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REVIEW

Impact of anastomotic leakage on long-term prognosis after colorectal cancer surgery

Valeria Tonini, Manuel Zanni

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Abstract

Colorectal cancer (CRC) is one of the most common malignancies in the world. Despite significant improvements in surgical technique, postoperative complications still occur in a fair percentage of patients undergoing colorectal surgery. The most feared complication is anastomotic leakage. It negatively affects short-term prognosis, with increased post-operative morbidity and mortality, higher hospitalization time and costs. Moreover, it may require further surgery with the creation of a permanent or temporary stoma. While there is no doubt about the negative impact of anastomotic dehiscence on the short-term prognosis of patients operated on for CRC, still under discussion is its impact on the long-term prognosis. Some authors have described an association between leakage and reduced overall survival, disease-free survival, and increased recurrence, while other Authors have found no real impact of dehiscence on long term prognosis. The purpose of this paper is to review all the literature about the impact of anastomotic dehiscence on long-term prognosis after CRC surgery. The main risk factors of leakage and early detection markers are also summarized.

Key Words: Anastomotic leakage; Colorectal surgery; Colon cancer; Rectal cancer; Long term prognosis; Long term survival

Core Tip: Colorectal cancer (CRC) is one of the most common malignancies in the world. Despite significant improvements in surgical technique, postoperative complications still occur in a fair percentage of patients undergoing colorectal surgery. The most feared complication is anastomotic leakage. It negatively affects short-term prognosis, with increased post-operative morbidity and mortality, higher hospitalization time and costs. Moreover, it may require further surgery with the creation of a permanent or temporary stoma. While there is no doubt about the negative impact of anastomotic dehiscence on the short-term prognosis of patients operated on for CRC, still under discussion is its impact on the long-term prognosis. Some authors have described an association between leakage and reduced overall survival, disease-free survival, and increased recurrence, while other authors have found no real impact of dehiscence on long term prognosis. The purpose of this paper is to review all the literature about the impact of anastomotic dehiscence on long-term prognosis after CRC surgery. The main risk factors of leakage and early detection markers are also summarized.

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INTRODUCTION

Definition, incidence and classification

Anastomotic leakage (AL) is a major cause of postoperative morbidity and mortality after colorectal cancer (CRC) surgery. AL is a defect of the intestinal wall integrity at the colorectal or colo-anal anastomosis site (including suture and staple lines of neorectal reservoirs) leading to a communication between the intra- and extraluminal compartments[1]. However, there are several definitions of AL in literature and most studies define it using clinical signs (pain, fever, tachycardia, peritonitis, purulent or fecal drainage), radiographic findings (fluid and/or gas-containing collections), and/or intraoperative features (peritoneal effusion and ruptured anastomosis)[1,2]. The use of different definitions in clinical studies can partly explain the considerable variations in AL reported rates. The incidence of AL reported in different studies is highly variable (2%-19%) and certainly influenced first of all by the surgeon's experience and the emergency or elective surgical setting. It is also influenced by the site of the anastomosis: It is lowest for ileocolic anastomoses (1%-3%) and highest for coloanal anastomoses (10%-20%)[3-5].

AL has been divided into "early" and "late" depending on whether AL is diagnosed within or after 30 d after surgery[6]. In general, early AL manifests with severe peritonitis and it is mainly related to a technical error in performing the anastomosis, usually due to mal vascularization of the intestinal stumps or tension at the anastomotic site[7]. In contrast, late AL is often associated with long-standing pelvic abscess[8] and is due to preexisting conditions in patients, such as local sepsis, poor nutrition, immunosuppression, morbid obesity, and radiation exposure[9].

AL is also classified according to severity into grade A, B and C. Grade A is represented by AL that does not require active therapeutic intervention, grade B by AL that requires active therapeutic intervention but manageable without re-laparotomy, and grade C by AL that requires re-laparotomy[1].

RISK FACTORS

Several risk factors for anastomotic dehiscence following colorectal surgery have been identified over the years. They can be classified for convenience into preoperative, intraoperative, and postoperative [10].

Preoperative risk factors commonly reported in the literature include male sex[7], obesity[11], tobacco habit, alcohol consumption, an American Society of Anaesthesiologistscore of 3 or higher[6], and prolonged corticosteroid intake[12]. Tumor location, size and stage must be considered among the risk factors. Akiyoshi *et al*[13] reported that tumor localization in the rectum, rather than the colon, was independently predictive of AL development on multivariate analysis.

The AL rate was 10 times higher (20.6% *vs* 2.3%) when the anastomotic region was located within 5 cm of the anal verge[14].

Low anterior resection (LAR) involves surgery in an anatomically confined space and when tumor size and/or stage increases, intrapelvic manipulation becomes limited and rectal dissection more challenging. In a series of 154 patients with rectal carcinoma, tumor size ≥ 5 cm in diameter was associated with a 4-fold increased risk of leakage[15]. Zhu *et al*[16] found that tumors greater than 3 cm

in diameter, as well as TNM stage, were independently associated with leakage.

Intraoperative risk factors include: The surgeon experience (and hospital size)[7], the number of linear stapler firings[7], left colic artery ligation[17], emergency surgery (patients with peritonitis and/or bowel obstruction are at higher risk of postoperative adverse events)[18], operative time[19] and blood loss during surgery. Intra-operatively, it is also important to ensure good vascularization of the anastomosed bowel segments. Indocyanine green (ICG) fluorescence angiography may help in this evaluation. In a recent meta-analysis, an incidence of anastomotic dehiscence was observed in 3.8% of cases in the ICG group and 7.8% in the control group in which ICG was not used[20].

Postoperative risk factors are anemia, hypoalbuminemia, and late initiation of enteral nutrition[21].

EARLY DETECTION AND MARKERS

Early detection of AL is crucial to treat patients limiting negative effects. Baeza-Murcia *et al*[22] analyzed the accuracy of C-reactive protein (CRP) and procalcitonin (PCT) for early detection of AL and have found that CRP is more accurate than PCT on both postoperative day (POD) 3 and 5. According to this study CRP measured on POD 5 is the most useful test for early diagnosis of AL and that values above 9.1 mg/dL are indicative of anastomotic dehiscence.

In a recent meta-analysis by Yeung *et al*[23] a CRP cutoff level of 14.8 mg/dL at POD 3 had a sensitivity and specificity of 95%, while CRP cut-off levels of 12.3 mg/dL at day 4, 11.5 mg/dL at day 5, 10.5 mg/dL at day 6, and 9.6 mg/dL at day 7 had a sensitivity and specificity of 100% for anastomotic dehiscence.

According to Garcia-Granero *et al*[24] and El Zaher *et al*[25], PCT is also a very good predictor of anastomotic dehiscence, particularly from POD 5 or higher. The predictive power of PCT may also be enhanced in combination with CRP or white blood cell, or both (area under the curve 0.92, 0.92, 0.93, respectively)[25]. A recent meta-analysis by Xu *et al*[26] shows that PCT at POD 3 has potential clinical value in the early diagnosis of AL and has better diagnostic accuracy in patients undergoing laparoscopic surgery. Cut-off values are recommended in the range of 0.7-1.3 ng/mL to ensure accurate diagnosis and safe discharge. However, PCT is a valid predictor only for patients with major clinical losses confirmed by radiology and presenting with severe clinical signs and symptoms that require a change in therapeutic management and in most cases a reintervention. Cousin *et al*[27] conducted a meta-analysis and concluded that PCT does not add value to CRP in the diagnosis of AL.

It can be said that CRP and PCT at POD 5 have a high negative predictive value, which would allow early and safe discharge.

Tavernier *et al*[28] considered 5 criteria for safe early discharge after laparoscopic colorectal surgery: A CRP level of less than 15 mg/dL, absence of fever during the entire hospital stay (temperature < 38 °C), return of bowel function (flatus with or without stool), adequate pain control with oral analgesics (pain less than 5 out of 10 on a 10-point visual analog scale) and tolerance of a solid diet. The negative predictive value in ruling out an anastomotic leak was 98.4% for all 5 criteria combined. The false-negative rate was 13.3%.

RELATIONSHIP BETWEEN AL AND SHORT-TERM PROGNOSIS

AL affects the outcome of surgery, worsening the short-term outcomes and increasing the time and cost of hospitalization[29,30]. The mortality related was reported to be between 0.8% and 27%[31]. Mortality was higher after leak from a colonic anastomosis than after leak from a rectal anastomosis (43.8% *vs* 7.1%)[31]. Bertelsen *et al*[32] found in a multicenter study a 4-fold increase in 30-d mortality in patients with AL[32]. According to a Cochrane review, AL is associated with a perioperative mortality rate of 2% to 24% and high morbidity, with the risk of a definitive ostomy exceeding 25%[33]. Warps *et al*[34] found an overall AL rate of 4.8%, ranging from 4.0% (right hemicolectomy) to 15.4% (subtotal colectomy). AL was predominantly managed with reintervention, ranging from 81.2% of cases after transversectomy to 92.4% after sigmoid resection. After reintervention, the highest mortality rates were observed for transversectomy (15.4%) and right hemicolectomy (14.4%) and the lowest for sigmoid resection (5.6%) and subtotal colectomy (5.9%). The intensive care unit admission rate was 62.6% overall (range 56.7%-69.2%) and the stoma rate ranged from 65.5% (right hemicolectomy) to 93.0% (sigmoid resection).

RELATIONSHIP BETWEEN AL AND LONG -TERM PROGNOSIS

While the short-term consequences of AL are well known, its impact on long-term prognosis in CRC patients is still debated.

In the literature, the first authors to concern themselves with outcomes related to anastomotic dehiscence after resective surgery for CRC were Phillips *et al*[35] and Sauven *et al*[36]. In both cases, the parameter evaluated was local recurrence (LR). In the first study, AL did not appear among the significant risk factors for recurrence, while in the second, anastomotic dehiscence was associated with an increased rate of LR. In the same years, Amato *et al*[37] evaluated the association between CRC and AL by focusing exclusively on patients with rectal tumors operated with an anterior resection. In this study, AL did not influence the recurrence rate.

In 1991, Akyol *et al*[38] performed a study on patients operated for left colon or rectal cancer and demonstrated an important influence of AL on recurrence and cancer-specific survival (CSS) at 24 mo. The independence of the impact of dehiscence on outcomes from tumor stage was highlighted. This was the first study that analyzed local and distant recurrence separately and used multivariate Cox regression.

Two years later, a study published by Fujita *et al*[39] showed the impact of AL on LR and disease-free survival (DFS). DFS is significantly lower in the AL group for patients with Duke stage A and B cancers but not for C and D. The importance of this work also lies in the separate evaluation of subjects with colon and rectal cancer.

Petersen *et al*[40] studied the influence of leakage on LR, CSS, overall survival (OS) and postoperative mortality. AL influence only LR and CSS, confirming the previous findings of Akyol *et al*[38]. Branagan *et al*[41] reached similar conclusions in 2005. Further studies[42-44] showed a correlation between AL and higher 30-d mortality, lower OS and CSS.

Law *et al*[45] in 2007 found a significant association between AL and 5-year CSS, 30-d mortality and recurrence (local and systemic).

According to the study by Eberhardt *et al*[46], AL does not change the risk of recurrence and mortality for colon cancer, whereas it does for rectal cancer. The article also offers an assessment of OS, CSS, LR and overall recurrence for each stage, as well as an analysis of these outcomes at both 1 and 5 years after surgery.

According to Marra *et al*[47], AL significantly reduces OS without affecting the risk of recurrence, while other studies[48-58] have found an impact of leakage on OS, recurrence, and DFS. However, Katoh *et al*[50] evaluated only patients with stage II CRC and Breugom *et al*[54] only patients with stage I-III colon cancer. To be precise, Park *et al*[56] in 2016 found an effect of AL on OS and DFS only for patients with rectal cancer. Nachiappan *et al*[52] found a reduction in OS in patients with AL who required reoperation compared with subjects without AL. Ramphal *et al*[58] demonstrated that LR develops with the same frequency in symptomatic and asymptomatic dehiscence.

Krarup *et al*[59-60] identified in patients with AL an increase in distant recurrence (DR) and in mortality. However, there was no significant association with LR. Nordholm-Carstensen *et al*[61] and Ng *et al*[62] evaluated the impact of AL in patients with stage IV CRC. The 3-year survival rate is affected by dehiscence for both colon (18.7% *vs* 44.6%) and rectum (53.7% *vs* 73.3%).

The first meta-analysis on this topic was performed by Mirnezami *et al*[63] on 22 studies. It reported an association between AL and LR, DR and cancer-specific mortality.

The subsequent meta-analysis by Ha *et al*[64] evaluated 34 studies and divided the results into two categories. In the first group rectal anastomosis data were analyzed, and AL was associated with increased LR and reduced OS, CSS, and DFS. There were no significant effect on distant recurrence. In the second group colic anastomoses were analyzed and AL was associated with reduced OS and DFS and there was no correlation with local or distant recurrence.

The studies by Sammour *et al*[65] and Goto *et al*[66] also analyzed CSS. They showed a significant reduction in 5-year OS for patients with AL, without finding differences in LR, CSS and postoperative mortality (in rectal carcinoma, leakage affects only the latter). The second one documented instead a reduction in OS (80. 8% *vs* 90.3%) and CSS (89.6% *vs* 95.1%), an increase in LR and no correlation with distant recurrence.

A subsequent meta-analysis conducted in 2020 by Bashir Mohamed *et al*[67] demonstrated a lack of significant effect of AL on recurrences, however it reduced OS, DFS and CSS.

Recent articles on this topic were written by Stormark *et al*[68] and Kryzauskas *et al*[69]. The former concluded that leakage only after surgery for stage III CRC is able to reduce survival, whereas the latter demonstrated that AL impaired disease-free and OS in patients undergoing sigmoid and rectal surgery.

Regarding rectal cancer alone, the first data of the new millennium showed an increase in LR and a decrease in CSS[70,71]. Subsequent studies can be divided into 3 categories. In the first group, there are studies that supported the absence of an impact of AL on cancer outcomes such as OS, CSS, DFS, LR and DR[72-79]. The second group covers studies defining AL as an independent prognostic factor for reduced OS, CSS, DFS and increased recurrence[80-83]. In the third group, we can place studies[84-88] midway between the first two categories, as the study of Noh *et al*[88], demonstrating that AL is associated with increased LR and reduced DFS, whereas its relationship with OS and distant recurrence is not significant. These findings were confirmed in a recent study by Peltrini *et al*[89].

To the above groups, we must also add studies evaluating also perioperative mortality. Ptok *et al*[90] and Hain *et al*[91] found an impact of dehiscence on 30-d mortality, DFS, and LR, whereas Eriksen *et al* [92] and Bertelsen *et al*[32] found an increase in 30-d mortality, but without a significant increase in LR. Bertelsen *et al*[32] also noted the lack of reduction in OS and impact on distant recurrence[32].

Lim *et al*[93] in 2015 classified ALs into 3 categories based on the consequences: (1) Generalized peritonitis; (2) Localized peritonitis with or without abscess; and (3) Fistula. Oncologic outcomes were evaluated separately for each type and reduced OS and LRFS (LR-free survival) were identified. According to Boström *et al*[94], leaks only impact OS if they require intervention.

In 2022, Dulskas *et al*[95] evaluated AL in patients undergoing right colectomy for CRC and concluded that AL is a factor that negatively affects long term prognosis. In contrast, a Dutch retrospective study found that disease recurrence is not associated with AL after CRC resection[96].

Koedam *et al*[97], analyzing data from the COLOR and COLOR II studies, show that ALs after rectal cancer surgery are associated with an increased rate of LR and a decreased DFS at 5-year follow-up. DR and OS are not significantly affected. Regarding colon cancer surgery, no significant effect of AL on long-term oncologic outcomes was observed, presumably because of a relatively low leakage rate. Strengths of this study include the randomized, multicenter design of the two included studies[98,99] and uniform study protocol for perioperative care and follow-up to limit practice variability.

All studies on this topic are summarized in Table 1.

CONCLUSION

AL appears to be an independent risk factor influencing long-term oncologic outcomes after rectal cancer surgery. On the other hand, regarding colon cancer, the results are still extremely heterogeneous and unclear. Further studies on patients undergoing resection for CRC are needed to confirm the oncological impact of AL.

Based on these data, we would recommend more frequent follow-up for patients with AL after CRC cancer surgery.

Table 1 Summary table of all studies reporting on anastomotic leakage and outcomes after colorectal cancer surgery

Ref.	Study	Period	Cancer	Patients	LR	DR	OS	CSS	DFS	30 d mortality	Follow-up (mo)	Stage	Leak's definition	AL rate (%)	LR rate (%)	Multivariate analysis
Phillips *et al* [35], 1984	PCS	1976-1980	C + R	1627	Yes	No	No	No	No	No	≥ 60	I, II, III	NR	8	14	No
Sauven *et al* [36], 1989	RCS	1978-1981	C + R	53	Yes	No	No	No	No	No	36	I, II, III, IV	Clin, Rad	19	13	No
Amato *et al* [37], 1991	PCS	1981-1995	R	78	Yes	No	No	No	No	No	≥ 24	I, II, III	Clin, Rad	17	12	No
Akyol *et al* [38], 1991	RCS	1985-1989	C + R	167	Yes	Yes	No	Yes	No	No	25	I, II, III, IV	Clin, Rad	19	18	Yes
Fujita *et al* [39], 1993	PCS	1970-1991	C/R	980	Yes	Yes	No	No	Yes	No	NR	I, II, III, IV	Clin, Rad	3	3	Yes
Pakkastie *et al*[100], 1995	PCS	1981-1990	R	116	Yes	No	Yes	No	Yes	No	48	I, II, III	Clin, Rad	16	28	No
Petersen *et al* [40], 1998	RCS	1985-1995	C + R	331	Yes	No	Yes	Yes	No	Yes	32	I, II, III, IV	Clin	8	9	Yes
Merkel *et al* [70], 2001	RCS	1978-1996	R	814	Yes	No	No	Yes	No	No	90	I, II, III	Clin	11	14	Yes
Bell *et al* [101], 2003	PCS	1971-1991	R	401	Yes	No	No	No	No	No	≥ 60	I, II, III	Clin, Rad	13	12	Yes
Law *et al* [102], 2004	PCS	1993-2002	R	622	Yes	No	No	Yes	No	No	39, 6	I, II, III	Clin, Rad, Endo	6	10	Yes
Walker *et al* [43], 2004	PCS	1971-1999	C + R	1722	No	No	Yes	No	No	No	≥ 60	I, II, III	Clin, Rad	5	NR	Yes
Branagan *et al*[41], 2005	PCS	1991-1995	C/R	1834	Yes	No	Yes	No	No	No	≥ 60	I, II, III	Clin, Rad	4	10	Yes
Eriksen *et al* [92], 2005	PCS	1993-1999	R	1958	Yes	No	Yes	No	No	Yes	45	I, II, III	Clin, Rad	12	11	Yes
McArdle *et al* [42], 2005	PCS	1991-1994	C + R	2235	No	No	Yes	Yes	No	Yes	≥ 60	I, II, III	Clin, Rad	4	NR	Yes

Choi *et al* [44], 2006	PCS	1996-2004	C + R	1417	No	No	Yes	No	No	No	NR	I, II, III, IV	Clin, Rad	2	NR	Yes
Ptok *et al*[90], 2007	RCS	2000-2001	R	2044	Yes	No	No	No	Yes	Yes	40	I, II, III	Clin, Rad, Endo	15	6	Yes
Law *et al*[45], 2007	PCS	1996-2004	C + R	1580	Yes	Yes	No	Yes	No	Yes	46	I, II, III, IV	Clin, Rad	4	6	Yes
Jung *et al* [71], 2008	RCS	1997-2003	R	1391	No	No	Yes	Yes	No	No	40	I, II, III	Clin, Rad	3	10	No
Lee *et al*[79], 2008	PCS	1996-2004	R	1278	Yes	No	Yes	No	Yes	No	45	I, II, III, IV	Clin, Rad, Endo	4	NR	Yes
den Dulk *et al* [87], 2009	RCS	1987-2002	R	2726	Yes	Yes	Yes	Yes	Yes	No	71	I, II, III	Clin, Rad, Endo	10	9	Yes
Eberhardt *et al*[46], 2009	PCS	1979-2007	C/R	468	Yes	Yes	Yes	Yes	No	No	94	I, II, III	Clin, Rad	33	6	Yes
Marra *et al* [47], 2009	RCS	1991-2004	C	440	Yes	Yes	Yes	No	No	Yes	63	I, II, III	Clin, Rad	3	6	No
Bertelsen *et al* [32], 2010	PCS	2001-2004	R	1494	Yes	Yes	Yes	No	No	Yes	45	I, II, III	Clin, Rad, Endo	11	7	Yes
Kube *et al* [48], 2010	PCS	2000-2004	C	28271	No	No	Yes	No	Yes	Yes	23	NR	Clin, Rad	3	NR	No
Boccola *et al* [49], 2011	PCS	1984-2004	C + R	1576	No	No	Yes	Yes	Yes	No	67	I, II, III, IV	Clin, Rad	7	NR	Yes
Jörgren *et al* [72], 2011	PCS	1995-1997	R	250	Yes	Yes	Yes	Yes	No	Yes	≥ 60	I, II, III	Clin, Rad, Endo	9	8	Yes
Katoh *et al* [50], 2011	RCS	1990-2000	C/R	207	No	No	No	No	Yes	No	116	II	Clin, Rad	6	NR	Yes
Lin *et al*[80], 2011	PCS	1993-2003	R	999	Yes	Yes	Yes	Yes	Yes	Yes	≥ 60	I, II, III	Clin, Rad	5	5	Yes
Smith *et al* [73], 2012	RCS	1991-2010	R	1127	Yes	No	Yes	Yes	No	Yes	74	I, II, III	Clin, Rad	4	5	Yes
Smith *et al* [103], 2013	RCS	1992-2010	R	184	Yes	No	Yes	Yes	No	No	30	IV	Clin, Rad	7	13	Yes
Krarup *et al* [59], 2014	RCS	2001-2008	C	8589	Yes	Yes	Yes	No	No	No	≥ 60	I, II, III	Clin, Rad	6	10	Yes
Bakker *et al* [104], 2014	RCS	2009-2011	C	15667	No	No	No	No	No	Yes	NR	I, II, III, IV	Clin, Rad	8	NR	Yes
Jäger *et al* [81], 2015	RCS	2003-2010	R	108	No	No	Yes	Yes	Yes	No	70	I, II, III	Clin, Rad	18	NR	Yes
Ke *et al*[78], 2015	RCS	2007-2011	R	653	Yes	Yes	No	No	Yes	No	47	I, II, III, IV	Clin, Rad	6	4	Yes
Ebinger *et al* [74], 2015	RCS	1991-2010	R	584	Yes	Yes	Yes	Yes	No	No	62	I, II, III	Clin, Rad, Endo	11	17	Yes
Jannasch *et al* [84], 2015	PCS	2000-2010	R	17867	Yes	No	Yes	No	Yes	No	30	I, II, III	Clin, Rad	12	9	Yes
Nachiappan *et al*[52], 2015	PCS	2004-2013	C + R	1048	Yes	Yes	Yes	No	Yes	No	40	I, II, III, IV	Clin, Rad	9	2	Yes
Kang *et al* [82], 2015	RCS	2006-2009	R	1083	Yes	No	Yes	No	Yes	Yes	54	I, II, III	Clin, Rad	6	2	Yes
Kulu *et al* [85], 2015	RCS	2002-2011	R	570	Yes	No	Yes	No	No	No	56	I, II, III	Clin, Rad, Endo	9	4	Yes
Krarup *et al* [60], 2015	RCS	2001-2008	C	8597	No	No	No	No	No	Yes	≥ 60	I, II, III	Clin, Rad	6	NR	Yes
Lim *et al*[93], 2015	RCS	2007-2011	R	2510	No	No	Yes	No	No	No	33	I, II, III, IV	Clin	6	NR	Yes
Kim *et al*[53], 2015	RCS	2008-2013	C + R	809	Yes	Yes	Yes	No	No	Yes	NR	I, II, III	Clin, Rad	4	4	Yes

Espín *et al* [77], 2015	RCS	2006-2008	R	1181	Yes	No	Yes	Yes	No	Yes	60	I, II, III	Clin	9	5	Yes
Breugom *et al* [54], 2016	RCS	2006-2008	C	761	No	No	Yes	No	Yes	No	60	I, II, III	NR	5	NR	Yes
Park *et al* [56], 2016	RCS	2000-2011	C/R	10477	Yes	Yes	Yes	No	Yes	Yes	45	I, II, III, IV	Clin, Rad	3	2	Yes
Sammour *et al*[65], 2018	PCS	1988-2015	C/R	4892	Yes	No	Yes	Yes	No	Yes	60	I, II, III, IV	Clin, Rad	4	C = 5/R = 2	Yes
Noh *et al*[88], 2016	RCS	2006-2012	R	1258	Yes	Yes	Yes	No	Yes	No	50	I, II, III, IV	Clin, Rad	8	5	Yes
Nordholm *et al*[61], 2017	RCS	2009-2013	C/R	774	No	No	Yes	No	No	Yes	36	IV	Clin, Rad	9	NR	Yes
Goto *et al* [66], 2017	RCS	2007-2008	C	3364	Yes	Yes	Yes	Yes	No	Yes	96	I, II, III, IV	Clin, Rad	3	1	Yes
Hain *et al* [91], 2017	RCS	2005-2014	R	428	Yes	No	No	No	No	Yes	40	I, II, III, IV	Clin, Rad	28	8	Yes
Hüttner *et al* [51], 2018	RCS	2001-2014	C	628	No	No	Yes	No	Yes	No	60	I, II, III	Rad	4	NR	Yes
Voron *et al* [57], 2019	RCS	1990-2015	C	1025	No	No	Yes	No	Yes	No	60	I, II, III, IV	Clin, Rad	4	NR	Yes
Boström *et al* [94], 2018	RCS	2007-2016	R	6948	No	No	Yes	No	No	No	60	I, II, III, IV	NR	10	NR	Yes
Ng *et al*[62], 2018	RCS	2002-2015	C + R	843	No	No	Yes	No	No	Yes	150	I, II, III, IV	Clin, Rad	6	NR	Yes
Ramphal *et al* [58], 2018	RCS	2005-2015	C + R	1984	Yes	Yes	Yes	No	Yes	Yes	48	I, II, III, IV	Clin, Rad	8	2	Yes
Furnée *et al* [86], 2019	RCS	2011	R	746	Yes	Yes	Yes	No	Yes	Yes	42	I, II, III	Rad	14	4	Yes
Allaix *et al* [83], 2020	RCS	1998-2013	R	532	Yes	Yes	Yes	No	Yes	No	80	I, II, III	Clin, Rad	8	6	Yes
Zimmermann *et al*[55], 2019	RCS	2001-2014	C + R	1122	Yes	Yes	Yes	No	Yes	No	63	I, II, III, IV	NR	8	1	Yes
Jang *et al*[76], 2019	RCS	2000-2013	R	698	Yes	Yes	Yes	Yes	Yes	No	48	I, II, III	Clin, Rad	7	17	Yes
Crippa *et al* [75], 2020	RCS	2000-2013	R	787	Yes	No	Yes	Yes	Yes	No	64	I, II, III, IV	Clin, Rad	5	2	Yes
Kryzauskas *et al*[69], 2020	PCS	2014-2018	C/R	900	No	No	Yes	No	Yes	Yes	NR	I, II, III, IV	Clin, Rad, Endo	C = 5/R = 11	NR	Yes
Dulskas *et al* [95], 2022	RCS	2014-2018	C	488	No	No	Yes	No	No	No	48	I, II, III, IV	Clin, Rad, Endo	5	NR	Yes
Arron *et al* [96], 2022	RCS	2008-2018	C/R	88154	No	No	No	Yes	Yes	No	NR	I, II, III, IV	Clin, Rad	C = 5/R = 8	NR	Yes
Koedam *et al* [97], 2022	RCS	1997-2010	C/R	1832	Yes	Yes	Yes	No	Yes	No	60	I, II, III (No T4)	Clin, Rad	C = 3/R = 11	C = 15/R = 13	Yes
Peltrini *et al* [89], 2022	RCS	2011-2017	R	367	Yes	Yes	Yes	No	Yes	No	60	I, II, III, IV	Clin, Rad, Endo	17	23	Yes

AL: Anastomotic leakage; LR: Local recurrence; DR: Distant recurrence; OS: Overall survival; CSS: Cancer-specific survival; DFS: Disease-free survival; PCS: Prospective cohort study; RCS: Retrospective cohort study; C: Colon cancer; R: rectal cancer; C + R: Colon and rectal cancer analyzed together; C/R: Colon and rectal cancer analyzed separately; NR: Not reported; Clin: Clinical; Rad: Radiological; Endo: Endoscopic.

FOOTNOTES

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REVIEW

Application of indocyanine green in surgery: A review of current evidence and implementation in trauma patients

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Abstract

Background: Modern surgical medicine strives to manage trauma while improving outcomes using functional imaging. Identification of viable tissues is crucial for the surgical management of polytrauma and burn patients presenting with soft tissue and hollow viscus injuries. Bowel anastomosis after trauma-related resection is associated with a high rate of leakage. The ability of the surgeon's bare eye to determine bowel viability remains limited, and the need for a more standardized objective assessment has not yet been fulfilled. Hence, there is a need for more precise diagnostic tools to enhance surgical evaluation and visualization to aid early diagnosis and timely management to minimize trauma-associated complications. Indocyanine green (ICG) coupled with fluorescence angiography is a potential solution for this problem. ICG is a fluorescent dye that responds to near-infrared irradiation. Methods: We conducted a narrative review to address the utility of ICG in the surgical management of patients with trauma as well as elective surgery. Discussion: ICG has many applications in different medical fields and has recently become an important clinical indicator for surgical guidance. However, there is a paucity of information regarding the use of this technology to treat traumas. Recently, angiography with ICG has been introduced in clinical practice to visualize and quantify organ perfusion under several conditions, leading to fewer cases of anastomotic insufficiency. This has great potential to bridge this gap and enhance the clinical outcomes of surgery and patient safety. However, there is no consensus on the ideal dose, time, and manner of administration nor the indications that ICG provides a genuine advantage through greater safety in trauma surgical settings. Conclusions: There is a scarcity of publications describing the use of ICG in trauma patients as a potentially useful strategy to facilitate intraoperative decisions and to limit the extent of surgical resection. This review will improve our understanding of the utility of intraoperative ICG fluorescence in guiding and assisting trauma

surgeons to deal with the intraoperative challenges and thus improve the patients' operative care and safety in the field of trauma surgery.

Key Words: Trauma; Indocyanine green; Fluorescence angiography; Perfusion imaging; Fluorescence guided surgery; Acute care surgery

Core Tip: There is no consensus on the ideal dose, time, and manner of administration of Indocyanine green Fluorescence (ICG) as well as its indications in the acute surgical settings. There is a scarcity of publications describing the use of ICG in trauma patients as a useful adjunct to facilitate intraoperative decisions and to safely limit the extent of surgical resection. ICG has been increasingly used for surgical guidance as an intraoperative localizing technique, tissue perfusion evaluation, and imaging for anatomy identification and leaks as well as to provide targeted therapies. This review explored the potential utility of ICG in trauma surgery.

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INTRODUCTION

Hollow viscus injury is relatively uncommon[1,2]. Early diagnosis and timely management are essential to minimize the associated complications[3,4]. Identifying structures that need to be resected and spared during traumatic surgery is of paramount importance. Surgical resection of the damaged or devascularized bowel segments is often required. In daily practice, resection is guided primarily by the surgeon's ability to recognize and assess injured segments using conventional room light (white-light imaging), which relies on visual inspection. Resection is often followed by immediate bowel anastomosis.

Bowel anastomosis after trauma-related bowel resection may be associated with high leak rates[5]. Although the etiology of these leaks may be multifactorial, tissue perfusion at the ends of the resected bowel remains one of the most important determining factors for anastomotic leaks and strictures[5,6].

Technological developments have transformed human lives and medical practice in several fields. The ability of the bare eye of surgeons to determine bowel viability remains limited, and the need to obtain a more standardized objective assessment has not been fulfilled[7]. There is a need for tools to enhance surgical evaluation and visualization while eliminating the risk of damage to vital structures. Fluorescence angiography (FA) with indocyanine green (ICG-FA) is a potential solution to this perplexing problem[7] and is used worldwide to assess visceral perfusion[8]. The fluorescent signal obtained following intravenous ICG injection is thought to be proportional to blood flow. This allows surgeons to address poor regional perfusion that is otherwise challenging to detect intraoperatively[9,10]. Evidence in elective surgeries is available; however, reports on this technology in trauma are sparse [11].

ICG is a fluorophore dye with fluorescent properties that respond to near-infrared (NIR) irradiation. ICG has many applications in different medical fields and has been used for several decades to determine the cardiac output, hepatic function, and fluorescence-guided surgery (FGS). Examples include intraoperative localization techniques (*e.g.*, sentinel lymph node mapping or metastasis), tissue perfusion evaluation (for resection and anastomosis), imaging for vital structure identification (*e.g.*, cholangiogram, ophthalmic structures, and neurovascular structures), leaks, and targeted therapies[8,12-15].

ICG for real-time tissue perfusion assessment is feasible in open and minimally invasive surgeries (MIS). This has been proposed as a potential solution to the limitations of bowel viability assessments, particularly for MIS[16]. Fluorescence angiography helps surgeons assess bowel perfusion and viability for better resection margins, preserve normally perfused bowel, and minimize the potential for ischemia-related anastomotic leaks[17]. It has great potential to bridge this gap and enhance the clinical outcomes of surgery and patient safety[18].

Advances in imaging and intraoperative tools have impacted medical and surgical practices and may help resolve this precision surgery dilemma[19,20]. Adopting technology for surgical procedures and trauma care is a natural process. Despite these advances, surgical complications remain high, with implications for mortality, cost, and long-term complications; thus, the game is not over[8,11,21-24]. We

conducted a narrative review to address the utility of ICG in the surgical management of patients with trauma as well as elective surgery. This will guide and help trauma surgeons to deal with the intraoperative challenges, improve the patients' operative care, and improve the safety in trauma surgery.

