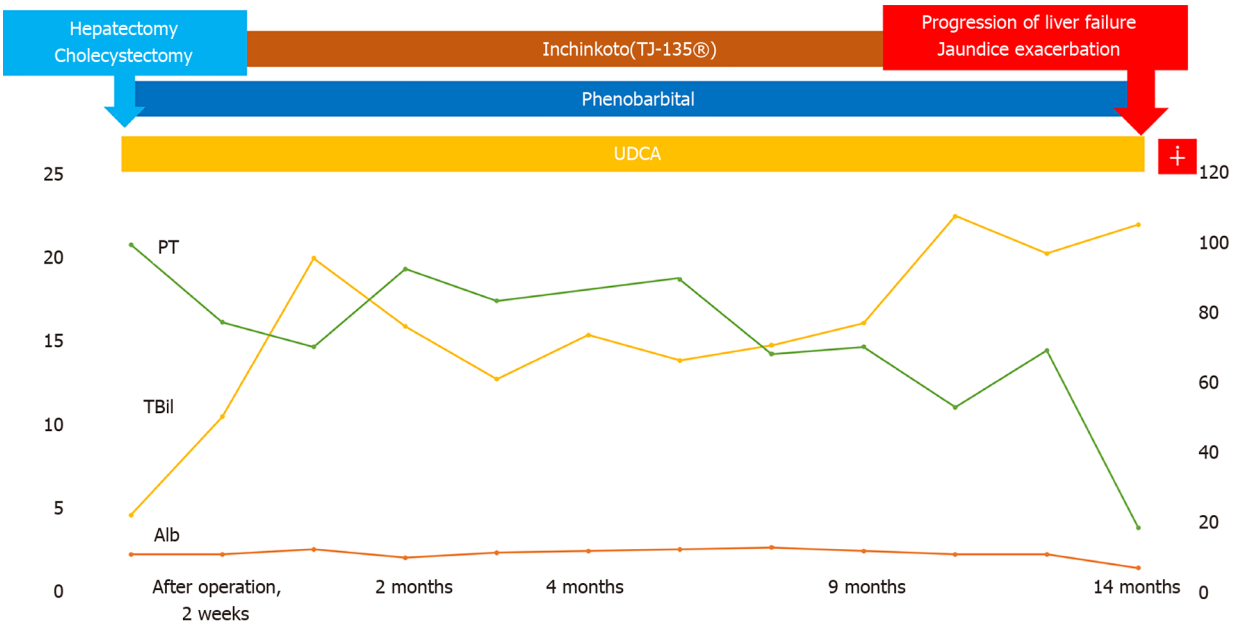

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Figure 7 Clinical course of case 2. UDCA: Ursodeoxycholic acid; PT: Prothrombin time; TBil; Total bilirubin; Alb: Albumin.

that the complication rate in UC is 2%–7.5%[11,12]. The incidence of ICC in PSC cases is 8%–20%[13-15], and approximately 10% of cases with ICC have been reported to be related to PSC[16]. We found 94 case reports in the English literature since 2000 by using PubMed with the keywords: Ulcerative colitis, cholangiocarcinoma, and primary sclerosing cholangitis.

There have been several reports on the relationship between the prevalence of PSC and the prevalence of ICC. Case-control studies reported from Sweden[17] and the United States[18] did not show a significant difference between the prevalence and incidence of ICC. A cohort study of the population of PSC patients was conducted on the association between IBD and ICC, but many of the reports indicated that there was no association[19,20]. However, in a case-control study conducted by Welzel *et al*[21], both UC and CD were reported as risk factors for ICC. Nevertheless, they did not consider the coexistence of PSC with ICC in these IBD patients, and the association between IBD and ICC remained unclear. In our report, case 1 was diagnosed with ICC 12 years after the onset of UC, and case 2 was diagnosed with ICC 27 years after the onset of UC. The average duration of UC of these patients was 20.5 years, which is a relatively long period of time. Therefore, in patients with coexisting UC and PSC, long-term screening of the liver and bile duct by imaging tests such as MRI and CT is necessary.

Early detection of ICC is difficult, and the accuracy rates of ultrasonography, CT, MRI, and other diagnostic imaging methods in cases without mass formation are as low as 48%, 38%, and 40%, respectively. The correct diagnosis rate of ICC by endoscopic retrograde cholangiopancreatography and magnetic resonance cholangiopancreatography was 23% and 21%, respectively[5,22]. Nevertheless, examination by both tumor marker CA19-9 and diagnostic imaging are useful for the diagnosis of ICC [5]. At the time of diagnosis, CA19-9 was high in our first case, but was below the threshold for

detection in our second case. Therefore, it is considered necessary to make a comprehensive diagnosis without relying solely on the value of tumor markers.

The 5-year survival rate for ICC is 39% for mass-forming lesions and 69% for intra-biliary lesions[23]. However, other reports state that no patients with tumor-forming lesions or peribiliary infiltrative lesions survived for more than 5 years[6,24]. Both our cases had mass-forming lesions and peribiliary infiltration, with a poor prognosis and an average survival duration of 15 mo from surgery to death.

As mentioned above, it is not uncommon for ICC to develop in cases of PSC with long-term follow-up. However, one of the patients presented here was largely asymptomatic, yet experienced a significant increase in tumor size at the time of discovery and ultimately died despite surgery and chemotherapy. Meanwhile, another patient had a relatively small lesion that could have been surgically removed; however, the patient died due to liver dysfunction which developed thereafter. With an unstable UC course, clinicians may be distracted by its progression and neglect to monitor the course of PSC. We have learned a valuable lesson – when CCC develops in patients with both IBD and PSC, the prognosis may be considerably worse. In both of our cases, there were tumor-forming lesions and periductal infiltration and the prognosis was poor, with an average survival time of 15 mo from surgery to death. Especially in the first case, the tumor was discovered when it was 10 cm in diameter, although the patient was largely asymptomatic until right lower abdominal pain began, suggesting that this tumor may grow relatively rapidly and almost asymptomatically.

Therefore, it is critical to perform regular imaging screening, such as MRI, during follow-up of patients with coexisting IBD and PSC, even if the patient is asymptomatic. This may aid ICC detection before periductal infiltration occurs.

CONCLUSION

We reported two patients with early-onset UC and PSC who developed ICC. Both cases followed an unfortunate course. Thus, in order to prevent similar scenarios from recurring, we should always consider ICC during the follow-up of patients with IBD and PSC and perform regular abdominal imaging examinations for its early detection.

FOOTNOTES

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CASE REPORT

Massive bleeding from a gastric artery pseudoaneurysm in hepatocellular carcinoma treated with atezolizumab plus bevacizumab: A case report

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Abstract

BACKGROUND

The combination of atezolizumab (ATZ) and bevacizumab (BVZ) was approved as first-line systemic therapy for advanced hepatocellular carcinoma (HCC) owing to its superior rates of response and patient survival. However, ATZ + BVZ is associated with increased risk of upper gastrointestinal (GI) bleeding, including arterial bleeding, which is rare and potentially fatal. We present a case of massive upper GI bleeding from a gastric pseudoaneurysm in a patient with advanced HCC who had been treated with ATZ + BVZ.

CASE SUMMARY

A 67-year-old man presented with severe upper GI bleeding after atezolizumab (ATZ) + bevacizumab (BVZ) therapy for HCC. Endoscopy failed to detect the bleeding site. Digital subtraction angiography revealed a gastric artery pseudoaneurysm and contrast extravasation from the inferior splenic artery and a branch of the left gastric artery. Successful hemostasis was achieved with embolization.

CONCLUSION

HCC patients who have been treated with ATZ + BVZ should be followed for 3 to 6 mo to monitor for development of massive GI bleeding. Diagnosis may require angiography. Embolization is an effective treatment.

Key Words: Atezolizumab; Bevacizumab; Hepatocellular carcinoma; Gastric artery pseudoaneurysm; Gastrointestinal bleeding; Case report

Core Tip: Atezolizumab (ATZ) + bevacizumab (BVZ) treatment increases the risk of bleeding in hepatocellular carcinoma (HCC) patients. Gastrointestinal (GI) bleeding is most common and usually arises from esophageal varices. We report a patient with advanced HCC who presented with massive upper GI bleeding from a gastric artery pseudoaneurysm after three cycles of ATZ + BVZ. Gastric artery pseudoaneurysm is rare and often asymptomatic. Mortality is high and emergency endovascular embolization is required. Patients receiving ATZ + BVZ treatment should be followed closely for GI bleeding. Arterial bleeding should be considered when massive GI bleeding occurs. Angiography may be required for diagnosis. Embolization has a role in treatment.

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INTRODUCTION

Primary liver cancer is the fourth leading cause of cancer-related death worldwide[1] and hepatocellular carcinoma (HCC) is the most common type of primary liver cancer[2]. Curative treatment options for early-stage HCC include resection, liver transplantation, and ablation. However, most HCC patients are diagnosed in an advanced stage[2]. In these patients, current guidelines recommend systemic therapy [3].

The multikinase inhibitor sorafenib is an effective first-line systemic agent for treating advanced HCC [4,5]. Lenvatinib, another multikinase inhibitor, is an accepted alternative[6]. Previous studies have shown that both provide modest improvement in survival[6,7]. However, multikinase inhibitors are associated with considerable toxicities which can impair quality of life. The IMbrave 150 trial showed that atezolizumab (ATZ), a programmed cell death ligand 1 antibody and immune checkpoint inhibitor, combined with bevacizumab (BVZ), a vascular endothelial growth factor (VEGF) antibody, achieved a better response rate and rates of progression-free and overall survival than sorafenib in patients with advanced metastatic or unresectable HCC[8]. Based on the trial's results, ATZ + BVZ was approved as first-line systemic therapy for advanced HCC in May 2020. However, compared with sorafenib, ATZ + BVZ was associated with a higher rate of bleeding overall (25.2% *vs* 17.3%) and higher rate of upper gastrointestinal (GI) bleeding (7% *vs* 4.5%). According to previous studies, variceal bleeding accounts for approximately 70% of all upper GI bleeding in HCC patients receiving BVZ or ATZ + BVZ; arterial GI bleeding is rare[9,10]. Here, we report an HCC patient who developed massive GI bleeding from a gastric artery pseudoaneurysm after treatment with ATZ + BVZ.

CASE PRESENTATION

Chief complaints

A 67-year-old man with advanced HCC was admitted to our hospital for massive upper GI bleeding after three cycles of ATZ+BVZ treatment.