INTRAOPERATIVE INDOCYANINE GREEN FLUORESCENCE GUIDANCE

Indocyanine green fluorescence (IO-ICGF) guidance is an evolving and exciting concept. The limitations of the human senses are well-documented: Sight and touch, which open the door for technological augmentation and support (guide) of the surgeon's visual and tactile localization. The need is amplified in MIS[16,17]. Evidence shows that surgeons' assessment of tissue perfusion concerning future anastomotic leaks has low sensitivity and specificity[25]. The potential benefits of such guidance include increased safety, reduced operating time, decreased need for second look operations, and decreased risk of complications such as leaks, infections, dehiscence, strictures, and reoperations. Proper resection margins are achieved by removing damaged tissue while protecting the normal tissue and enhancing adequate healing.

Residual ischemia on extrapolation resembles residual tumors after surgical resection; residual ischemia strongly predicts anastomotic failure, and residual tumors predict tumor recurrence. In the event of cancer, histopathological evaluation of the margins of frozen sections (FS) is a viable intraoperative solution for some tumors. Nonetheless, the literature discloses various FS-related problems, and the FS results differ by up to 15% from the permanent pathological data. However, solutions for residual ischemia are yet to be adequately addressed[26]. This problem can be exploited for the use of IO imaging, such as computed tomography/magnetic resonance imaging, as described in Neuro Surgical practice with apparent complexities of the cost, the needed space, logistics, and the potential interruption of operative time, which makes them non-practical solutions in many setups[27].

ICG, as an example of FGS, has been a strong competitor since 1948 in the search for a practical solution to the dilemma of perfusion assessment. ICG was first used in biological applications in 1956 and was authorized by the Food and Drug Administration (FDA) for diagnostic use in cardiocirculatory and hepatic functions[28].

Fluorescence angiography is a potential solution to the perfusion problem with reported high sensitivity, specificity, contrast, safety, low cost, ease of use, and seamless real-time imaging utility when it comes to interrupting operative processes[27,29]. ICG is the primary agent with a long history of use and high safety profile.

Owing to several merits, FGS has excellent potential for improving surgical practices and associated outcomes. It can direct IO image-guidance margin assessments and detect microscopic tumors, residual lesions, and tissue perfusion. Furthermore, it may aid in avoiding surgical complications, and the benefits of ICG may open new applications in various trauma-related subspecialities. Nonetheless, most surgeons continue to rely heavily on conventional visual and tactile cues and preoperative imaging to make resection decisions[19,20].

There is explosive interest in FGS research, fluorescence imaging devices, and system development and adoption. Nevertheless, a common problem is that evolving technology requires long standardization[18,30]. These arrangements include a wide range of technological issues, such as determining the appropriate agents (fluorophores or dyes), specific indications and clinical utility, acquiring supporting data and evidence, selecting the correct dose, and determining the optimal time for administration (whether before the operation, intraoperatively, or both). Nevertheless, the adoption of FGS is on the rise. The industry is actively introducing new probes and devices, including improved portable cameras with real-time imaging and easy non-distracting integration, enriching this attention and growing interest[18,31].

Furthermore, other technical aspects of this technology need to be addressed in the future: whether we need a subjective dose (individualized) is also a possible way to optimize the tissue dosage and effects; can we measure real-time quantity at the tissue level? Tissue-to-background ratio optimization is an ongoing discussion in the literature[32]. A recent consensus paper surveyed 19 international experts in FGS and reported strong agreement on its safety and effectiveness. Although it is no longer considered experimental, there is a considerable need to study ICG administration details (dose, concentration, route, and timing for optimal use)[18].

In many oncological practices, using NIR fluorescence imaging with ICG has become commonplace, both in open surgery and MIS, such as during staging laparoscopy for cancer[33]. This fact makes ICG the primary available dye with considerable literature support and wide use. The equipment available is designed to handle this agent and is one of the few FDA-approved agents.

Regarding MIS, Laparoscopic systems [high-definition (HD) cameras attached to a laparoscope with an NIR filter to detect fluorescence] were reported by Boni *et al*[34]. NIFICG allows real-time direct image assessment of tissue perfusion and vascularization related to anastomotic and stapler line leaks [35]. A full HD image 1 S camera, switching to NIR mode within a few seconds after the injection of ICG, provides real-time angiography of bowel perfusion before the anastomosis and another additional dose after establishing the anastomosis to confirm anastomotic perfusion with adequate vascularization.

TECHNOLOGY AND APPROVED FLUOROPHORES

The imaging step requires an NIR fluorescent agent (or fluorophore) and imaging system to excite and detect fluorophore signals within milliseconds. Two approved generic agents are used clinically by the FDA and the European Medicines Agency: ICG and methylene blue. Methylene blue is a weak fluorescent dye with low yield, which is why it is not commonly used. On the other hand, ICG is the most widely used fluorophore for this purpose for all the reasons mentioned above; historical, safe, and practical. There is increasing interest in the development of new tracers for expanding clinical applications[29].

CHARACTERIZATION, METABOLIZATION, ADMINISTRATION, AND OPTICAL PROPERTIES OF ICG

ICG is a water-soluble, anionic, amphiphilic tri-carbo-cyanine iodide dye probe with a molecular weight of 776 Da[36,37]. It binds to plasma proteins, has a short half-life (150-180 s), and is rapidly eliminated by hepatic clearance[37,38]. It was used in human health at the Mayo Clinic after it was launched as a dye in photography by the Kodak research facilities in 1955. The FDA approved it in 1959 as an indicator material (*e.g.*, photometric hepatic function diagnostics and fluorescence angiography) in circulatory, hepatic, cardiac output, and ophthalmic research. It is injected intravenously and depending on liver function, has a half-life of approximately 3-4 min in the body[8,38]. ICG sodium salt is often available in powder form and is soluble in a variety of solvents; 5% (depending on the batch) sodium iodide is typically added to improve its solubility[15]. ICG is limited to the vascular system after forming a strong bond with plasma proteins. ICG is only eliminated from the circulation by the liver and converted to bile[15]. The recommended dose is 2.5 mg before indulging in the anastomosis performance or 0.2-0.5 mg/kg[34,39,40]. The vasculature was visible within 60 s, and the anastomotic site was visible on NIR fluorescence imaging[41-43]. A second bolus of 2.5 mg, usually 15 min after the first injection, can be repeated if the signal begins to fade. Good perfusion supports completing the anastomosis as planned; furthermore, the check for perfusion(ischemia) should be performed before or after the anastomosis or both[44]. A similar dosage is also used for liver resection margins, where liver segment perfusion happens within one-two minutes (similar time frame). There are two routes: The peripheral veins and portal vein[45-47].

The lag in advancing the technique was related to the technical limitations associated with film-based photography. Since 1980, several technological challenges have been resolved, owing to the invention of new camera types, improved films, and higher-resolution photometric measurement tools. ICG is now routinely used in medicine, which has happened in the meantime. Since its early inception in the medical field, more than 5000 scientific papers on ICG in Surgery have been published worldwide[15].

ICG exhibited NIR absorption and fluorescence spectra. Both parameters varied significantly, depending on the concentration and solvent used[48]. ICG emits fluorescence between 750 nm and 950 nm and absorbs mostly between 600 nm and 900 nm[48]. The significant overlap between the absorption and fluorescence spectra caused ICG to absorb light significantly. The fluorescence spectra were highly diverse. It reaches its highest levels in water at 820 nm and in blood at approximately 830 nm[48]. ICG becomes a fluorescent (or light-emitting) form of luminescence upon excitation with a specific wavelength of light (about 820 nm) in the NIR spectrum.

Furthermore, NIR light (700-900 nm) is more valuable than visible light, as it allows for up to 10 mm of tissue penetration, provides maximum tissue contrast because auto-fluorescence is not observed, and maximizes signal-to-background ratios[49]. The emitted signal can be detected even within deep structures because it is transmitted through the tissue. This feature allows for less invasive real-time imaging of vessels and lymphatic ducts inside organs during surgery[50,51]. NIR ray illumination of ICG generates NIR fluorescence, permitting real-time transcutaneous intraoperative visualization of structures, such as superficial lymphatics and vessels. Merging these signals with normal RGB (red, green, and blue) color videos facilitates anatomical orientation, recording, and analysis.

Several NIR fluorescence imaging devices have been developed for intraoperative clinical use. Despite differences in the technical parameters, all these devices offer the surgeon an image of the NIR fluorescence signal[52]. Color imaging using imaging systems such as the HyperEye Medical System can simultaneously detect NIR rays under ambient light with outstanding diagnostic precision[53].

Literature on ICG use in trauma is limited, and our search identified only a few reports. The first is a recent case series demonstrating the utility of this technique in guiding anastomosis after post-traumatic damage-controlled resection. In one case, it led to further resection; in the other two, it assured good perfusion and permitted anastomosis without subsequent leaks[54].

Secondly, a retrospective study by Yamaguchi *et al*[11] explored the use of ICG NIR fluorescence to reduce postoperative complications in operative cases of mesenteric and bowel injuries. They concluded that ICG NIR tended to be associated with fewer complications after traumatic damage, regardless of the need for resection. This procedure is easy and quick. However, the study had several limitations. The authors called for randomized controlled trials to explore this technology for its routine use in

stable patients[11]. Unfortunately, in the setup of trauma, recruitment would be very challenging.

Furthermore, Aggarwal *et al*[55] reported a case of ICG FA guiding the resection of post-traumatic bowel ischemic ileal strictures. It provides real-time objective perfusion assessment to show the length of the ischemic segment to be resected.

Despite the availability of few reports (even small case series), Smyth *et al*[56] commented on the use of ICG in trauma settings to predict anastomotic leaks considering it a very new and promising concept [54,56].

SAFETY AND ADVERSE EVENTS ASSOCIATED WITH ICG

ICG has been used successfully in clinical research for over 50 years, has been shown to have a favorable safety profile, and is rarely associated with adverse reactions. ICG is very safe, with rare cases of anaphylaxis and caution regarding potential cross-reactions in patients with iodine sensitivity[57]. It has a long history of use, and a high safety index with rarely reported allergies (1:10000) supports this growing interest[28,37]. The intestinal mucosal membrane does not absorb ICG, and therefore, its toxicity is minimal. It is microsomal digested in the liver and eliminated by the liver and bile ducts. There are risks associated with administration during pregnancy[58].

It has been understood that ICG breaks down into harmful waste products when exposed to UV radiation, producing a multitude of as-yet-unidentified compounds[59,60]. In one of every 42000 instances, people experienced minor side effects, including sore throats and heat flashes[58,59]. Anaphylactic shock, hypotension, tachycardia, dyspnea, and urticaria were only seen in a few instances; the risk of severe side effects increases in patients with chronic renal impairment[58,60].

THE NEED FOR ICG IN TRAUMA SURGERY

Anastomotic leakage is a perplexing and frequently clinically challenging issue in elective and emergency surgeries with significant morbidity and mortality. Hypoperfusion near resection margins is thought to be a powerful indicator of anastomotic failure and subsequent leakage[5]. Gross surgical assessment is the gold standard for perfusion (vascularity) assessment[11]. This assessment involved visual inspection, palpation of the mesentery, and intraoperative ultrasound assessment. Naked eye assessment is limited, whereas palpation and ultrasound assessments may not be an option for MIS[25]. There is an urgent need to augment perfusion assessment using a simple and affordable tool without interrupting the flow of the surgery[8], and it can also be applied for MIS.

The merits of Intraoperative NIR fluorescence or simple fluorescence imaging include high contrast, low cost, safety (no ionizing radiation, low incidence of allergic reactions), ease of use, high sensitivity, and specificity[27,31,61], and the MIS option make it the best available solution.

Along with other oncological surgical benefits, such as lymph node mapping and tumor tissue identification, intraoperative vascularity assessment may increase the extent of resection, shorten the surgical time, protect viable tissues, lessen the need for second-look surgeries, and identify vital structures. As a result, there has been growing acceptance in recent years. Our literature review found that tissue perfusion adequacy is the primary determinant of visceral tissue viability[62] and is the main reason for its use during trauma. Theoretically, all the other reported uses are potential areas for use in trauma surgery, with only a few supporting reports.

The recent clinical trials on the use of ICG in trauma and surgery

Table 1 summarizes most of the concurrent clinical trials addressing the utility of ICG in trauma (n = 18) and general surgery (n = 13), and most of the latter was for cancer surgery. Moreover, Figure 1 illustrates the different utilities of ICG that also can be used as an algorithm for bowel injury management.

THE USES OF ICG IN TRAUMA

The use of ICG in trauma surgery is primarily associated with anatomical identification (visualization of vital structures). Examples include the cystic duct, ureters, nerves, vessels (angiography), and thoracic ducts (lymphography)[11]. Every operation has the unique risk of causing inadvertent harm to a neighboring vital structure. Effective intraoperative procedures are required to locate and safeguard structures. Based on their clearance characteristics, fluorescence imaging with ICG can identify and map the biliary tree, cystic artery, and ureter *via* different routes of administration[8].

Biliary mapping/leak detection after DCS in severe liver injuries (fluorescence cholangiography)

This technique has not been reported to be used in trauma patients; however, it has been extensively

Table 1 Recent clinical trials for indocyanine green fluorescence use in trauma and surgery

Trial title	Subject/field	Status
ICG fluorescence imaging in trauma patients	Bone/soft tissue perfusion in fracture patients and surgical site infection	Completed
ICG fluorescence imaging in open fracture trauma patients	Open extremity fracture	Recruiting
ICG 24 h Prior to operative treatment of orthopedic infection	Bone trauma and soft tissue infection	Active, not recruiting
The role of indocyanine green angiography fluorescence on intestinal resections in pediatric surgery	Intestinal resection margins during elective and emergency pediatric surgeries	Completed
ICG fluorescence imaging in lower extremity amputation patients	Lower extremity amputation in and trauma	Recruiting
ICG fluorescence imaging in post-traumatic infection	Trauma injury	Recruiting
Feasibility and usability of intraoperative fluorescent angiography with indocyanine green in penetrating abdominal trauma	Abdominal trauma	Completed
Non-invasive measuring of cerebral perfusion after severe brain injury with near-infrared-spectroscopy and ICG	Subarachnoid hemorrhage, intracerebral hemorrhage, TBI	Recruiting
Dynamic contrast-enhanced fluorescence arthroscopy of meniscus pilot	Knee injury	Recruiting
ICG 24 h prior to operative treatment of orthopedic infection	Trauma injury, infection	Active not recruiting
A study assessing circulation around surgical incisions at the time of laparotomy closure	Laparotomy	Completed
Application	Fractures, comminuted, surgical wound dehiscence, necrosis	Terminated has results
NIRST and ICG-based perfusion imaging in acute compartment syndrome	Compartment syndrome lower limb, forearm	Recruiting
ICG and SPY imaging for assessment of burn healing	Burns	Completed
NIR arthroscopic fluorescence angiography of menisci	Meniscus rupture	Not yet recruiting
Detection of cerebral ischemia with a non-invasive neurometabolic optical monitor	TBI, ischemic stroke, intracerebral hemorrhage	Completed
A new multi-parameter neuromonitoring system to save patients' lives in stroke and brain injury	Subarachnoid hemorrhage	Completed
Pilot study to assess the use of spy elite for assessment of amputation healing	Wound healing lower extremity amputation	Completed
Near-infrared fluorescence with indocyanine green for identification of sentinels and parathyroid during thyroidectomy	Thyroid cancer	Unknown
Near infrared fluorescence imaging with ICG	Lung cancer	Completed
A study of perfusion of colorectal anastomosis using FLAG-trial	Colorectal cancer	Completed
Near-infrared fluorescence imaging as a supportive tool for localization of deep infiltrating endometriosis during laparoscopy	Endometriosis	Completed
Prospective evaluation of near-infrared fluorescence imaging use as a supportive tool in deep infiltrating endometriosis surgery	Endometriosis	Completed
NIF-guided ramie using ICG *vs* OTE feasibility randomized controlled trial	Esophageal cancer	Recruiting
Falcon: A multicenter randomized controlled trial	Cholecystitis	Unknown status
Quantitative ICG fluorescence angiography in colorectal surgery	Colorectal cancer	Recruiting

Effect and long-term outcomes of indocyanine green fluorescence imaging method *vs* modified inflation-deflation method in identification of intersegmental plane	Lung cancer	Recruiting
Intraoperative ICG fluorescence angiography in colorectal surgery to prevent anastomotic leakage	Colorectal cancer	Not yet recruiting
Synapse 3D with intravascular ICG	Lung cancer	Not yet recruiting
The role of ICG fluorescence imaging on anastomotic leak in robotic colorectal surgery	Colorectal diseases	Unknown status
ICG molecular fluorescence imaging technique using in diagnosis and treatment of primary liver cancer	Liver cancer	Recruiting

Adopted from: https://clinicaltrials.gov/ct2/results?cond=indocyanine+green+fluorescence+clinical+trials&term=&cntry=&state=&city=&dist= & https://clinicaltrials.gov/ct2/results?cond=Indocyanine+Green+%28ICG%29+Fluorescence+in+trauma&term=&cntry=&state=&city=&dist= & https://clinicaltrials.gov/ct2/show/NCT04245111; https://clinicaltrials.gov/ct2/results?cond=Trauma&term=ICG&cntry=&state=&city=&dist=. Accessed on 11 January 2023. ICG: Indocyanine green; NIR: Near-infrared; FLAG: Fluorescence angiography; TBI: Traumatic brain injury; NIRST: Near-infrared spectroscopic tomography; OTE: Open transthoracic esophagectomy.

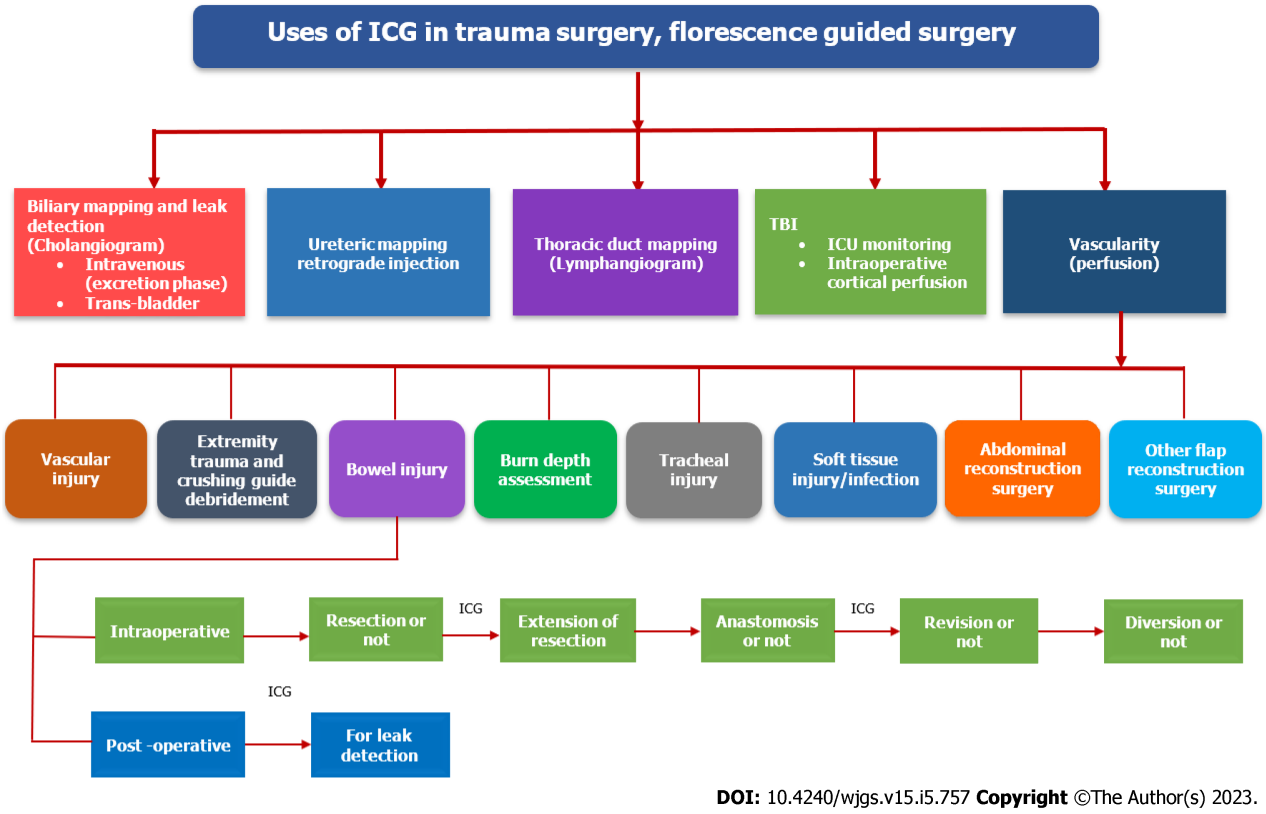

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Figure 1 Utility of indocyanine green in trauma and surgery. ICG: Indocyanine green; TBI: Traumatic brain injury.

studied and utilized in biliary surgery. The literature has shown no agreement on dosage and time; the biliary in elective should be done roughly 5 h beforehand for the best contrast, and mapping may start as soon as 30 min after the IV injection and can be repeated[52]. This is a potential limitation in emergency setup and trauma; though intra-gall bladder injection is a feasible alternative route; no substantial evidence is available[63]; although it may be used as an alternative to other cholangiogram techniques such as traditional trans-cystic or methylene blue in cases when it is necessary to rule out bile duct damage or bile leaks after penetrating trauma or during second-look laparotomy for serious liver injuries. If identified, the leaking duct should have been overlooked. No consensus on the optimal dose was reached in published literature; however, a dose of 5 mg was injected 3-7 h before incision in elective cases, but even shorter intervals were described, with no significant practical differences[52,64].

Ureteric mapping using ICG

The use of ureteric mapping is less widespread than other available agents, such as methylene blue or the newer ZW800-1, a novel dye exclusively secreted by the kidneys[62]. Santi *et al*[65], in a recent report

on the use of ICG for laparoscopic colorectal resections, commented on the avoidance of iatrogenic ureteric injuries through injection of the dye through the urinary catheter to identify the ureter in difficult dissection due to adhesions when the tumor is tightly attached to the ureter; the ICG solution was retrogradely injected through a ureteric catheter. Siddighi *et al*[66] reported 10 cases of retrograde ICG injection using a 6F ureteral catheter, allowing ureteral identification in colorectal, urological, and gynecological surgeries. The literature reflects the search for renally excreted fluorophores that permit non-invasive ureteric visualization. Mahalingam *et al*[67] reported UreterGow-11 as the most promising, with near-exclusive renal excretion and observed fluorescence for more than 12 h with optical and biodistribution characteristics. Once again, we might infer a possible use in situations of challenging trauma exploration with retroperitoneal and pelvic hematoma to identify these structures and to attempt to safeguard them.

ICG for thoracic duct in chylothorax

Transthoracic esophagectomy may result in a dangerous complication called chylothorax. It hinders oral intake, lengthens hospital stay, and is detrimental to overall survival[68]. Additionally, a thoracic duct (TD) lesion decreases body fluids and albumin, which causes hypovolemia1 and depletes T-cells[69]. Even with a high-definition thoracoscopy, intraoperative TD identification is often tricky. The best preventative approach to stop lesions is precise intraoperative diagnosis of TD. However, it is often tricky to identify the TD route or leaking location intraoperatively[70]. The same report commented on the intraoperative use of ICG with NIR fluorescence during minimally invasive esophageal surgery as an emerging approach for assessing gastric conduit perfusion. Vecchiato *et al*[70] percutaneously injected ICG (0.5 mg/kg solution) in the inguinal nodes of 19 patients undergoing MIS esophagectomy. The rationale for this was to identify the duct. The prone position was used before the thoracoscopy. The TD was determined after a mean of 52.7 min from injection time. No postoperative chylothorax or adverse effects of ICG green were observed. This study concluded that it is simple, effective, and not time-consuming and may become a new standard to prevent postoperative chylothorax[70].

Other case reports have described the inguinal injections of indocyanine green. Controlling postoperative leaks allows easy visualization of lymphatic leakage points during minimally invasive video-assisted thoracotomy (VATS). A potential trauma application is in cases of traumatic chylothorax, a rare entity that is difficult to control[71].

Jardinet *et al*[72] described a technique to facilitate thoracic duct identification and ligation control when required during robot-assisted esophagectomy. Lymphangiography-guided injection of indocyanine green into the right groin of a patient in the left-lateral position. Coratti *et al*[73] further simplified the complex intranodal injection of ICG subcutaneously 12-18 h before surgery compared with the operator-dependent United States-guided procedure. There have been no reports of trauma; however, extrapolation represents a potential use of traumatic chylothorax to identify and control leakage from the duct during operative management, whether open or minimally invasive approaches like VATS.

ICG in traumatic brain injury

Traumatic brain injury (TBI) pathophysiology of TBI is primarily related to the structural integrity of the brain. Multimodal monitoring is gaining popularity in the critical care of patients with TBI. ICG-NIR fluorescence has been used for TBI treatment. Although ICG has been described in ophthalmic studies for a long time[28], ICG and other fluorescent dyes have not been used in emergency neurosurgical interventions and traumatic brain injuries in contrast to elective tumor resections[74].

Although ICG is currently a research technique under study with limited clinical applications to meet numerous necessary characteristics, head injuries represent a possible application area. Potential clinical applications of NIR spectroscopy with ICG for non-invasive bedside continuous neuromonitoring include benefits in terms of logistics, radiation exposure, and cost. It can help measure brain perfusion and blood-brain barrier integrity in a critical care setup; however, several limitations exist. One of them is that the available devices do not correlate with invasive techniques for ischemic episodes, which is a significant drawback[75].

Kamp *et al*[76] used intraoperative ICG cortical perfusion assessment to predict long-term severe head injuries and short-term outcomes. This small retrospective study was based on using ICG FA to monitor regional cerebral blood flow during decompressive craniectomies. Microscopic add-on tool to assess ICG-induced Fluorescence. Ten patients underwent a standard surgical procedure and fluorescence assessment immediately after decompression. The parameters were correlated with 3-mo outcomes (favorable or unfavorable based on the Glasgow Outcome Scale and modified Rankin Scale). The authors concluded that the ICG-derived fluorescence curve was different in unfavorable patients. Fluorescence reflects underlying increased ICP, capillary leaks, and venous congestion, which are common pathophysiological changes in the body in response to severe TBIs.

This technology can potentially delineate outcomes if more extensive studies are conducted, and the heterogeneity of patients can be mitigated[76]. It is not currently a type of surgical guidance, experimental neuromonitoring, or exploratory prognostic tool to predict functional outcomes. The use of ICG-NIR technology in all stages of TBI treatment appears promising. It can be used to identify clinically important biomarkers from patients and provide more information about their comprehensive

physiological state.

Assessment of vascularity post-trauma (tissue perfusion)

The Intraoperative evaluation of tissue perfusion in patients with peripheral artery disease or vascular injury is crucial for predicting wound healing or symptom improvement. Currently, there are no commonly accepted standards for monitoring intraoperative tissue perfusion[77].

Tissue perfusion is critical for determining the return of normal function and post-injury healing. Decreased perfusion results in ischemia and contributes to secondary damage and healing failures. Identifying hypoperfusion at one or both bowel segments to be anastomosed dictates the broadening of resection margins and the need for new anastomosis or revision[78]. This information can also inform decisions to create a protective stoma for challenging and risky anastomoses. Simply put, it is probably the most important application in general and trauma to assist in intraoperative decision-making. The ICG-based imaging system was developed to examine the most recent degree of necrosis, capillary perfusion inside the tissue in question, and real-time arterial blood flow[77]. With the passage of the fluorophore in tissues after peripheral injection, illumination of the tissues under assessment generates fluorescence signals that correlate with the microvascular flow, that is, perfusion.

Bowel injury: As previously mentioned, anastomotic failures and leaks are among the most frequently challenging clinical problems after the restoration of resected bowel continuity[5,6,79,80].

The current standard of care supports intraoperative clinical evaluation of anastomotic perfusion by operating surgeons. Observing the color of the bowel, bleeding at the borders, and peristalsis of the segment are examples of visual and tactile feedback used in the subjective processes. Which is still a blind process with interobserver variability among surgeons; Furthermore, in traumatic cases, the naked eye is limited in appreciating the extent of blunt damage to the bowel, and it is mesentery and blood vessels; palpation is limited and is not an option in minimally invasive surgical options[25,31].

Historical techniques have been described; however, owing to their limitations, many have failed in terms of popularity and practice. Traditional intraoperative imaging (non-optical): These systems are costly, complex, space-demanding, and interrupt the operative flow, which makes them non-practical and available only in a few centers[81].

IO fluorescence imaging has many advantages that support its practical value in helping with visualization and providing surgeon guidance (*e.g.*, surgical GPS). As mentioned, it has many benefits, such as high contrast, sensitivity, specificity, low cost, user-friendliness, and absence of ionization, and thus, a high safety profile. Therefore, these applications have been widely investigated[27,29-31,82].

Literature reflects an increase in the use of this technology to guide resection and anastomosis to solve this issue by reducing the incidence of leaks and their sequelae related to fistula formation, reoperation, permanent stomas, bowel dysfunction, wound-related complications, stricture formation, quality of life, and mortality. It appears to be a reliable predictive tool to address the need to reduce anastomotic leaks in cancer-related resection of the colon, rectum, and other GI locations[5,82,83].

Arezzo *et al*[84], in a recent systematic review and individual participant database meta-analysis, assessed the effectiveness of ICG NIR intraoperative imaging in determining anastomosis perfusion in rectal cancer surgery and concluded that it has the potential to reduce the risk of anastomotic leaks compared to standard practice, independent of other factors such as sex, age, BMI, and anal border distance. In addition, more extensive, prospective, and randomized studies on this topic will help determine whether the occurrence of AL may be decreased by the routine use of ICG fluorescence imaging during surgery for rectal cancer[84].

ICG fluorescence blood flow speed in the gastric conduit wall can predict anastomotic leakage after esophagectomy, and microvascular perfusion of the capillary vessels of the gastric conduit may be impaired by systemic atherosclerosis. Why is ICG a perfect candidate for perfusion imaging[85]? This could be because it binds to plasma proteins and thus remains intravascular after the IV injection. Many reports on the use of ICG in esophagogastric and colorectal anastomoses, often after selecting the anastomotic site, help determine the right site with an influence site change between 3.7%-40.0%. Also reported on decreasing the anastomotic leak rate; in a systematic review, Degett *et al*[86] reported a decrease from 8.5% to 3.3% in the ICG group. In an earlier article, Campbell *et al*[87] reported a drop in the leak in the esophagus from 20% to 0%. Nevertheless, others reported no significant difference; even after a site change of 5%, the leak did not change significantly in a retrospective colorectal analysis[88]. This feasible technique can be conveniently obtained with minimal added time to the operations[89].

Extremity trauma, guide debridement, and decision on wound closure: Another potential application is to guide vital tissue and perfusion assessments in crushed limbs and combined vascular and orthopedic injuries to the extremities and infected wounds.

The surgical goal was timely and meticulous debridement was performed. ICG can help surgeons interpret the local circulation (perfusion) and demarcate debridement zones (identify necrotic devitalized tissues, both soft and bony). The wound (tissue) status is dynamic and may change over time. Factors such as aggressive debridement, infection, and local complications, may have contributed to this finding. Nevertheless, it remains an excellent area for bedside technique utilization. There are few reports of orthopedic and vascular trauma and other surgical wounds[90].

In addition, it can potentially guide decisions regarding wound closure and predict smooth healing, which might be an issue in some traumatic injuries, especially after angioembolization. These cases are challenging because of the double hits of the original trauma and ischemic tissue injury. Controlling bleeding by interventional radiology embolization or surgical ligation often results in collateral damage; the second hit is ischemia and extensive tissue necrosis[77,91]. Michi *et al*[92], in a recent systematic review regarding the use of ICG to assess bony perfusion, concluded that studies and evidence were limited and more clinical studies are needed.

Endoscopic anastomotic assessments such as tracheal anastomosis have potential clinical applications. In a prospective study, Schweiger *et al*[93] reported the feasibility of ICG perfusion assessment during bronchoscopy for elective cases and was theoretically feasible in selected post-traumatic cases.

War-related traumatic soft tissue and orthopedic injuries: One known challenge in high-energy war-related injury mechanisms, such as blast and ballistic injuries, is determining the viability of soft and bony structures in heavily contaminated fields. This is further confounded by the evolving and secondary infection-related necrosis. Green *et al*[94] reviewed and illustrated the use of IO fluorescence angiography for case series of war-related trauma. He reported the ability of this adjunctive tool to critically and rapidly assess traumatized tissue perfusion to avoid near misses, morbidities, and perfusion-related problems, by objectively permitting effective surgical modifications and enhancing clinical outcomes. Nineteen percent (35 patients) required operative modifications for better-perfused tissues; nine patients used NIR ICG for bowel perfusion[94].

Reconstructive surgery: In cases where tissue perfusion is a concern and clinical and physical assessments are unclear, ICG angiography can be a beneficial tool (adjunct) for serving hands and reconstructive surgeons. ICG real-time angiography visualizes contemporary tissue physiology and enhances decision-making during crushing and traumatic avulsions. The flow to digit tips is a particulate example where small-vessel spasms (common and proper digital vessels) confound the clinical assessment. Ghareeb *et al*[95] described three cases in which this utility proved to be of great help (two were traumatic, while the third was a case of Reynaud's ischemia): Injection of 5 mL dye solution with a 10cc NS flush. At the same time, the tissues of concern were centered on the device's screen. The device was activated, the initial fluorescence test of the arterial inflow was followed, and the scan was repeated for 10 min to check for venous outflow and congestion. A repeat is feasible within 10-15 min, and data can be stored, allowing comparison with normally perfused tissues.

Moreover, the percentage of fluorescence helps quantify the perfusion adequacy. These findings can help salvage decisions and attempt revascularization, replantation, or conservative amputation[95]. Mothes *et al*[96] modified ICG angiography treatments and predicted failure in a superior manner to traditional clinical indicators (capillary refill, turgor, bleeding, and temperature)[93]. Along with the guidance of free flaps in identifying perforators in the abdomen, thigh, and forearm to facilitate flap creation and predict flap necrosis and loss[96-98].

Similarly, lower-limb trauma and vascular injury applications are also of great interest because the convenience of quickly repeating ICG angiography compromises circulation both during surgical exploration and postoperatively compared to traditional angiography[99]. This versatility provides clinicians with an advantage in terms of tissue perfusion and viability. It permits a precise surgical plan in complex situations and injuries, and consent and counseling can be performed in collaboration with an awake patient[100,101].

These advantages have also been reported for bony flap reconstruction[101]. The cut-off tissue viability determination was 30%, which is the current device manufacturer's recommendation[102,103].

ICG helps in intraoperative and postoperative flap design, especially with newer systems such as the VsionSense real-time fusion image of both NIR and white light with highlighted perfusion NS flow scale color-coded to enhance the interpretation of anatomy and perfusion. Bigdeli *et al*[104] addressed this technique in 8 patients and proved its practicability.

In a recent systematic review, Li *et al*[105] concluded that ICG for detecting flap perforators and microcirculation(perfusion) evaluation informs surgical decision-making regarding the selection of dominant cutaneous nerves, anastomosis quality, and thrombosis identification[105].

Patel *et al*[106] used ICG to identify poorly perfused tissues in complex abdominal reconstruction. Concerning the potential to decrease delayed healing, the authors reported accuracy in identifying perfusion, abnormalities, and skin viability in complex hernia repairs. Thus, wound healing-related complications. Adams *et al*[107], in a recent scoping review of ICG in complex abdominal wall reconstruction, suggested a role, while others did not. Therefore, guidelines on ICGFA in this aspect will require more studies and future meta-analyses[107].

The tool expands the armamentarium for reconstructive surgeries. It is highly useful for decision-making during accurate debridement and soft tissue coverage of extensive plantar degloving before obvious demarcation, reducing the number of interventions and risk of infection[108].

Application of ICG in the detection of intestinal fistula (leaks)

Peng *et al*[109] reported a new preliminary application of ICG imaging in a postoperative case in which the initial fistula was identified using oral methylene blue dye, imaging contrast leakage, and ICG

fluorescence in the drain. Subsequently, on follow-up, the output decreased and cleared. The first two tests failed to demonstrate the leak, and ICG showed a persistent leak on fluorescence imaging of the drained fluid. The patient received 25 mg of oral ICG in 50 mL sterilized water. After approximately one hour, at the bedside, the NIR system detected ICG fluorescence in the drainage fluid at the bedside. The output decline with a fluorescence check was used to determine fistula closure. Therefore, the treatment was terminated. This reflects the low sensitivity and high false-negative rates of the contrast and methylene blue studies. This case report presents ICG as a highly sensitive, convenient, and low-cost bedside imaging modality without the risk of radiation or side effects[109,110].

Application in burns depth assessment

The assessment of burn depth remains challenging, and its determination of burn depth is critical in deciding the treatment approach for thermal injuries[111]. The current trend is the early excision of deep dermal and full-thickness burns, followed by wound grafting to reduce costs, infection concerns, and severe scarring. Assessment of sites with unknown burn depths remains difficult. The traditional approach is subjective clinical judgment. Many objective clinical assessment techniques have been tested but did not gain acceptance. ICG video angiography helps assess vascular patency, precise marking of burns, and depth estimation and has the advantages of being a practical, accurate, and effective adjunct.

Additionally, it enables the dynamic follow-up (objective, qualitative, and quantitative) of changes in burn wound depth throughout the acute post-burn period to improve prompt therapies[107]. Moreover, animal studies have also performed histopathological comparisons[112-114]. A recent prospective multicenter, double-blind study demonstrated the guidance of ICGA with excellent healing (closure) rates and concluded that it is a competent method for their purpose. In a previous prospective triple-blinded experimental study, the same author came to the same conclusion regarding the superiority of ICGA over clinical assessment (100% diagnostic accuracy *vs*. 50% for clinical evaluation) in identifying excising burns of unknown depth and stronger associations with long-term wound outcomes[115]. In a recent animal study, Second Window Indocyanine Green imaging was shown to be a potential imaging modality to objectively predict burn wound healing potential and guide intraoperative burn excision [116]. Simply put, it helps reduce unnecessary excision and prevent inadequate excision with better secondary results regarding the number of surgeries, healing, length of stay, and indirect costs[112-114,116,117].

Technological limitations of ICG

The comprehensive evaluation of NIR FI in the past decades was mainly in non-traumatic situations. This technology is used for the anatomical identification of tumors (both primary and secondary), vital structure identification, mapping of structures, and assessment of perfusion. There is still wide variation in agent dosage and administration timing among different tissues and applications[86]. Intraoperative perfusion assessment techniques such as transabdominal Doppler ultrasound, transabdominal laser Doppler flowmetry, and oxygen spectroscopy have not been widely accepted because such techniques cannot be easily applied in routine clinical practice or have not proven reliable. A disadvantage of ICG-enhanced Fluorescence is that the assessment of the fluorescence intensity is subjective, making it a real-time intraoperative navigation modality.

However, the use of ICG in routine practice, particularly in trauma surgery, is currently lagging. This technique is simple, straightforward, and easy to implement. The logistics and costs are feasible[11,54-56,86]. Therefore, there is a need to develop a consensus regarding the choice, dosage, and timing of treatment. There is a need for prospective trials on whether it effectively predicts or decreases the risk of anastomotic leaks. It identifies other vital structures such as nerves, ureters, bile ducts, and thoracic ducts.

Unfortunately, published studies lack a quantitative comparison of fluorescence signals. There is a risk of overestimating the fluorescence signals in vascularized tissues due to the NIR fluorophore's over-time diffusion. Diana *et al*[118] attempted to address this drawback and developed a quantitative software-based analysis. The software calculated the peak slope of the fluorescence signal stiffness. Virtual bowel perfusion cartography is fashioned and overlaid on white-light images, allowing real-time quantitative perfusion assessment[118-121]. Several custom and commercial Quantification of ICG fluorescence (Q-ICG) software solutions uses inflow parameters rather than intensity parameters as well as mass-adjusted ICG dosing and fixed camera position[122].

A recent survey of colorectal surgeons in Italy concluded that FI is widely used; however, its indications and methods vary. The perception and acceptance among surgeons are not sufficient to determine whether this additional technological tool is essential. This reflects the need for future research to develop a solid foundation for implications in the practice of colorectal surgery and to extrapolate this to other fields of surgery, including trauma.

FUTURE PERSPECTIVES

Despite expanded clinical trials, fluorescent agents, and imaging systems for intraoperative FI, there

currently needs to be a standardized strategy for evaluating the imaging system performance and post-acquisition image processing[19,123]. There is a paucity of high-level evidence and the need for rigorous ways to address this continuous shortfall despite recent increases in publications, notably the number of meta-analyses and systematic reviews and the poor quality of the included data. Therefore, surgeons need to embrace and explore technological adjuncts to guided surgery[124].

Currently, two fluorescent compounds are FDA-approved and are used clinically (ICG and methylene blue). There is increasing interest in expanding fluorescence-guided surgery, and there is a need to develop other tissue-specific agents that would enhance surgical anatomical identification and protect important structures, such as nerve-specific agents, which are currently at the animal study level, to avoid accidental nerve damage with their sequelae[125].

The future is anticipated to accelerate the development of specific molecular tracers that are expected to introduce a paradigm shift in surgical decisions regarding resection based on additional molecular information. Fluorescein- and 5-aminolevulinic acid-induced protoporphyrin IX (PpIX-an endogenous metabolic fluorophore) imaging for neurosurgery and certain superficial cancers such as the urinary bladder. Technology (*i.e.*, FGS systems and imaging) is evolving in terms of specifications and performance differences. Desirable criteria or optimum systems have been published to define standards of care for evaluating new systems. A set of desirable criteria were presented to guide the evaluation of the instruments in this regard including: (1) Real-time overlay of white-light and fluorescence images; (2) operation within ambient room lighting; (3) nanomolar-level sensitivity; (4) quantitative capabilities; (5) simultaneous multiple fluorophore imaging; and (6) ergonomic utility for open surgery[30,126]. There is no perfect system; nevertheless, knowing the differences and limitations of available systems helps define clinical utility more precisely.

Furthermore, hybrid tracers (radioactive and fluorescent) are being researched to aid in expanding image navigation and precision procedures in elective settings, as well as oncologic excision[127]. Quantitative assessment of suitable or unsuitable pre-anastomotic perfusion is not well determined, mostly because most real-time imaging systems cannot assess tissue perfusion. However, some experimental studies have evaluated fluorescence quantification in animal models[124]. A technological upgrade would undoubtedly benefit the outcome of ICG application; nonetheless, system development has recently undergone a significant trial to establish a benchmark.

There is an interest in the objective assessment of tissue perfusion as a predictor of healing failure, which is performed in a poorly perfused segment of the bowel and is subjective based on the surgeon's experience with the previously mentioned limitations of human senses and ill-defined experience. This review discusses ICG-based fluorescence angiography as a practical solution. However, there are other options, such as hyperspectral imaging (HIS). Briefly, the tissue was illuminated with a broadband light source, and reflectance was measured with an image sensor in various bands of the electromagnetic spectrum in the visual and NIR range (400-1000 nm). Tissue composition permits absorption, scattering, or reflection; measuring this information works like a tissue fingerprint and can be used to measure perfusion status without the need for an exogenous fluorophore, and it can easily be repeated. The clinical use of this technique has been less studied in the literature, and the comparison of this technique with older ICG FA is limited. Pfahl *et al*[127] combined the data of the two techniques for the first time after an initial surgeon transaction-line decision; however, before resection, the complementary information of the two techniques may provide better tissue vascularization data. They concluded that more studies are needed to define the roles and recommend the routine integration of these techniques. Therefore, the future may determine the most promising, reliable, and safe method for assessing tissue perfusion during surgical resection and anastomosis in different disease processes, including trauma, tumors, and inflammatory bowel disease.

The combined application of ICG-FA and HIS within one imaging system may provide supportive and complementary information regarding tissue vascularization, minimize perioperative mortality, and shorten the surgical time. Different degrees of infusion[127]. To compensate for the scarcity of approved fluorophores, some groups have used NIR coating of equipment with materials that have a similar spectral ICG range to allow the use of already available ICG cameras such as ureteric stents, magnetic anastomotic devices, tumor endoscopic clips for laparoscopic identification, and Foley[128]. The future may integrate the artificial intelligence system with functional imaging into the challenging trauma surgery arena.

REVIEW LIMITATIONS

This narrative review is based on an interpretation of the literature on the topic rather than a systematic literature review. This study overlooks a few of these issues. Additionally, the arguments and views presented in this review are based on the authors' interpretation of NIR FA, which remains a novel tool. The heterogeneity between published studies may limit the possibility of conducting a meta-analysis.

CONCLUSION

FGS is a surgical navigation tool with evolving uses. Although ICG is extensively used for various reasons in monitoring organ perfusion, developments in existing systems are continually being made to define standards, quantify fluorescent signals, and discover new prospective tracers. This represents a paradigm change and the possibility of using molecular data in surgical decision-making for trauma, elective, and emergency surgeries. ICG, a relatively safe, sensitive, and nonspecific fluorophore widely used in NIR fluorescence imaging, can help surgeons to operate on injured patients. Minimizing the risk of anastomotic leakage remains a core goal of clinical practice. The large-scale use of ICG and further standardization and training of this technique are necessary to obtain specific and robust evidence to confirm its clinical value and define specific indications in trauma surgery. Additionally, a successful program for the development and application of FGS would require solid collaboration with optical engineers (for the development of hardware), computer scientists (for the development of the software), chemists (for the engineering of fluorophores), and medical professionals to enable clinical translation. Defining the therapeutic value of this method in trauma, including the timing, doses, and damage pattern indications, further research, including prospective trials, could offer great information and value for both surgeons and patients.

FOOTNOTES

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MINIREVIEWS

Global dissemination of minimally invasive living donor hepatectomy: What are the barriers?

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Abstract

Minimally invasive donor hepatectomy (MIDH) is a relatively novel procedure that can potentially increase donor safety and contribute to faster rehabilitation of donors. After an initial period in which donor safety was not effectively validated, MIDH currently seems to provide improved results, provided that it is conducted by experienced surgeons. Appropriate selection criteria are crucial to achieve better outcomes in terms of complications, blood loss, operative time, and hospital stay. Beyond a pure laparoscopic technique, various approaches have been recommended such as hand-assisted, laparoscopic-assisted, and robotic donation. The latter has shown equal outcomes compared to open and laparoscopic approaches. A steep learning curve seems to exist in MIDH, mainly due to the fragility of the liver parenchyma and the experience needed for adequate control of bleeding. This review investigated the challenges and the opportunities of MIDH and the barriers to its global dissemination. Surgeons need expertise in liver transplantation, hepatobiliary surgery, and minimally invasive techniques to perform MIDH. Barriers can be categorized into surgeon-related, institutional-related, and accessibility. More robust data and the creation of international registries are needed for further evaluation of the technique and the acceptance from more centers worldwide.

Key Words: Minimally invasive donor hepatectomy; Liver transplantation; Living donation; Laparoscopic donor hepatectomy; Global surgery

Core Tip: Living donor liver transplantation provides an excellent option for expanding the donor pool. Minimally invasive donor hepatectomy can potentially minimize complications of hepatectomy to the donors and have a better cosmetic effect. This approach demands expertise and experience in both liver surgery and minimally invasive techniques to maximize its potential.

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INTRODUCTION

Living donor liver transplantation (LDLT) represents a valuable choice for end-stage liver disease, especially in regions with a limited donor pool[1]. In children with rapidly progressive liver failure, full pediatric grafts, reduced-size grafts, and split grafts from cadaveric donors may not be available in time [2]. Liver grafts from living donors provide comparable or potentially better short-term graft function and long-term survival rates, especially in children, compared to whole and split cadaver liver grafts[3-5]. The occurrence of donor morbidity and mortality is the main obstacle to broad utilization of living liver donors.

Complications from the hepatectomy operation are the main contributing factors to donor morbidity. Significant complications may include biliary (*e.g.*, bile duct injury, leak), infective, or vascular (*i.e.*, bleeding). Other complications, such as bowel obstruction, incisional hernias, and prolonged operative stay, can also contribute to donor morbidity[6]. Minimally invasive donor hepatectomy (MIDH) has been proposed to minimize donor complications. Potential advantages of MIDH, inherent to the minimally invasive approach, are better cosmetic results, reduced postoperative pain, faster recovery, and earlier return to daily activities[7]. MIDH was first described in France when cases of adult left lateral sectionectomy (LLS) and subsequent successful pediatric transplantation were reported[8]. The aim of this review was to describe the parameters that affect the efficiency of MIDH as well as identify barriers to its global dissemination.

INITIAL CONCERNS

In the United States, LDLT reached a peak in 2001 accounting for 10% of the total number of liver transplants (LTs)[9]. However, a marked decrease followed reports of complications reaching up to 40% [6,10], especially for right hepatectomy (RH)[11]. As a result, in 2019, the year with the most LTs in the United States (8896), only 5.3% of LT recipients received a graft from a living donor[12], with the majority of those being right grafts. This proportion contrasts with that of living kidney donation, which surpasses 30%[13]. In living donor nephrectomy, several meta-analyses and randomized trials have established that a laparoscopic approach is associated with decreased morbidity, less postoperative pain, shorter hospital stay, and lower costs[14-16]. Living donor nephrectomy is not considered a particularly technically challenging procedure, as the kidney is removed intact with its associated pedicle and ureter, without the need for parenchymal transection. On the other hand, MIDH requires recovery of partial vascular and biliary pedicles as well as parenchymal transection[17]. These factors along with anatomical complexity and the size of the liver itself have slowed down its progression[18]. The two main targets of minimally invasive liver procurement in living donors are donor safety and fast rehabilitation. The risk of mortality and morbidity of liver resection in a living donor depends on three parameters: physiologic status (*e.g.*, comorbidities); proportion of liver mass removed associated with proportional risk of postoperative liver failure; and the amount of intraoperative blood loss and subsequent need for allogeneic transfusion[19]. As a result, to minimize morbidity in living donors, transplant teams must focus on the best surgical technique and leave an adequate liver remnant with the lowest blood loss. It is still unknown whether a minimally invasive technique can achieve these goals[19].

Systematic reviews of laparoscopic liver resections have confirmed growing safety of this approach when performed by experienced surgeons, suggesting that it may offer significantly fewer complications, less blood loss, and shorter length of stay compared to an open technique[20,21]. It must be noted, however, that retrieving a liver graft from a living donor is not entirely equivalent to a conventional hepatectomy since vascular pedicles of the resected part must be preserved[8].

A statement from the 2008 International Laparoscopic Liver Resection Consensus Conference in Louisville was that MIDH is the most controversial part of laparoscopic liver surgery. Donor safety has not been validated yet, and the technique is limited only to a few specialized centers as it is not easily reproducible[22]. In the Second International Consensus Conference on laparoscopic liver resections held in Morioka in 2015, it was argued that MIDH is non-inferior to the standard approach in terms of donor safety, but the procedure was not recommended due to lack of convincing data on postoperative morbidity[23]. After the first positive results of MIDH, an expert consensus was held in Seoul in order to establish clear recommendations for the safe widespread adoption of MIDH[24]. The results demonstrated that MIDH offers superior outcomes compared to an open approach, provided that the procedure is performed in high-volume centers by surgical teams with high experience in both MIDH and laparoscopy. Moreover, data from the United States suggest that donors are more willing to undergo living donation through a laparoscopic than a conventional approach[25].

LAPAROSCOPIC LIVING LLS FOR CHILDREN

Whereas MIDH has evolved into different variations (hand-assisted, laparoscopic-assisted, pure laparoscopic), LLS has been exclusively proposed as a purely laparoscopic technique with mobilization and creation of the graft through 4-5 trocars and extraction *via* a remote incision. The left lateral segment is a favorable anatomic entity for pure laparoscopic resection because of its anterior position and limited number of anatomic variations[26]. Following the first achievements in France[8,27], Belgium[28], and South Korea[29], the safety and reproducibility of the procedure were confirmed by Scatton *et al*[30]. The authors noted that after a learning phase, the median hospital stay gradually decreased, median blood loss stabilized around 50 mL, and Clavien-Dindo grade II or higher complications were less frequent. However, it was emphasized that the procedure requires at least two experienced surgeons in order to follow the required learning curve[30]. Soubrane *et al*[27] stated that MIDH yields at least equal short-term outcomes compared to laparoscopic donor nephrectomy. Subsequent studies continued to report less estimated blood loss and shorter length of stay but longer operative time for pure laparoscopic LLS compared to an open approach[31-34].

RH FOR ADULTS

Adult-to-adult MIDH can be performed with either the right or left hemi liver, with each option having its own advantages and disadvantages. While RH provides the recipient with an adequate volume of transplanted liver parenchyma, it has raised much concern about donor safety with reported postoperative complications rates up to 40%[6]. The laparoscopic approach was advocated in multiple centers to minimize these complications. MIDH of the right liver is more difficult than the left due to the extensive mobilization required, as it is deeply seated below the rib cage[35].

Due to inherent difficulties of the procedure, various techniques were recommended that allowed the surgeon to avoid a large subcostal incision and to keep the familiarity of open dissection and resection. These hybrid techniques, such as hand-assisted or laparoscopic-assisted[22], can represent a transitional approach for many centers before moving to pure laparoscopy. The choice of the technique depends on the surgeon's expertise and experience. It is important that if anatomic integrity is in jeopardy, then conversion to open is the inevitable solution.

The first report of the hybrid technique in MIDH was from Chicago. The team used the hand-assisted technique and noted that it provides better tactile perception, crucial for the dissection of the hilum[36]. Surgeons from different centers used either midline[25,37-39] or transverse incisions[40], whereas Choi *et al*[41] presented 40 donor hepatectomies with a single port.

Pure laparoscopic right donor hepatectomy is technically more challenging. It was first reported by Soubrane *et al*[19], with the graft being removed from a suprapubic incision without any postoperative complications. After adoption of the technique from several centers worldwide, results have shown non-inferiority in terms of postoperative complications, estimated blood loss, and length of stay[42-46].

LEFT HEPATECTOMY FOR ADULTS

There is evidence that left lobe hepatectomies are associated with significantly lower morbidity compared to RH. The lower morbidity is mainly due to fewer biliary and pulmonary complications, potentially due to smaller graft size[47,48]. The left lobe can be a choice when graft-to-weight ratio is > 0.8 or between 0.6 and 0.8, provided that the recipient has a model for end stage liver disease score < 15. The main risk of left lobe donation is the small-for-size syndrome that eventually leads to graft failure in the recipient. Reports from left donor hepatectomy have resulted in positive outcomes[37,49,50], whereas Soubrane *et al*[51] in a multinational study demonstrated no difference in morbidity between

right and left hepatectomy. During left lobe MIDH, the right liver is mobilized and rotated through the midline incision to allow hybrid surgery. Marubashi *et al*[49] noted that for a successful operation, it is the right lobe volume that has a greater impact rather than abdominal depth.

SELECTION CRITERIA

Careful donor selection is considered of paramount importance for MIDH. Pretransplant evaluation includes a thorough medical assessment. Of particular importance are any cardiovascular, renal, pulmonary, or coagulopathic comorbidities as well as an infectious disease and psychiatric assessment. Several centers exclude patients with arterial hypertension and psychiatric disorders[49]. In addition, standard liver function tests, hepatitis B and C serology, and chest and abdominal radiographs are always utilized. A triphasic liver computed tomography scan with volumetric calculations and assessment of vasculature is also invariably performed.

Magnetic resonance cholangiopancreatography provides accurate and precise images of the biliary tree and can define the appropriate division point for the hepatic duct, especially in D1 biliary anomaly (right posterior duct draining into the left bile duct) (Table 1). Incorrect identification of biliary anatomy may require intraoperative cholangiography[30], yet it demands expertise, increased cost, and more operative time[52]. Indocyanine green fluorescence cholangiography not only captures images but also enables a bile leak test using methylene blue injected through the cholangiography tube[34].

Surgeons from different centers have defined specific criteria of liver anatomy for a potential liver donor. Kim *et al*[43] accepted only donors who had a single and long right hepatic duct, artery, and portal vein. They also excluded grafts that exceeded 650 g. Gautier *et al*[31] considered separate drainage of segments 2 and 3 as a setback for MIDH as it can cause difficulties with stapling and lead to intraoperative bleeding. Rotellar *et al*[42] agreed that single hilar elements defined the best candidates, but everyone should be considered on a case-by-case basis.

Portal vein variations (Table 1) used to be considered a contraindication for MIDH candidates, yet there are reports that showed encouraging results even for these donors[44,45]. After acquiring consistent, reproducible, and standardized techniques through cumulative surgical experience, it will be possible to expand these existing criteria.

CONVERSION

Any incident that might compromise donor safety or graft integrity should lead to conversion to an open approach. Conversion is not by itself a complication but implies that some unfavorable event occurred during the procedure[51]. Most common causes for conversion to an open approach are failure to recognize biliary duct or hepatic hilum anatomy, vessel injury that led to significant bleeding, and poor exposure due to extensive adipose tissue in donors with a high body mass index (BMI).

Scatton *et al*[30] reported 4 conversions (6%) out of 70 MIDH procedures, of which 66 were LLS and 1 was LH. Reasons for conversions were left portal vein branch injury, poor exposure, and uncertainty regarding biliary anatomy. None of the conversions were associated with acute or uncontrolled bleeding or need for transfusion, and all converted donors had an uneventful recovery. Choi *et al*[41] mentioned a conversion rate of 10% (2/20) in traditional hand-assisted MIDH and 5% (2/40) in single-port hand-assisted MIDH due to right hepatic vein and adrenal gland injury. In single-port surgeries, instruments commonly collide in tight abdominal spaces, referred to as "sword fighting" or the "chopstick" effect[53]. For liver surgeries through the umbilicus, the instruments are too short to reach the entire liver surface. Soubrane *et al*[51] reported a conversion rate of 4.1% with 17 conversions from 412 MIDH due to portal vein injury, uncertainty regarding identification of important structures, and difficult hilum dissection, whereas Rhu *et al*[45] found a 5.0% rate due to portal vein narrowing and injury, donor steatosis during intraoperative biopsy, and inferior vena cava injury.

COMPLICATIONS

It should be emphasized that a 30-d follow-up underestimates morbidity after a liver resection; robust studies for a hepatectomy should cover at least a 90-d follow-up after the operation[54]. The Clavien-Dindo classification, although extensively used, tends to consider only the most severe adverse events and does not consider other less severe complications[55] (Table 2). A recently proposed continuous score, the comprehensive complication index, summarizes all of the postoperative complications and represents the most sensitive tool to estimate the real overall morbidity burden of a procedure[56]. The complication rate in MIDH ranges from 0% to 40%[34,57], but in the majority of studies it lies between 10%-26%[39,45,51,58]. Most common complications are wound complications, pleural effusions, biliary leakage, or stricture (Table 3). Most reports showed no statistically significant difference in the

Table 1 Biliary duct and portal vein variations

Biliary duct variations	
A	Normal bifurcation (57%)
B	Trifurcation of 3 ducts (12%)
C	Right anterior (C1, 16%) or right posterior (C2, 4%) duct draining into common hepatic duct
D	Right posterior (D1, 5%) or right anterior (D2, 1%) duct draining into left hepatic duct
E	Absence of hepatic duct confluence (3%)
F	Drainage of right posterior duct into cystic duct (2%)
Portal vein variations	
I	Classical anatomy
II	Trifurcation
III	Right posterior vein as first branch of main portal vein
IV	Segment VII branch separate branch of right portal vein
V	Segment VI branch separate branch of right portal vein

Table 2 Clavien-Dindo classification for donor and recipient complications[55]

Grade	Definition
I	Non-life threatening. Requires only bedside interventions, postoperative bleeding requiring three units of packed red blood cells, no prolongation of hospital or ICU stay longer than twice the population median
II	No residual disability. Any complication that is potentially life threatening, or requires use of four units of packed red blood cells, or prolongation of hospital stay for > 4 wk or ICU stay for > 5 d
III	Residual disability. Any complication with residual or lasting functional disability or development of malignant disease
IV	Liver failure or death. Requires liver transplantation (grade IVA) or results in death (grade IVB)

ICU: Intensive care unit.

Table 3 Reported complications of minimally invasive living donor hepatectomy

Grade	Complication
I	Fever, gastroenteritis, gastric ulcer, occipital alopecia, pneumothorax without drainage, wound infection, suprapubic hematoma, ileus, arm neuropraxia, atelectasis, transient neuropenia
II	Gastroparesis, pulmonary infection, segment IV infarction, bile duct stenosis, pancreatitis, cystitis, incisional port-size hernia
IIIa	Biliary leakage, fluid collection, bladder injury, portal vein thrombosis or stenosis
IIIb	Abdominal abscess, intra-abdominal bleeding

complication rate between MIDH and an open approach, but this may be attributed to the small sample size of most studies. Rhu *et al*[45] made an interesting point that complications were significantly higher during the first quartile of operations, which reflects potential difficulties due to surgeon inexperience with the approach. Broering *et al*[33] also stated that the complication rate decreased from 26.7% to 9.7% after acquiring the appropriate experience in the initial period. Morbidity rates were equivalent between right and left MIDH[51] and among different portal vein variations[45].

Biliary complications are among the most serious in MIDH. Takahara *et al*[59] mentioned three bile leakages, although each stump had been double-clipped with hem-o-lock clip and looked perfectly secure at the end of the operation. It was hypothesized that the clips dropped off due to ischemic changes postoperatively. Regarding incisional complications, open living donor hepatectomy requires a large, bilateral subcostal incision with major muscular transection, leading to several days of pain and multiple weeks of discomfort[8]. During that incision, sensitive nerve endings (ventral rami of intercostal nerves T8 and T9) are divided, which might lead to permanent abdominal wall anesthesia [8]. On the contrary, suprapubic incisions are usually well tolerated without gynecological sequelae, and incisional hernias are rare. In addition, they are almost invisible when they are made low enough in the

pubic hair area[8]. Attention is needed during suture transfixion in the abdominal wall closure, as bladder trauma might occur[17]. Small incisions that are made for the trocars are predisposed to local ischemia and wound infections, yet these complications are much less frequent in MIDH than the conventional approach[60].

There is a theoretical increased risk of gas embolism because of pneumoperitoneum. However, pneumoperitoneum is established by carbon dioxide insufflation, a gas with solubility greater than that of nitrogen[22]. Several experimental studies have established that carbon dioxide absorption into systemic circulation is not associated with hemodynamic instability[22].

The mortality risk of living donor lobectomy is estimated to be 0.2% worldwide[61], with LLS having lower rates (0.05%-0.10%). It is generally accepted that adult-to-adult donation has greater morbidity, and possibly mortality, than adult-to-child donations, as right lobes are mostly used for adults, thus the tissue volume removed is larger and operative time longer.

It should be noted that the outcomes of surgical interventions in living donors should not be estimated separately from the results of recipients. In kidney transplantation, Troppmann *et al*[62] found that laparoscopic nephrectomy is associated with delayed graft function and increased acute rejection rate. The causes about this finding were unclear, but a possible factor is the hemodynamic disturbance in kidney vasculature due to the pneumoperitoneum. On the other hand in almost all the studies comparing laparoscopic and open living donor hepatectomy, the authors did not find any difference between MIDH and the conventional approach in terms of vascular and biliary complications, graft survival, and overall survival of recipients[31,33,34,42]. MIDH does not add risk to the recipient even in cases of portal vein variations[45]. Hong *et al*[44] were the only team that noted a higher rate of biliary complications to the recipients after MIDH, a finding which was attributed to the longer warm ischemia time and the increased likelihood of multiple bile duct openings.

BLOOD LOSS

A strong initial reluctance in the development of MIDH was the management of hemorrhage under laparoscopy. With technical refinements and growing expertise during the past three decades, multiple reports have validated decreased blood loss and lower transfusion rates during laparoscopy[63,64]. Meticulous parenchymal transection and the "cut surface effect" of pneumoperitoneum (*i.e.* tamponade-like effect on transected surface by increased intra-abdominal pressure) have contributed to minimal blood loss during MIDH[30], as the main source of bleeding is the venous backflow. Some authors suggest transiently increasing the pneumoperitoneum pressure to 14-16 mmHg in order to minimize bleeding[30]. The greatest risk of intraoperative hemorrhage occurs during the parenchymal dissection, which in a laparoscopic approach is performed very accurately and under magnification. Division of the hepatic vein is also crucial as slipping of the vascular clamp may lead to massive bleeding[65].

Results from comparative studies between MIDH and the conventional approach showed decreased [31,33,59,66] or similar[25,39,44,45] estimated blood loss in MIDH. However, the authors emphasized that the absence of a statistically significant difference was due to insufficient power related to inadequate sample size[25]. Therefore, there might be an advantage of less blood loss in MIDH than an open approach.

OPERATIVE TIME AND HOSPITAL COST

MIDH tends to last longer, especially during the initial learning period of surgeons[33,44,49,59,67]. It is expected that additional experience in hilar dissection will lead eventually to reduced operative time [49]. Baker *et al*[25] found an association between increased body mass index and longer operation time, whereas Rhu *et al*[66] emphasized that after the first 100 cases the operative time shortened. Although material costs were higher in MIDH, they were balanced by lower time-related operation costs. Therefore, there was no difference found by Baker *et al*[25]. In another case series, MIDH was a significantly more expensive procedure than the open procedure[39].

PAIN CONTROL AND HOSPITAL STAY

Kurosaki *et al*[37] used decreased supplemental analgesia in MIDH compared to patients who underwent open hepatectomy. A reduced amount or shorter use of analgesics was also found in multiple case series[33,39,41,43] yet that finding was not consistently demonstrated[49,65].

Postoperative length of stay is greatly influenced by institutional and healthcare system policies. In Eastern countries like Japan and South Korea, the policy is to admit donors in the hospital until they are able to return to normal daily function[49]. Additionally, some Eastern national healthcare systems do not require patients to be discharged even after they have recovered from the operation[45,65,67]. In

Western countries there seems to be an enhanced recovery protocol. In a few reports there is no statistically significant decrease in the length of stay between MIDH and the open approach[25,57]. However, the majority of centers present shorter length of stay in the MIDH group[33,45,67].

ROBOTIC DONATION

The Robotic approach is much less established than the laparoscopic approach, but it is considered safe and feasible in expert hands. The first robotic LDLT was accomplished by Giulianotti *et al*[68] in 2012 from a 53-year-old man to his 61-year-old brother, using the Da Vinci Robotic Surgical System. Compared to a pure laparoscopic approach, robotic evolution is slow and delayed. Potential advantages are the amplified and more stable view and better precision of movements. The Da Vinci surgical system can rotate in all directions with 90° articulation and 7° of freedom, which allows for a broader range of movements compared to the human hand. The latter allows manipulation and suturing in the retrohepatic space at angles not possible with rigid instruments. On the contrary, the surgeon loses the tactile feedback and is also dependent on a trained bedside assistant who changes the robotic instruments during parenchymal transection[69].

The latest studies have shown that robotic transplantation is feasible and achieves similar short-term outcomes compared to a laparoscopic procedure[69] but with increased perioperative cost, as medical insurance plans usually do not cover it. Another barrier to dissemination of this technique is the need for high center specialization and surgical instruments; only ultrasonic scalpels, hem-o-lock clips, and staplers can be used during robotic liver surgery[70].