History of present illness

The patient had been treated with transcatheter arterial chemoembolization (TACE) twice and surgical resection. Owing to HCC progression, he had more recently been treated with sorafenib and four radiofrequency ablation procedures. He was referred to our hospital for evaluation of right upper quadrant abdominal pain in January 2021. Contrast-enhanced abdominal magnetic resonance imaging (MRI) showed multiple enhancing nodules in all segments of the liver (Figure 1A). He underwent TACE twice as well as lenvatinib treatment. Nonetheless, his HCC progressed (Figure 1B). Combination of ATZ (1200 mg) and BVZ (15 mg/kg) every 3 wk was therefore initiated. Blood testing revealed a white blood cell count of 2.83 × 10^9/L, hemoglobin concentration of 127 g/L, and platelet count of 149 × 10^9/L. Child–Pugh score was 6 (Class A), indicating preserved liver function. Prothrombin time was 2 s longer than normal. Concentrations of the tumor markers des-gamma-carboxyprothrombin and alpha fetoprotein were elevated (29787 mAU/mL and 0.8 ng/mL, respectively). After three cycles, MRI showed continued progression but no remarkable gastroesophageal varices (Figure 1C and D). The

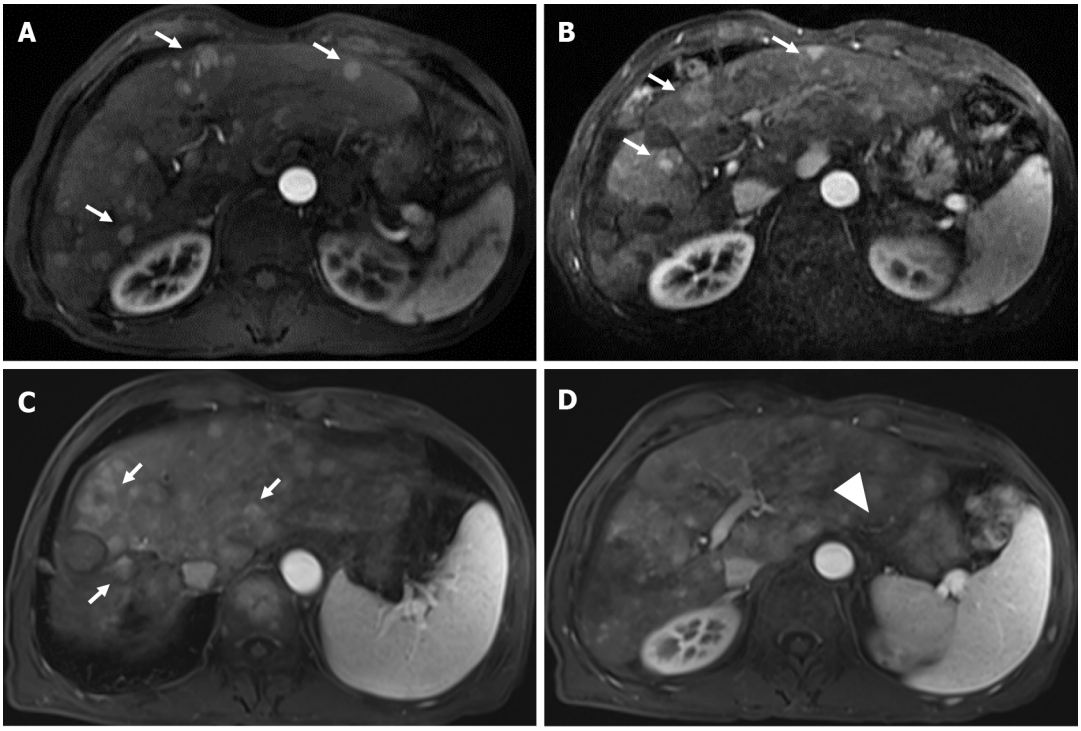

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Figure 1 Pseudoaneurysm bleeding after atezolizumab–bevacizumab treatment. A: Magnetic resonance imaging (MRI) of the abdomen revealed multifocal enhancing hepatocellular carcinoma lesions in the liver (white arrows); B: After transcatheter arterial chemoembolization and lenvatinib treatment, MRI showed disease progression (white arrows); C and D: After three cycles of atezolizumab plus bevacizumab, MRI showed progressive disease (white arrows) but no remarkable gastroesophageal varices (white arrowhead).

patient then underwent another TACE procedure which showed no contrast extravasation in the gastric area (Figure 2). He was discharged without complications. Ten days later, he was admitted to the hospital because of massive hematochezia and melanemesis. The patient's clinical course is shown in Figure 3.

History of past illness

The patient had a history of hepatitis C, cirrhosis, and HCC diagnosed 3 years ago. He also had a remote history of gastric carcinoma treated with partial gastrectomy 30 years previously.

Personal and family history

No specific personal and family history.

Physical examination

On admission, he exhibited signs of hypovolemic shock: Paleness, sweating and low blood pressure (64/38 mmHg).

Laboratory examinations

Hemoglobin concentration and platelet count were 59 g/L and 98 × 10^9/L, respectively. Prothrombin time was 5 s longer than normal.

Imaging examinations

His condition did not improve despite infusion of intravenous fluids and a transfusion of packed red blood cells. Because acute upper GI bleeding was suspected, GI endoscopy was performed, which revealed fresh blood and blood clots within the stomach (Figure 4). The blood could not be removed with repeated washings. Esophageal varices and red wale signs were not observed; however, visualization was limited. Because hemostasis could not be achieved, he underwent emergency digital subtraction angiography (DSA), which showed contrast extravasation from a gastric artery pseudoaneurysm, the inferior splenic artery, and a branch of the left gastric artery (Figure 5A).

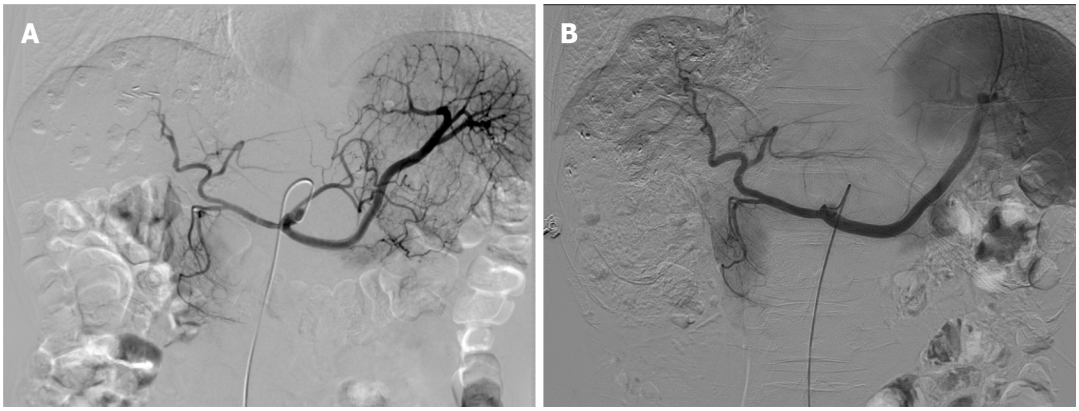

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Figure 2 Selective digital subtraction angiography showed no extravasation of contrast medium in the gastric area. A: Digital subtraction angiography in March 2021; B: Digital subtraction angiography in September 2021.

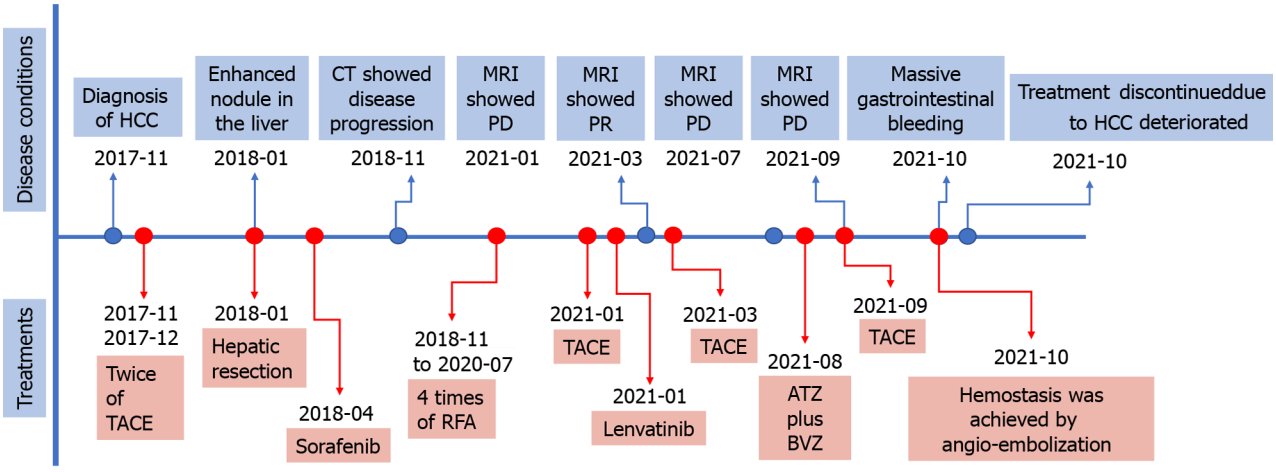

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Figure 3 Treatment and disease status timeline. HCC: Hepatocellular carcinoma; TACE: Transcatheter arterial chemoembolization; CT: Computed tomography; RFA: Radiofrequency ablation; MRI: Magnetic resonance imaging; PD: Progressive disease; PR: Partial response; ATZ: Atezolizumab; BVZ: Bevacizumab.

FINAL DIAGNOSIS

The final diagnosis was acute massive upper GI bleeding from a gastric pseudoaneurysm.

TREATMENT

The pseudoaneurysm was successfully embolized with a mixture of lipiodol (2 mL) and liquid glue (0.5 mL) (Figure 5B-D).

OUTCOME AND FOLLOW-UP

Although embolization resulted in hemostasis and marked improvement in general condition, the patient later developed liver failure and hepatic encephalopathy. Further treatment was discontinued at the family's request. Unfortunately, he died because of disease deterioration 6 d later.

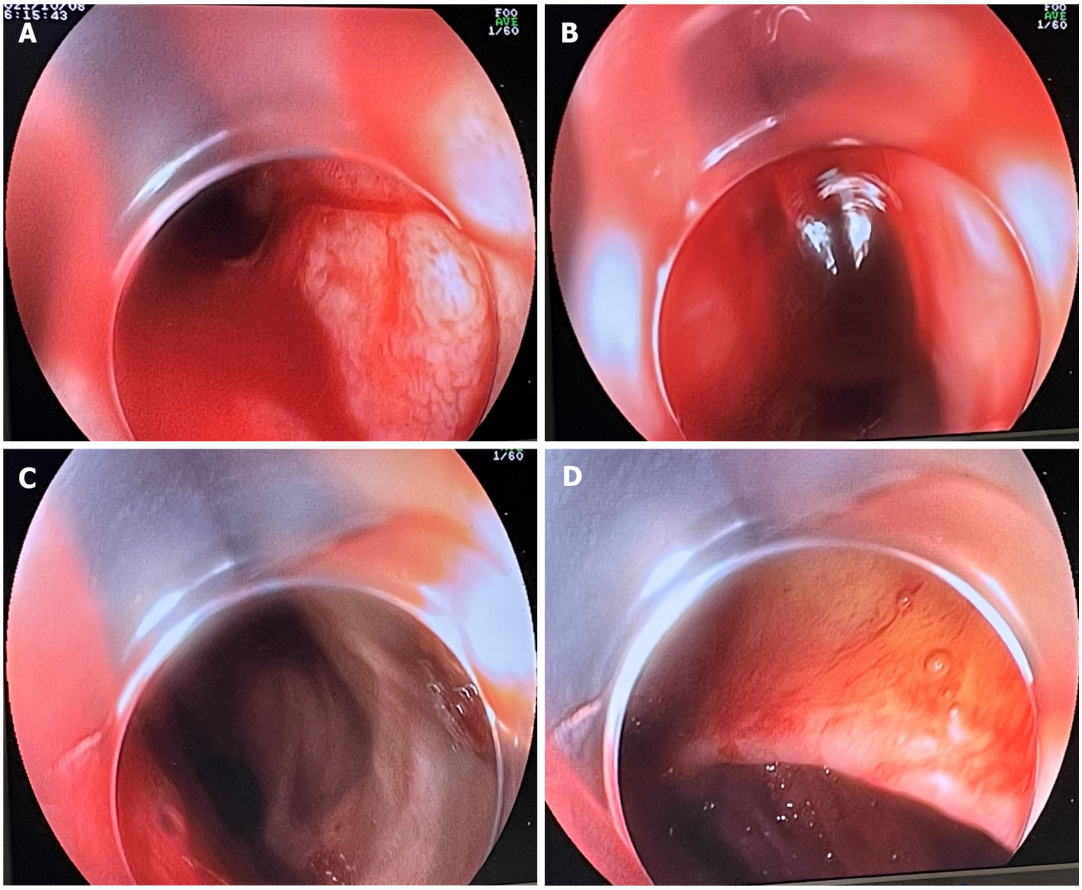

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Figure 4 The findings of gastrointestinal endoscopy performed by the time of massive upper gastrointestinal bleeding. Visualization was limited because of massive fresh blood and blood clots within the stomach. A-C: No remarkable esophageal varices or red wale signs were observed in esophagus and fundus of stomach; D: No recurrence of gastric carcinoma or anastomotic bleeding was detected.