Two studies that compared robotic with open donor hepatectomy found non-inferiority of the robotic technique in terms of complications and blood loss[70,71]. Currently, there are no data indicating superiority of a robotic approach compared to an open or laparoscopic approach. Troisi *et al*[72] did not find any favorable outcome to justify the higher cost of the robotic approach compared to a laparoscopic one. They also emphasized that a robotic to open conversion takes longer than a laparoscopic to open conversion. Therefore, it is crucial to apply all the laparoscopic techniques to control unexpected bleeding before converting[72]. In any case, the robotic approach is still very limited in geographic spread and requires much more experience than laparoscopy. Forthcoming introduction of new robotic systems that could support haptic feedback or cavitron ultrasonic surgical aspirator devices will contribute to further spread of robotic hepatectomy.

LEARNING CURVE

A major barrier in the global dissemination of MIDH is that it requires significant experience both in liver and laparoscopic surgery. A multinational study on global dissemination of MIDH revealed that 65.6% of the surgeons had performed > 50 laparoscopic hepatectomies and 43.8% had performed > 50 open donor hepatectomies before their first MIDH[24]. The steep learning curve is due to the fragility of the liver parenchyma and familiarity with the control of challenging bleeding situations[71]. Several reports have emphasized that a minimum of 15-60 procedures depending on the extent of the resection are required before optimal results can be obtained[73]. Scatton *et al*[30] showed that preliminary experience with at least 20 donors is needed before achieving optimal hemostasis and postoperative course. It should be noted, however, that defining a single surgical case cutoff is unrealistic, as experience and outcomes vary amongst different surgical teams.

Rhu *et al*[66] reported no change in operative time from first to second quartile of a surgeon's operations over time but reported a significant decrease from the second to the third quartile and from the third to the fourth. His team was able to reduce the operative time after 50 laparoscopic cases[66]. In order to define the learning curve, Lee *et al*[74] used two variables: estimated blood loss and operative time. The learning period was defined as the period before reaching a plateau in those two parameters. They showed that the experienced phase started after 15 cases, with significantly less estimated blood loss and operative time than the learning phase.

Broering *et al*[70] argued that robotic major hepatectomy could also have a short learning curve, with a mastering phase reached at 15 procedures. Chen *et al*[71] divided the learning curve of robotic hepatectomy into three phases: initial (1-15); intermediate (15-25); and mature (25-52). A learning effect was demonstrated by shorter operative time and hospital stay after phase 1 and less blood loss after phase 2. The robotic approach with the double console offers a safe form of teaching, as the proctor can guide the surgeon through the dissection and take control if it is necessary[70].

BARRIERS TO GLOBAL DISSEMINATION AND FUTURE DIRECTIONS

MIDH is a promising technique to expand the liver donor pool while ensuring the safety of both the

Table 4 Barriers to global dissemination of minimally invasive donor hepatectomy

Barriers	
Institutional barriers	Donor safety: concerns for compromised donor safety when using MIS approaches (*e.g.*, control of bleeding, parenchymal transection). High-risk: donor morbidity and mortality can compromise institutional reputation and even suspension of living donor transplantation program. Limited evidence: existing studies selecting for most ideal patients
Surgeon-related barriers	Learning curve: high surgical experience in both minimally invasive liver surgery and living donor hepatectomy. Limited MIS experience by liver surgeons. Transplant surgeons in some countries do not frequently practice HPB surgery
Accessibility	Localization of expertise in very few centers worldwide. Need for proctoring by surgical experts to start MIDH program (*e.g.*, fly in experts from specialist centers to proctor first cases, local surgeons fly to specialist centers to observe). Resources: need for specialized technology (*e.g.*, CUSA)

CUSA: Cavitron ultrasonic surgical aspirator; HPB: Hepato-pancreato-biliary; MIDH: Minimally invasive donor hepatectomy; MIS: Minimally invasive surgery.

donor and the recipient. Although evidence for the efficacy and safety of this technique is increasing, there are several barriers currently limiting a more widespread utilization. These barriers may be categorized as those related to the transplant program institution, barriers related to the individual surgeon considering the technique, and finally accessibility concerns (Table 4). MIDH may eventually become more widespread globally; however, the technique is best utilized only at specialized LT centers around the world.

LDLT represents a highly validated choice of liver grafts; yet every effort must be made in order not to expose donors to potential risks. Any increase in morbidity would be a huge price for the sake of possibly reduced postoperative pain or hospital stay[75]. Donors are otherwise healthy people who altruistically and electively decide to donate a part of their liver. Therefore, every effort should focus on rendering their postoperative course complication-free. Every effort should be made to advocate not only for the physical but also the psychological well-being of living liver donors. In order to recruit more living liver donors to fulfill the continuously increasing demand for liver grafts, it is necessary to optimize the postoperative course for donors[76].

So far, the benefits of MIDH are limited to retrospective or case-control studies; current literature lacks strong evidence, mainly due to ethical concerns that prevent conducting a randomized controlled trial between MIDH and the open approach[77]. Since the first report of MIDH[8], the procedure has been limited to a few centers worldwide. The creation of an international registry, especially in Eastern countries where the technique is more widespread, should be undertaken for further assessment of the approach.

Although preliminary reports tend to support the benefits of MIDH, future challenges must include standardization of the technique to achieve a certain degree of reproducibility among new surgeons. A multinational study from ten LT centers from both Eastern and Western countries over a 10-year period showed that donor safety is not compromised under MIDH, with low transfusion and conversion rates [24]. The study revealed that right MIDH is most prevalent in South Korea and LLS in Europe and the Middle East[24]. Teams in the eastern hemisphere are not as conservative in the use of grafts with anatomical variations as they are in the West, maybe due to scarcity of deceased donors in the East[24]. Further studies and more robust data on short-term and long-term outcomes are needed to evaluate donor selection, learning curve, donor's quality of life, and global dissemination of the technique.

CONCLUSION

Living transplant donation constitutes a promising opportunity for increasing the liver donor pool. However, LDLT has been limited in utilization. Minimally invasive approaches may offer an opportunity to increase grafts from living donors. MIDH offers donors the advantages of minimally invasive techniques, while there is increasing evidence that it is a safe and effective approach for both the donor and the recipient at the hands of experienced surgeons. Several barriers at the institutional and individual surgeon level limit the more widespread dissemination of MIDH to more specialized liver centers globally. International collaborative efforts can promote progress in the field of MIDH.

FOOTNOTES

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MINIREVIEWS

Post-COVID-19 cholangiopathy: Current understanding and management options

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Abstract

Post-coronavirus disease 2019 (COVID-19) cholangiopathy (PCC) is a rare but life-threatening complication of COVID-19 infection. PCC typically presents when patients recovering from the contagion and manifests as cholestasis in patients with no history of pre-existing liver disease. The pathogenesis of PCC is little understood. Hepatic injury in PCC could be mediated by the predilection of severe acute respiratory syndrome coronavirus 2 for cholangiocytes. Though PCC shows some resemblance to secondary sclerosing cholangitis in critically ill patients, it is considered as a separate and unique entity in the literature. Various treatment options like ursodeoxycholic acid, steroids, plasmapheresis, and endoscopic retrograde cholangiopancreatography guided interventions have been tried but with limited success. We have noticed significant improvement in liver function with antiplatelet therapy in a couple of patients. PCC can progress to end-stage liver disease necessitating liver transplantation. In this article, we discuss the current knowledge of PCC focusing on its pathophysiology, clinical manifestations, and management strategies.

Key Words: COVID-19; Liver; Post-COVID-19 syndrome; Long haulers; Cholangiopathy; Cholestasis

Core Tip: Post-coronavirus disease 2019 (COVID-19) cholangiopathy (PCC) is a rare complication of COVID-19 infection with gruesome prognosis. There is no proven treatment for this entity and patients often end up in liver transplantation. This review focusses on pathophysiology, clinical manifestations and management strategies of PCC along with our experience with antiplatelets in managing patients with PCC.

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INTRODUCTION

World health organization declared coronavirus disease 2019 (COVID-19) as a global pandemic in March 2020[1]. Though severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) mainly affects the respiratory system, studies have demonstrated that organotropism of the virus can cause multisystem inflammation[2,3]. Hypercoagulability associated fatal cardiovascular, cerebrovascular, and gastrointestinal complications have been reported. Derangements in liver function tests (LFT) are the most frequent hepatic manifestation of COVID-19, and its incidence among hospitalized COVID-19 patients varies between 14% to 83%[4-10]. However, the spectrum of liver injury due to COVID-19 extends beyond just abnormalities in LFT. Other attributed hepatic effects of this contagion include vascular thromboses, cholangiopathy, and COVID-19 vaccine-related auto-immune hepatitis[11-13]. Remarkably, 'Long haul COVID' or 'post-COVID syndrome' (a collective term used to denote the persistence of symptoms or development of delayed complications beyond four weeks after the initial presentation of COVID-19) has also been known to adversely affect the liver[14,15].

Although COVID-19 results most commonly in a hepatocellular pattern of liver injury, severe cholestasis has also been occasionally noted[16-20]. Roth *et al*[13] labeled this unique entity of severe cholestasis as post-COVID-19 cholangiopathy (PCC)[21]. PCC typically presents when patients recover from COVID-19 and manifests as cholestasis in patients with no history of pre-existing liver disease. PCC is diagnosed in less than 1% of patients hospitalized for COVID-19[22]. Literature regarding this newly described entity is sparse, and the natural course of the disease remains unknown. We searched PubMed, *Reference Citation Analysis* (RCA), and Web of Science using Mesh words such as "post-Covid-19 cholangiopathy", "COVID-19 sclerosing cholangiopathy", "Covid-19 and liver", and "COVID-19 and liver transplantation". The data on pathogenesis, histology, imaging findings, clinical features, management, and outcomes were collected. This review summarizes the current knowledge of PCC, focusing on its pathophysiology, clinical manifestations, and management strategies.

PARTHENOGENESIS

SARS-CoV-2 utilizes angiotensin converting enzyme 2 (ACE2) receptor to enter the host cell and the internalisation process is aided by the host cell transmembrane serine protease 2. ACE2 receptors are expressed in various human organs including lung, liver, intestine, kidney, and heart[23,24]. The binding of SARS-CoV-2 to ACE2 receptor impairs ACE2 activity leading to the enhanced effect of angiotensin-2 resulting in an inflammatory and hypercoagulable state. In the liver, ACE2 receptors are more intensely expressed on cholangiocytes (59.7%) than on hepatocytes[24]. Cholangiocytes modify hepatocyte-derived bile acids, and the tight junction between these cells is essential for bile acid accumulation and excretion. Experimental studies using liver ductal organoid culture showed that SARS-CoV-2 can cause dysregulation of genes engaged in tight junction formation and bile acid transportation, thereby resulting in an impaired barrier and defective bile acid transportation. This mechanism of injury has been purported as the cause for direct cholangiocytic injury and consequent bile acid accumulation, resulting in severe and prolonged hepatic damage caused by COVID-19[25].

Ischemia injury, especially to the cholangiocytes has also been implicated in the causality of PCC. ACE2 receptors are expressed on vascular endothelial cells and SARS-CoV-2 can lead to uncontrolled inflammation through the interleukin (IL)-6 signaling pathway. Endothelitis results in hypercoagulability and thrombosis of the peribiliary vascular plexus aggravating biliary ischemia. Shreds of evidence in favor of this hypothesis include endothelial swelling with luminal narrowing of the hepatic arterioles and portal venous endophlebitis reported on histological examination of PCC specimens.

Furthermore, improvement in liver function on treatment with antiplatelets in two of our patients (detailed below) also implicates the role of microvascular events in the pathogenesis of PCC[26]. On the contrary, a few studies noted no significant microvascular thrombi in their patients' livers with PCC[22,27,28].

Due to their similar clinicopathological features, many researchers believe that PCC is a variant of secondary sclerosing cholangitis in critically ill patients (SSC-CIP). SSC-CIP is a rare form of secondary sclerosing cholangitis which occurs in patients with no history of hepatobiliary disease after a long intensive care unit stay for various conditions requiring prolonged mechanical ventilation and high-dose vasopressors. SSC-CIP was first described by Scheppach *et al*[29]. The pathogenesis of SSC-CIP is not fully elucidated, but the main mechanism appears to be bile duct ischemia. Other proposed causes include changes in the composition of the bile and biliary infection[30]. Ischemia leads to necrosis and sloughing of biliary epithelium resulting in biliary cast formation. Ischemia can also damage hepato-biliary transporters involved in the protective barrier mechanism of cholangiocytes from toxic bile salts. Progression to cirrhosis may occur over several months[31,32]. SSC-CIP has a mortality of over 50% in severe cases and up to a fifth of patients require a liver transplant (LT)[33,34]. Damages to extra and intrahepatic biliary ducts, cholangiocyte necrosis and biliary epithelial destruction, ductular reaction, and progressive fibrosis portal tracts are features common to PCC and SSC-CIP. Though PCC is typically described in patients with severe COVID-19 who required prolonged mechanical ventilation, few authors have reported cases of severe cholestasis in patients with mild to moderate COVID-19[17,18]. In contrast to acquired immunodeficiency syndrome cholangiopathy, the opportunistic infection has not been implicated as an etiological factor of PCC.

Some authors attributed PCC to ketamine related hepatobiliary damage, a condition called Ketamine induced cholangiopathy. Ketamine is metabolised in the liver and is used for sedation of patients with respiratory distress. Two recent articles reported patients with severe COVID-19 developed cholestatic liver disease with features of sclerosing cholangitis after exposure to ketamine. Nonetheless, a majority of other reports of PCC do not mention the use of ketamine. Antiviral drugs, particularly remdesivir and immunomodulatory agents like tocilizumab (IL-6 receptor antagonist) used in the management of COVID-19 are known to cause hepatic injury. The use of these agents has not been uniformly reported in any of the published cases of PCC. Moreover, there is insufficient evidence to prove that these medications may cause cholangiopathy.

CLINICAL, BIOCHEMICAL & IMAGING FEATURES

Patients with PCC are predominantly males (80%) and their median age at presentation is over 50 years [13,23,35-37] (Table 1). Patients typically present with jaundice with or without pruritus several weeks or months after the initial admission in intensive care units for severe COVID-19[13,37]. Significantly, these patients have no prior history of liver disease. Diabetes mellitus is the most common comorbid condition reported[37]. LFTs at the time of admission following COVID-19 diagnosis are almost always near-normal. In a cohort of 24 patients with PCC from various German centers, the median serum total bilirubin level at admission was 0.6 mg/dL (N: 0.6-1.2 mg/dL), while at the time of diagnosis of PCC it was 11.9 mg/dL[37]. The highest serum total bilirubin level reported in a patient with PCC was 42.4 mg/dL[16]. Gross elevation of serum alkaline phosphatase (ALP) levels, with peak levels above 1000 U/L (N: 20-140 U/L) have been commonly reported[13,22,27]. Remarkably, these biochemical changes in PCC are similar to that observed in patients with SSC-CIP[37].

In a series of 12 cases reported by Faruqui *et al*[22] mean interval between the initial diagnosis of COVID-19 and the diagnosis of PCC by magnetic resonance cholangiopancreatography (MRCP) was 118 d. All 12 patients in their series, showed some structural changes in the biliary system on MRCP [35]. Intrahepatic bile duct strictures and the beaded appearance of intrahepatic bile ducts were the most commonly noted findings[13,22]. Ghafoor *et al*[35] studied magnetic resonance imaging/MRCP of 17 patients with PCC, and noted that none of the patients had cirrhosis or vascular thrombosis. Strictures in the form of beading of intrahepatic bile ducts were seen in 14 (82.3%) patients and biliary casts were seen in 2 (11.8%) patients. In addition to biliary abnormalities, liver contour irregularities and signal intensity changes in PCC livers can also be ascertained on MRCP.

HISTOPATHOLOGY

On macroscopic examination, the PCC livers are described to have a greenish discoloration[13,38,39] (Figure 1A). Brightfield microscopy may show portal/periportal fibrous expansion with bile ductular proliferation and degenerative cholangiocyte injury accompanied by leucocytes[13,39]. Loss of interlobular bile ducts has been described in PCC (Figure 1B). Ductular bile plugs and bile lakes are reported. Lobular disarray, hepatocanalicular bilirubinostasis with rosetting, and patchy lobular inflammation may be seen. Hilar bile ducts with inflammation and fibrosis have been described. Portal veins may show fibrin thrombi (Figure 1C). A case from the authors' series also showed Mallory Denk bodies

Table 1 A summary of reported cases of post-coronavirus disease 2019 cholangiopathy in the literature

Ref.	Number of patients	Age, median (range)	Sex	Time interval between COVID-19 diagnosis and presentation with features of PCC	Peak bilirubin (mg/dL)	Peak ALP (U/L)	MRCP	Biopsy	Treatment	Outcome reported
Edwards *et al*[21], 2020	1	59	Male	Time to elevation of bilirubin: 15 d. Peak at 79 d	14.6	4000	Beading of intrahepatic ducts	Not reported	ERCP for sludge clearance	Alive (planning biopsy to decide on liver transplantation)
Roth *et al* [13], 2021	3	34 (25-40)	2 males, 1 female	Around 6 mo	Patient 1-7 gm/dL, patient 2-24 and patient 3-15	16 × ULN	Two of three: Hepatomegaly. One of three: Extrahepatic bile ducts dilatation and one of three: Intrahepatic bile ducts strictures and dilatations with beaded aspect or solely dilatation	Two of three: Mild and moderate bile ducts paucity. Three of three moderate ductular reaction, cholangiocytes swelling and regenerative changes with portal tract inflammation, hepatic artery endothelial swelling, hepatic veins endophlebitis and periportal fibrosis	Conservative	Two patients discharged home, one still hospitalized
Faruqui *et al*[22], 2021	12	58 (38-73)	Male: 92%; female: 8%	Mean interval-118 d	Range: 2-35	Range: 965-2544	Eleven of twelve patents showed beaded images of intrahepatic bile ducts, seven of twelve patients showed bile ducts thickening and hyperenhancement, ten of twelve patients showed peribiliary diffusion high signal	Performed in four of twelve pts. Acute or chronic large bile ducts obstruction, mild fibrosis of some portal tracts, Keratin 7 immunostain positivity	UDCA. UDCA slightly improved some lab tests (AST and ALT) but GGT and ALP remained elevated	Four of twelve died for complications consequent to sclerosing cholangiopathy, 2/12 listed for transplantation, 5/12 continuing conservative management
Durazo *et al*[27], 2021	1	47	Male	Around 2 mo	19	1644	Mild intrahepatic bile ducts dilatation with focal strictures and beaded aspect, no dilatation of CBD	Inflammatory mononuclear infiltrates of bile ducts walls with increased collagen deposition, liver abscesses and bile lakes associated with bile duct injury with vacuolization and neutrophilia. Endothelial cell swelling, lumen obliteration of arterial vessels and obliterative portal venopathy	Liver transplantation	Alive with normal LFT at 7 mo after liver transplantation
Tafreshi *et al*[42], 2021	1	38	Male	Cholestasis at a few months after initial hospital admission	9.8	3665	Mild dilatation of intrahepatic bile ducts with beaded aspect, dilatation of CBD and periportal oedema	Cholangiocytes injury, ductular proliferation, canalicular cholestasis, a bile lake and focal bridging fibrosis	Under evaluation for liver transplantation	Under evaluation for liver transplantation

Lee *et al* [38], 2021	1	64	Male	51 d	7.8	1600	Mild intrahepatic biliary ductal dilatation and mild patchy T2 hyperintensity within the right hemiliver, concerning for cholangitis	Explant pathology: Bridging fibrosis, severe bile duct injury, ductular reaction and leucocytes and plasma cells infiltrate	Liver transplantation	Alive at 8 mo and returned to work
Klindt *et al* [43], 2021	1	47	Male	Around 50 d	18	1700	Alterations of medium and small intrahepatic bile ducts	Enlarged portal tracts with phlogistic infiltrate, ductular reaction with degenerative alterations of bile duct epithelium; focal biliary metaplasia of periportal hepatocytes. A few bile infarcts and perivenular canalicular cholestasis	Liver transplantation	Alive
Rojas *et al* [44], 2021	1	29	Female	Around 2 mo	19	6000	Only a cystic lesion in liver segment V	Low periportal phlogistic infiltrate without necrosis but with a severe obstructive cholestatic pattern	UDCA and cholestyramine	Slight improvement at the time of reporting
Bütikofer *et al*[28], 2021	4	59 (54-67)	Male: 3, female: 1	70-153 d	3.81-26.05	(12.85-21.26) × ULN	Diffuse irregularities of the bile ducts with dilatations and strictures	Portal inflammation with pericellular fibrosis	UDCA	2 patients: Deceased. 1 patient: Listed for liver transplantation (MELD-17). 1 patient: Persistently marked increased ALP and GGT at 9 mo of follow up
Rela *et al* [16], 2022	1	50	Male	4 wk	42.4	248	Mild prominence of central intrahepatic, common hepatic, and common bile ducts with minimal beading of the right posterior sectoral and segment 2 ducts	Mild portal tract inflammation with lymphocytes, histiocytes and few eosinophils, with loss of interlobular bile ducts	Auxiliary partial orthotopic liver transplantation	Asymptomatic at 6 mo follow-up with good graft function and recovering function in native liver remnant
Kulkarni *et al*[17], 2022	15	Unvaccinated: 59 (24-67). Vaccinated: 52 (29-67)	Unvaccinated: Male (8/8, 100%). Vaccinated: Male (5/7, 71.4%)	The median time to the development of cholestasis was 35 (19-44) d and in vaccinated group and 39.5 (27-57) in the unvaccinated group	Unvaccinated group: 22.95 (4.2-48.5), vaccinated group 17 (8.3-32.4)	312 (239-517) U/L in the vaccinated group and 571.5 (368-1058) U/L in the unvaccinated group	Normal in all patients	Architectural distortion, fibrosis, cholestasis, and ductular reaction with duct openia in unvaccinated group. Cholestasis and inflammation and no fibrosis in vaccinated group	UDCA. Plasma exchange: 5. Oral steroids: 4	2-died. 2-liver transplantation. 2-listed for liver transplantation. 1-declined liver transplantation. 2-recovered. All 7 in vaccinated group recovered
Mayorquín-Aguilar *et al*[45], 2022	3	46 (45-52)	Male	12-14 wk in two patients and 20 d in another patient	17.32 (5.8-22.7)	1328 (705-1695)	Irregular morphology of intrahepatic and extrahepatic bile ducts. Multiple areas of stenosis in the distal intrahepatic bile ducts	Intracanalicular cholestasis, portal inflammation, ductular reaction, and moderate portal fibrosis	UDCA, cholestyramine, and sertraline	Persisitent cholestasis in one patient and disease progressed to cirrhosis in another patient. Third patient expired due to unrelated cause

Hunyady *et al*[37], 2023	24	57 (19-73)	Out of 24 patients, 20 were male, 4 females	91 d (IQR: 64-154 d)	Peak bilirubin 24.3 mg/dL. Median bilirubin 11.9 mg/dL (6.0-24.3)	Peak ALP 1100 U/L. Median ALP 925 U/L. (555-1100)	Strictures or dilatation of biliary system, rarefication of biliary tree including contrast filling defects or detection of biliary casts	-	UDCA in 16 (66.7%) patients, ERCP with sphincterotomy done in 20 (83.3%) patients. Cast extraction done in 11 (45.8% patients). 3 patients underwent liver transplantation	3 patients underwent liver transplantation. 2 patients had transplant free survival

ULN: Upper limit of normal; UDCA: Ursodeoxycholic acid; COVID-19: Coronavirus disease 2019; ALP: Alkaline phosphatase; PCC: Post-coronavirus disease 2019 cholangiopathy; IQR: Interquartile range; ERCP: Endoscopic retrograde cholangiopancreatography; GGT: Gamma glutamyl transpeptidase; MELD: Model for end-stage liver disease; CBD: Cannabidiol; LFT: Liver function test; MRCP: Magnetic resonance cholangiopancreatography; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

along with patchy sinusoidal dilatation and congestion with hepatocyte atrophy (Figure 1D). In late cases, bridging fibrosis and cirrhosis have been reported[13,38]. Immunostaining with CK7 may show biliary metaplasia of hepatocytes (Figure 1E). Pathognomonic findings of PCC on immunohistochemistry include a granular cytoplasmic positivity for SARS-CoV-2 within hepatocytes and sinusoidal macrophages (Figure 1F).

TREATMENT

Given that PCC is a recently described disease arising out of the COVID-19 pandemic, little is known about its natural history. Anecdotal evidence of various treatment modalities is present in the literature, and currently, there is no well-defined treatment algorithm. Though universally used for PCC, medical treatment with ursodeoxycholic acid and cholestyramine does not seem to offer much clinical or biochemical improvement. Antiplatelet medications have serendipitously shown benefits (two patients from the authors' series). However, the exact indication, timing, dose, and duration of this regimen remain unknown. Franzini *et al*[40] recently published a video demonstration of their experience with cholangioscopy (SpyGlass®) to assess bile duct changes and removal of biliary casts. In patients with biliary casts or cholangitis, interventions using endoscopic retrograde cholangiopancreatography may offer transient improvement of the clinical condition, but abnormal liver functions are likely to persist even after an anatomical clearance of the extrahepatic ducts[13,36].

LIVER TRANSPLANTATION FOR PCC

In most patients, the disease causes progressive biliary injury with worsening cholestasis and recurrent infections[16,22]. The first successful LT for PCC was reported by Durazo *et al*[27]. A 47-year-old man with PCC and worsening liver and renal function underwent deceased donor liver transplantation on day 108 from the initial presentation with COVID-19. Histopathology of the explanted liver showed features of severe sclerosing cholangitis with hepatic abscesses. The patient improved well and graft

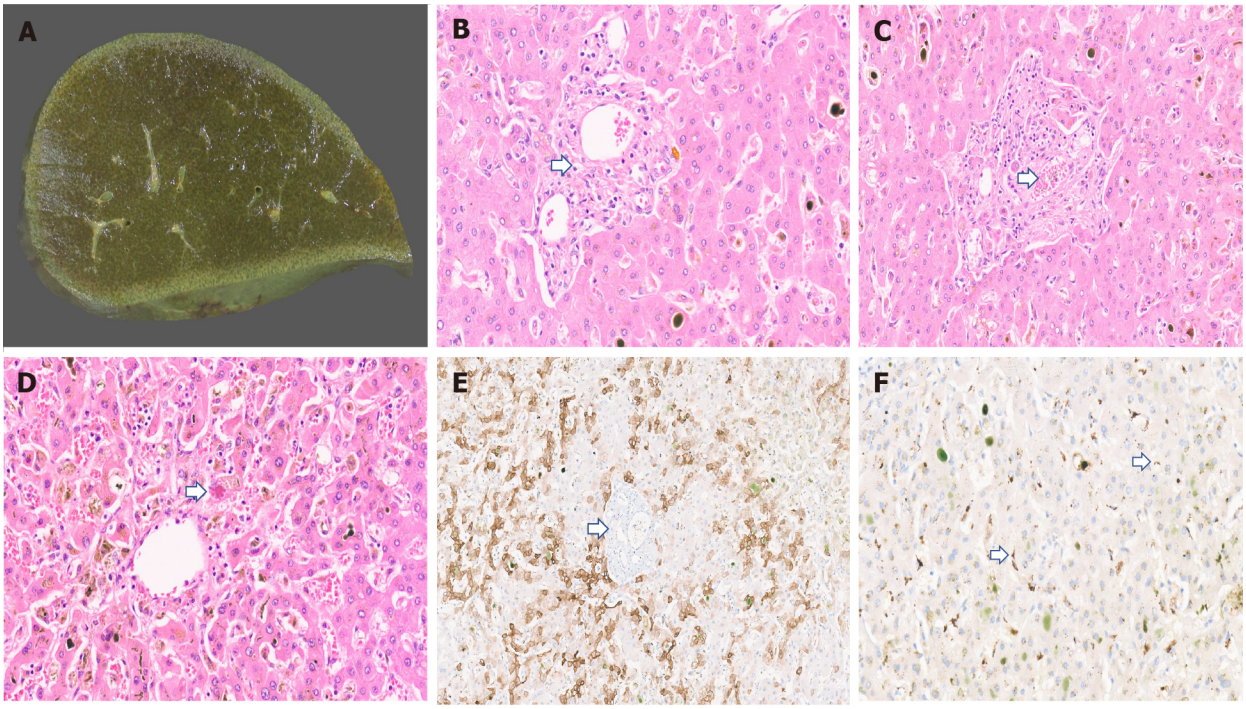

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Figure 1 Histopathology imaging. A: Explant liver cut surface with greenish discolouration; B: Explant liver displaying duct loss (arrow) and bilirubinostasis [× 20, hematoxylin and eosin (H&E)]; C: Fibrin thrombi in portal vein (arrow, × 18, H&E); D: Mallory Denk body in a hepatocyte (arrow) and mild lobular inflammation (× 18, H&E); E: CK7 immunostaining with duct loss (arrow) and biliary metaplasia of hepatocytes (× 15); F: Severe acute respiratory syndrome coronavirus 2 immunostaining with granular brown positivity in hepatocytes and macrophages (arrow, × 15).

function was normal at 7 mo after LT. Subsequently, various authors reported their experience with LT for patients with PCC[16,22,38]. Our team reported a living donor auxiliary right lobe LT (APOLT) in a 50-year-old patient at 12 wk after the initial diagnosis of COVID-19. The patient underwent a right trisectionectomy with caudate lobectomy. The right lobe was retrieved robotically from a related donor and implanted orthotopically. Interestingly, hepatobiliary scintigraphy at six months follow-up showed 90% and 10% in the graft and native livers respectively, reflecting some native liver recovery[16]. The authors' premise was that since the natural course of PCC is unknown, there remains the possibility of spontaneous liver recovery. Thus, the allograft in APOLT potentially acts as a bridge till native regeneration occurs, providing the patient with a realistic possibility of becoming immunosuppression-free. While LT is an effective curative option for patients with PCC, it is naïve to offer it to every patient with PCC. It is also sobering to realise that several variables of this management continue to be undefined. These include vital data to define which cohort of patients are likely to recover without an LT. It is likely that these questions will have answers as experience grows with this disease entity.

COVID-19 VACCINATION AND PCC

In the current era of near-universal COVID-19 vaccination, it is important to re-evaluate the natural course of PCC. Vaccination has been shown to reduce the severity of COVID-19 and improve outcomes [41]. Kulkarni *et al*[17] compared 8 unvaccinated patients with 7 vaccinated patients with post-COVID-19 cholestasis and showed that serum ALP and gamma glutamyl transpeptidase (GGT) were significantly lower in the vaccinated group. Furthermore, all patients in the vaccinated group improved with conservative management while a majority in the unvaccinated group required LT. Again, literature in this regard is scarce, but intuitively, COVID-19 vaccination is likely to play a positive role in preventing/attenuating the course of PCC.

OUR EXPERIENCE

Our experience with PCC is limited to four patients. All of them presented with severe cholestatic jaundice following initial recovery from COVID-19 illness[26] (Table 2). All were men in their 5th or 6th decade of life. Unlike other reported series, only half of our patients had a history of mechanical ventilation for their COVID-19 related respiratory illness. Clinical recovery from COVID-19 was

Table 2 A summary of authors' experience with post coronavirus disease 2019 cholangiopathy

Case	Age/sex	ICU admission for COVID	Mechanical ventilation for COVID	Medications received for COVID	LFT at initial admission for COVID	LFT (peak values)	Time interval[1]	MRCP	Biopsy	Treatment	Outcome
1	67/male	Yes (hypoxia-high flow oxygen)	No	Remdesivir, methylprednisolone	Bilirubin 0.84 mg/dL, AST 54 U/L, ALT 32 U/L, ALP 127 U/L, GGT 78 U/L and albumin 4.1 mg/dL	Bilirubin 12.7 mg/dL, AST 322 U/L, ALT 527 U/L, ALP 474 U/L and GGT 1318 U/L, albumin 3.2 g/dL, INR 0.98	4 wk	Normal except for cholelithiasis	Mild portal fibrous expansion with diffuse loss of interlobular bile ducts	Prednisolone, ursodeoxycholic acid	Hyperbilirubinemia continued to worsen. Expired of pneumonia
2	50/male	Yes	Yes	Methylprednisolone, Remdesivir, antibiotics and thromboprophylaxis	Bilirubin 0.5 mg/dL, AST 43 U/L, ALT 57 U/L, ALP 60 U/L, GGT 64 U/L, albumin 2.8 mg/dL	Bilirubin 31.3 mg/dL, ALP 248 U/L, GGT 355 U/L, AST 176 U/L and ALT 200 U/L	6 wk	Mild prominence of central intrahepatic, common hepatic, and common bile ducts with minimal beading of the right posterior sectoral and segment 2 ducts	Mild portal tract inflammation with lymphocytes, histiocytes and few eosinophils, with loss of interlobular bile ducts	Auxiliary partial orthotopic liver transplantation	Asymptomatic at 6 mo follow-up with good graft function and recovering function in native liver remnant
3	58/male	No	No	Doxycycline, ivermectin, methylprednisolone. Remdesivir, paracetamol along with zinc and other vitamin supplements	Bilirubin 1.99 mg/dL, AST 145 U/L, ALT 140 U/L, ALP 70 U/L, GGT 65 U/L and albumin 4.1 g/dL	Bilirubin 10 mg/dL, AST 167 U/L, ALT 181 U/L, ALP 532 U/L and GGT 728 U/L	6 wk	Normal	Bile duct degenerative changes in majority of portal tracts along with prominent centrilobular hepatocanalicular bilirubinostasis	Aspirin, clopidogrel, prednisolone, ursodeoxycholic acid	Improved, LFT at 18 mo of follow up. Bilirubin 1.3 mg/dL, AST 101 U/L, ALT 101 U/L, ALP 309 U/L
4	52/male	Yes	Yes	Amoxycillin, remedesivir, IV methyl prednisolone	Bilirubin 1 mg/dL, albumin 4.2 g/dL, ALT 25 U/L, AST 49 U/L, ALP 110 U/L, GGT 62 U/L	Bilirubin 33.9 mg/dL ALP 390 U/L, ALT 41 U/L, GGT 94 U/L, AST 58 U/L	6 wk	Normal	Bile ducts showed mild injury, lobular bilirubinostasis	Therapeutic plasma exchange, aspirin, clopidogrel, prednisolone, ursodeoxycholic acid	Improved, LFT at 6 mo of follow up. Bilirubin 1.1 mg/dL, ALP 101 U/L, AST 23 U/L, ALT 32 U/L

[1]Time interval between coronavirus disease 2019 (COVID-19) diagnosis and presentation with features of post-COVID-19 cholangiopathy.