DISCUSSION

We report a patient who presented with massive bleeding after receiving ATZ + BVZ treatment for progressive HCC. Although endoscopy failed to detect a bleeding source, DSA revealed a gastric artery pseudoaneurysm and contrast extravasation from the inferior splenic artery and a branch of the left gastric artery. Hemostasis was achieved after successful embolization.

ATZ is a humanized immunoglobulin G1 monoclonal antibody which selectively targets programmed cell death ligand 1 on tumor-infiltrating immune cells or tumor cells and prevents ligand interactions with programmed cell death protein 1 and the costimulatory molecule B7-1 on activated T-cells. This enables inhibition of effector T-cells and induces tumor cell death[11,12]. ATZ is associated with a wide range of immune-related adverse events that can involve almost any organ[13]. In the IMbrave150 study[8], the most common ones were hepatitis (53%), rash (22%), and hypothyroidism (14%); incidence of GI bleeding was relatively low.

BVZ is a recombinant humanized monoclonal immunoglobulin G antibody which binds VEGF and blocks its interaction with receptors on endothelial cells to inhibit tumor angiogenesis and growth[14]. VEGF-A is an important growth factor which induces vascular permeability, stimulates extracellular matrix remodeling, and creates new blood vessels[15]. BVZ inhibits normal and pathological angiogenesis *via* targeting VEGF-A. In the IMbrave150 study[8], GI bleeding (3%), pulmonary hemorrhage (0.3%), and subarachnoid hemorrhage (0.3%) were adverse events which led to withdrawal of treatment. The cause of the gastric pseudoaneurysm in our patient remains unclear; however, based on the inhibitory effect of BVZ on VEGF and angiogenesis, BVZ may have been involved. Gastric artery pseudoaneurysms are rare and usually cause no symptoms; they are typically found after rupture[16]. Causes include pancreatitis, trauma, peptic ulcer, atherosclerosis, iatrogenic, and connective tissue disorders[17]. Computed tomography angiography is the most sensitive noninvasive diagnostic modality for detecting pseudoaneurysms[18]. The early diagnosis of gastric pseudoaneurysm by computed tomography angiography was unavailable because the patient had no related symptom or laboratory abnormalities until he suffered from massive upper GI bleeding. Shord *et al*[19] reported pseudoaneurysms of the left internal iliac artery and superior rectal artery, respectively, in two patients who received BVZ therapy for metastatic colorectal cancer. Our patient had no history of anticoagulant

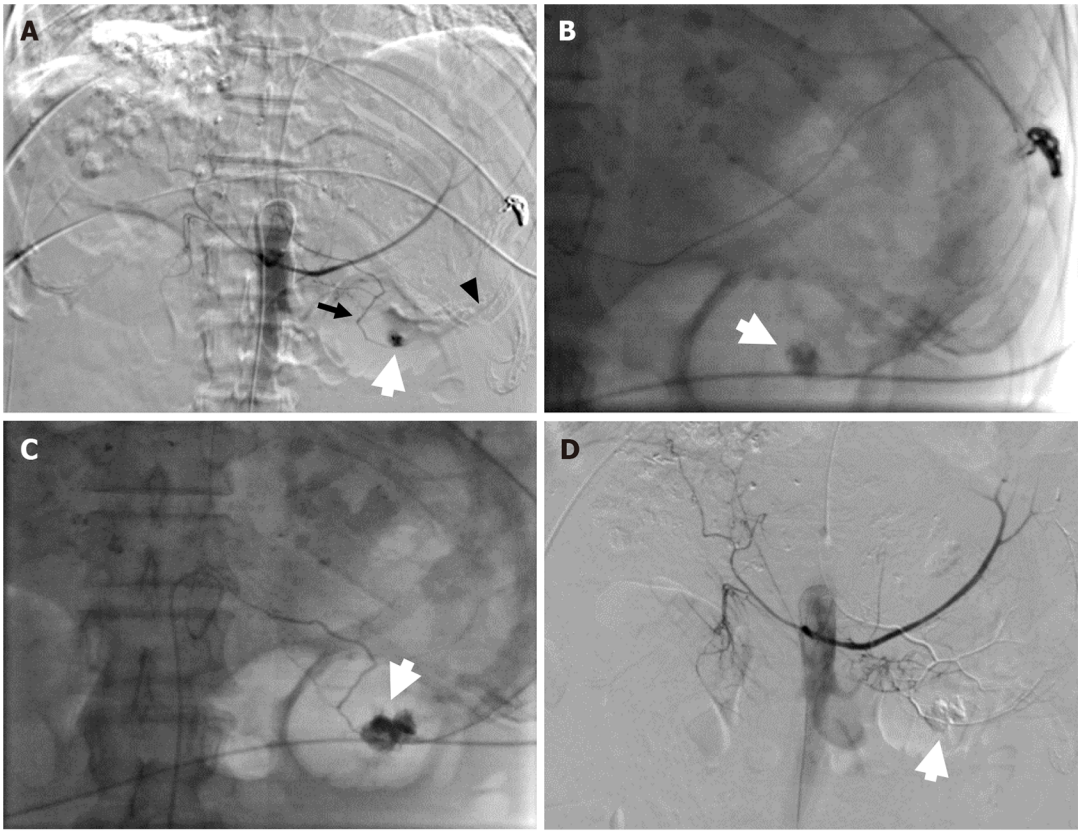

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Figure 5 Emergency angiography. A: Selective digital subtraction angiography of the celiac trunk showed extravasation of contrast medium (white arrow) from the inferior splenic artery (black arrow), a branch of the left gastric artery (black arrow head), and a pseudoaneurysm of the gastric artery; B and C: The pseudoaneurysm (white arrow) was embolized using liquid glue and lipiodol; D: After embolization, the pseudoaneurysm (white arrow) and active bleeding were no longer visible.

use or cardiovascular or other diseases associated with increased risk of bleeding. As a result, BVZ may have been the cause of his gastric artery pseudoaneurysm and bleeding. Moreover, deterioration of HCC can also be the cause of bleeding.

Because the patient had a remote history of gastric carcinoma and partial gastrectomy and the site of bleeding was in the stomach, recurrence of gastric carcinoma and anastomotic bleeding should be taken into consideration. Unfortunately, we did not perform endoscopy before ATZ + BVZ was administered or before bleeding began. GI endoscopy at the time of bleeding failed to detect the bleeding site because of limited visualization. However, the gastrectomy was performed approximately 30 years prior and the recurrence rate more than 10 years after curative gastrectomy is lower than 0.2%[20]. In addition, DSA performed before the massive bleeding occurred showed no pseudoaneurysm in the gastric area. Therefore, these possibilities are unlikely. In a meta-analysis of the risk of high-grade bleeding in patients with various cancers treated with BVZ, the risk was significantly higher in those who received 5 mg/kg per wk than those who received 2.5 mg/kg per wk[21]. However, none of the studies included in the meta-analysis examined patients with HCC. HCC patients typically receive doses of BVZ (15 mg/kg) and ATZ (1200 mg) on the same day administered every 3 wk[8]. BVZ dosing adjustments have not been established at present. Our patient received the standard recommended BVZ dose; therefore, it is not likely to have been the cause of bleeding.

Acute GI bleeding from varices or nonvariceal lesions can be fatal in patients with cirrhosis or HCC. Careful monitoring and appropriate intervention are important. Visceral artery pseudoaneurysms require immediate treatment because their rupture rate is high[22] and endovascular embolization using coils and/or liquid glue is effective. In our patient, owing to his poor physical condition and the massive degree of bleeding, embolization was successfully performed using a mixture of liquid glue and lipiodol.

In HCC patients undergoing treatment with ATZ + BVZ, we recommend GI endoscopy before and after therapy. Patients with a high risk of bleeding should be followed for 3 to 6 mo[23]. Any pseudoaneurysms identified should be embolized under DSA guidance.

CONCLUSION

In this study, we report a case of massive GI bleeding from a gastric pseudoaneurysm in patient after ATZ + BVZ treatment for HCC. Awareness of this rare and life-threatening complication allows specific diagnostic evaluation and timely intervention. Angioembolization of the pseudoaneurysm guided by DSA is preferred whenever a pseudoaneurysm becomes apparent.

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FOOTNOTES

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CASE REPORT

Bedside ultrasound-guided water injection assists endoscopically treatment in esophageal perforation caused by foreign bodies: A case report

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Abstract

BACKGROUND

Fishbone migration from the esophagus to the neck is relatively uncommon in clinical practice. Several complications secondary to esophageal perforation after ingestion of a fishbone have been described in the literature. Typically, a fishbone is detected and diagnosed by imaging examination and is usually removed by a neck incision.

CASE SUMMARY

Herein, we report a case of a 76-year-old patient with a fishbone in the neck that had migrated from the esophagus and that was in close proximity to the common carotid artery, and the patient experienced dysphagia. An endoscopically-guided neck incision was made over the insertion point in the esophagus, but the surgery failed due to having a blurred image at the insertion site during the operation. After injection of normal saline laterally to the fishbone in the neck under ultrasound guidance, the purulent fluid outflowed to the piriform recess along the sinus tract. With endoscopic guidance, the position of the fish bone was precisely located along the direction of liquid outflow, the sinus tract was separated, and the fish bone was removed. To the best of our knowledge, this is the first case report describing bedside ultrasound-guided water injection positioning combined with endoscopy in the treatment of a cervical esophageal perforation with an abscess.

CONCLUSION

In conclusion, the fishbone could be located by the water injection method under the guidance of ultrasound and could be accurately located along the outflow

direction of the purulent fluid of the sinus by the endoscope and was removed by incising the sinus. This method can be a nonoperative treatment option for foreign body-induced esophageal perforation.

Key Words: Esophageal perforation; Foreign body removal; Fishbone; Beside ultrasound-guided; Endoscopy; Case report

Core Tip: Fishbones are very common foreign bodies in upper gastrointestinal tracts in clinical practice. The most common fishbone stuck sites are the oropharynx, oral cavity, and esophagus. However, they are movable under the action of esophageal peristalsis, food swallowing and normal pleural pressure, which may cause severe complications if not treated in time. Under the guidance of ultrasound, the fishbone can be accurately located under the endoscope, and the fishbone can be removed by incising the sinus. This method can be an optimal alternative for treating patients with esophageal perforation and reducing surgical trauma.

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INTRODUCTION

In clinical practice, fishbones are very common in upper gastrointestinal tracts of patients[1] and are associated with the highest risk of gastrointestinal perforation[2]. In adults, the most common stuck sites of fish bones are the oropharynx, oral cavity, and esophagus[3]. Most patients can be discharged after outpatient treatment[4]. However, some foreign bodies, such as fishbones, can move under the action of esophageal peristalsis, food swallowing, and normal pleural pressure. If not treated in time, these sharp foreign bodies may penetrate the esophageal wall, causing an esophageal perforation, and surrounding organs or main blood vessels, causing severe complications[5]. Esophageal perforation is defined as a foreign body penetrating the outer wall of the esophagus[6]. When the fishbone completely penetrates the esophagus and enters the neck, a cervical sinus will be formed over time. Patients may experience symptoms such as dysphagia, pain, hemoptysis, and fever. Computed tomography (CT) and X-ray examinations can detect foreign bodies such as fishbones in the esophagus. For the treatment of esophageal perforation, different surgical methods are required for different types of fishbones, for different locations of perforation, and for the various complications after perforation. Most migratory fish bones in the neck can be removed by making a lateral incision into the neck[7]. However, this method is usually traumatic to the tissue and can lead to severe bleeding. Therefore, in this case, we chose to use the bedside ultrasound-guided water injection positioning method combined with endoscopy to remove a neck-located fishbone, which had migrated from the esophagus. This method can accurately remove the fishbone with less trauma and bleeding.

CASE PRESENTATION

Chief complaints

A 76-year-old Chinese man was admitted to our hospital due to pain during swallowing for 1 wk that was caused by accidental swallowing of a "fishbone".

History of present illness

The patient had mistakenly swallowed a "fish bone" 26 d prior. However, no foreign body was found during the laryngoscopy examination, and the pain gradually eased. One week prior, the pain in the right throat was aggravated, and it was accompanied by difficulty swallowing. After removing the "epiglottis abscess" and after a course of anti-infection treatment, the patient still had pain during swallowing and dysphagia and had pain in his right neck and shoulder. After the outpatient CT review of the esophagus, the patient was admitted to the hospital and was diagnosed with "foreign bodies in

the throat".

History of past illness

The patient had no history of hypertension, diabetes, viral hepatitis or tuberculosis. He had no known drug or food allergies. He also denied any history of surgery, trauma, or blood transfusions.

Personal and family history

The patient denied any history of smoking or drinking or any abnormal family history.

Physical examination

On physical examination, the vital signs were as follows: Body temperature, 36.4 °C; blood pressure, 126/79 mmHg; heart rate, 69 beats per min; and respiratory rate, 19 breaths per min. He was well developed and moderately nourished. He had an active position. The skin was not jaundiced. There are no special general appearances. The patient had no pitting edema. The patient's superficial lymph nodes in his neck were not found to be enlarged.

Laboratory examinations

No abnormalities were found in coagulation function, blood biochemical parameters, routine blood, or urine analysis.

Imaging examinations

Laryngoscopy examination showed that the pharynx was slightly congested, the bilateral tonsils were not enlarged, and a raised mass of approximately 1.0 cm × 1.0 cm was seen on the right side of the lingual surface of the epiglottis. The surgical site had recovered well with no obvious pus exudation. Both vocal cords were smooth and showed good movement capacity. The right piriform fossa was obviously swollen, and there was no obvious foreign body in the laryngopharynx. Ultrasonography revealed a band of hyperechoic echoes on the right side of the neck (Figure 1A). The sagittal plane of the CT scan showed a high-density strip in the right of the neck (Figure 1B).

FURTHER DIAGNOSTIC WORK-UP

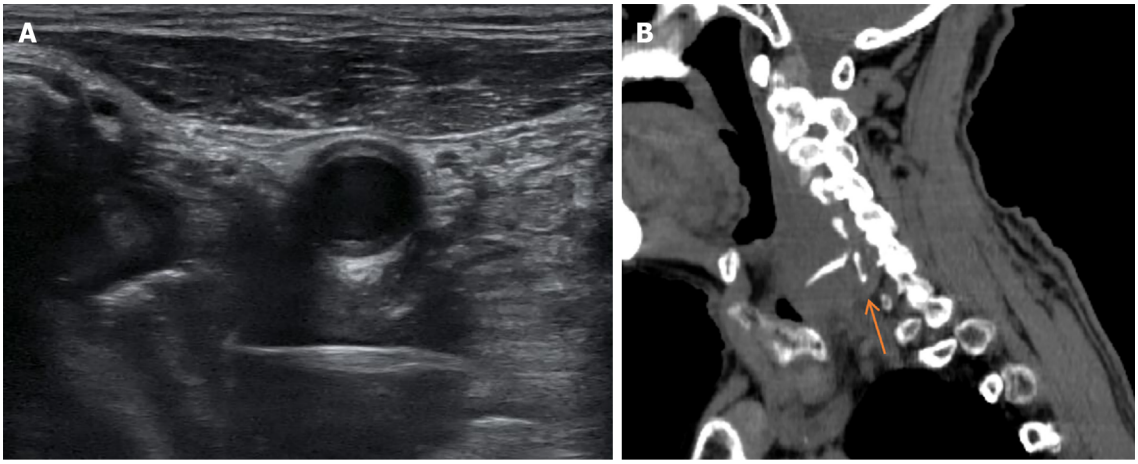
The patient was diagnosed clearly, and no further examination was necessary.

FINAL DIAGNOSIS

Combined with the medical history and examination results, the final diagnosis was "a foreign body in the right paralaryngopharynx and a foreign body with abscess formation".

TREATMENT

Therefore, surgery was performed on the patient in collaboration with a gastroenterologist and ultrasound physician after the patient signed an informed consent form. During the operation, the mucosa of the lateral wall of the right piriform fossa was obviously swollen, and a mucosal breach was seen. An incision was made at the mucosal breach of the lateral wall of the right piriform fossa. Blunt dissection was performed, but no foreign body was detected. Then, under the guidance of bedside ultrasound positioning, a 23 G/9.0 cm fine needle was found punctured into the cavity where the fishbone was located (Figure 2A). After injection of normal saline, a small amount of purulent fluid overflowing from the dissected lateral wall of the right piriform fossa was observed under video endoscopy and laryngoscopy (Figure 2B). Under endoscopy, the sinus tract was separated until the end of the foreign body was located by ultrasound, and the head of the foreign body (fishbone) was exposed (Figure 2C). Then, a fishbone with a length of 2.5 cm was removed using forceps (Figure 2D). We then withdrew the puncture needle from the neck, adjusted the supporting laryngoscope to expose the epiglottis abscess, and cut the epiglottis abscess with a surgical scimitar. A small amount of pus was seen overflowing. After the pus was completely removed, the swelling on the lingual surface of the epiglottis completely disappeared. After withdrawing the supporting laryngoscope, we completed the operation successfully.



DOI: 10.4240/wjgs.v15.i6.1240 **Copyright** ©The Author(s) 2023.

Figure 1 Imaging examinations. A: Ultrasound scan still image of the fishbone which was shown as a band of hyperechoic echoes on the right side of the neck; B: The Sigittal computed tomography shows the suspected fish bone.

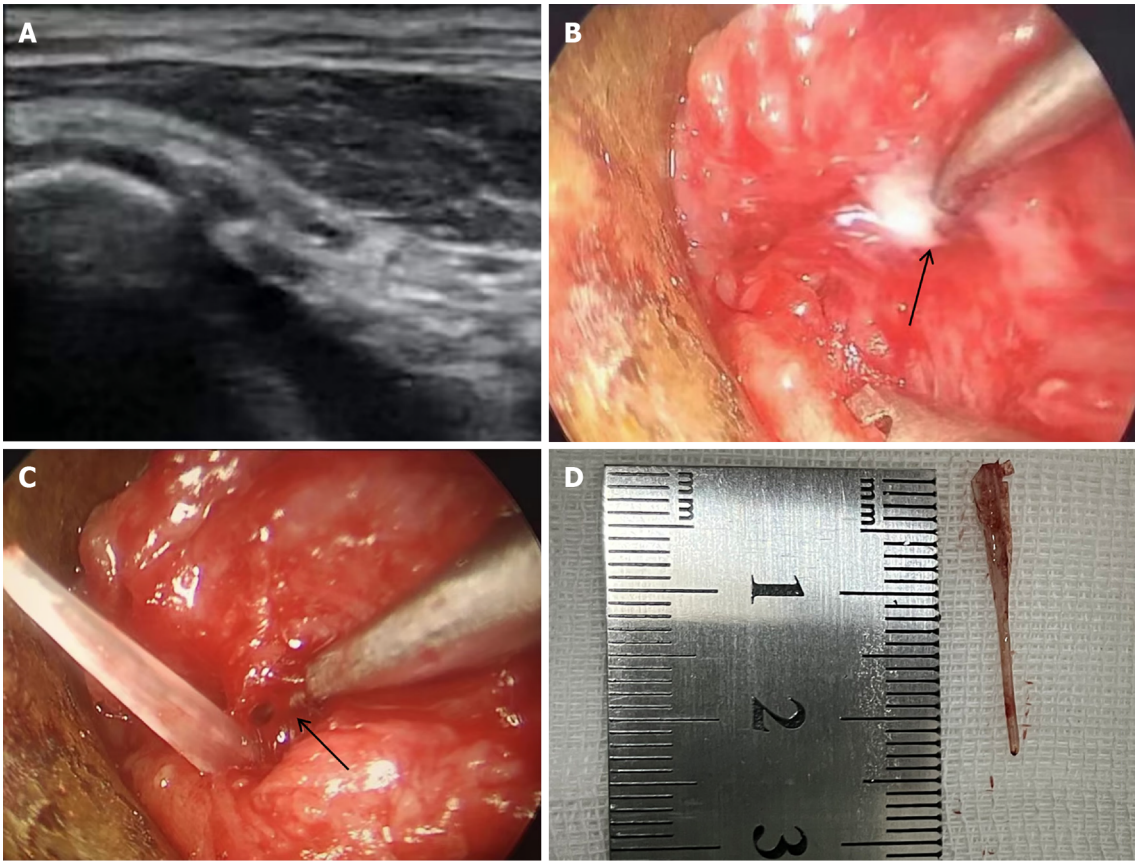


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Figure 2 Operation. A: Ultrasound imaging: The needle was punctured into the cavity where the fishbone was located; B: Endoscopy examination: A small amount of purulent fluid was seen overflowing from the dissected lateral wall of the right piriform fossa under video endoscopy and laryngoscope; C: Endoscopy examination: The head of the foreign body (fishbone) was exposed; D: Fishbone removed: The removed fish bone measured 2.5 cm in diameter.

OUTCOME AND FOLLOW-UP

The patient was treated with antibiotics for 3 d after the operation and was discharged from the hospital without symptoms, including neck pain, fever, hematemesis, and melena.

DISCUSSION

Ingested esophageal foreign bodies are commonly seen in the adult population. Due to the different eating habits of people in China compared to people in Western countries, foreign bodies found in Chinese people are mostly fishbones, jujube shells, and poultry bones[8]. Most ingested foreign bodies pass through the gastrointestinal tract spontaneously without causing complications; however, some foreign bodies may stay in the gastrointestinal tract and cause serious complications. Approximately 20% of patients require nonsurgical intervention; in a few cases, all the standard treatment options are ineffective and may cause the patient to require surgery[9]. Esophageal perforation caused by foreign bodies is still an urgent problem to be solved.