COVID: Coronavirus disease; ALP: Alkaline phosphatase; GGT: Gamma glutamyl transpeptidase; MELD: Model for end-stage liver disease; LFT: Liver function test; MRCP: Magnetic resonance cholangiopancreatography; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ICU: Intensive care unit; INR: International normalized ratio.

complete and all of them had been discharged between 7 and 21 d. None of them had a history of any underlying liver disease. LFTs were uniformly unremarkable at the time of COVID-19. All these patients were readmitted with fatigue and jaundice four to six weeks following their COVID-19 and a couple of them developed pruritus. Peak enzymes were aspartate aminotransferase 4-8 times upper limit normal (ULN), alanine aminotransferase 3-10 ULN, ALP 4-6 ULN, and GGT 5-15 ULN. Peak bilirubin varied between 15 to 42 mg/dL (N: 0.6-1.2 mg/dL). Interestingly, none of them developed coagulopathy,

ascites, or hepatic encephalopathy. Abdominal imaging in 3 patients was unremarkable. MRCP of one patient demonstrated mild prominence of central intrahepatic, common hepatic, and common bile ducts with minimal beading of the right posterior sectoral and segment 2 ducts. Liver biopsies showed loss of interlobular bile ducts, degenerative features in residual ducts, hepatocanalicular bilirubinostasis, and fibrin thrombi in some vessels.

Of the 4 patients, one died of worsening symptoms and sepsis. The second patient developed progressive jaundice and underwent APOLT (described above)[16]. He remains well on 9 mo follow-up and is due to have a hepatobiliary scintigraphy at 12 mo to reassess native liver regeneration. The third patient remained symptomatic with worsening hyperbilirubinemia and was listed for LT. On evaluation, he was noted to have double-vessel coronary artery disease which required stenting. Following stent placement, he was commenced on aspirin and clopidogrel. Interestingly, there was a significant improvement in LFT within six weeks of initiating antiplatelet therapy. He was discharged home without the need for a LT and his clinical improvement was attributed to anti-platelet drugs. With this experience, the fourth patient was commenced early on antiplatelet therapy and he too had a remarkable improvement in his clinical and biochemical status. Both these patients remain well on 6- and 7-mo' follow-up respectively. This finding underpins the theory of microvascular events in the pathogenesis of PCC.

CONCLUSION

PCC is a recently described entity of severe cholestasis that has been recognized in patients recovering from severe COVID-19 infection. While the exact etiopathogenesis remains unknown, purported theories include SSC-CIP, microthromboses, direct liver injury, and autoimmune etiology among others. Although relatively uncommon at present, it is likely that this disease will be more commonly encountered in the near future. Its natural course remains undefined, but with accumulating evidence several successful management strategies have been proposed. There remains a need for concentrated, multicenter studies to further elucidate this disease which can potentially have high morbidity if not identified and managed appropriately.

FOOTNOTES

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MINIREVIEWS

Changing trends in the minimally invasive surgery for corrosive esophagogastric stricture

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Abstract

Esophagogastric stricture is the troublesome long-term complication of corrosive ingestion with a significant adverse impact on the quality of life. Surgery remains the mainstay of therapy in patients where endoscopic treatment is not feasible or fails to dilate the stricture. Conventional surgical management of esophageal stricture is open esophageal bypass using gastric or colon conduit. Colon is the commonly used esophageal substitute, particularly in those with high pharyngoesophageal strictures and in patients with accompanying gastric strictures. Traditionally colon bypass is performed using an open technique that requires a long midline incision from the xiphisternum to the suprapubic area, with adverse cosmetic outcomes and long-term complications like an incisional hernia. As most of the affected patients are in the second or third decade of life minimally invasive approach is an attractive proposition. However, minimally invasive surgery for corrosive esophagogastric stricture is slow to evolve due to the complex nature of the surgical procedure. With advancements in laparoscopic skills and instrumentation, the feasibility and safety of minimally invasive surgery in corrosive esophagogastric stricture have been documented. Initial series have mainly used a laparoscopic-assisted approach, whereas more recent studies have shown the safety of a total laparoscopic approach. The changing trend from laparoscopic assisted procedure to a totally minimally invasive technique for corrosive esophagogastric stricture should be carefully disseminated to preclude adverse long-term outcomes. Also, well-designed trials with long-term follow-ups are required to document the superiority of minimally invasive surgery for corrosive esophagogastric stricture. The present review focuses on the challenges and changing trends in the minimally invasive treatment of corrosive esophagogastric stricture.

Key Words: Robotics; Laparoscopy; Surgery; Caustics; Bypass; Stricture

Core Tip: Most patients with corrosive esophagogastric stricture are young adults in the most productive period of their lives. Hence, minimally invasive surgery for corrosive stricture is an attractive proposition. However, minimally invasive surgery for corrosive esophagogastric stricture is slow to evolve due to complex operative steps. With advances in laparoscopic technology, there is a changing trend from laparoscopic-assisted approaches to totally minimally invasive techniques. However, assessing the patency of the vascular arcade remains a challenge during the laparoscopic approach. The challenges and limitations highlighted in the present review could guide future research on minimally invasive surgery in corrosive esophagogastric stricture.

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INTRODUCTION

Consumption of corrosive substances remains a significant public health concern, especially in developing countries. Stricture of the upper aerodigestive tract is one of the most feared long-term complications of corrosive ingestion. Children and young adults in the most productive period of their lives make up about 80% of the population affected by corrosive injuries globally[1]. While less common in western countries, corrosive esophageal injuries are the most frequent cause of benign esophageal obstruction in developing countries[2]. The social and economic repercussions of severe corrosive injuries are substantial. Consequences include a significant negative social impact due to the stress of prolonged treatment, delayed recovery, and negative body image secondary to unpleasant laparotomy scars, which cause families to dissolve and increase the chances of repeat suicidal ideation in patients.

Innovations and advancements in minimally invasive surgery allowed its application in various gastrointestinal surgical disorders. The short-term benefits of minimally invasive surgery are well known and include early ambulation and postoperative recovery, decreased postoperative pain, and analgesic requirement[3-5]. Also, the excellent cosmetic outcome is an added advantage considering the age group of the affected population. The long-term benefits of minimally invasive surgery are reduced incision-related complications such as incisional hernia. However, minimally invasive surgery for corrosive esophageal injury is slow to evolve due to the complexity of the esophageal bypass procedure [5,6]. Also, surgeons primarily focused on restoring oro-enteral continuity and reestablishing a euphagic state rather than the minimally invasive approach. However, growing experience in various minimally invasive gastrointestinal surgical procedures allowed its application in corrosive esophagogastric strictures.

Initial minimally invasive series for corrosive esophagogastric strictures reported hybrid approaches (hand-assisted or mini-laparotomy) because of limited instrumentation and experience[7-9]. However, with the advancement of laparoscopic technology, energy sources, and better instrumentation, a few series reported the safety and feasibility of the total minimally invasive procedure[10,11]. As the number of patients reported in each series is limited, the present review aims to provide an overview of the changing trends in minimally invasive surgery for corrosive esophagogastric strictures. Also, the current challenges and future perspectives in the minimally invasive management of corrosive esophagogastric strictures will be highlighted in this review.

SEARCH STRATEGY

All the authors did a PubMed search of relevant articles. Further, the articles' reference lists were also searched for additional appropriate studies. The keywords and combinations included in the search were: "Caustics"; "stricture"; "bypass"; "corrosive stricture" and "laparoscopic"; "colon conduit" and "Laparoscopic"; "colon bypass" and "robotic"; "gastric stricture" and "Laparoscopic"; "esophageal stricture" and " laparoscopic"; "gastric conduit" and "Laparoscopic"; "gastric stricture" and "robotic"; "corrosive stricture" and "esophagectomy" and "laparoscopic ". The search was limited to publications in English literature. All the authors agreed that the articles selected for review were relevant.

MINIMALLY INVASIVE SURGERY FOR ESOPHAGEAL STRICTURE: GASTRIC TRANSPOSITION

The two most frequently utilized conduits have been the stomach and the colon. While the colon has traditionally been the favored option, comparable results have been reported with gastric conduits in selected patients[3,7-9]. The use of a gastric conduit for the esophageal bypass procedure would be contingent upon the presence of a normal well-vascularized stomach, with no evidence of any stricture in the body or antrum and the absence of a high esophageal or hypopharyngeal stricture. The retrosternal gastric pull-up is an acceptable alternative to colon bypass in these patients. Traditionally, gastric transposition in corrosive stricture has been carried out using an open surgical method.

Technique

Javed *et al*[10] reported the technical feasibility and safety of the laparoscopic approach in four patients with corrosive stricture of the esophagus who had failed endoscopic therapy. The suitability of the stomach as a prospective conduit was evaluated based on the barium swallow. A computed tomography (CT) scan of the abdomen was used in patients for whom a complete barium examination was not possible because of a tight esophageal stricture. Findings from previous surgical records at the time of the feeding jejunostomy also guided decision-making. However, the final decision regarding the appropriateness of the stomach as a conduit was decided at the time of surgery after direct evaluation with a laparoscope.

The procedure was performed using four laparoscopic ports, and the conduit was based on right gastroepiploic vessels. An adequate retrosternal tunnel is created under vision till the level of the thoracic inlet. The stomach is delivered into the neck with the help of Ryle's tube placed through the neck incision and advanced into the abdomen *via* the retrosternal tunnel. Gentle handling of the conduit and preserving vascular supply are vital principles to ensure an excellent postoperative outcome.

Outcome

The mean duration of the surgery was 260 min, and none of the patients required blood transfusions or postoperative ventilation. All patients were ambulated on postoperative day one. Oral liquids were started between the fifth and seventh postoperative days after a gastrograffin study. One patient had transient hoarseness and another a mild chest infection, but none had an anastomotic leak. The mean hospital stay was 7.75 d. Long-term follow-up results are not available. However, all patients were euphagic to a solid diet at a mean follow-up of 6.5 mo[10].

Limitations

In most patients with corrosive injury, using gastric conduit is not a viable option due to the frequent involvement of the stomach in the scarring process, particularly after acid ingestion. As a reliable evaluation of the stomach is not feasible in patients with high-grade esophageal stricture, gastric stricture manifesting in the postoperative period is not uncommon. In patients with high pharyngeal strictures, the length of the stomach conduit may be a concern. Also, functional results of gastric conduit tend to deteriorate with time, with symptomatic reflux, stricture, and columnar metaplasia of the residual squamous epithelium above the anastomosis. Additionally, when a gastric conduit is utilized, the function of the gastric reservoir is lost.

COLONIC TRANSPOSITION

Indications

The colon is the most frequently used esophageal substitute in corrosive injury patients, particularly those with high pharyngoesophageal strictures and accompanying gastric strictures[11-14]. Such substantial lesions of the upper aerodigestive tract necessitate a longer and more versatile conduit, which the colon can offer[15,16]. Relative vascular impairment at the tip of the gastric conduit predisposes to anastomotic complications. At the same time, a robust blood supply of the colon conduit minimizes the risk of anastomotic leaks and strictures[15-18]. However, using the colon requires a minimum of three anastomoses instead of one needed with gastric conduit[17,18].

Various centers have used different parts of the colon as a conduit which may be the right, left, or mid-colon. Ananthakrishnan *et al*[14] have previously documented good long-term outcomes with open mid-colon esophageal bypass, a variation of the traditional left colon esophageal bypass. The mid-colon bypass offers a longer colon segment than other standard colon bypasses, thereby enabling tension-free cervical anastomoses. Additionally, using the terminal ileum to deliver the colon through the retrosternal tunnel to the neck protects the vascular pedicle and arcade from trauma. Also, the initial passage of the widest portion of the colon (cecum), through the retrosternal region minimizes the trauma on the subsequent colon segments. Resection of the terminal ileum and cecum in the neck permits using a colon segment that is comparatively unaffected by the trauma caused by conduit

transfer[19].

An esophageal bypass without esophagectomy provides numerous advantages over esophageal resection. Corrosive injuries, especially those caused by acid, result in extensive periesophageal fibrosis, making esophageal resection hazardous with complications including bleeding, laryngeal nerve injury, thoracic duct damage, and tracheal lacerations[20-23]. Esophageal resection disproportionately increases the complexity and morbidity of the surgery than its claimed benefit of preventing cancer, whose prevalence is exaggerated[16,17,22]. Additional benefits include a reduction in operation duration and the avoidance of thoracotomy or blind hiatal dissection[17,18,21].

Traditionally colon bypass is performed using an open technique that requires a long laparotomy incision, frequently linked to suboptimal cosmetic results and long-term complications like incisional hernia. These consequences can be mitigated by adopting a minimally invasive approach, which has been recently demonstrated to be both safe and feasible[15,19-21]. While the initial series used hand-assisted and laparoscopic-assisted techniques, the feasibility of total laparoscopic colon bypass has been recently documented.

Hand-assisted laparoscopic surgery

The hand-assisted laparoscopy combines traditional laparoscopy with the capability of putting a hand intraperitoneally. The hand-assisted technique improved exposure and allowed manual exploration, blunt dissection, and immediate control of hemostasis[20]. The hand port offers abdominal access for the surgeon's hand while maintaining the pneumoperitoneum. After colon mobilization, gastrointestinal continuity and extracorporeal anastomosis (coloenterostomy and colocolostomy) were carried out through the incision to implant the hand port device[21].

Lin *et al*[21] demonstrated the safety and feasibility of Hand-assisted laparoscopic colonic mobilization for esophageal reconstruction in seven patients with esophageal stricture secondary to caustic ingestion. The procedure was performed with the patient in the lithotomy posture, and the surgeon stood between the patient's legs (Table 1). The pneumo sleeve device was attached to the 7-cm supraumbilical midline incision. The camera port was positioned around 5 cm below the umbilicus, with two additional 10-mm ports placed into the bilateral flanks. The surgeon's right hand, wrapped with a conventional glove, was inserted into a plastic sleeve with perforated fingers (Pneumo Sleeve), and then covered with a second traditional glove. The colon was mobilized using the ultrasonic shears, the pneumo device was subsequently removed, and the colon was exteriorized *via* the wound protector. The conventional left colon esophagocoloplasty extending from the hepatic flexure to the splenic flexure based on the ascending branch of the left colic artery was performed.

Outcomes of hand-assisted laparoscopic surgery

In the study by Lin *et al*[21], the mean (range) operative time was 3.9 (3.2-5.0) h, with the mean (range) operative time of 62 (45-75) min for hand-assisted laparoscopic colonic mobilization. Two of the seven patients had cologastric anastomosis combined with gastrojejunostomy due to the associated gastric antropyloric stricture (Table 2). Postoperatively, no patients experienced any anastomotic complications, and all are euphagic at 18 mo follow-up. One patient had a mild abdominal wound infection. The mean (range) hospital stay was 9.1 (8.0-13.0) d[21].

Laparoscopy assisted colonic transposition

Proponents of laparoscopic-assisted techniques believe that intracorporeal suturing, a rate-limiting step in laparoscopy, can be eliminated. Also, adding a minilaparotomy does not contribute to the disfigurement because most patients have incision scars due to the earlier feeding procedure while offering comfort to the surgeon[24].

Banerjee *et al*[24] utilized laparoscopy for left colic artery-based colonic mobilization and retrosternal tunneling in ten patients with acid-induced esophageal strictures. The assessment of the adequacy of conduit perfusion and subsequent colonic transection was performed through a mini laparotomy (Table 1). The laparoscopic procedure was performed with the patient in the supine posture with legs split and the neck extended to the right. Four laparoscopic trocars were used. During descending and ascending colon mobilization, the surgeon stood to the patient's right and left, respectively.

Lateral to medial mobilization of the descending, ascending, and transverse colon was performed sequentially. After releasing the falciform ligament from the anterior abdominal wall, the Xiphisternum was palpated with the non-dominant hand and pressed down to visualize its location on the monitor. At the junction of xiphisternum and sternum, the diaphragm was incised using ultrasonic shears to create a retrosternal tunnel. A U-shaped collar incision was used if the patient were to undergo a pharyngolaryngectomy. Otherwise, a left pre-sternomastoid incision was made for exposure of the esophagus alone. In patients where the larynx was salvageable, anastomosis to the pyriform fossa helped in preventing laryngectomy.

A mini-laparotomy was performed through the previous upper abdominal incision for feeding jejunostomy. The right colic, middle colic, and ileocolic vessels were clamped with bulldog clamps to confirm adequate perfusion by the left colic vessels. As per the required length of the colon for transposition transection was done at the transverse/ascending/ileo-ascending colon to create an

Table 1 Studies on laparoscopic colon transposition showing baseline and intraoperative variables

Ref.	Total No. patients	Surgery	Colon used	Arterial pedicle	Route	Blood loss (mL)	Operative duration
Lin *et al* [21], 2002	7	Hand-assisted laparoscopic colon mobilization	Transverse colon	Ascending branch of left colic artery	Retrosternal	100 (50-350)	3.9 h (3.2-5.0)
Esteves *et al* [4], 2010	3/5 corrosive	Laparoscopic-assisted esophagectomy and colonic interposition	Transverse colon	Double vascular pedicle (left colic artery and marginal paracolic arcade)	Posterior mediastinal	-	3.6 h (3.0-4.0)
Maurer *et al* [5], 2013	20	Laparoscopic transhiatal esophagectomy + laparoscopic assisted colonic transposition	Transverse colon	-	Posterior mediastinal	-	8.3 h
Javed *et al* [18], 2013	4	Total laparoscopic esophageal bypass	Ascending, transverse colon	Left colic artery	Retrosternal	100 (80-120)	6.1 h (5.3-7.0)
Banerjee *et al*[24], 2017	10	Laparoscopic-assisted colonic transposition	Ascending, transverse colon	Left colic artery	Retrosternal	150 (100-200)	240 m (210-300)
Gurram *et al*[19], 2020	7	Laparoscopic midcolon esophageal bypass	Mid colon	Left colic artery	Retrosternal	200 (100-400)	440 m (390-600)

Table 2 Studies on laparoscopic colon transposition showing postoperative outcomes

Ref.	Anastomotic leak	Anastomotic stricture	Wound infection	Other complications	Hospital stay (d)	Follow up (mo)
Lin *et al*[21], 2002	Absent	Absent	1	None	9.1 (8.0-13.0)	18.2
Esteves *et al* [4], 2010	Absent	1 (cervical dilatation)	Absent	1-atelectasis; 1-pneumonia; 2-pneumothorax; 1-cervical stenosis (persistent fibrotic esophagus)	6 (9-18)	20.4 (10.0-29.0)
Maurer *et al* [5], 2013	6-cervical anastomotic leak (resolved spontaneously)	11-anastomotic stricture	-	6-pneumothorax; 5-pleural effusion; 3-atelectasis; 6-vagal nerve injury	26.8	-
Javed *et al* [18], 2013	1 minor leak (cervical)	Absent	Absent	None	-	5 (3-6)
Banerjee *et al* [24], 2017	1 (resolved spontaneously)	1 (dilatation thrice)	Absent	1-transient left recurrent laryngeal nerve paresis	-	11 (5-24)
Gurram *et al* [19], 2020	1 (segmental conduit ischemia)	Absent	Absent	2- postoperative pneumonia	9 (8-42)	14 (7-42)

isoperistaltic conduit based on the left colic artery. Using a camera sleeve as a retrosternal sheath and a Foley catheter attached to the cranial tip of the conduit with a silk suture, the conduit was delivered atraumatically into the neck with gentle traction[25].

The cervical esophagus was longitudinally opened, and a side-to-side esophago-colic anastomosis was performed using an interrupted 4-0 polydioxanone suture to create a wide anastomosis. In patients with stricture immediately below the cricopharynx, the esophageal slit was widened by extending it superiorly into the hypopharynx. Those who underwent partial laryngectomy received a side-to-end pyriform fossa-colic anastomosis. On the other hand, those who underwent total pharyngolaryngectomy had end-to-end pharyngo-colic anastomosis constructed at the base of the tongue. The conduit's slack was rectified and secured to the diaphragmatic hiatus. Beyond the DJ flexure, the conduit was anastomosed to the proximal jejunum using stapled/hand-sewn side-to-side anastomosis. Just distal to the anastomosis, the colon was divided while maintaining the integrity of the marginal arcade and the colonic continuity restored.

Outcomes of laparoscopy assisted colonic transposition

In the study by Banerjee *et al*[24], acid-induced strictures in ten adults (5 males and 5 females) were treated. Two individuals had duodenal involvement in addition to several esophageal and gastric strictures. Three patients had strictures of the pharynx and larynx, requiring suprahyoid pharyngolaryngectomy (n = 2) or partial laryngectomy (n = 1). The mean (range) operative time was 240 (210-300) min with a mean (range) blood loss of 150 (100-200) mL. Postoperatively one patient

developed a cervical anastomotic leak on ninth postoperative day, which healed with conservative management (Table 2). One patient developed proximal anastomotic stricture, requiring dilatation. One patient had transient left recurrent laryngeal nerve paresis, which resolved spontaneously. All the patients were euphagic to solid oral diet[24].

Total laparoscopic colonic transposition

Advancements in laparoscopic technology and instrumentation facilitated total laparoscopic colonic transposition, as documented in recent studies[18,19]. The critical steps of total laparoscopic colonic transposition are described here.

Patient and port position: After inducing general anesthesia, the patient was positioned in the supine position with a leg split. A soft wedge or sandbag is kept under the shoulders, the neck is extended to the right, and the arms are tucked to the side of the body. Pneumoperitoneum was established using a 12 mm infraumbilical trocar. Five more additional ports were installed. In addition to an epigastric port to create a retrosternal tunnel, two working and two assistant trocars were inserted in the pararectal area. The patient's previous jejunostomy or gastrostomy, if present, would be removed if it interfered with the surgical procedure. Later in the surgery, the gastrostomy could be utilized to construct a side-to-side cologastric anastomosis.

Trial clamping of vascular pedicles and assessment of the adequacy of perfusion: The operative surgeon stands on the patient's left side and uses the two left pararectal ports as working trocars during the initial dissection. The ileocolic vessels are identified after providing traction to the terminal small bowel mesentery, looped, and secured with a laparoscopic vascular clamp (Figure 1). In patients with separate origin of the right colic artery; the vessel is dissected and clamped. After controlling the ileocolic pedicle and, if present, the right colic artery, the lesser sac is entered by dividing the gastrocolic omentum. Right colic veins draining to the gastrocolic trunk are divided. Middle colic vessels are dissected at their origin proximal to its bifurcation and clamped using a laparoscopic vascular clamp (Figure 1). To prevent retrograde perfusion of colonic conduit through the ileal arcade, a laparoscopic vascular clamp is applied to the mesentery of the terminal ileum. With the laparoscopic bulldog clamps in place, the sufficiency of the colonic vascular arcade is assessed. The surgeon briefly releases the pneumoperitoneum before proceeding to the neck to commence dissection.

Neck dissection: The neck is entered using a gently curved left-sided linear neck incision from the suprasternal notch to the upper part of the neck. Less frequently, a more cosmetic transverse skin crease neck incision may be used, although its application is restricted to lower esophageal strictures[18]. The incision is deepened further *via* the platysma while dividing the inferior belly of the omohyoid. The middle thyroid vein and occasionally the anterior jugular vein must be ligated because they impede the operative field. The thyroid gland is retracted medially away from the field with the use of a thyroid stitch. The cricoid cartilage is now palpated, the cervical esophagus is recognized, and its lumen is palpated either over a prepositioned Ryle's tube or an esophageal bougie introduced by the anesthesiologist. Stay sutures are placed posteriorly above and below the targeted esophagotomy site to facilitate esophagotomy and subsequent anastomosis. Finger dissection is used to create a short retrosternal tunnel from the neck incision (Figure 1). The pneumoperitoneum is recreated after the incision has been covered with surgical gauze to prevent gas leakage.

Retrosternal tunnel creation: The surgeon shifts from the left side of the patient to stand between the patient's legs and utilizes the upper two working trocars. The epigastric trocar will be used to finish the retrosternal tunnel creation and colonic transposition to the neck. In order to get sufficient exposure, the falciform ligament is split. Percutaneous insertion of a needle in the subxiphoid region facilitates identification of the most inferior point of the retrosternal region and prevent unintentional pleural or pericardial perforation. To enter the retrosternal space, the peritoneum is split at the needle's entry point. The loose connective tissue of the retrosternal area opens easily with the blunt dissection aided by pneumoperitoneum. This region is bounded anteriorly by the posterior surface of the sternum, and posteriorly on both sides by the pericardium and bilateral pleurae (Figure 1). The camera light further transilluminates the sternum and guides the progression of retrosternal tunnel creation. Observing the assistant surgeon's fingers placed into the neck incision verifies that the retrosternal tunnel has been completed (Figure 1).

Colonic transposition: With bulldog clamps in place, the conduit's vascularity was examined by observing the cecum's color and pulsations. An ideal colonic conduit should be pink, demonstrate peristalsis when stimulated, and have visible arterial pulsations to the terminal portion of the conduit with no obviously distended veins[19]. Once the surgeon was satisfied with the vascularity of the colon conduit, the previously clamped vessels were ligated at the origin and divided. The terminal ileum was divided near the ileocecal junction using a laparoscopic linear cutter. The umbilical tape placed through the retrosternal tunnel is tied to the ileum. The colonic conduit is transferred to the neck by gently pulling with umbilical tape and pushing it using endoscopic bowel graspers (Figure 1). The conduit should be handled carefully, and the mesocolon's lie checked again. After delivering the conduit to the

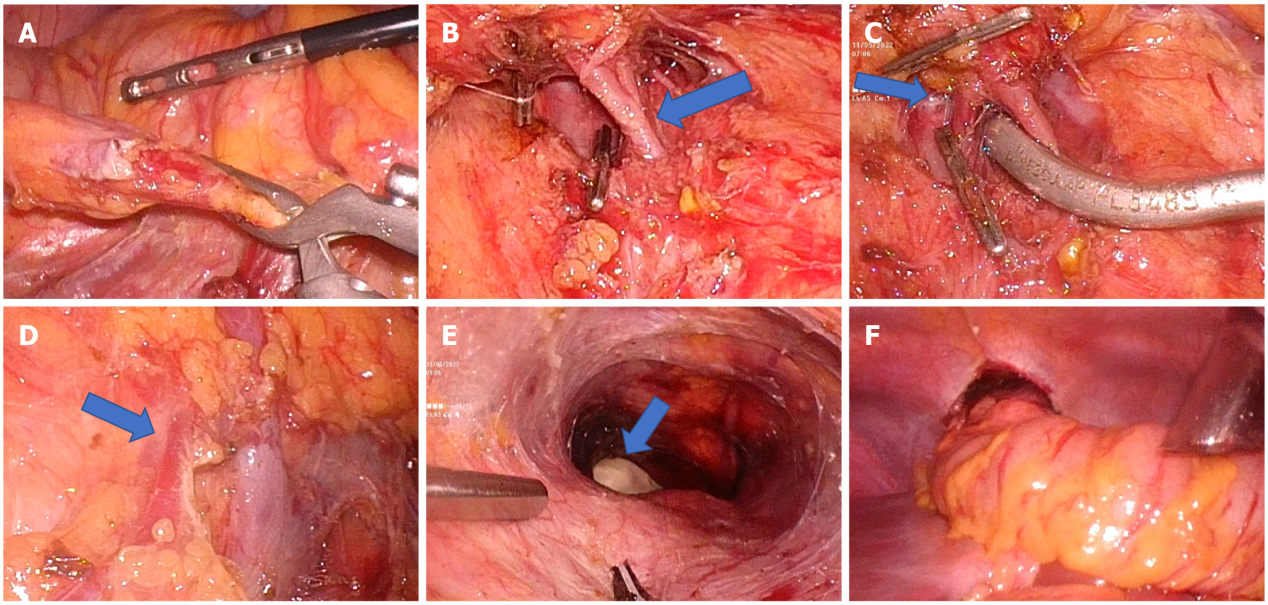

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Figure 1 Laparoscopic mid-colon esophageal bypass. A: Ileocolic pedicle dissected and bulldog clamp applied (marked with arrow); B: Middle colic artery dissected. Early division of the middle colic artery can be seen (marked with an arrow). Metal clips were applied on the right colic artery; C: Bulldog clamp applied on the middle colic artery proximal to the bifurcation. Middle colic vein draining to superior mesenteric vein seen (marked with arrow); D: The right colic vein (marked with arrow) joins with the gastrocolic trunk; E: Completion of retrosternal tunnel creation guided by assistant surgeon fingers; F: Transfer of colon conduit to the neck through the retrosternal tunnel.

neck, the lower end of the colon was divided with a laparoscopic linear cutter where the colon meets the stomach or jejunum (in diffuse gastric stricture) without tension. The colonic conduit was checked for redundancy. During distal colonic transection, the mesocolon was opened close to the bowel wall to protect the marginal arcade.

Reconstruction: A wide side-to-side, single-layer esophago/pharyngocolic anastomosis was created using interrupted polydioxanone 3-0 suture (Figure 2). The anastomosis should be as posterior and as wide as possible. The lower end of the colonic conduit is anastomosed to the anterior gastric wall in a side-to-side fashion using a laparoscopic linear cutter (Figure 2). The gastrostomy site may be used for cologastric anastomosis if the patient had a previous feeding gastrostomy. The stapler entry site is closed with a 3-0 polydioxanone suture. Laparoscopic Billroth-I gastrectomy or gastrojejunostomy is performed in patients with associated antropyloric stricture. The lower end of the colonic conduit is anastomosed to the jejunum in patients with a diffuse gastric stricture. The procedure concludes with the restoration of the colonic continuity with the aid of a stapled side-to-side ileocolic anastomosis (Figure 2).

Outcomes of total laparoscopic colonic transposition

In the series published by Javed *et al*[18] four patients with suicidal acid ingestion underwent total laparoscopic colon transposition. The average duration of surgery was 370 min, with an average blood loss of 100 mL (Table 2). None of the patients required any blood transfusions or ventilator support after surgery. In the laparoscopic group, all patients were ambulated earlier, and considerably fewer analgesics were required (P = 0.01)[18]. In a retrospective study, Gurram *et al*[19] analyzed 15 patients who underwent esophagacoloplasty for caustic stricture. Seven patients who underwent the laparoscopic procedure were compared with the eight patients who had an open mid-colon esophageal bypass. The laparoscopic group required considerably less postoperative analgesia (3 d *vs* 5 d, P = 0.02) and lesser intraoperative blood loss (200 mL *vs* 350 mL, P = 0.03). Operative time was shorter in the laparoscopic group (440 min *vs* 510 min), but the difference was not statistically significant (P = 0.93). Surgical complications, intensive care unit length of stay, total postoperative hospital stay, and medium-term swallowing outcomes were comparable between the two groups[19].

Limitations of total laparoscopic colonic transposition

Esophagocoloplasty is a technically challenging surgery that necessitates advanced laparoscopic skills. A colonic bypass requires a minimum of three anastomoses, whereas a laparoscopic gastric bypass requires only one. In addition, the median operation time is more for laparoscopic colonic pull-up compared to laparoscopic gastric pullup (370 min *vs* 180 min)[18]. Transillumination of the mesocolon is used to evaluate the vascular arcade during an open mid-colon bypass, which is not possible during

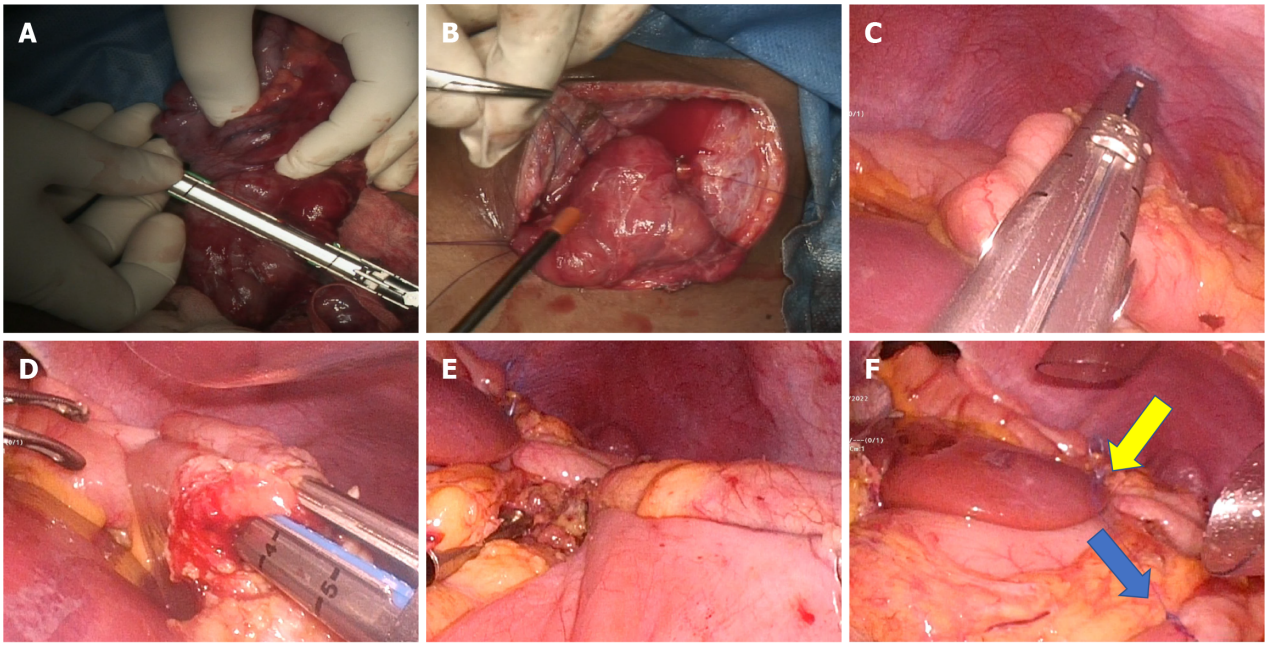

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Figure 2 Reconstruction. A: Cecum and terminal ileum stapled and divided; B: Completed cervical esophago-colic anastomosis; C: Lower end of colon divided with a laparoscopic stapler; D: Stapled cologastric anastomosis; E: Stapled ileocolic anastomosis; F: Completed ileocolic (blue arrow) and cologastric (yellow arrow) anastomosis.

laparoscopy and necessitates a preoperative cross-sectional imaging to rule out substantial vascular anomalies. Also, unlike open approach adequacy of perfusion can be evaluated only by visual assessment of arterial pulsations in the marginal arcade and appendices epiploicae. Hence, it is essential to understand the limitations of the laparoscopic colonic transposition and to have a low threshold for conversion if the vascular anatomy cannot be precisely identified. The dangers of misjudgment and poor evaluation during a laparoscopic procedure greatly outweigh the benefits of a laparoscopic technique.