X-ray and endoscopic examinations are the most commonly used methods for detecting fishbones in the upper gastrointestinal tract; however, their accuracy and consistency are lower than those of neck-based CT scans. Magnetic resonance imaging (MRI) has advantages in estimating the extent of soft tissue inflammation caused by foreign bodies and detecting adjacent structures such as cervical blood vessels and nerves, but MRI is not sensitive in diagnosing foreign bodies. Thus, CT is the gold standard for the examination of fishbones in the neck[10].

Endoscopic removal is a safe and effective treatment method for sharp-pointed food impactions[11]. Food that is causing an esophageal obstruction can be gently pushed into the stomach, while foreign bodies that are unsuitable or unable to be pushed into the stomach can be removed by a snare, graspers, a stone extraction mesh basket, a balloon, a holmium laser and other tools after the types and positions are identified endoscopically[12]. However, for patients showing throat and neck discomfort after eating fish without fishbones detected by endoscopy, the possibility of esophageal perforation combined with the fishbone migrating to other locations should be considered[13], as constriction of swallowing muscles and peristalsis of the esophagus can force the fishbone to penetrate the mucosa and move out of the oropharynx[14]. An abscess can be formed 3-4 d after the fishbone moves out of the oropharynx into the neck[15]. In this case, since the fishbone is in the nontraditional position, endoscopic ultrasonography is very promising in accurately locating its position. In this study, the water injection method was adopted, by which normal saline was injected into the abscess formed by the fishbone. Then, purulent normal saline flowed along the sinus tract into the piriform recess. We accurately positioned the fishbone from the piriform crypt in the direction of the outflow. It has been reported that for cases where the insertion point of the fishbone can be seen clearly, the method of injecting normal saline containing methylene blue through the esophagus under ultrasound-guided endoscopy can be used, which can precisely locate the fishbone. By cutting an incision along the stained tract under the endoscope, the fishbone can be removed easily[16]. Therefore, we suggest that for foreign bodies that have been in the neck for a long time, which formed an abscess cavity, normal saline injection positioning can be used to locate the foreign body, and then a neck incision can be performed under the endoscope to remove the foreign body. This surgical protocol yields smaller incisions and less bleeding and avoids perforation and reoperation.

Ultrasound examination, a highly operator-dependent and nonradiation examination technology, has been less commonly used in the detection of neck fishbones in recent years[17]. As ultrasound examination has the advantages of real-time imaging and low cost, the combination of bedside ultrasound and endoscopic techniques may provide a beneficial solution for the diagnosis and treatment of patients with esophageal perforation combined with a migratory fishbone in the neck.

CONCLUSION

Under the guidance of ultrasound, the fishbone can be located by the water injection method. Then, the foreign body can be accurately located endoscopically and along the outflow direction of the sinus purulent fluid, and the fishbone can be removed by incising the sinus. This method can be an optimal plan for treating patients with esophageal perforation caused by foreign bodies. It can effectively improve the efficiency of endoscopic removal of free foreign bodies in the neck, reducing the surgical incision area and avoiding intraoperative bleeding and extensive tissue damage.

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FOOTNOTES

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CASE REPORT

Modified stomach-partitioning gastrojejunostomy for initially unresectable advanced gastric cancer with outlet obstruction: A case report

Xin-Xin Shao, Quan Xu, Bing-Zhi Wang, Yan-Tao Tian

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Abstract

BACKGROUND

Chemotherapy followed by gastrojejunostomy remains the main treatment for unresectable gastric cancer (GC) in the middle- or lower-third regions with gastric outlet obstruction (GOO). Radical surgery is performed as part of a multimodal treatment strategy for selected patients who respond well to chemotherapy. This study describes a case of successful radical resection with completely laparoscopic subtotal gastrectomy after a modified stomach-partitioning gastrojejunostomy (SPGJ) for obstruction relief, in a patient with GOO.

CASE SUMMARY

During the initial esophagogastroduodenoscopy, an advanced growth was detected in the lower part of the stomach, which caused an obstruction in the pyloric ring. Following this, a computed tomography (CT) scan revealed the presence of lymph node metastases and tumor invasion in the duodenum, but no evidence of distant metastasis was found. Consequently, we performed a modified SPGJ, a complete laparoscopic SPGJ combined with No. 4sb lymph node dissection, for obstruction relief. Seven courses of adjuvant capecitabine plus oxaliplatin combined with Toripalimab (programmed death ligand-1 inhibitor) were administered thereafter. A preoperative CT showed partial response; therefore, completely laparoscopic radical subtotal gastrectomy with D2 lymphadenectomy was performed after conversion therapy, and pathological complete remission was achieved.

CONCLUSION
Laparoscopic SPGJ combined with No. 4sb lymph node dissection was an effective surgical technique for initially unresectable GC with GOO.

Key Words: Gastrojejunostomy; Gastric cancer; Gastric outlet obstruction; Conversion therapy; Curative resection; Case report

Core Tip: Radical resection, which may improve long-term survival, is often challenging in unresectable gastric cancer (GC) with gastric outlet obstruction (GOO) due to the management of complete gastrointestinal anastomoses and abdominal adhesions caused by gastrojejunostomy. We present a successful case of radical resection after laparoscopic stomach-partitioning gastrojejunostomy (SPGJ) combined with No. 4sb lymph node dissection, followed by conversion therapy; pathological complete remission was achieved. This case suggests that laparoscopic SPGJ combined with No. 4sb lymph node dissection is an option for initially unresectable GC with GOO.

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INTRODUCTION

Gastric cancer (GC) is one of the most common malignancies globally. In 2020, there were 768793 GC-related deaths, accounting for approximately 7.7% of total cancer deaths among 185 countries[1]. As GC is rarely detected at an early stage, the morbidity and mortality rates are high, with 5-year survival rates ranging from 20% to 40% in most countries[2,3]. Curative resection is essential for long-term survival. For patients with unresectable or metastatic GC, the median survival time is 4.3 mo with best supportive care[4], which can be extended to 10.5-11.6 mo with chemotherapy[5]. For unresectable GC in the middle- or lower-third with gastric outlet obstruction (GOO), chemotherapy followed by gastrojejunostomy remains the main therapeutic approach. Treatment modalities of adjuvant combination therapy, include combined targeted drugs or hyperthermic intraperitoneal perfusion chemotherapy[6-8]. For gastric adenocarcinoma, nivolumab plus chemotherapy demonstrated superior overall survival *vs* chemotherapy alone at the 12-mo follow-up in the randomized, global CheckMate 649 phase 3 trial[9]. The development of agents for GC has encouraged us to perform radical surgery for patients with initially unresectable GC who were converted to resectable status following their response to chemotherapy plus programmed death (PD)-1 inhibitor.

However, radical surgery is often challenging for patients who have undergone gastrojejunostomy. We report a successful case of radical resection utilizing completely laparoscopic subtotal gastrectomy with D2 lymph node dissection after completely laparoscopic stomach-partitioning gastrojejunostomy (SPGJ) combined with No. 4sb lymph node dissection, followed by adjuvant capecitabine plus oxaliplatin (CAPOX) combined with Toripalimab (PD-1 inhibitor), in a patient with GOO.

CASE PRESENTATION

Chief complaints

A 58-year-old woman presented with abdominal distension and vomiting.

History of present illness

The patient had previously attended a local hospital complaining of abdominal distension and vomiting. During the esophagogastroduodenoscopy (EGD), it was observed that there was an advanced growth located in the lower part of the stomach, causing a narrowing that made it difficult for the scope to pass through. Pathological examination of the biopsy confirmed the diagnosis of cancer. Afterwards, she was admitted to our hospital where she underwent a comprehensive medical examination and treatment.

History of past illness

The patient had been successfully treated for right breast cancer with surgery and adjuvant chemotherapy 17 years earlier.

Personal and family history

There was no record of smoking or alcohol consumption in the patient's medical history, and there was no pertinent family medical history.

Physical examination

Mild tenderness was noted in the upper abdomen.

Laboratory examinations

No positive findings were obtained from standard laboratory examinations (including routine blood, and liver function, renal function, and tumor markers).

Imaging examinations

EGD detected an advanced lesion in the lower part of the stomach. The lesion was obstructing the pyloric ring and invading the duodenum (Figure 1A-C). Histological examination of the biopsies led to a diagnosis of poorly differentiated adenocarcinoma (Figure 1D). Computed tomography (CT) showed lymph node metastases and tumor invasion into the duodenum (Figure 1E-H) without distant metastases. Pathological examination revealed human epidermal growth factor receptor 2 negative, Ki-67 (+, 90%), and pMMR based on immunohistochemistry.

FINAL DIAGNOSIS

The final diagnosis was GC cT4aN2M0 c Stage III, according to the American Joint Committee on Cancer TNM Staging Classification for Carcinoma of the Stomach (8th ed, 2017).

TREATMENT

Completely laparoscopic SPGJ combined with No. 4sb lymph node dissection

The staging laparoscopy indicated the absence of liver metastases or spreading, and the lavage cytology test results were negative. It was also confirmed that the lower part of the stomach body was immobile due to cancerous invasion into the duodenum. After the left gastroepiploic vessels were severed at their origin near the splenic tail, No. 4sb lymph nodes were dissected. The stomach was transected with a 60 mm linear stapler, from the greater curvature, extending 2 cm from the lesser curvature, at least 5 cm proximal to the tumor or site of obstruction. Thereafter, a small opening was made in the jejunum at the antimesenteric border, 25 cm from the ligament of Treitz. A second opening was made in the stapling line on the greater curvature side of the gastric stump. Next, gastrojejunostomy was performed using a laparoscopic linear stapler. Using the same equipment, the proximal and distal jejunum were anastomosed to form a jejunojejunostomy, 60 mm in length. The anastomotic stoma was established 15 cm from the ligament of Treitz and 25 cm from the gastrojejunostomy anastomosis (Figure 2). The surgery lasted for 1 h and 10 min, and the total amount of blood loss was 20 mL. No intra- and post-operative complications were observed. Post-operative upper digestive tract radiography indicated a good passage to the jejunum and drainage route in the lesser curvature (Figure 3A). The time to oral feeding was 3 d, and the post-operative hospital stay was 6 d.

Conversion therapy and toxicities

Twenty days after laparoscopic SPGJ, seven courses of CAPOX combined with Toripalimab (capecitabine 1500 mg/d on days 1-14, oxaliplatin 100 mg/m^2 on day 1, and Toripalimab 240 mg/d on day 1, Q3W) were performed. With this regimen, only grade 2 elevations in leukopenia were observed, and no serious adverse events of grade 3 or greater according to the Common Terminology Criteria for Adverse Events version 5.0 were detected.

Radiological assessment

After conversion therapy, EGD showed a good drainage route in the lesser curvature and detected shrinkage of the primary tumor, allowing the endoscope to pass (Figure 3B and C). CT showed significant reduction in size of primary tumor and metastatic lymph nodes (Figure 4A-D). Clinical response was defined as a partial response on radiological examination according to the Response Evaluation Criteria in Solid Tumors criteria version 1.0. The preoperative diagnosis was ycT3N0M0 yc Stage IIB.