GASTRIC STRICTURE

Acid ingestion is more common in developing countries compared to alkali ingestion. The corrosive gastric stricture is a late complication of corrosive-induced gastric injury and is usually linked to acid consumption. Acids cause coagulation necrosis, while alkalis cause liquefaction necrosis[26]. The adage, "acids lick the esophagus and bite the pyloric antrum", highlights the risk of gastric stricture secondary to acid ingestion[27]. The antropyloric region of the stomach is most frequently affected because of reflux pylorospasm, which results in a prolonged contact time. Antropyloric stricture in the absence of high-grade esophageal stricture manifests as gastric outlet obstruction. Endoscopic assessment and barium studies can typically determine the extent of gastric involvement in patients with isolated gastric strictures[28]. However, neither of these procedures can be utilized to evaluate the type of gastric injury in individuals with absolute dysphagia. Often, a CT scan would be required in such a circumstance. A plain abdomen radiograph performed after an overnight fast is frequently a less expensive alternative if it reveals a gastric air-fluid level suggestive of gastric outlet obstruction[29]. As with esophageal strictures, the importance of gastrectomy to avoid malignant transformation has been exaggerated[2]. In more than 750 esophageal and 2000 gastric stricture patients, Hsu *et al*[30] observed no cases of cancer resulting from corrosive intake. Endoscopic therapy of gastric stricture is often associated with poor long-term outcomes, necessitating surgery in most patients.

For management purposes, gastric strictures are divided into five categories. Of this type I and type II represent localized short prepyloric strictures and strictures extending proximally up to the antrum, respectively[2]. The surgery of choice for patients with isolated type I and II gastric strictures is a limited resection with gastroduodenal reconstruction, maintaining physiological continuity while avoiding dumping syndrome and bile reflux. Loop gastrojejunostomy should be performed on patients in whom an esophageal stricture can be ruled out with certainty, as gastrojejunostomy precludes the use of the stomach as a conduit. However, if gastrojejunostomy is required retrocolic route should be avoided, since it increases the technical complexity of future colonic bypass by interfering with the vascular arcade[2].

Type III strictures are mid-gastric strictures involving the body and sparing the proximal and distal portion of the stomach, often requiring distal gastrectomy with Polya reconstruction. As the anastomosis is typically non-dependent in type III stricture, gastrojejunostomy should generally be avoided.

Type IV are diffuse gastric strictures producing a linitis plastica like appearance. A substantial amount of the corrosive swallowed will cause a widespread stomach contraction. In healthy, fit patients, total gastrectomy with esophagojejunostomy and feeding jejunostomy is the recommended surgical procedure.

Type V gastric strictures are associated with a stricture of the first part of the duodenum. The management of type V gastric stricture is a challenge. Since aggressive resection is associated with severe problems in these individuals, antecolic dependent gastrojejunostomy is considered a safer treatment option[2].

Compared to the esophageal stricture laparoscopic approach is feasible in a significant proportion of patients with isolated gastric stricture due to less complex surgical steps.

Laparoscopy assisted gastro-jejunostomy

Shah *et al* evaluated the surgical outcomes of 30 patients with corrosive-induced gastric outlet obstruction who underwent laparoscopic-assisted (n = 15) versus open gastrojejunostomy (n = 15)[31]. The intraoperative findings and postoperative complications were recorded and compared between approaches. Shah *et al*[31] reported that the laparoscopic assisted gastrojejunostomy group required a smaller incision (4-5 cm *vs* 9-10 cm) and fewer intraoperative blood transfusions (2 patients *vs* 8 patients). Postoperatively, patients in the laparoscopic-assisted group experienced lesser post-operative pain with no incidence of wound infections (0 patient *vs* 4 patients). Early drain and suture removal result in quicker hospital discharge with minimal post-operative morbidity and no significant increase in the total duration or cost of the operation[31].

Total laparoscopic gastro-jejunostomy

Raikwar *et al*[32] analyzed demographic characteristics, injury grade, location, mode of consumption, performed surgery, parameters before and after surgery, body weight, nutritional status, and mortality in a series of 35 patients. One patient underwent laparotomy, and Billroth II gastrectomy at the initial visit, while the rest underwent feeding jejunostomy for nutritional optimization. Thirteen patients subsequently underwent gastrojejunostomy, of which two underwent a laparoscopic procedure. Subasinghe *et al*[33] demonstrated the effectiveness of laparoscopic gastrojejunostomy in two patients with homicidal corrosive acid ingestion resulting in antral stricture. Both patients underwent laparoscopic stapled gastrojejunostomy with a mean operative time of 3 h. Oral intake was allowed by the fourth and sixth postoperative day, which they tolerated well, demonstrating the efficacy of laparoscopic gastrojejunostomy[33]. The safety and feasibility of laparoscopic gastrojejunostomy have also been documented in a few case reports[34,35].

Laparoscopic antro-duodenostomy

Traditionally, corrosive-induced gastric outlet obstruction secondary to short pyloric stricture is managed with a Billroth I gastrectomy or bypass gastrojejunostomy. Heineke Mickulicz pyloroplasty is occasionally sufficient in individuals with partial gastric outlet obstruction due to moderate mucosal damage[36]. Following the footsteps of laparoscopic repair of neonatal duodenal atresia, some studies described and demonstrated the feasibility of laparoscopic diamond antroduodenostomy as a less invasive alternative for managing pyloric cicatricial obstruction in five pediatric patients[37,38]. For laparoscopic antroduodenostomy, monopolar cautery is used to make a transverse enterotomy in the healthy pyloric antrum, and a longitudinal one in the first portion of the duodenum. A diamond antroduodenostomy was created using single-layered interrupted intracorporeal sliding tumble-square knots. No abdominal drains were placed. A diluted contrast agent was administered through the nasogastric tube under the C-arm 24 h after surgery to evaluate anastomotic integrity and gastric motility. Patients were gradually allowed oral fluids when deemed appropriate and were discharged home the next day.

In the study by Seleim *et al*[38], the operation time ranged from 72 min to 89 min, with an average of 81 min. Contrast examinations on postoperative day 1, ruled out any radiological leaks, with delayed gastric emptying demonstrated in two cases. Seleim *et al*[38], demonstrated an average weight gain of 2.35 kg (almost 24% of preoperative weight)in the postoperative period. At a mean follow-up of 13.5 mo, no recurrence of obstructive symptoms nor dumping was observed, with excellent cosmetic outcomes [38].

Laparoscopic Billroth I gastrectomy

In patients with isolated antropyloric stricture, Billroth I gastrectomy is preferred over gastrojejunostomy as it restores physiological alimentary continuity, thereby maintaining autocrine and paracrine signaling and feedback mechanisms. Also, in patients with a concurrent esophageal stricture Billroth I gastrectomy does not interfere with future colon conduit formation and esophageal bypass[39].

Nagaraj *et al*[40] reported two patients with corrosive acid ingestion managed with total laparoscopic double-stapled Billroth-I gastrectomy. One patient presented with progressive dysphagia and, on evaluation, was found to have antropyloric stricture with concomitant esophageal stricture amenable to endoscopic dilatation. The second patient had isolated antropyloric stricture with symptoms of gastric outlet obstruction[40].

The patient was positioned supine with her legs split. The procedure was performed with five laparoscopic ports like any upper gastrointestinal laparoscopic surgery. The primary surgeon stands to the patient's left, the assistant surgeon to the right, and the camera surgeon between the legs. The lesser sac is entered by dividing the gastrocolic omentum using ultrasonic shears. Subsequently right gastroepiploic vessels were clipped and divided. Creation of a retrogastric tunnel is completed by dividing the gastrohepatic ligament and right gastric artery branches using ultrasonic shears. An umbilical tape placed through the retro gastric tunnel is snugly tied to the antropyloric region to facilitate duodenal mobilization and provide traction during stapler application.

Stapled transection of the healthy portion of the stomach proximal to the stricture was performed with green or black reloads depending upon the stomach thickness (Figure 3). After gastric transection, one gastrotomy was made on the greater curvature proximal to the stapler line and a second one at the pyloric level. One jaw of a 60-mm blue laparoscopic linear cutter was positioned through the greater curve gastrotomy, and the stomach was brought anterior to the duodenum. The other stapler jaw was placed through the pyloric gastrotomy into the duodenum. The umbilical tape traction facilitates the stapling procedure. The firing of the stapler generates a V-shaped gastroduodenostomy between the stomach's posterior wall and the duodenum's anterior wall. The stapler entry site was closed with a laparoscopic linear cutter to complete the gastroduodenostomy using a double-stapled technique (Figure 3).

The modified linear stapling approach described by Nagaraj *et al*[40], as opposed to a circular stapler for gastroduodenostomy, does not require a mini-laparotomy. The most prevalent approach employing a linear stapler is a delta-shaped gastroduodenostomy, which is technically challenging and requires more staplers[41]. The technical difficulties of performing a completely laparoscopic gastroduodenal anastomosis are primarily due to the challenge in aligning gastric remnant and duodenal stump. In the technique described by Nagaraj *et al*[40], the duodenum is not cut until the very end, which allows for improved traction and orientation during the stapling procedure. The last stapler used to seal the gastroduodenostomy simultaneously transect the duodenum.

CHALLENGES AND FUTURE PERSPECTIVES

In a minimally invasive colon bypass, transillumination of the elevated colon to evaluate the vascular arcade is not possible. However, the limitation can be partially overcome by utilizing the near-infrared light for Indocyanine green fluorescence angiography, which is a real-time method to evaluate the organ perfusion. With the advent of a robotic platform and laparoscopic camera with inbuilt indocyanine green fluorescence technology, it should be feasible to objectively evaluate the vascular arcade (Figure 4). Also, minimally invasive approach can be potentially used for ischemic preconditioning. In this technique one of the major vessels, usually the ileocolic or middle colic pedicle, is ligated to promote vascular flow through marginal arcade.

The creation of a retrosternal tunnel in a laparoscopic approach is technically challenging because of the absence of any conventional landmarks. Insertion of a long needle percutaneously at the level of the xiphisternum facilitates precise identification and creation of a retrosternal tunnel without inadvertent damage to the pleura or pericardium.

Most patients with corrosive stricture will be referred for definitive management after a feeding procedure usually feeding jejunostomy. Hence, care should be taken to avoid iatrogenic bowel injury during initial trocar insertion and adhesiolysis. Performing feeding jejunostomy laparoscopically could minimize the adhesion-related challenges during definitive surgery.

CONCLUSION

As most patients with corrosive esophagogastric stricture are young adults minimally invasive approach is an attractive proposition. However, due to complexity of the surgery and technical challenges, minimally invasive surgery for corrosive esophagogastric stricture has lagged compared to other benign gastrointestinal orders. With improvements in laparoscopic instrumentation and technological advances, minimally invasive surgery for corrosive stricture is gaining momentum. There is a changing trend from laparoscopic assisted procedure to totally minimally invasive approach. However, carefully disseminating a minimally invasive approach for corrosive esophagogastric stricture is imperative to preclude adverse long-term outcomes. Technological advances like indocyanine green fluorescence help to improve the safety of the surgical procedure using a minimally invasive approach. However, well-designed trials with long-term follow-ups are required to document the superiority of

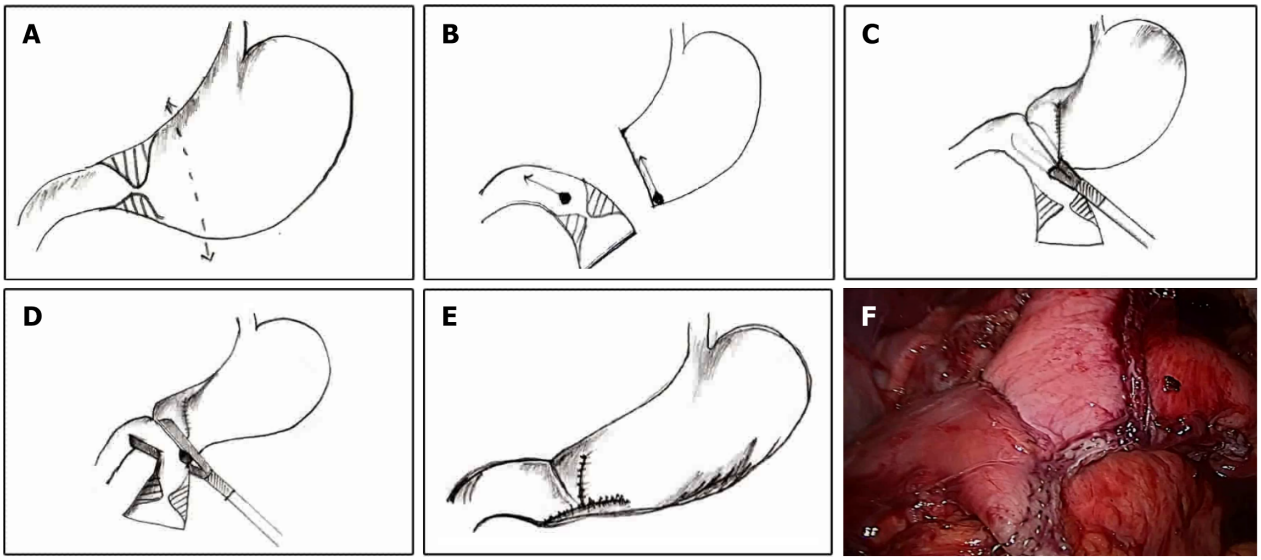

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Figure 3 Steps of laparoscopic Billroth I gastrectomy. A: Line of gastric transection proximal to the level of stricture; B: Completed gastric transection; C: Stapled gastroduodenostomy performed with the specimen in continuity; D-F: Final stapler simultaneously close the stapler entry site and transects duodenum (E) gastroduodenostomy completed using double-stapled technique (F) picture of completed anastomosis in a patient.

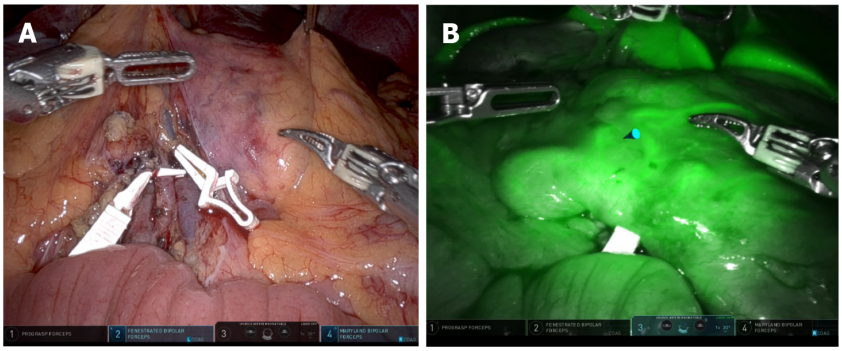

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Figure 4 Robotic mid-colon esophageal bypass. A: Bulldog clamps placed on the middle colic vessels; B: Indocyanine green fluorescence demonstrates patent vascular arcade.

minimally invasive surgery for corrosive esophagogastric stricture.

FOOTNOTES

Author contributions: Satish D and Kalayarasan R did the literature search; Satish D wrote the first draft of the review; Kalayarasan R conceptualized the work, supervised the writing, gave intellectual inputs, and critically revised the manuscript.

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Distribution of splenic artery lymph nodes and splenic hilar lymph nodes

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Abstract

BACKGROUND

Total gastrectomy with splenectomy is the standard treatment for advanced proximal gastric cancer with greater-curvature invasion. As an alternative to splenectomy, laparoscopic spleen-preserving splenic hilar lymph node (LN) dissection (SPSHLD) has been developed. With SPSHLD, the posterior splenic hilar LNs are left behind.

AIM

To clarify the distribution of splenic hilar (No. 10) and splenic artery (No. 11p and 11d) LNs and to verify the possibility of omitting posterior LN dissection in laparoscopic SPSHLD from an anatomical standpoint.

METHODS

Hematoxylin & eosin-stained specimens were prepared from six cadavers, and the distribution of LN No. 10, 11p, and 11d was evaluated. In addition, heatmaps were constructed and three-dimensional reconstructions were created to visualize the LN distribution for qualitative evaluation.

RESULTS

There was little difference in the number of No. 10 LNs between the anterior and posterior sides. For LN No. 11p and 11d, the anterior LNs were more numerous than the posterior LNs in all cases. The number of posterior LNs increased toward the hilar side. Heatmaps and three-dimensional reconstructions showed that LN No. 11p was more abundant in the superficial area, while LN No. 11d and 10 were more abundant in the deep intervascular area.

CONCLUSION
The number of posterior LNs increased toward the hilum and was not neglectable. Thus, surgeons should consider that some posterior No. 10 and No. 11d LNs may remain after SPSHLD.

Key Words: Gastric cancer; Laparoscopic gastrectomy; Anatomy; Splenic hilar lymph node; Laparoscopic spleen-preserving splenic hilar lymph node dissection

Core Tip: Recently, laparoscopic spleen-preserving splenic hilar lymph node (LN) dissection (SPSHLD) has emerged as a viable alternative to splenectomy for advanced proximal gastric cancer with greater curvature invasion. However, laparoscopic SPSHLD has been observed to leave behind the posterior splenic hilar LNs. In this study, we aimed to clarify the distribution of splenic hilar and splenic artery LNs by examining cadavers, and to evaluate the possibility of omitting posterior LN dissection in laparoscopic SPSHLD from an anatomical perspective. Our findings revealed that the number of posterior LNs increased towards the hilum and was not negligible. Therefore, it is crucial for surgeons to consider that some posterior LNs may remain after SPSHLD.

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INTRODUCTION

Total gastrectomy with splenectomy is a standard treatment for locally advanced proximal gastric cancer with greater-curvature infiltration in East Asian countries[1,2]. Splenectomy is performed with the aim of achieving complete retrieval of splenic hilar lymph nodes (LNs), as well as LNs along the splenic artery, although the procedure increases the incidence of postoperative pancreas-related complications[1,3-5]. To avoid these potentially fatal complications, a new surgical technique named laparoscopic spleen-preserving splenic hilar LN dissection (SPSHLD) has been developed, and its use is widespread in some countries[3,4,6-8].

According to the Japanese Classification of Gastric Carcinoma[9], No. 10 LNs are defined as splenic hilar LNs adjacent to the splenic artery and distal to the pancreatic tail, as well as those on the roots of the short gastric arteries and those along the left gastroepiploic artery proximal to its gastric branch. The LNs along the splenic artery are referred to as No. 11 LNs, which are subdivided into No. 11p (proximal splenic artery LNs from the origin of the splenic artery to halfway between its origin and the pancreatic tail end) and No. 11d (distal splenic artery LNs from halfway between the origin of the splenic artery and the pancreatic tail end to the end of the pancreatic tail) LNs.

Both anterior and posterior splenic hilar LNs are completely retrieved with splenectomy; however, it is challenging to dissect the posterior LNs of the splenic hilum and the LNs along the splenic artery with laparoscopic SPSHLD in which the spleen is not mobilized[7,8]. For SPSHLD to be accepted as a standard procedure for locally advanced proximal gastric cancer with greater-curvature infiltration, omission of posterior splenic hilar LNs must be justified from both the clinical and anatomical standpoints.

Several reports have demonstrated the feasibility of laparoscopic SPSHLD from the clinical standpoint[8,10,11], but no studies have examined the distribution of splenic hilar LNs from the anatomical standpoint. Demonstrating the detailed distribution pattern of the anterior and posterior LNs would allow the feasibility of laparoscopic SPSHLD to be evaluated from an anatomical standpoint. Therefore, this study aimed to clarify the anatomical distribution of the splenic hilar (No. 10) and splenic artery (No. 11p and 11d) LNs. In addition, the number of anterior and posterior LNs was counted to clarify whether LN dissection without spleen mobilization can be justified from the anatomical standpoint. We also created three-dimensional (3D) images to clarify the anatomy around the splenic hilar and splenic artery LNs.

MATERIALS AND METHODS

Cadavers

In this study, we examined six Japanese cadavers (four male and two female) aged between 74 and 99 years (Table 1). The cadavers were donated to the Department of Clinical Anatomy of Tokyo Medical and Dental University. All donors had previously signed documents agreeing to donate their bodies and had provided written consent for use in anatomical studies. The format of the document concurred with the Act on Body Donation for Medical and Dental Education under Japanese law. The study protocol was approved by our institutional review board (M2018-210). This study excluded the cadavers of individuals with esophageal, gastric, splenic, or pancreatic cancer. The cadavers were fixed by arterial perfusion with 8% formalin and preserved in 30% alcohol to prevent fungal growth and maintain the softness of the tissues.

Histological examination

The esophagus, stomach, duodenum, spleen, pancreas, and vessels were resected from the cadavers in an en-bloc fashion (Figure 1A). Tissue blocks from the body of the pancreas to the splenic hilum were made from the specimens (Figure 1B). The short gastric arteries were dissected at the root, and the specimens consisted of the splenic hilum along with the pancreatic parenchyma. The tissue blocks were post-fixed, followed by defatting, demineralization, and paraffin embedding. Next, we made histological sections by cutting them into 5-μm-thick specimens at 1.0-mm intervals of width in the sagittal plane. Hematoxylin & eosin (H&E) staining was conducted to evaluate the structure of the organs and vasculature (Figure 2A and B). In H&E staining, LNs had a characteristic appearance with a dense core and were blue-purple because of hematoxylin staining, while the surrounding tissue was pink-red because of eosin staining. We also marked the splenic artery LNs and the splenic hilar LNs on H&E-stained sections (Figure 2C). We then evaluated the distribution of the splenic hilar LNs and the splenic artery LNs on H&E-stained specimens. We counted the number of anterior and posterior splenic artery LNs in each of the six cadavers, followed by the number of anterior and posterior splenic hilar LNs in five of these cadavers.

Heatmap creation

To assess whether the number of LNs that could not be dissected by laparoscopic SPSHLD was acceptable, we determined the number of anterior and posterior LNs.

To clarify the difficulty in dissecting each LN, we created heatmaps and 3D images to objectively show the locations of the LNs and surrounding organs. The contours of the pancreas, spleen, blood vessels, and LNs were traced on H&E-stained sections. Anatomically similar sections from the same cadaver were overlaid to create schemas, and the frequency of the LNs was represented as heatmaps (Figure 3). We made the heatmaps using the color scale function of Microsoft Excel for Mac (version 16.16.27[202012]; Microsoft Corp., Redmond). The scale was set to show that the number of LNs increased as the color changed from yellow to red.

3D reconstruction creation

We used serial tissue sections from one of the six cadavers to perform 3D reconstruction. First, the traced images from a typical case were superimposed to create 3D images of the blood vessels and LNs. In addition, we generated 3D images by extracting only the regions of the distal splenic artery LNs and the splenic hilar LNs using Autodesk AutoCAD for Mac (product version R.47.M193).

Definition of anterior and posterior LNs

We defined the LNs within the range of laparoscopic LN dissection as anterior and posterior LNs. In the region of the No. 11 LNs, the splenic artery was divided into two patterns: one in which the splenic artery was located anterior to the splenic vein, and the other in which the splenic artery was located posterior to the splenic vein. When the splenic artery was shallower than the splenic vein, the posterior side was defined as the area bounded by the pancreatic parenchyma, splenic vein, and retroperitoneum (Figure 4A). In the region of the No. 10 LNs (Figure 4B), the anterior side was defined as the area ventral to the line connecting the midpoint of vessels with a long diameter of ≥ 1.5 mm, while the dorsal region was defined as the posterior side (Figure 4C).

RESULTS

The number of LNs on the anterior and posterior sides of the No. 10 and No. 11 LNs in each case are shown in Table 1. The No. 11 LNs of all of the cadavers were more frequently anterior than posterior. The number of No. 10 LNs varied from case to case. In three cadavers (cases 2, 4, and 6), there were more No. 10 LNs on the anterior side than on the posterior side. In two cadavers (cases 3 and 5), there were more No. 10 LNs on the posterior side than on the anterior side.

Table 1 Characteristics of cadavers

Case No.	1	2	3	4	5	6
Age (yr)	75	81	79	96	99	85
Sex	Male	Male	Male	Female	Female	Female
Weight (kg)	38	59	40	41	30	42
Cause of death	Bronchial pneumonia	DIC	Pneumonia	Senility	Senility	Liver failure
Patient history	Lung cancer	Miliary tuberculosis,post-CABG surgery	NA	Breast cancer, Melanoma	NA	Liver cancer, hepatic cirrhosis

DIC: Disseminated intravascular coagulation; CABG: Coronary artery bypass graft; LN: Lymph node; NA: Not available.

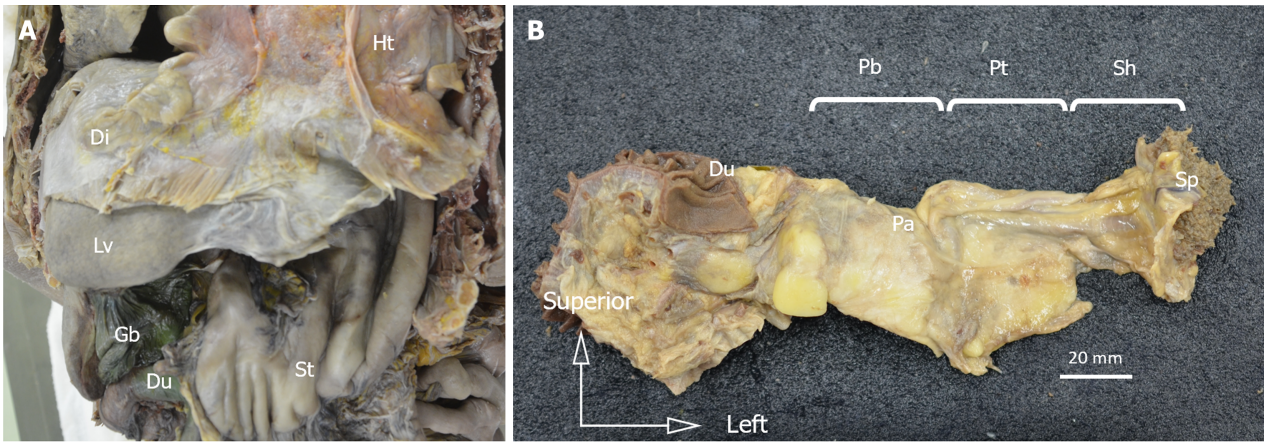

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Figure 1 Resected specimens. Resected specimens. A: Laparotomy was performed, and the esophagus, stomach, duodenum, spleen, pancreas, and vessels were resected in an en-bloc fashion; B: The duodenal bulb, horizontal leg, and lower bile duct were removed, and the duodenum, pancreas, spleen, and surrounding tissue were dissected from the retroperitoneum in an en-bloc fashion. Ht: Heart; Di: Diaphragm; Lv: Liver; St: Stomach; Du: Duodenum; Gb: Gallbladder; Pa: Pancreas; Pb: Pancreatic body; Pt: Pancreatic tail; Sh: Splenic hilum; Sp: Spleen.

The mean number of No. 10 LNs per case was 11.5 on the anterior side and 10.7 on the posterior side. The mean number of No. 10 LNs per section was 1.08 on the anterior side and 1.00 on the posterior side. There was little difference in the number of No. 10 LNs between the anterior and posterior sides.

Next, we examined the No. 11p and No. 11d LNs separately. The number of anterior and posterior No. 11p and No. 11d LNs is shown in Table 2. The mean number of No. 11p LNs per case was 27.8 on the anterior side and 3.7 on the posterior side, and the mean number of No. 11d LNs per case was 25.3 on the anterior side and 7.7 on the posterior side. The mean number of No. 11p LNs per section was 1.46 on the anterior side and 0.19 on the posterior side, and the mean number of No. 11d LNs per section was 0.89 on the anterior side and 0.27 on the posterior side. For No. 11p and No. 11d LNs, all cases had more LNs on the anterior side than on the posterior side.

The number of No. 11p, No. 11d, and No. 10 LNs per section, as shown in Table 2 and Table 3, are summarized in Table 4. The anterior side had a larger number of No. 11p, No. 11d, and No. 10 LNs than the posterior side. In addition, the number of posterior LNs increased as they moved to the hilar (distal) side. Therefore, we calculated the ratio of posterior LNs to anterior LNs for LN No. 11p, 11d, and 10 for all cases. We also calculated the ratio of the total number of posterior LNs to the total number of anterior LNs for LN Nos. 11p, 11d, and 10 for all cases. These ratios are summarized in Table 5. The number of posterior LNs increased toward the splenic hilum (distal side).

The heatmaps for the No. 10 LNs of the five cases are shown in Figure 5. The arrangement of the hilar vessels varied widely, and some No. 10 LNs existed intravascularly. In terms of the mean number of LNs, there were more anterior LNs than posterior LNs. However, some LNs existed deeply between the splenic hilar vessels.

The heatmaps for the No. 11 LNs are shown in Figure 6. We distinguished the No. 11 LNs into No. 11p and No. 11d LNs and evaluated them separately because the localization of these LNs differed between the proximal and distal sides. The number of posterior LNs tended to increase toward the spleen. As shown in the heatmap of the No. 11p LNs in Figure 6, in case 6, the No. 11p LNs tended to be more abundant in the superficial location, while the No. 11d LNs tended to be more common in more

Table 2 Distribution of No. 10 and No. 11 lymph nodes

	Case No.							
	1	2	3	4	5	6	Avg. (LN/case)	Avg. (LN/slice)
No. 10								
No. of slices	0	18	4	18	19	5		
Anterior nodes	NA	40	3	12	12	2	11.5	1.08
Posterior nodes	NA	25	4	6	29	0	10.7	1.00
No. 11								
No. of slices	52	51	44	31	43	66		
Anterior nodes	31	94	61	20	36	77	53.2	1.23
Posterior nodes	8	10	19	7	10	14	11.3	0.26

The distribution of No. 10 and 11 lymph nodes (LNs) in each cadaver is shown. The number of LNs on the anterior and posterior sides and the number of microslides studied are also shown. No. 10, No. 10 LNs; No. 11, No. 11 LNs; No. of slices: Number of microslides; Avg. (LN/case): Mean number of LNs per case; Avg. (LN/slice): Mean number of LNs per microslide. LN: Lymph node; NA: Not available.

Table 3 Distribution of No. 11p and 11d lymph nodes

	Case No.							
	1	2	3	4	5	6	Avg. (LN/case)	Avg. (LN/slice)
No. 11p								
No. of slices	14	27	15	9	16	33		
Anterior nodes	14	52	20	8	21	52	27.8	1.46
Posterior nodes	2	6	2	1	5	6	3.7	0.19
No. 11d								
No. of slices	38	24	29	22	27	33		
Anterior nodes	17	42	41	12	15	25	25.3	0.88
Posterior nodes	6	4	17	6	5	8	7.7	0.27

The distribution of No. 11p and 11d lymph nodes (LNs) in each cadaver is shown. We also noted the number of LNs on the anterior and posterior sides, the number of vessels, and the number of microslides. No. 11p, No. 11p LNs; No. 11d, No. 11d LNs; No. of slices: Number of microslides; Avg. (LN/case): Mean number of LNs per case; Avg. (LN/slice): Mean number of LNs per microslide.

Table 4 Number of lymph nodes per microslide

	No. 11p	No. 11d	No. 10
Anterior node	1.46	0.88	1.08
Posterior node	0.19	0.27	1.00
	→		Hilar side

The number of No. 11p, 11d, and 10 lymph nodes per microslide is shown.

deeply intervascular locations. Some No. 11d LNs were located on the posterior side or were surrounded by the hilar vessels.

We generated 3D images of the No. 11 and No. 10 LNs (Figure 7A). The splenic hilum side had an intricate structure of vessels and LNs. Figure 7B shows that the No. 11p LNs existed on the surface of a single splenic artery. For the No. 11d and No. 10 LNs, the vascular branch was complicated, and the splenic hilar vessels covered the posterior LNs.

Table 5 Posterior/anterior lymph node ratio

Lymph node		Case No.						
		1	2	3	4	5	6	Total
↓	No. 11p	0.14	0.12	0.10	0.13	0.24	0.12	0.13
	No. 11d	0.35	0.10	0.41	0.50	0.33	0.32	0.30
Hilar side	No. 10	NA	0.63	1.33	0.50	2.42	0.00	0.93

The posterior/anterior lymph node (LN) ratio and the average of these ratios were calculated for each cadaver. Total: Sum of the number of posterior LNs in all cases divided by the sum of the number of anterior LNs in all cases. NA: Not available.

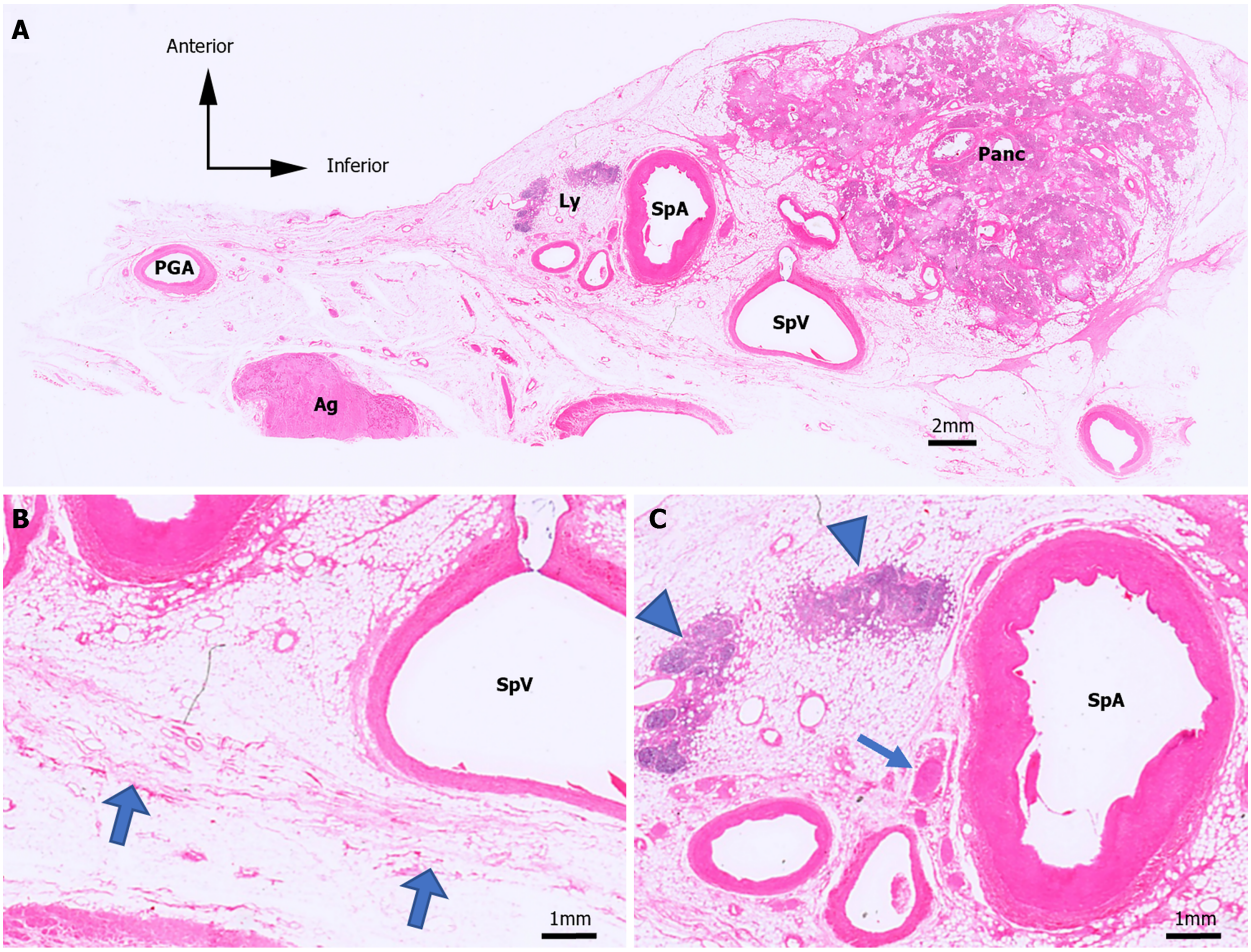

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Figure 2 Hematoxylin & eosin-stained microslides. Hematoxylin & eosin (H&E)-stained microslides. A: H&E-stained images of the No. 11 lymph node (LN) region in case 1; B and C: Enlarged image of A. The retroperitoneal layer can be seen as fibrous structures, indicated by the thick arrows. H&E, hematoxylin and eosin; Panc: Pancreas; SpA: Splenic artery; SpV: Splenic vein; Ly: Lymph; Ag: Adrenal gland; PGA: Post-gastric artery; Arrowhead: Lymph node; Arrow: Nerve; Thick arrow: Border with the retroperitoneal region.

DISCUSSION

In this study, we report the results of an anatomical study on six cadavers in which we examined the distribution of No. 10 and No. 11 LNs. Importantly, we observed that the number of posterior LNs increased toward the hilum.

Comparison with previous studies

Lymphatic flow of proximal gastric cancers, especially those located along the greater curvature, drains to splenic hilar LNs *via* the left gastroepiploic artery, short gastric artery, celiac artery, and posterior gastric artery[12]. Therefore, the incidence of metastasis in No. 10 and splenic hilar LNs in advanced proximal gastric cancer were 9.8%-20.9% and 8.1%-27.9%, respectively[12,13]. Total gastrectomy with

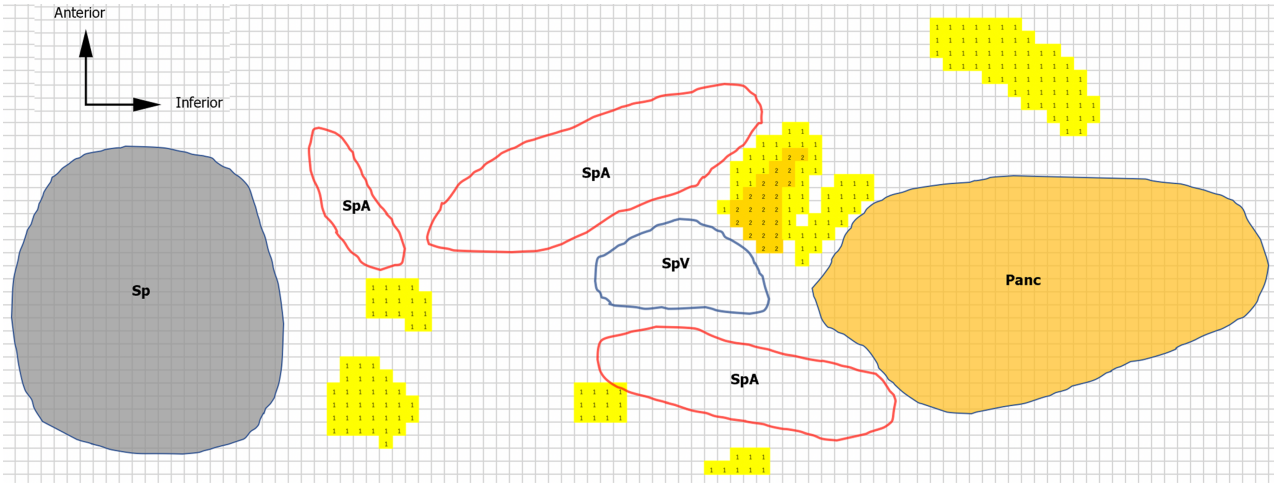

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Figure 3 Heatmap and color scale. We traced the major structures [*i.e.*, pancreatic parenchyma, spleen, splenic artery, splenic vein, and lymph nodes (LNs)] around the No. 11d LN region in case 4. The number of LNs is represented as a heatmap. We made the heatmap using the color scale function of Microsoft Excel for Mac (version 16.16.27[202012]). The scale is set to show that the number of LNs increases as the color changes from yellow to red. The colored cells with numbers are LN heatmaps. LN: Lymph node; Sp: Spleen; Panc: Pancreas; SpA: Splenic artery; SpV: Splenic vein.

splenectomy is the standard treatment for locally advanced proximal gastric cancer with greater-curvature invasion[1,2]. However, this procedure has rarely been performed with the laparoscopic approach. Recently, large randomized controlled trials from Asia have demonstrated the non-inferiority of laparoscopic surgery for locally advanced gastric cancer[14-16], and laparoscopic surgery has thus become more popular recently. With the development of laparoscopic instruments and techniques, laparoscopic total gastrectomy became possible. Since then, outstanding surgeons in East Asia have started to perform laparoscopic SPSHLD[6,7]. Previous reports have insisted that the majority of No. 10 LNs are located on the anterior side, while posterior No. 10 LNs are rarely found[8,17]. However, the present study found that the number of posterior No. 10 LNs was not neglectable and was almost equal to, or even outnumbered, the number of anterior No. 10 LNs in some cases.

This discrepancy is probably because small LNs, which were counted as LNs in this study, might be overlooked in clinical practice. In clinical practice, surgeons visually remove the LNs from surgically resected specimens. Therefore, small LNs, which can be recognized under the microscope, but that are difficult to identify with the naked eye, are rarely counted. Indeed, small LNs of < 1 mm in size, which are usually ignored in clinical practice, were counted as LNs in the present study. Another probable reason is that in previous reports, some LNs, which were assumed to be on the posterior side in this study, might have been dissected as anterior LNs due to certain manipulations, such as elevation of the stomach, leading to displacement of the LNs from the posterior to the anterior side. As a result, it became difficult to completely distinguish the anterior LNs from the posterior LNs intraoperatively. Therefore, the distribution of the anterior and posterior LNs in this study (in which anatomical findings were considered) was different from that of previous studies (in which surgical findings were considered).

The novelty of this study lies in the use of autopsy to define the posterior and anterior LNs in detail and to determine the distribution and number of LNs based on serial sections. Furthermore, in this study, the distribution and number of LNs were visualized using a new analysis method of heatmapping and 3D reconstruction of serial sections, and the variability and complexity of the LN distribution were qualitatively verified.

Clinical implications

The No. 10 and No. 11d LNs varied in their distribution, as shown in Figures 5 and 6. This variation could be attributed to the variety of vascular running and branching patterns in this region.

Studies have reported that the running patterns of the distal splenic artery and the splenic hilar vessels vary greatly[18,19]. Indeed, the branching patterns were not identical among the cadavers in the present study, as shown in Figures 5 and 6. This tendency became more obvious toward the distal end of the splenic artery. The traditional running pattern of the splenic artery is that it divides from a single splenic artery trunk into two or three branching vessels, which further branch into smaller vessels at the hilum[18]. These small vessels also have multiple branching patterns and can be divided into eight major categories. Although rare, the splenic artery may also branch near the celiac trunk[19]. Compared with the number of reports on the branching patterns of blood vessels, the branching patterns of lymphatic vessels have seldom been reported. However, as the lymphatic vessels usually run along the blood vessels, they are thought to have equally as numerous running patterns and LN distribution

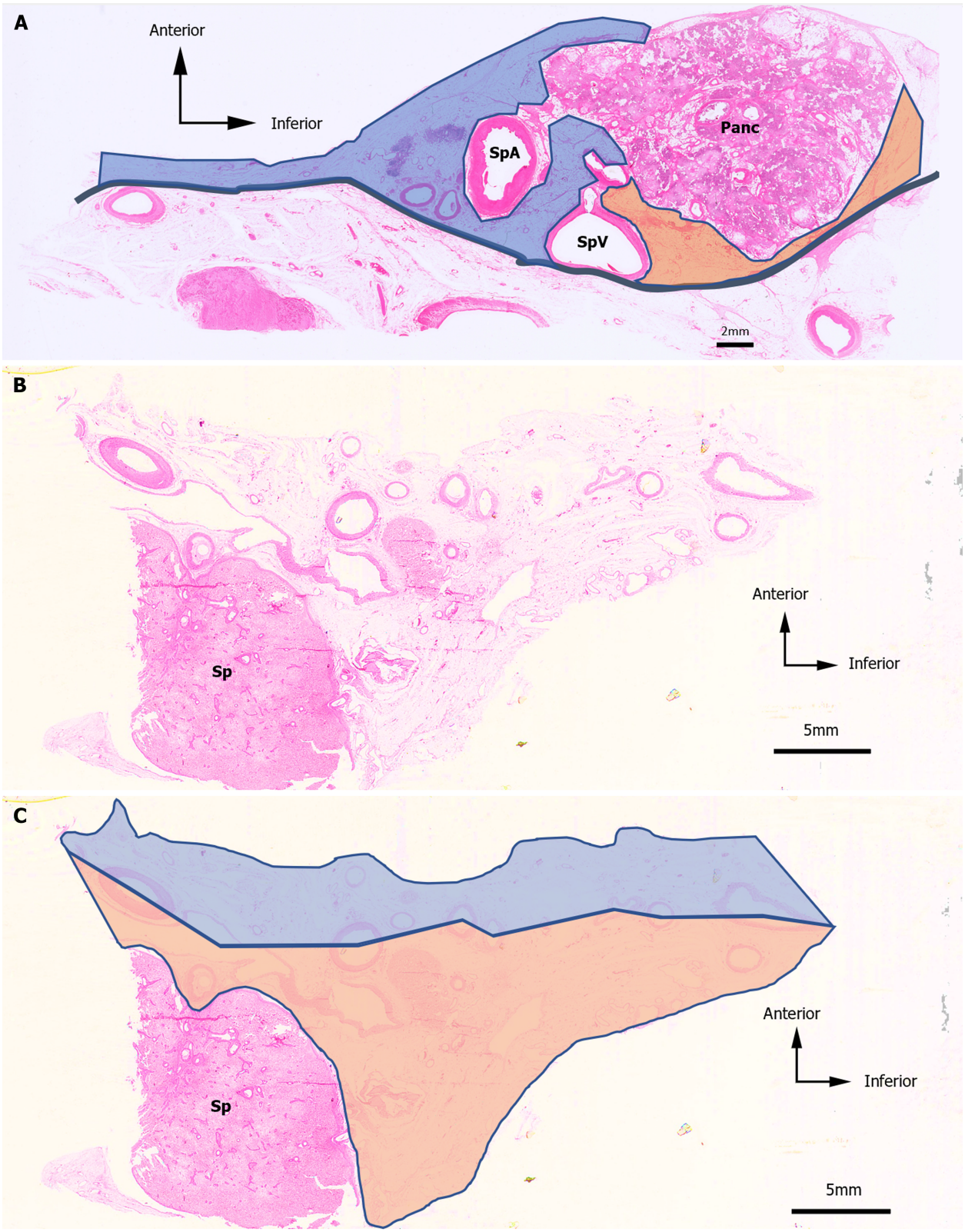

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Figure 4 Hematoxylin & eosin-stained images and an example of the anterior side and the posterior side. Hematoxylin & eosin (H&E)-stained images and an example of the anterior side and the posterior side. A: H&E-stained images of the No. 11 lymph node (LN) region in case 1. The anterior side is represented by the blue area, and the posterior side is represented by the orange area; B: H&E-stained images of the No. 10 LN region in case 4; C: The anterior side is represented as the blue area, and the posterior side is represented as the orange area. H&E: Hematoxylin and eosin; LN: Lymph node; Panc: Pancreas; SpA: Splenic artery; SpV: Splenic vein; Sp: Spleen.

patterns in the distal splenic artery and splenic hilar regions as the splenic vessels.

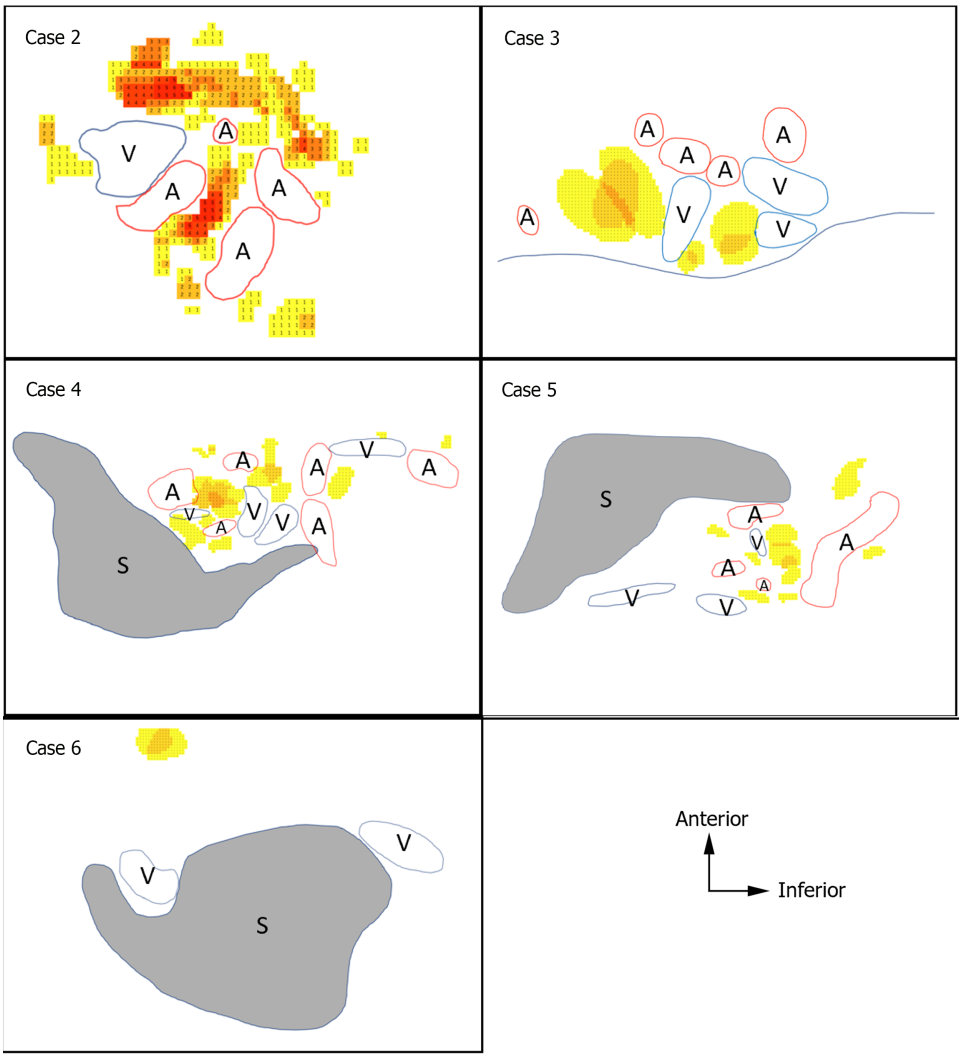

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Figure 5 Heatmaps of the splenic hilum region. Heatmaps of the splenic hilum region. Heatmaps of the five cadavers studied for the splenic hilum utilizing the color scale of Microsoft Excel for Mac (version 16.16.27[202012]). The scale is set to show that the number of lymph nodes (LNs) increases as the color changes from yellow to red. The colored cells with numbers are LN heatmaps. A: Splenic artery; V: Splenic vein; S: Spleen; LN: Lymph node.

The No. 10 and No. 11d LNs can be dissected as en-bloc specimens with splenectomy, regardless of their distribution. However, the posterior LNs may be left behind in vascular-sparing SPSHLD.

Our study showed that the number of posterior LNs increased toward the splenic hilum. This means that the number of LNs that may be left behind without splenectomy was high. Although a magnified view of laparoscopic surgery could enable surgeons to perform meticulous LN dissection by skeletonizing the blood vessels, retrieval of posterior LNs surrounded by multiple blood vessels or intertwined with each other is still technically demanding and difficult to perform, even with laparoscopic SPSHLD. Thus, surgeons should be cautious about omitting posterior LN dissection from the anatomical viewpoint.

Although the technical safety of SPSHLD has been demonstrated previously[8,20], the oncological safety of SPSHLD remains unclear. The efficacy of LN dissection should be comprehensively examined, and a variety of factors, such as the rate of metastasis, procedure-related complications, the local control rate, and survival outcomes, should be considered. Nevertheless, a survival analysis needs to be conducted to clarify these points.

The anterior/posterior ratio of No. 10 LNs, as well as the number of No. 10 LNs, differed widely among the cadavers examined in this study. The number of No. 10 LNs was small in cases 3 and 6, which was probably due to the short distance between the pancreatic tail and the spleen in these cases. Moreover, the number of sections in these cases was smaller than in the other cases.

Different from the No. 10 LNs, most of the No. 11p LNs were located in the anterior region. In addition, the splenic artery running pattern was relatively simple and did not branch at this level in most cases. Different from the No. 10 and No. 11d LNs, which were located deep between the vessels, the No. 11p LNs were identified at a resectable depth using the typical laparoscopic procedure without pancreatic mobilization.

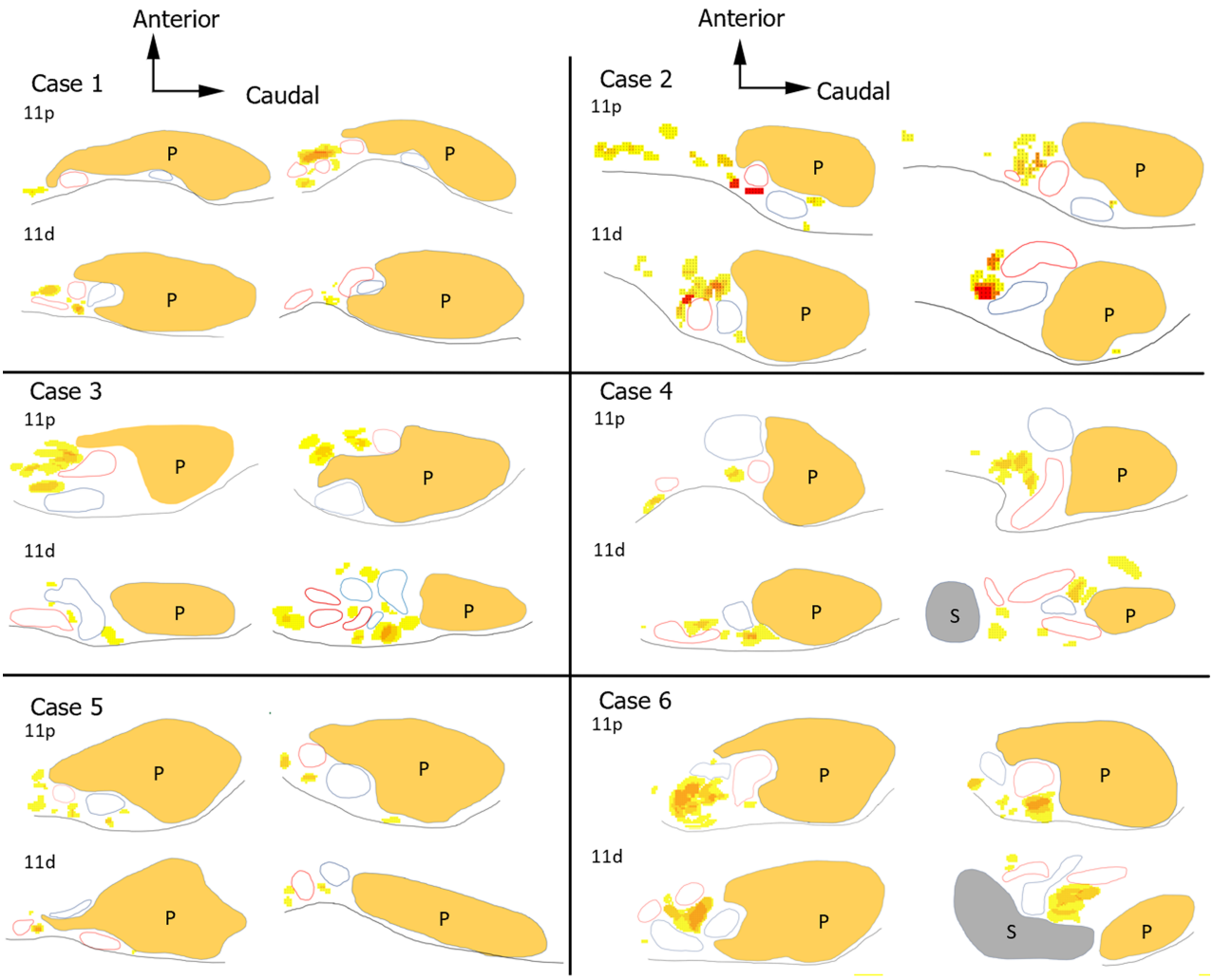

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Figure 6 Heatmaps of the splenic artery lymph node region. Heatmaps of the splenic artery lymph node (LN) region. Heatmaps of the No. 11p and No. 11d LN regions in each case. The color scale settings are the same as in Figure 5. LN: Lymph node; 11p: No. 11p lymph node; 11d: No. 11d lymph node; P: Pancreas; S: Spleen.

Limitations

To separate No. 10 LNs into those that were difficult to dissect by laparoscopic SPSHLD without pancreatic mobilization and those that were not, LNs behind vessels greater than 1.5 mm in diameter were defined as posterior in this study. However, anterior and posterior as defined in this study do not necessarily correspond to clinical anterior and posterior. The number of LNs in each may vary depending on how the definitions are determined. However, even qualitative assessment methods such as heat maps showed more LNs deep in the posterior compared with previous studies. Therefore, the conclusion that there were more posterior splenic hilar LNs compared with previous studies remains unchanged.

Another limitation is that this study did not investigate lymphatic flow from the gastric side to posterior splenic hilar LNs in proximal advanced gastric cancer. Therefore, the results do not directly relate the dissection of posterior LNs to recurrence. Cadavers with gastric cancer were excluded from assessing the neutral distribution of hilar LNs. If posterior No. 10 LNs receive little lymphatic flow from the stomach, the anterior LNs may be more often positive for metastases in gastric cancer. Further studies focusing only on proximal advanced gastric cancer are expected.

CONCLUSION

In this anatomical study of six cadavers, we found that several splenic hilar and distal splenic artery LNs might be left behind following anterior LN dissection by SPSHLD, as the anterior/posterior LN ratio of these areas was lower than expected. Most of the No. 11p LNs were located at the anterior side,

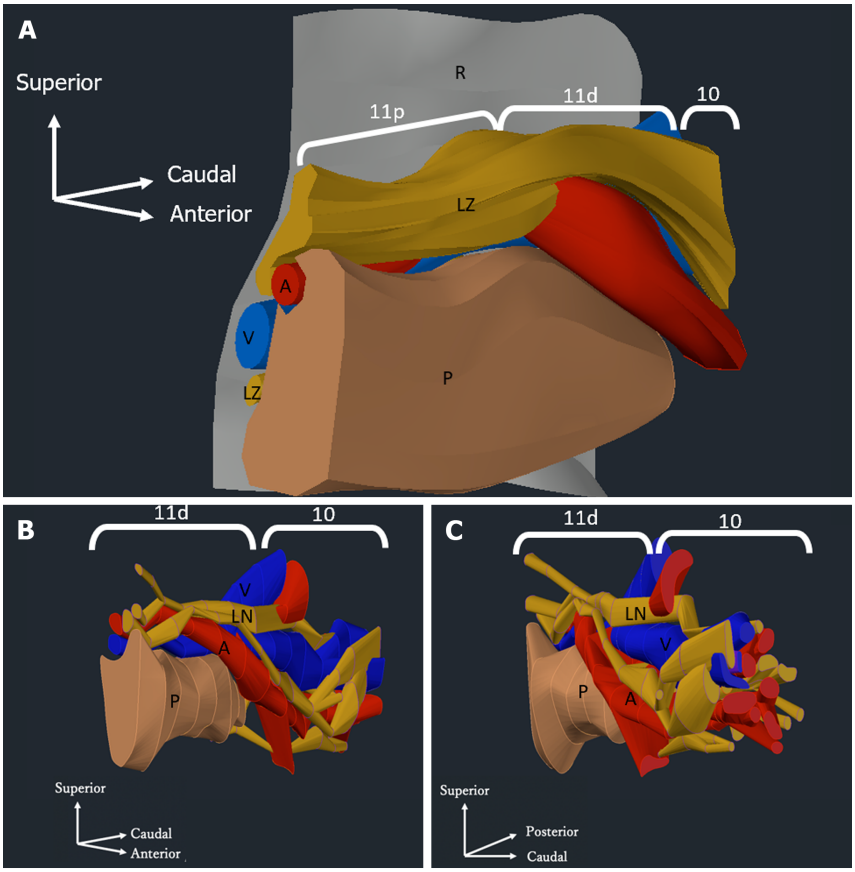

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Figure 7 Three-dimensional model of the distribution of the pancreas, splenic artery, splenic vein, and lymph nodes. Three-dimensional model of the distribution of the pancreas, splenic artery, splenic vein, and lymph nodes (LNs). A: Three-dimensional model of the distribution of the pancreatic parenchyma, splenic artery, splenic vein, and LNs in the No. 11 region in case 2. The yellow zones represent the areas that contain LNs and surrounding tissues; B and C: Three-dimensional model showing the distribution of the pancreatic parenchyma, splenic artery, splenic vein, and LNs in the region of LN No. 11p and LN No. 10 in case 2. The yellow zones represent the LNs. Three-dimensional model viewed from the pancreatic head toward the splenic hilum. The retroperitoneal side is on the left (B). Three-dimensional model of the splenic hilum looking toward the pancreatic head. The retroperitoneal side is on the right (C). Brown: Pancreatic parenchyma; Red: Splenic artery; Blue: Splenic vein; Yellow: Lymph nodes; Gray: Border with the retroperitoneum; R: Retroperitoneal; LZ: Lymph node zone; A: Splenic artery; V: Splenic vein; P: Pancreas; LN: Lymph node; 11p: No. 11p lymph node; 11d: No. 11d lymph node; 10: No. 10 lymph node.

and conventional laparoscopy would be sufficient for No. 11p LN dissection. Our results suggest that surgeons should consider that some posterior No. 10 and No. 11d LNs may be left behind after SPSHLD when applying this procedure in clinical practice. The feasibility of the procedure should be reviewed if future clinical trials show an increase in hilar LN recurrence in laparoscopic SPSHLD cases.

ARTICLE HIGHLIGHTS

Research background

In East Asian countries, the standard treatment for locally advanced proximal gastric cancer with invasion of the greater-curvature is total gastrectomy with splenectomy. The splenic hilar and splenic artery lymph nodes (LNs) are usually dissected in this procedure. However, this procedure increases the risk of postoperative pancreatic complications. To avoid these complications, laparoscopic spleen-preserving splenic hilar LN dissection (SPSHLD) has been developed and is widely used in some countries.

Research motivation

Performing laparoscopic SPSHLD without spleen mobilization makes it challenging to dissect posterior splenic hilar LNs and LNs along the splenic artery. While previous studies have demonstrated the clinical feasibility of laparoscopic SPSHLD, anatomical studies have not been performed. Therefore, we sought to justify the omission of the posterior splenic portal LN from an anatomical perspective.

Research objectives

To evaluate the feasibility of laparoscopic SPSHLD from an anatomical standpoint, this study aimed to demonstrate the detailed distribution pattern of the anterior and posterior LNs, clarify the anatomical distribution of the splenic hilar (No. 10) and splenic artery (No. 11p and 11d) LNs, and count the number of anterior and posterior LNs.

Research methods

This study examined six Japanese cadavers fixed by arterial perfusion with 8% formalin and preserved in 30% alcohol. The distribution of the splenic hilar LNs and splenic artery LNs was evaluated by creating histological sections, followed by hematoxylin & eosin staining to assess the structure of the organs and vasculature. In addition, the number of anterior and posterior LNs was counted, and three-dimensional reconstructions of their distributions were created.

Research results

This research uncovered a pattern where No. 11 LNs exhibited a greater frequency on the anterior side than on the posterior side, whereas No. 10 LNs showed minimal variability in number. The mean LN count was observed to be higher on the anterior side for No. 11p, No. 11d, and No. 10 LNs. Additionally, the number of LNs on the posterior side tended to increase toward the splenic hilum. Heat maps and three-dimensional images were generated to illustrate the spatial distribution and location of the LNs, showing that some LNs were intravascular or surrounded by the hilar vessels.

Research conclusions

The ratio of anterior to posterior splenic hilar and splenic artery LNs may be lower than expected, and the number of posterior LNs increased toward the hilum. Our study suggests that surgeons should be aware that some posterior No. 10 and 11d LNs may be left behind after SPSHLD when using this procedure in clinical practice.

Research perspectives

In laparoscopic SPSHLD, some LNs may not be retrieved, which should be considered by surgeons.

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FOOTNOTES

Author contributions: Umebayashi Y, Muro S, Tokunaga M, Saito T, Sato Y, Tanioka T, Kinugasa Y and Akita K designed and coordinated the study; Umebayashi Y, Muro S and Saito T acquired data; Umebayashi Y and Muro S analyzed data; Umebayashi Y, Muro S, Sato Y, Tokunaga M and Akita K interpreted the data; Umebayashi Y, Muro S, Tokunaga M and Akita K drafted the manuscript; all authors approved the final version of the article.

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ORIGINAL ARTICLE

Case Control Study

Preservation of left colic artery in laparoscopic colorectal operation: The benefit challenge

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Abstract

BACKGROUND

During laparoscopic resection for colorectal cancer, there is controversy regarding whether the left colic artery (LCA) should be preserved at its origin.

AIM

To investigate the prognostic significance of preservation of the LCA in colorectal cancer surgery.

METHODS

Patients were divided into two groups. The high ligation (H-L) technique (refers to ligation performed 1 cm from the beginning of the inferior mesenteric artery) group consisted of 46 patients, and the low ligation (L-L) technique (refers to ligation performed below the initiation of the LCA) group consisted of 148 patients. Operative time, blood loss, lymph nodes with tumor invasion, post-operative complications and recovery time, recurrence rate, and 5-year survival rate were compared between the two groups.

RESULTS

The average number of lymph nodes detected in postoperative pathological specimens was 17.4/person in the H-L group and 15.9/person in the L-L group. There were 20 patients (43%) with positive lymph nodes (lymph node metastasis) in the H-L group and 60 patients (41%) in the L-L group. No statistical differences were found between the groups. Complications occurred in 12 cases (26%) in the H-L group and in 26 cases (18%) in the L-L group. The incidences of postoperative anastomotic complications and functional urinary complications were significantly lower in the L-L group. The 5-year survival rates in H-L and L-L groups were 81.7% and 81.6%, respectively, and relapse-free survival rates were 74.3% and 77.1%, respectively. The two groups were similar statistically.