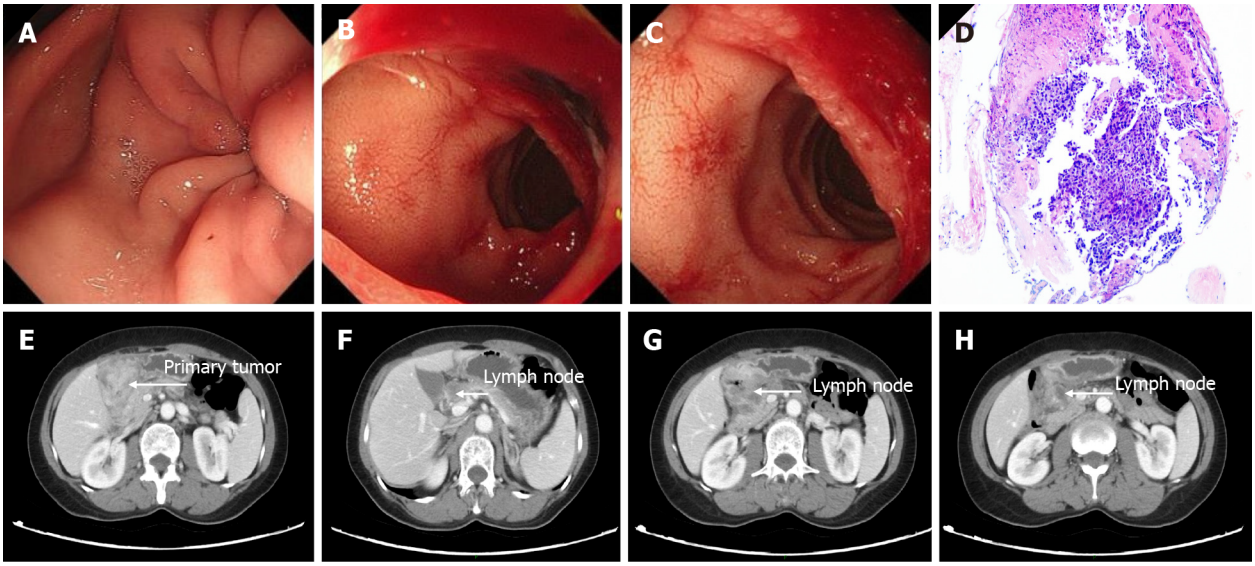

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Figure 1 Clinical data of the patient at the initial diagnosis. A-C: Normal endoscopic showing primary tumor invasion to the antrum (A), pyloric ring (B), and duodenum (C); D: Pathological examination of the endoscopic biopsy revealed a poorly differentiated adenocarcinoma; E-H: Initial computed tomography showing primary tumor invasion to the duodenum (E) and lymph node metastases (F-H).

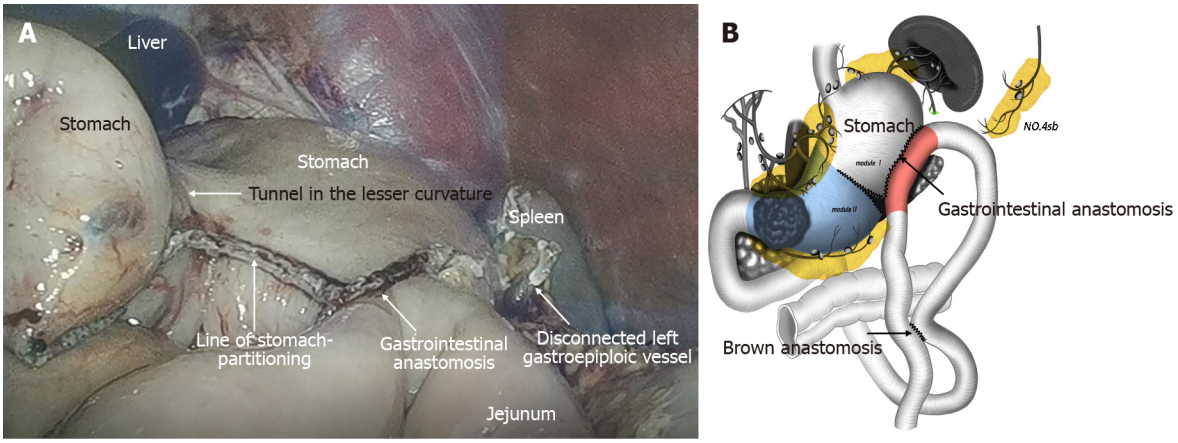

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Figure 2 Stomach-partitioning gastrojejunostomy and Braun anastomosis combined with No. 4sb lymph node dissection. A: Intraoperative laparoscopic images; B: Illustration of the modified stomach-partitioning gastrojejunostomy.

Completely laparoscopic subtotal gastrectomy with D2 lymph node dissection

Following dissection of the adhesions between the omentum and the abdominal wall, it was confirmed that there were no liver metastases or spreading. Rapid lavage cytology results showed the absence of cancer cells in the ascites. Infra-pyloric dissection was performed by ligating the right gastro-epiploic vessels. The duodenum was divided at 2 cm below the pyloric ring using a 60 mm linear stapler. Negative margins were confirmed by intraoperative frozen pathology. The right gastric artery was ligated from its origin in the right hepatic artery. The peritoneum over the porta hepatis and the lesser omentum were excised. The supra-pancreatic dissection continued with the removal of No. 8a and No. 12a lymph nodes. After ligation of the right gastric vein, the pancreatic capsule was dissected from the root of the left gastric artery to the proximal splenic artery. The left gastric artery was then transected. The proximal splenic artery was skeletonized to dissect the No. 11 lymph nodes. The No. 3 and No. 1 lymph nodes were then dissected along the lesser curvature of the stomach. After D2 lymphadenectomy, the stomach was divided along the SPGJ line using a 60 mm linear stapler. The anastomoses created in previous operations were used throughout (Figure 5). The total operation time was 1 h and 55 min and the total blood loss was 50 mL. No intra- and post-operative complications were observed. The time to oral feeding was 1 d, and the post-operative hospital stay was 5 d.

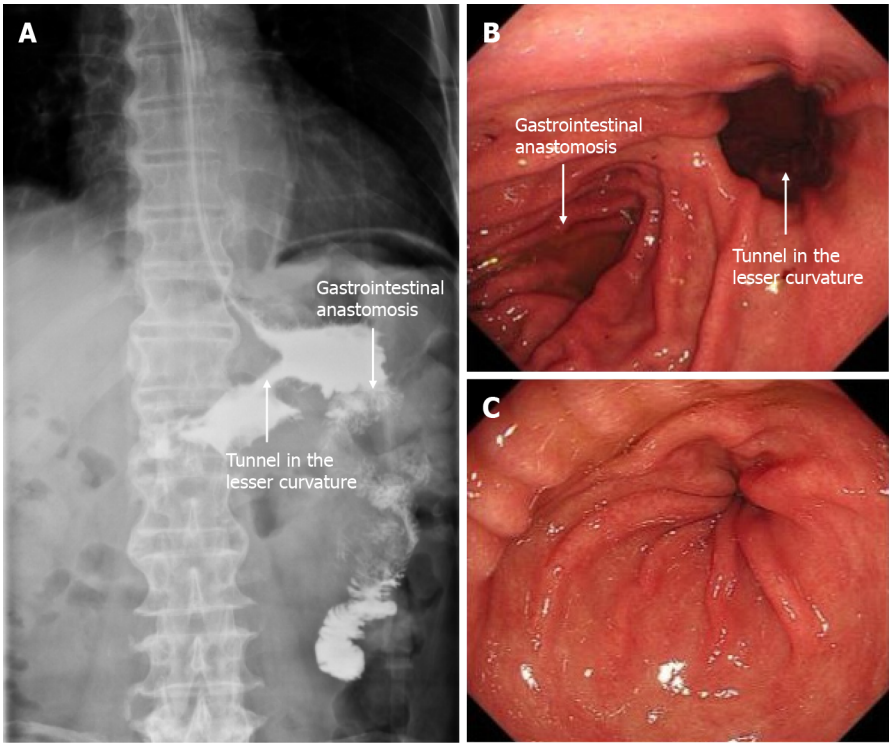

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Figure 3 Clinical data of the patient after operation and conversion therapy. A: Upper digestive tract radiography showed a good passage to the jejunum; B: Endoscopic showing good drainage route in the lesser curvature; C: Endoscopic evidence of good reduction of primary tumor.

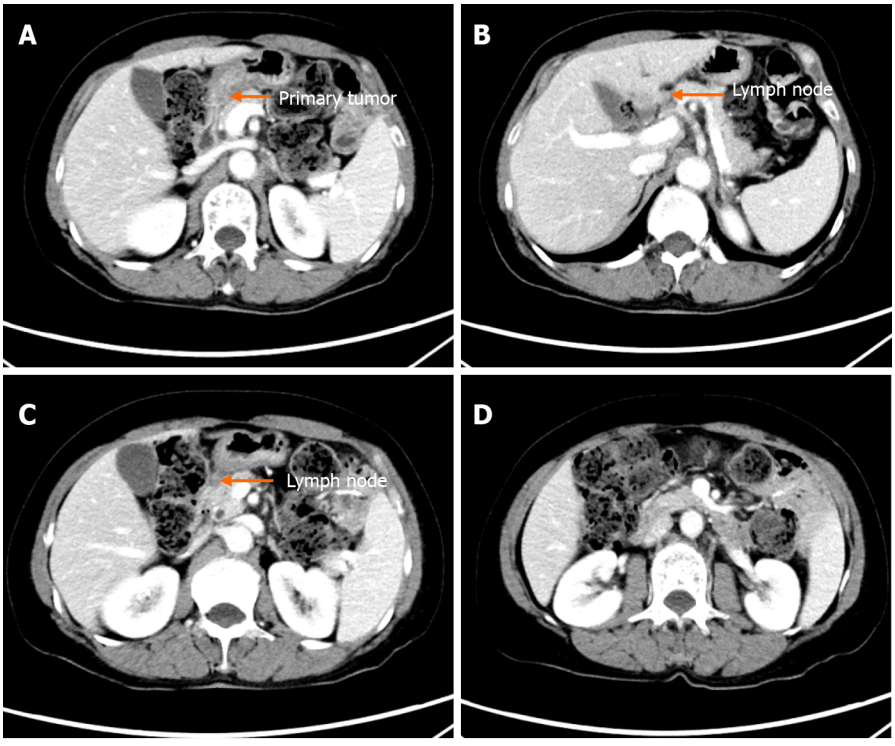

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Figure 4 Computed tomography findings after conversion therapy. A: Primary tumor reduction; B-D: Metastatic lymph node reduction.

OUTCOME AND FOLLOW-UP

Pathological complete remission was achieved (Figure 6). Post-operative therapy was not performed due to the good response to the seven courses of preoperative therapy. No recurrences were observed

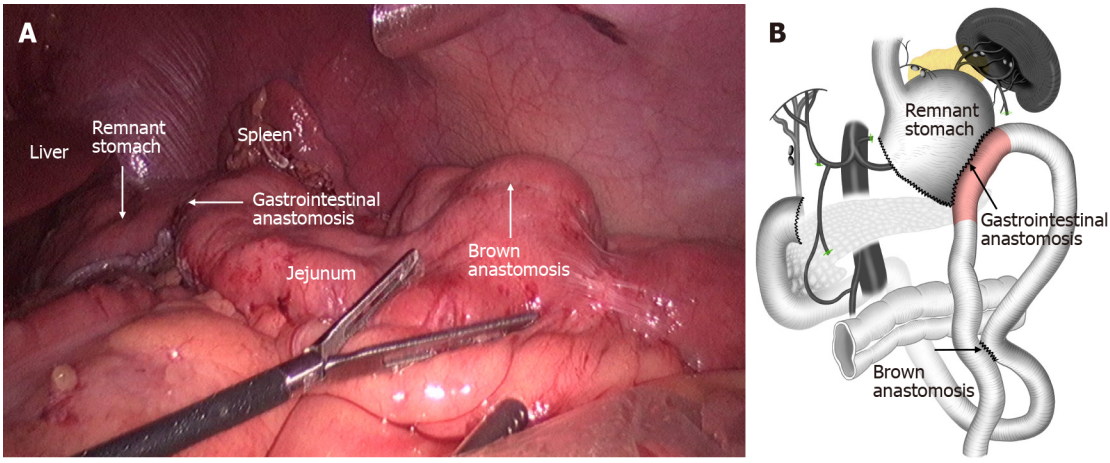

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Figure 5 Subtotal gastrectomy with D2 lymph node dissection. A: Intraoperative laparoscopic images; B: Illustration of the gastrectomy, the anastomoses completed in the previous operation were preserved.

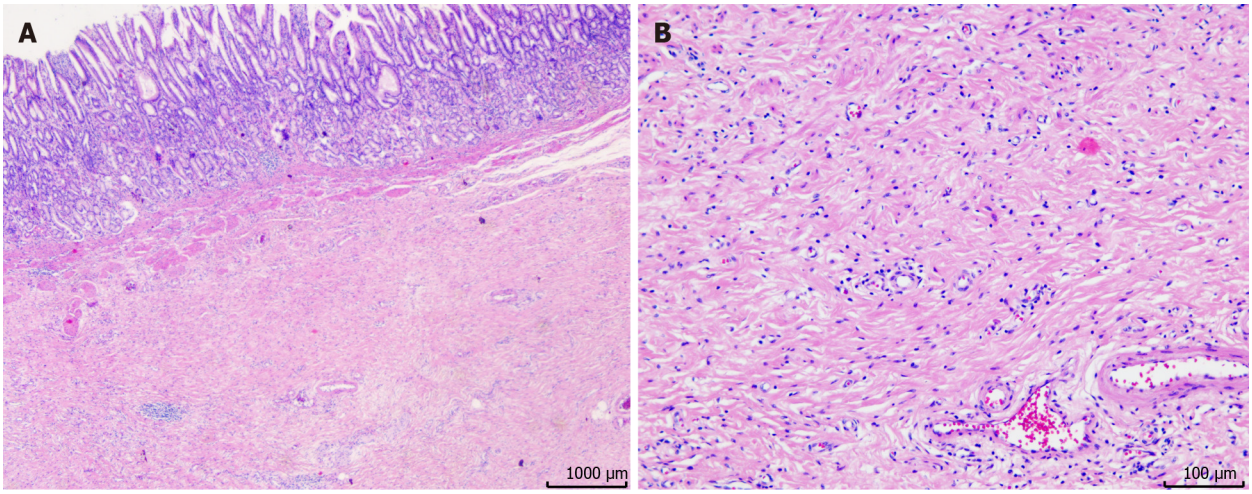

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Figure 6 Post-operative pathology showed no residual tumor cells, and a pathological complete response was achieved. A: Hematoxylin and eosin staining results, × 4; B: Hematoxylin and eosin staining results, × 40.

17 mo post-operatively. Table 1 shows the timeline from the onset of symptoms to the completion of treatment.

DISCUSSION

We present the successful case of a radical resection performed with a completely laparoscopic subtotal gastrectomy with D2 lymph node dissection after laparoscopic SPGJ combined with No. 4sb lymph node dissection, followed by CAPOX combined with Toripalimab for advanced GC with GOO.

Chemotherapy is one of the main treatments for advanced GC. GOO is a common condition among patients suffering from unresectable distal gastric tumors, which present with nausea and vomiting, and can cause dehydration, weight loss, and impaired chemotherapy tolerance for patients, hastening their demise. Traditionally, duodenal stent or gastrojejunostomy have been recommended as first-line treatment options for unresectable GC with GOO. For patients with good performance status and a favorable prognosis, the latter option is regarded as the preferred primary treatment[10].

Yamaguchi *et al*[11] reported long-term survivors in patients who underwent conversion surgery for stage IV GC. Therefore, radical surgery is performed during the treatment as part of a multimodal treatment strategy for selected patients who respond well to chemotherapy[11]. Many clinical trials have been performed for immunotherapy as a first-line treatment for advanced GC/gastroesophageal junction carcinoma and revealed encouraging results. The objective response rate was 60% and 67% in

Table 1 Timeline from the onset of symptoms to the completion of treatment

Time series	Symptoms and treatment details
9 mo ago	She presented with symptoms of abdominal distension and vomiting and visited a hospital
	A gastric tube was inserted to drain food residue from the stomach
8 mo ago	Staging laparoscopy confirmed no liver metastasis, no dissemination, and negative lavage cytological results
	Laparoscopic stomach-partitioning gastrojejunostomy and Braun anastomosis combined with No. 4sb lymph node dissection were performed
1-7 mo ago	CAPOX + Toripalimab 1-7
The date of radical surgery	Completely laparoscopic subtotal gastrectomy with D2 lymph node dissection was done
11 mo after surgery	CT shows no recurrence

CT: Computed tomography; CAPOX: Capecitabine plus oxaliplatin.

the cohort 2 study of KEYNOTE059 and ATTRACTION-04, respectively, when immune checkpoint inhibitors combined with chemotherapy were used as first-line therapy[12-14]. The development of agents for GC has encouraged us to perform radical surgery.

However, for patients who undergo gastrojejunostomy, radical surgery is often challenging for the following reasons: First, abdominal adhesions are often severe due to previous operations, especially laparotomy; this can cause significant interference in locating normal tissue spaces, dissecting lymph nodes, excising tumors, and anastomosing; Second, if the original anastomosis requires removal, the difficulty and risk of the operation greatly increases. Therefore, sufficient negative margins should be ensured. Moreover, No. 4sb lymph node dissection, especially in cases where the original anastomosis is retained, enables the short gastric vessels to be easily injured, which may cause gastric ischemia and spleen laceration, resulting in bleeding.

To solve these problems, we modified the operation based on the SPGJ[15] and named it the modular two-stage laparoscopic gastrectomy (MTLG). In MTLG, the gastrectomy and gastrointestinal anastomoses are divided into two modules and two stages. Module I was located on the upper side of the SPGJ line. Stage I surgery was performed for total laparoscopic SPGJ and Braun anastomosis combined with No. 4sb lymph node dissection. Module II was located inferiorly, and stage II surgery was offered for total laparoscopic subtotal gastrectomy with D2 lymphadenectomy (Figures 2B and 5B).

As a result, we observed the following advantages of MTLG: First, the incidence of post-operative complications was low, and operations could be completed using total laparoscopy to ensure less invasiveness, rapid post-operative recovery, and minimal abdominal adhesions. Second, SPGJ utilization: (1) Reduced the risk of bleeding from lesions caused by food stimulation; (2) Prevented the tumor from spreading to the gastrojejunal anastomosis; (3) Improved gastric emptying while maintaining endoscopic access to the region distal to the bypass; and (4) Obviated duodenal stump leaks. Third, it was conducive for SPGJ after No. 4sb lymph node dissection. Furthermore, patients only required subtotal gastrectomy with D2 lymphadenectomy in stage II surgery after conversion therapy to avoid anastomotic stomas, short gastric blood vessels, and splenic injuries caused by No. 4sb lymph node dissection. The anastomosis completed in the first stage continued to be used, and the two modules did not interfere with each other. Fourth, adding the Braun anastomosis to the gastrojejunostomy reconstruction could reduce the incidence of reflux gastritis. Fifth, even in the case of unsuccessful conversion, patients were able to eat soon after, and decreased post-operative morbidity, improved quality of life, and better prognosis after SPGJ were achieved[16].

CONCLUSION

Laparoscopic SPGJ combined with No. 4sb lymph node dissection is safe and effective for GOO. This procedure followed by chemotherapy and immunotherapy may be an effective treatment strategy before radical surgery.

FOOTNOTES

Author contributions: Shao XX and Xu Q contributed equally to this study. Shao XX and Xu Q contributed to writing-original draft of the manuscript; Shao XX, Xu Q, Wang BZ, and Tian YY involved in the writing-review and editing of the manuscript; Shao XX, Xu Q, and Tian YY were major in the conceptualization; Tian YY contributed to the project

administration and supervision; and all the authors have approved the final version of the manuscript.

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CASE REPORT

Small bowel diverticulum with enterolith causing intestinal obstruction: A case report

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Abstract

BACKGROUND

Small bowel diverticula are rare in clinics, and small intestinal obstruction caused by coprolites is rarer and difficult to diagnose early. The true incidence of these diverticula may be underestimated due to their clinical symptoms not differing from those of small bowel obstruction resulting from other causes. It is common in the elderly, although it can occur at any age.

CASE SUMMARY

This is a case report of a 78-year-old man with epigastric pain for 5 d. Conservative treatment does not effectively relieve pain, inflammatory indicators are elevated, and computed tomography suggests jejunal intussusception and mild ischemic changes in the intestinal wall. Laparoscopic exploration showed that the left upper abdominal loop was slightly edematous, the jejunum mass at the near Flex ligament was palpable, the size was about 7 cm × 8 cm, the local movement was slight, and the diverticulum was seen 10 cm downward, and the local small intestine was dilated and edema. Segmentectomy was performed. After the short parenteral nutrition after surgery, the fluid and enteral nutrition solution were pumped through the jejunostomy tube, and the patient was discharged after the treatment was stable, and the jejunostomy tube was removed in an outpatient clinic one month after the operation. Postoperative pathology: Jejunectomy specimen: (1) Small intestinal diverticulum with chronic inflammation, ulcer with full-thickness activity, and necrosis of the intestinal wall in some areas; (2) also see that the hard object is consistent with stone changes; and (3) the incision margin on both sides shows chronic inflammation of mucosal tissue.

CONCLUSION

Clinically, the diagnosis of small bowel diverticulum is difficult to distinguish from jejunal intussusception. Combined with the patient's condition, rule out

other possibilities after a timely disease diagnosis. According to the patient's body tolerance adopt personalized surgical methods to achieve better recovery after surgery.

Key Words: Small bowel diverticulum; Surgery; Complications; Case report

Core Tip: Small bowel diverticulum is clinically rare because it lacks specific clinical symptoms and has many complications. This case report presents a patient with a small bowel diverticulum with fecalith-causing intestinal obstruction diagnosed and treated by the Department of General Surgery of Jiangsu Provincial Hospital of Traditional Chinese Medicine.

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INTRODUCTION

Small bowel diverticulum disease is a rare disease in clinical practice, with an incidence of approximately 5%. Clinically, small bowel diverticula can be divided into two subtypes depending on their pathogenesis: Congenital and acquired diverticula of the small intestine. These in turn include Meckel's diverticulum (*i.e.*, distal ileal diverticulum), duodenal diverticulum and jejunal diverticulum[1]. Patients with small bowel diverticulum disease are usually asymptomatic, and the lesions are mostly noticed during radiological examinations or laparotomy for other abdominal disorders. Laparotomy is usually the gold standard for confirming small bowel diverticulum[2]. Symptoms such as bloating, epigastric pain, and nausea are sometimes present but ignored because they are not specific. When complications occur, patients may also develop diverticulitis, bleeding, stone formation, and secondary ileus[3].

CASE PRESENTATION

Chief complaints

Epigastric pain intercropping for 5 d.

History of present illness

This was a 78-year-old male patient with no obvious cause of epigastric pain, accompanied by sweating, occasional pantothenic acid belching, no nausea and vomiting, stomachache, irregular stools, and no melena. He visited Jiangsu Provincial Hospital of Traditional Chinese Medicine on September 22, 2022, and did not have any weight loss, changes in bowel habits, fever, or other symptoms in the past six months.

History of past illness

The patient had a history of appendix surgery and type 2 diabetes, and he had no history of a colonic diverticulum.

Personal and family history

The patient had no relevant personal or family history.

Physical examination

On September 23, 2022, the patient had left upper quadrant tenderness, no palpable mass, no rebound tenderness, or other signs of peritonitis. A digital rectal examination found no abnormal symptoms.

Laboratory examinations

The patient's hypersensitive C-reactive protein level was 2.87 mg/L, and the leukocyte count was 15.16 × 10^9/L.

Imaging examinations

On September 22, 2022, computed tomography (CT) of the whole abdomen showed that he possibly had a left upper quadrant jejunal intussusception (Figure 1A). On September 23, 2022, CT showed left upper quadrant jejunal intussusception and mild ischemic changes in the intestinal wall (Figure 1B).

FINAL DIAGNOSIS

Small bowel diverticulum with a fecalith causing intestinal obstruction.

TREATMENT

On September 23, 2022, laparoscopic exploration revealed no obvious exudation in the abdominal cavity, slight edema of the left upper abdominal intestinal loop, a jejunal mass near Qu's ligament, with a size of approximately 7 cm × 8 cm, local slight activity; the diverticulum was 10 cm distally; and there was obvious local small intestinal dilation edema. Jejunectomy anastomosis: A median incision was made into the upper abdomen, approximately 8 cm long, and the skin, white line, and peritoneum were separated to enter into the peritoneum layer by layer. The incision was placed into an incision protective sleeve. Breaking of the adhesions around the beginning of Qucker's ligament, separation and severing of the mesenteric vessels around the mass, ligation, and disconnection of the mesangium were performed to cut the small intestine approximately 15 cm below the lesion. After the small intestine was severed at Treitz's ligament, the stapler nail seat was placed, and jejunal side anastomosis was performed with a 25-tube stapler. The patency of the anastomosis was checked. A 4-0 Vijo line was used to strengthen the anastomosis and close the mesangium. Jejunocentesis catheterization was performed 30 cm below the anastomotic port; jejunostomy was performed, 3-0 sutures were used to suture the intestinal wall to form a 1 cm tunnel, and the sutures were suspended to the abdominal wall, allowing the jejunostomy tube to exit from the left upper quadrant.

OUTCOME AND FOLLOW-UP

After parenteral nutrition support was given for a short amount of time after surgery, the fluid and enteral nutrition solution were pumped through the jejunostomy tube, and the patient was discharged after stable treatment. The jejunostomy tube was removed one month after surgery. The postoperative pathology results were as follows: Jejunectomy specimens: (1) There was a small intestinal diverticulum with chronic inflammation, full-thickness inflammatory ulcers, and intestinal wall necrosis in some areas; (2) the quality of hard objects is consistent with stone changes; and (3) the resection margin on both sides shows chronic inflammation of mucosal tissue (Figure 2).

DISCUSSION

Acquired jejunal diverticulum is a pseudodiverticulum that invades only the mucosal layer and the submucosal layer, and it was first reported by de Bree *et al*[4]. It is more common in people in their sixties and seventies, and is seen more in men than in women. As in this patient, small bowel diverticula are usually multiple, and these diverticula provide a pocket for the stagnation of intestinal contents, leading to the formation of intestinal stones. Intestinal stones are rare and can be divided into true and pseudo stones according to their quality. Pseudo stones are formed by the accumulation of feces, fruits, and other exotic substances, while true stones are deposited by substances that digest the chyle layer.

The causes of intestinal stones are more complex and closely related to the patient's eating habits. Related studies have shown that the intake of persimmons, dates, hawthorn and other foods rich in tannic acid is an important cause of inducing fecalith intestinal obstruction; tannic acid and gastric acid form colloidal substances; and protein to form tannic acid protein can be mixed with food residues to form intestinal stones[5]. This patient had a history of diabetes, which can lead to autonomic lesions and reduce gastric emptying function, and it is also one of the important causes of intestinal fecalith formation[6]. In terms of diagnosis, patients with small bowel diverticular disease are usually asymptomatic. When complications occur, patients also show manifestations associated with complications. Diagnosis can be aided by ultrasound, CT, or small bowel enema[3]. Currently, contrast-enhanced CT remains the first choice for the diagnosis of small bowel diverticulum[7], but the diverticular presentation on CT is difficult to distinguish from the intestinal tube with fluid accumulation. Intestinal stones usually appear on CT as round or oval clumps at the site of obstruction and contain mottled gas that appears to be specific. However, small bowel stones can also present as gas-free

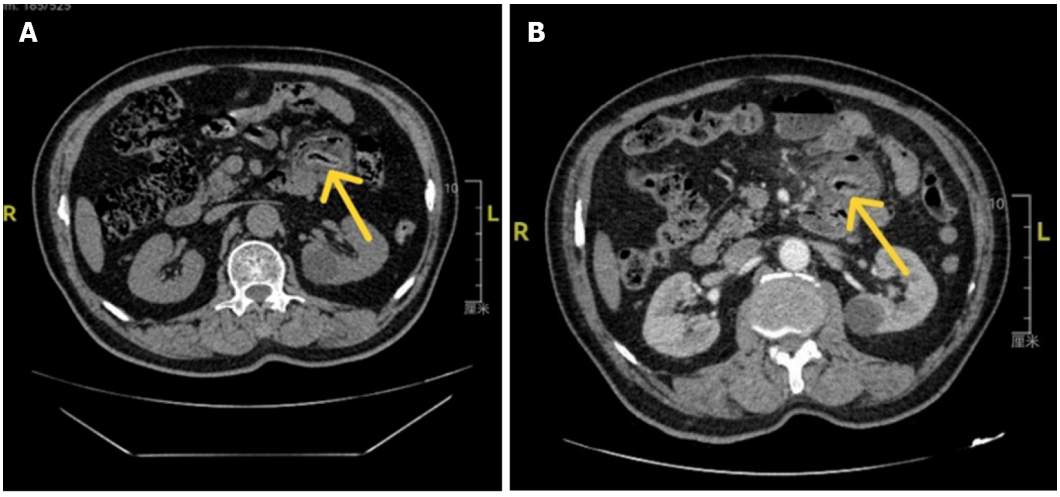

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Figure 1 Computed tomography image. A: 2022-09-22 non-scan computed tomography (CT); B: 2022-09-23 contrasted CT (arrow shows diverticular location).

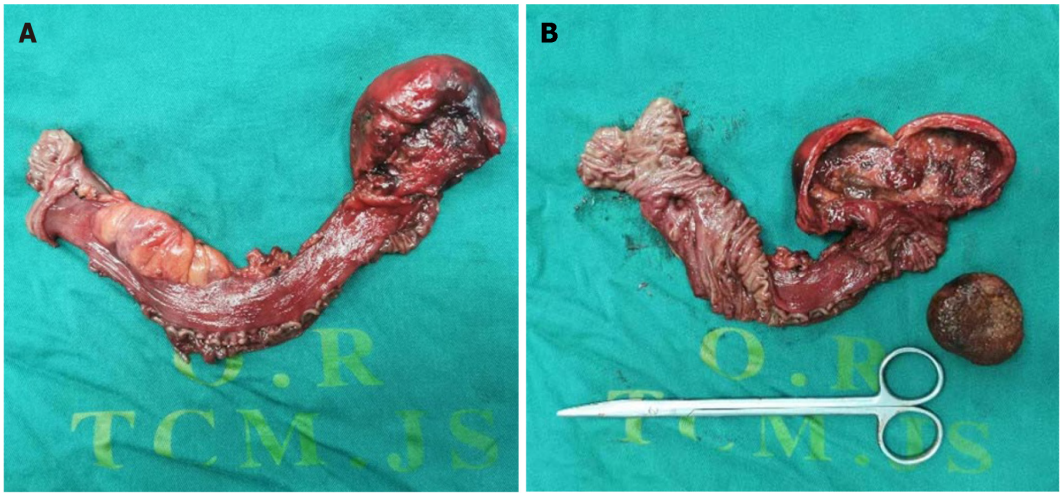

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Figure 2 Small bowel resection specimen. A: Small intestinal diverticulum about 7 cm × 8 cm × 3 cm; B: Intestinal stones are about 4.5 cm × 4.0 cm × 2.0 cm.

soft tissue masses that are difficult to distinguish from intussusception[3]. In this patient, chronic fecalith formation was caused by small intestinal diverticula, and the internal fecalith shadow and local loop edema made the CT imaging findings similar to those of intussusception. During intraoperative laparotomy, we consider that small intestinal tumors such as stromal tumors are more likely to be observed during a comprehensive operation due to local chronic inflammatory adhesions, edema of local intestinal loops, and solid manifestations of internal fecal stone filling. It was not until the surgical specimen was dissected *ex vivo* that the patient's mass was found to be a small intestinal diverticulum with local fecalith formation in the small intestinal lumen. The rarity and specificity of this case led to a misdiagnosis before surgery.

For treatment, patients with small bowel diverticular disease do not require any treatment in the absence of clinical symptoms, and conservative treatment should be considered when accompanied by diverticulitis. If conservative treatment is ineffective or accompanied by other complications, such as bleeding, obstruction, and perforation, surgery should be performed immediately. Small intestinal stones can be crushed and squeezed into areas of the intestine distal to the cecum so that they can pass naturally[8]. CT showed ischemic changes in the intestinal wall, and the patient required surgery to prevent bowel syndrome[9].

Due to the advanced age of the patient, long-term parenteral nutrition support is associated with complications such as catheter infection, liver damage, and metabolic disorders[10]. Moreover, advanced age is also a high-risk factor for anastomotic fistula, and the mortality rate of high anastomotic fistula is 21.4%[11]. Therefore, based on previous experience and Ojo *et al*[12] systematic reviews, enteral

IVF is safe and effective in improving the quality of life of patients. We placed a trans jejunostomy tube during surgery to pump fluid and enteral nutrition solution after surgery. As a result, patients can discontinue parenteral nutrition support as soon as possible and obtain a better and faster recovery after surgery.

In summary, the small intestinal diverticulum of this patient was accompanied by fecalith intestinal obstruction due to the special quality and size of the fecaliths. CT imaging and physical examination could not fully determine the quality, resulting in a misdiagnosis, and the diagnosis was not confirmed until after the autopsy specimen examination. In addition, the patient discontinued enteral nutrition support as soon as possible after surgery, and the method of pumping the nutrient solution through the jejunostomy tube was safer than long-term enteral nutrition support. Such means could be used as a common surgical method for elderly patients.

CONCLUSION

Clinically, small bowel diverticulum is difficult to distinguish from jejunal intussusception, and early diagnosis and surgery are the main means of appropriate management.

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FOOTNOTES

Author contributions: Wang LW and Chen P wrote and edited the original draft; Liu XX and Liu J provided a lot of help in the operation; Jiang ZW directed the writing of the manuscript; all authors have read and approved the final manuscript.

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