CONCLUSION
Complete mesenteric resection combined with lymph node dissection around the inferior mesenteric artery root while preserving the LCA is a beneficial surgical approach during laparoscopic resection for colorectal cancer.

Key Words: Cancer; Complete mesenteric resection; Inferior mesenteric artery; Urinary complications; Lymph

Core Tip: Colorectal cancer is a common disease. The operative method is related to the prognosis. We studied the correlation between different ligation sites of the inferior mesenteric artery and curative effect. There were 20 patients (43%) in the high ligation group and 60 patients (41%) in the low ligation group with positive lymph nodes. There was no significant difference in survival between the two groups. However, the incidences of postoperative anastomotic complications and functional urinary complications were significantly lower in the L-L group. This study confirmed that preservation of the left colic artery should be recommended in the surgery.

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INTRODUCTION

During laparoscopic resection of colorectal cancer there is controversy about the ligation site of the inferior mesenteric artery (IMA). There are currently two main opinions. Some doctors believe that the ligature should be performed at the beginning of IMA (high ligation, H-L), while others believe that the ligature should be performed after the dissection of the left colic artery (LCA) [preserving the LCA, low ligation (L-L)][1]. H-L, which is beneficial for removal of lymphatic tissue from the root of the IMA completely (especially lymph node No. 253), allows accurate staging of the postoperative tumor stage. H-L technology is easier to perform, and the anastomosis is essentially tension-free for complete mesenteric release. It is also easy for beginners to learn. However, because the anastomotic blood supply after high tie comes exclusively from the superior mesenteric vessels, for some patients, especially those with congenital absence of the marginal aortic arch, the anastomotic blood supply is significantly reduced, which increases the chance of intestinal fistula. Furthermore, autonomic nerve injury impacts postoperative bowel and urinary function recovery[2].

According to the Japan Colon and Rectal Cancer Association, the positive rate of lymph node metastasis around the root of the IMA root was 3.6% for colon cancer (stage T3-T4) and 5.1% for rectal cancer from 2011 to 2021, which were similar to statistics in Europe and the United States. Therefore, dissecting lymph node (LND) No. 253 is a necessary surgical step[3]. There are insufficient data to support whether simultaneous No. 253 LND while preserving the LCA and autonomic nerves can achieve satisfactory outcomes while reducing adverse events and complications. To overcome the shortcomings of the traditional surgical approach, we performed a surgical trial of L-L of the IMA combined with dissection of peri-IMA LND. We evaluated the patients' clinical data and prognosis between the L-L and H-L approaches.

MATERIALS AND METHODS

Clinical data

A retrospective case-control study including patients with sigmoid or rectal cancer treated surgically in the Department of General Surgery, Beijing Friendship Hospital, Capital Medical University were prospectively recorded and retrospectively analyzed between February 2014 to February 2016. According to the location of the vessel ligation the patients were divided into two groups, the H-L group and L-L group (Figure 1). The diagnostic criteria of colorectal cancer were postoperative pathological examination.

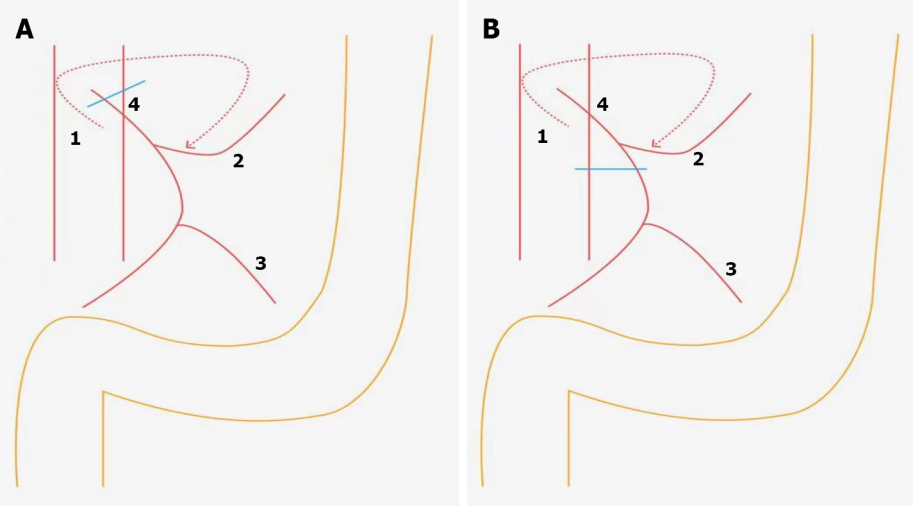

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Figure 1 The diagram of ligation site of the inferior mesenteric artery in colorectal cancer surgery. A: High tie; B: Low tie. 1: Inferior mesenteric artery; 2: Left colic artery; 3: The first branch of the sigmoid artery; 4: Lymph node around the origin of the inferior mesenteric artery.

Inclusion criteria were: (1) Patients with clearly diagnosed colorectal cancer who had preoperative indications for surgery diagnosed by magnetic resonance imaging or computed tomography; (2) No invasion of the adipose tissue surrounding the intestinal tract and no encapsulation of major vascular structures; and (3) No distant metastasis or peritoneal implantation.

Exclusion criteria were: (1) Patients with acute perforation or obstruction prior to surgery; (2) Patients with abdominal perineal resection combined with radical resection of rectal cancer; and (3) Patients with concurrent intestinal lesions.

The study was approved by the Ethics Committee of Beijing Friendship Hospital Affiliated to Capital Medical University, with the approval No. PM6475.

Monitoring indexes

Clinical data characteristics of all enrolled patients were analyzed, including age of onset, sex, tumor site, operation time, blood loss, number of lymph nodes with tumor metastasis (positive nodes), number of lymph nodes around the IMA root, total number of lymph nodes in the sample, recovery time of intestinal function, and national standard tumor staging. The tumor staging was defined according to the TNM staging System (7th edition) updated by the United Cancer Council and the United International Cancer Center.

The subjects were regularly examined in the outpatient department after discharge and were routinely examined in the outpatient department every 6 mo from discharge. The last follow-up date was September 15, 2022. The 5-year survival rate and recurrence-free survival rate were observed. Among them, overall survival referred to the time from the date of the operation to the date of death by the tumor. Patients were followed-up regularly by performing 1-2 colonoscopies or computed tomography examinations annually.

Surgical modality and grouping

The surgical modalities were radical resection of sigmoid or rectal cancer. The location of the IMA ligation site (preserving or not preserving the LCA) was determined by each surgeon on a case-by-case basis according to the presence of intraoperative bleeding, visibly enlarged lymph nodes around the artery, the operator's skill, and the ease of separating the vessels.

Statistical analysis

Data with normal distribution were expressed as mean ± standard deviation, and the χ^2 test was adopted to check whether the population rates of independent samples were the same. The *t*-test was used to compare whether the sample means of two independent samples were statistically significant. The 5-year survival rate between the two groups was compared by the log-rank test. We used SAS statistical software (version 23.0; IBM Corp.) for all analyses, and $P < 0.05$ was considered statistically significant.

RESULTS

Clinical data

This study involved 194 patients, who were divided into two groups according to the location of the vessel ligation: 46 in the H-L group, where the ligation was performed at the root of the IMA; and 148 in the L-L group (preservation LCA in the operation), where the vessel ligation was performed at the beginning of the LCA (Figures 1 and 2). No. 253 LND was also performed in both groups. There were no statistical differences in age, sex, and tumor site between the two groups as shown in Table 1.

Pathological analysis after LND

The average number of lymph nodes detected was 17.4/person for the H-L group and 15.9/person for the L-L group in postoperative pathological specimens. There were 20 patients (43%) in the H-L group and 60 patients (41%) in the L-L group with positive lymph nodes. We found no significant difference between the two groups. Regarding the IMA root lymph nodes (No. 253), there were 2 positive cases in the H-L group (4%) and 5 positive cases in the L-L group (3%). There was still no significant difference between the two groups. The recovery time of bowel function was shorter in the L-L group (Table 2).

No metastasis was found in the lymph nodes of 114 patients (58%), while positive lymph nodes were observed in 80 patients (42%), including 7 cases (3%) at station 3 (No. 253), 5 of which had positive station 1 and 2 lymph nodes. Positive lymph nodes were observed most often at station 1 and station 2 but rarely at station 3.

Complications

Complications occurred in 12 cases (26%) in the H-L group and 26 cases (18%) in the L-L group. Wound infection (n = 17) was the most common complication in both groups, and the incidences of postoperative anastomotic complications and functional urinary complications were significantly lower in the L-L group. The incidences of other complications were similar between the two groups (Table 3).

Five-year relapse-free and survival rates

There were 11 cases (24%) in the H-L group and 32 cases (22%) in the L-L group of postoperative recurrence, which was similar between the two groups. There were 2 cases (4%) in the H-L group and 6 cases (4%) in the L-L group of local lymph node recurrence, with no significant difference between the groups. The most common organ of recurrence in the H-L group (4 cases, 9%) and the L-L group (11 cases, 7%) was the lung, with no significant difference between the groups (Table 4).

The 5-year survival rates in the H-L and L-L groups were 81.7% and 81.6%, respectively, and the relapse-free survival rates were 74.3% and 77.1%, respectively. The two groups were similar statistically. In patients with lymph node metastases the 5-year survival rates were 68.1% *vs* 66.2% and the relapse-free survival rates were 65.3% *vs* 64.9% in the H-L and L-L groups, respectively, with no significant differences.

DISCUSSION

The presence or absence of lymph node metastasis is significantly related to the prognosis of patients with colorectal cancer, and detailed examination of each surgical specimen is an important index. According to the American Joint Committee on Cancer/Union for International Cancer Control guidelines, a minimum of 12 lymph nodes must be diagnosed in postoperative specimens. However, clinically reaching the recommended number of lymph nodes is sometimes very difficult[4]. In such cases, fine dissection of the intestinal vessels, especially the IMA, is essential to achieve the recommended number of lymph nodes. Therefore, choosing high- or low-tie IMA ligation remains controversial.

Except for a few colon cancers without lymphatic metastases in early stages, LND at the root of the IMA is a key step. Considering the completeness of tumor treatment, IMA ligation at the root is the standard procedure in many hospitals in China. An analysis by Rutegård *et al*[5] found that only 8.7% of patients had positive IMA root lymph nodes, and the rate of positive IMA root lymph nodes in this study was 4%. This is an important finding suggesting that No. 253 LND should be performed in all patients with distal colorectal cancer; otherwise approximately 4%-8%[6] of patients may have residual tumor at this site. The second reason for this anatomical dissection is the phenomenon of skip metastasis, which was found in the No. 253 lymph nodes of 2 cases in our study. This coincides with the findings of Mari *et al*[7], which identified this metastasis in 1.9% of the patients. Therefore, these findings provide a theoretical basis for LND at the IMA root.

In the present study, there was no difference in the number of lymph nodes obtained by high-tie or low-tie, the number of positive lymph nodes, and the ratio of positive-to-harvested lymph nodes, including the number of lymph nodes at the IMA root, suggesting that complete LND is still feasible even without IMA ligation. The rate of metastasis in the IMA root lymph nodes was relatively constant

Table 1 Comparison of the patients' preoperative clinical data

Group	High ligation group, *n* = 46	Low ligation group, *n* = 148	*P* value
Sex as male/female	28/18	90/58	0.897
Age in yr, mean ± SD	58.3 ± 10.1	60.4 ± 9.4	0.645
Tumor site			0.178
Sigmoid colon	16	46	-
Recto-sigmoid junction	13	34	-
Upper rectum	10	39	-
Lower rectum	7	29	-

SD: Standard deviation.

Table 2 Surgical data

Variable	High ligation group, *n* = 46	Low ligation group, *n* = 148	*P* value
Operative time in min, mean ± SD	210.0 ± 34.2	232.0 ± 28.3	0.482
Blood loss in mL, mean ± SD	145.0 ± 30.3	187.0 ± 50.3	0.165
Patients with positive lymph nodes, *n*	20	60	0.854
Number of lymph nodes dissected, mean	17.4	15.9	0.203
Patients with positive lymph nodes in the root of the inferior mesenteric artery, D253	2	5	0.372
Time to recovery of bowel function in d, mean ± SD	5.0 ± 1.8	3.0 ± 1.2	0.042

SD: Standard deviation.

Table 3 Comparison of postoperative complications, *n* (%)

Complication	High ligation group, *n* = 46	Low ligation group, *n* = 148	*P* value
Number of complications	12 (26)	26 (186)	0.436
Wound infection	4 (9)	13 (9)	0.286
Stress ulcers	2 (4)	6 (4)	0.316
Anastomotic fistula and stricture	3 (7)	5 (3)	0.045
Urinary dysfunction	3 (7)	2 (1)	0.029

Table 4 Postoperative recurrence

Recurrence site	High ligation group, *n* = 46	Low ligation group, *n* = 148	*P* value
Overall recurrence rate	11 (24%)	32 (21%)	0.607
Liver	3	9	-
Lung	4	11	-
Lymph nodes	2	6	-
Local recurrence (intestinal tract)	0	2	-
Peritoneum	2	4	-

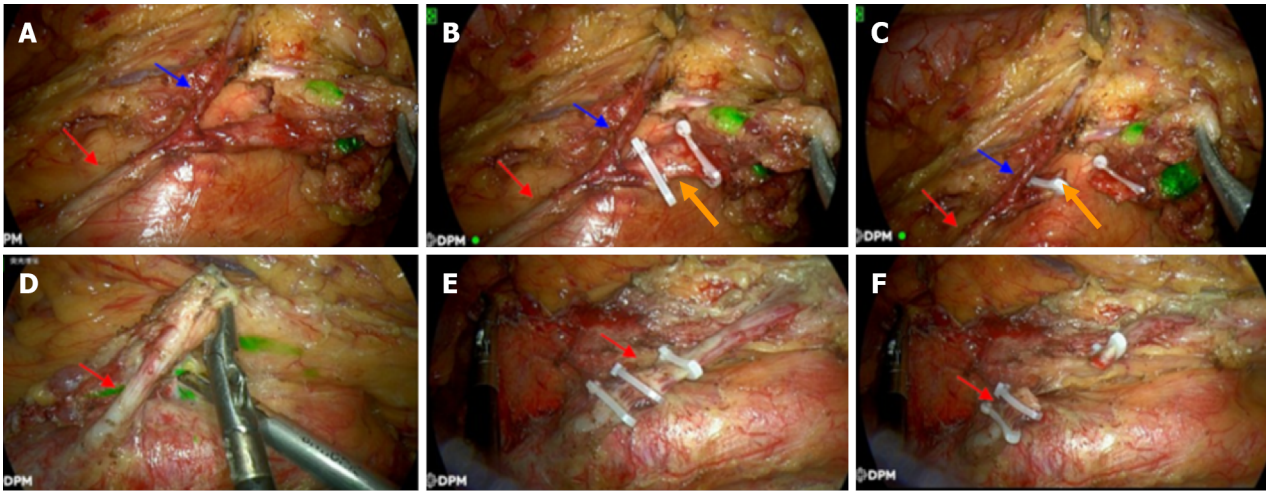

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Figure 2 The intraoperative photographs of the ligation site of the inferior mesenteric artery in colorectal cancer surgery. A-C: Low ligation combined with lymph node dissection around the origin of the inferior mesenteric artery (low tie with lymph node); D-F: High ligation combined with lymph node dissection around the origin of the inferior mesenteric artery (high tie with LND). Red arrows: The route of the inferior mesenteric artery; Blue arrows: Left colic artery; Orange arrows: Superior rectal artery.

with or without high ligation. During LND, careful vascular dissection and complete mesenteric resection are more important than the ligation site. Postoperative survival was not related to the tie level in this study but rather to the completeness of radical surgery. With advances in surgical techniques, more studies have observed no significant difference between the two ligation levels regarding LND. In fact, all clinical cases of local recurrence have occurred in incomplete or near-complete rectal mesenteric resections.

To prevent such an insurmountable problem as anastomotic leak after colorectal resection, more hospitals are selectively preserving the LCA to maintain anastomotic blood flow, benefiting from continuous advances in surgical techniques for colon cancer. The incidence of intestinal fistula in rectal cancer in China has ranged from 5% to 26% in the past 5 years[8]. Tension-free anastomosis and good blood supply are the two main considerations to reduce this serious complication. High-tie can reduce blood flow to the colon leading to intestinal ischemia, which may eventually lead to anastomotic leak or stricture and is a common postoperative complication. In this study, there was a significant increase in the incidence of anastomotic stricture in the H-L group. This was confirmed by intraoperative Doppler ultrasonography and the use of indocyanine green angiography in a study by Ogino *et al*[9], which revealed a 50% decrease in anastomotic blood flow after high tie. Treating anastomotic fistula or stricture is difficult once it occurs. There may also be cases of autonomic nerve disorders (*e.g.*, urinary and sexual dysfunction) owing to disruption of the IMA root plexus (Table 3).

The level of IMA ligation is partly related to the freeness of the proximal colon. In many studies, high tie of the IMA resulted in better free bowel[10]. Some researchers believe that high ligation of the IMA allows adequate free colon and ensures a tension-free colonic anastomosis. However, inadequate free bowel can now be completely resolved by technical means, such as ligation of the inferior mesenteric vein at the level of the lower margin of the pancreas and freeing the splenic flexure of the descending colon[11]. Another advantage of this surgical approach is that because the LCA is preserved it is also possible to reoperate on the residual colon if secondary carcinoma occurs in the ascending or transverse colon after surgery for sigmoid or rectal cancer[12]. Therefore, IMA LND based on LCA preservation has become the main surgical approach in some hospitals. The key in this approach is total mesenteric resection and clearance of group D3 lymph nodes (such as No. 253)[13,14].

In this study, 194 patients underwent radical surgery for sigmoid or rectal cancer, and we compared the postoperative complication rates, recurrence rates, and prognosis of high *vs* low IMA ligation combined with LND. The results showed that the incidence of anastomotic leak was significantly lower in the low ligation plus LND group. Furthermore, the incidence of postoperative urinary dysfunction was significantly lower, and the recovery time of bowel function was shorter[15]. In addition, there was no significant difference in the 5-year survival and relapse-free survival rates for all enrolled patients. These results demonstrate the reliability of preserving the LCA while performing LND.

CONCLUSION

High ligation of IMA in colorectal cancer operation is a simple method that can clean the lymph nodes

completely. However, the incidence of intestinal fistula increased significantly, and the postoperative recovery was slow[16]. In this study, with the investigation of the prognostic impact of the ligation site of IMA in colorectal cancer surgery in 194 patients, it is found that complete mesenteric resection and IMA root LND while preserving the LCA is a more reliable and safe surgical approach in patients undergoing colorectal cancer surgery.

ARTICLE HIGHLIGHTS

Research background

Sigmoid and rectal tumors are the most common intestinal tumors, accounting for 80% of all colorectal cancers. Surgery is still the preferred and primary treatment of intestinal tumors, and the anatomical basis is total mesangectomy. However, a critical point is that the location of ligation of the inferior mesenteric artery (IMA) is still under debate.

Research motivation

At present, there are two mainstream methods used in laparoscopic colorectal cancer surgery. One is high ligation (H-L), that is, ligation at the beginning of the IMA, and the other is low ligation (L-L) at the distal end of the left colic artery. The two methods have their own advantages. Therefore, we systematically compared the two methods to provide a reference basis for surgeons to choose.

Research objectives

To investigate the prognostic significance of the ligation site of the IMA in colorectal cancer surgery.

Research methods

We retrospectively analyzed the data of 194 patients undergoing radical R0 resection at Beijing Friendship Hospital between February 2014 to February 2016. Operative time, blood loss, positive lymph nodes and the number of dissected lymph nodes, postoperative complications and recovery, recurrence rate, and 5-year survival rate were compared between the H-L group and L-L group.

Research results

The average number of lymph nodes detected in postoperative pathological specimens was 17.4/person in the H-L group and 15.9/person in the L-L group. There were 20 patients (43%) in the H-L group and 60 patients (41%) in the L-L group with positive lymph nodes, with no statistical differences between the groups. Complications occurred in 12 cases (26%) in the H-L group and 26 cases (18%) in the L-L group, with no significant difference in the incidence between the groups. The incidences of postoperative anastomotic complications and functional urinary complications were significantly lower in the L-L group. The incidence of other complications was similar between the two groups. The 5-year survival rates in the H-L and L-L groups were 81.7% and 81.6%, respectively, and relapse-free survival rates were 74.3% and 77.1%, respectively. The two groups were similar statistically.

Research conclusions

Complete mesenteric resection and IMA root lymph node dissection while preserving the LCA is a more reliable and safe surgical approach during laparoscopic resection for colorectal cancer.

Research perspectives

Our study demonstrated that LCA preservation is highly feasible at its origin in most cases. A preoperative computed tomography scan could predict the feasibility of the determined origin of the LCA (spread out or not) and the route (near or far away from the inferior mesenteric vein) of the LCA. In the future, multicenter prospective studies with a larger sample size are required to verify our results.

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FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Surgical management of high-grade pancreatic injuries: Insights from a high-volume pancreaticobiliary specialty unit

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Abstract

BACKGROUND

The management of high-grade pancreatic trauma is controversial.

AIM

To review our single-institution experience on the surgical management of blunt and penetrating pancreatic injuries.

METHODS

A retrospective review of records was performed on all patients undergoing surgical intervention for high-grade pancreatic injuries [American Association for the Surgery of Trauma (AAST) Grade III or greater] at the Royal North Shore Hospital in Sydney between January 2001 and December 2022. Morbidity and mortality outcomes were reviewed, and major diagnostic and operative challenges were identified.

RESULTS

Over a twenty-year period, 14 patients underwent pancreatic resection for high-grade injuries. Seven patients sustained AAST Grade III injuries and 7 were classified as Grades IV or V. Nine underwent distal pancreatectomy and 5 underwent pancreaticoduodenectomy (PD). Overall, there was a predominance of blunt aetiologies (11/14). Concomitant intra-abdominal injuries were observed in 11 patients and traumatic haemorrhage in 6 patients. Three patients developed clinically relevant pancreatic fistulas and there was one in-hospital mortality

secondary to multi-organ failure. Among stable presentations, pancreatic ductal injuries were missed in two-thirds of cases (7/12) on initial computed tomography imaging and subsequently diagnosed on repeat imaging or endoscopic retrograde cholangiopancreatography. All patients who sustained complex pancreaticoduodenal trauma underwent PD without mortality. The management of pancreatic trauma is evolving. Our experience provides valuable and locally relevant insights into future management strategies.

CONCLUSION

We advocate that high-grade pancreatic trauma should be managed in high-volume hepato-pancreato-biliary specialty surgical units. Pancreatic resections including PD may be indicated and safely performed with appropriate specialist surgical, gastroenterology, and interventional radiology support in tertiary centres.

Key Words: Pancreas; Trauma; Injury; Pancreatectomy; Pancreaticoduodenectomy; Damage control surgery

Core Tip: The management of pancreatic trauma is evolving. This study presents a single-centre series of patients undergoing operative management for pancreatic trauma in Australia. We advocate that high-grade pancreatic trauma should be managed in high-volume hepato-pancreato-biliary specialty surgical units. Penetrating and blunt trauma presentations are associated with varied patterns of injury. There is a growing role for endovascular and endoscopic techniques in the contemporary management of pancreatic trauma. Pancreatic resections including pancreaticoduodenectomy may be indicated and safely performed with appropriate specialist surgical, gastroenterology, and interventional radiology support in tertiary centres.

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INTRODUCTION

Pancreatic injuries are relatively uncommon, but present with significant diagnostic and therapeutic challenges. Occurring in less than 2% of all trauma presentations and 1%-12% of abdominal trauma[1-3], they are associated with morbidity and mortality rates as high as 40%[4-7]. Diagnosis is difficult as clinical examination and standard imaging modalities are unreliable in the early phase of injury. As the pancreas is mostly retroperitoneal, initial signs and symptoms are non-specific and are frequently overlooked in the presence of concomitant injuries. Furthermore, blunt and penetrating aetiologies tend to be associated with different patterns of injury. Patients presenting with penetrating trauma or with hemodynamic instability typically proceed to exploratory laparotomy without prior imaging, where pancreatic injuries are evaluated intraoperatively. Meanwhile, stable patients presenting with blunt abdominal trauma tend to be imaged and managed conservatively[3].

Recommendations from the American Association for the Surgery of Trauma (AAST)[8] consider the location and extent of parenchymal injury and main pancreatic duct integrity as key determinants for definitive management[6,9]. For distal injuries with duct disruption (Grade III), distal pancreatectomy (DP) is the mainstay of treatment. The management of proximal injuries (Grades IV and V) is more complex by comparison. In select cases, proximal injuries with no devitalization of the pancreatic head or those involving the duodenum and ampulla may be managed with external drainage. More commonly, combined pancreaticoduodenal injuries tend to require surgical repair, with concurrent duodenal decompression with diversion or pyloric exclusion procedures. In exceptional circumstances, Whipple's resection or pancreaticoduodenectomy (PD) may be indicated where repair is not feasible.

Despite these pathways, the management of high-grade pancreatic injuries is debated, especially in patients with haemodynamic instability. In modern trauma management, those who are critically injured typically proceed to damage control surgery with staged reconstruction[10,11]. This involves a laparotomy with the primary objective of haemorrhage and contamination control, with return to theatre for definitive repair once physiological stabilisation has been achieved. This has been the preferred approach as definitive surgery in the presence of deranged physiology in the acute setting has

historically been associated with adverse outcomes. As such, the trauma PD is typically performed as a two-stage procedure, with resection performed at the initial laparotomy followed by completion of anastomoses at reoperation within 48 h[12]. Despite limited evidence, this has been widely adopted due to the perceived risk of increased morbidity and mortality associated extensive reconstruction at index laparotomy. However, delayed definitive management is not without major complications, which would favour immediate reconstruction where it can be safely achieved.

Due to its rarity, the management of high-grade pancreatic trauma is not standardised, and retrospective cohort and observational studies are invaluable in informing current standards of care. The literature consists predominantly of studies conducted in regions such as North America and South Africa, where penetrating abdominal trauma occur with high prevalence. However, blunt abdominal trauma is more common than penetrating trauma in Australasian centres. While pancreatic injuries are estimated to occur in 20%-30% of penetrating abdominal trauma, they are observed in less than 2% of blunt trauma cases worldwide[13]. Furthermore, trauma services are not centralised in Australian healthcare settings. These regional differences are likely to have important implications for patient management and outcomes.

This study reviews the experience of a high-volume hepato-pancreato-biliary specialty unit within a low-volume trauma centre in Australia. Our findings aim to provide valuable and locally relevant insights into the management of pancreatic trauma, providing a compelling argument for single stage pancreatic trauma management in units that perform a high volume of elective hepato-pancreato-biliary procedures.

MATERIALS AND METHODS

Following district ethics approval, a retrospective review of records was conducted for all patients presenting to a single tertiary centre who required pancreatectomy for high-grade pancreatic injuries (AAST Grade III or greater) from 2001-2022.

Patients were identified from a prospectively maintained database. Patient demographics (age and sex), injury characteristics (mechanism and associated injuries) and clinical data, pertaining to the initial presentation [haemodynamic stability and Glasgow Coma Scale (GCS) score on admission], diagnostic details (investigations and findings), surgical procedures, and morbidity and mortality outcomes were extracted. Pancreatic injuries were graded according to the AAST Organ Injury Scale[8]. Descriptive statistical analyses were performed on using SPSS version 28.0 (IBM Corporation, Armonk, NY).

RESULTS

Patient cohort and injury characteristics

From January 2001 to December 2022 a total of 14 patients (median age 23 years, 8/14 male) underwent pancreatectomy following blunt (n = 11) and penetrating (n = 3) trauma. Nine underwent DP and 5 underwent Whipple's resection. Seven patients sustained AAST Grade III injuries and 7 were classified as Grades IV to V, involving proximal injuries. Demographic and clinical characteristics of this study cohort are summarised in Table 1. The median length of stay was 15.3 d (range 3.1–40.4). Pancreatectomy-specific complications occurred in 7 patients, including intraabdominal sepsis (n = 4) and clinically-relevant pancreatic fistula (n = 3). There was one in-hospital mortality.

Blunt trauma

Among the patients presenting with pancreatic injury associated with blunt abdominal trauma, the mean age was 20 years (range, 17–38) and 7 patients were male. Seven patients were classified as AAST Grade III and 4 as Grade IV. The most common cause of blunt injury was motor vehicle accidents (n = 6). All but one was associated with major organ injuries requiring surgical intervention, including injury to the liver, spleen, kidneys, and small bowel. Two patients sustained additional injury to major vascular structures, including transection of the thoracic aorta and renal arteries. Three patients were hemodynamically unstable at the time of presentation and proceeded to surgery on the day of injury, of which 2 underwent damage control laparotomies. Pancreatic injuries were identified on computed tomography (CT) performed *en route* to theatre in one case and intraoperatively in the other. Among stable presentations, the median injury-to-surgery time was 3.5 d. Ten patients were investigated with imaging prior to surgery; pancreatic injury was missed in 5 cases and subsequently detected on repeat imaging. Grades III and IV were definitively diagnosed by initial CT (n = 3); delayed CT (n = 3, ranging from 2-30 d from injury); magnetic resonance cholangiopancreatography (MRCP) (n = 3); endoscopic retrograde cholangiopancreatography (ERCP) (n = 1); and intraoperatively (n = 1). Among patients managed for blunt trauma, 9 proceeded to DP and 2 to PD. Two patients developed major postoperative complications and there was one in-hospital mortality. A summary of pancreatic injuries associated with blunt trauma is presented in Table 2.

Table 1 Study population and characteristics

	Blunt *n* = 11	Penetrating *n* = 3
Patient demographics		
Age (yr, range)	20 (17 - 38)	32 (26 – 51)
Sex (male, %)	8	1
Injury characteristics		
Mechanism		
Motor vehicle accident	5	0
Gunshot	0	1
Stabbing	0	2
Sporting injury	5	0
Fall	1	0
Shock (BP < 90 mmHg)	3	1
Grade		
III	7	0
IV	4	1
V	0	2
Associated abdominal injuries		
Organ injuries	8	3
Vascular injuries	3	3
Intervention		
Time to operation		
< 12 h	4	3
> 12 h	7	0
Procedure		
DP	9	0
PD	2	3
Outcomes		
In-hospital mortality	1	0
Unplanned return to theatre	1	0
Length of stay	14.0 (3.1 – 39.0)	34.6 (19.7 – 40.4)
Postoperative complication		
Postoperative pancreatitis / fistula	1	2
Haemorrhage	0	0
Intraabdominal sepsis	2	2

BP: Blood pressure; PD: Pancreaticoduodenectomy; DP: Distal pancreatectomy.

Penetrating trauma

Among patients presenting with penetrating trauma, the mean age was 32 years (range, 26-51), with 2/3 patients being female. Two patients sustained knife trauma, and one a gunshot injury. All involved proximal injuries to the head of the pancreas. Two were classified as AAST Grade V injuries, involving major disruption of the pancreatic head combined with duodenal injury. All had associated injuries to solid organs and major vascular structures. Two were investigated with CT imaging prior to surgery. All penetrating injuries were managed with PD with immediate reconstruction at index laparotomy. Major complications were reported in 2 cases, and there were no mortalities. A summary of pancreatic

Table 2 Summary of cases: Blunt abdominal trauma resulting in high-grade pancreatic injuries

Patient		Mechanism	Pancreatic injury	Associated injuries	Vascular injury	AAST grade	Haemodynamic stability	Pre-operative transfusion requirements	Investigations prior to OT	Primary procedure, post-injury day	Other	LOS	Outcome
1	17F	Fall	Pancreatic body laceration	Splenic infarct	Nil	III	Stable; FAST positive	Nil	CTAP; MRCP; ERCP + Stent	DP and splenectomy, 10 d from injury (undetected injury on initial imaging)	Nil	20.8	Uncomplicated recovery
2	38F	MVA	Pancreatic head laceration; Associated with intraperitoneal haemorrhage	CBD avulsion; Liver laceration; Fractures–ribs; L2-3 transverse processes, right radius	Nil	IV	Stable	2U pRBCs	CTAP, MRCP	PD, 7 d from injury (transferred from regional centre, initially for conservative management)		17.8	Persistent intraabdominal collections requiring two CT-guided drainage procedures
3	36F	MVA	Transected pancreatic neck; Associated with large left retroperitoneal haematoma	Right tension pneumothorax; Left haemothorax; Multiple liver lacerations; Small and large bowel perforations; Left renal hilar laceration	Transection of left renal artery, suspected thoracic aortic injury	IV	Unstable	MTP, 26U pRBC, 18 FFP, 5 Plt, 47 Cryo, 1L albumin, 1g TXA	None	DP and splenectomy	Damage control surgery in hybrid theatre: Laparotomy with four quadrants packing and cross clamping of supracoeliac aorta. Angioembolisation of left renal artery performed; Pancreatic neck transection was noted and a temporary drain placed. Temporary abdominal closure with negative pressure dressing; Ongoing MTP and resuscitation for next 48 hours. Patient remained intubated; Definitive operative intervention 72 h from initial laparotomy: En block resection of distal pancreas and spleen, and distal transverse colonic resection without anastomosis.	3.1	In-hospital mortality (secondary to multi-organ failure)
4	29M	MBA	Transected head of pancreas	Liver laceration; Duodenal laceration; Radius and proximal phalanx fractures	Nil	IV	Unstable; FAST positive	7U pRBC	CTAP–deterioration en route to OT	Emergency PD, < 24 h from injury	Right wrist ORIF and closed reduction of 5th digit	15.0	
5	20M	MVA	Transacted pancreas at junction of tail and body; Associated with major disruption	Splenic laceration	Nil	III	Stable	Nil	CTAP; ERCP and pancreatogram	DP and splenectomy, 2 d from injury	Nil	13.0	Uncomplicated recovery

			of MPD										
6	19M	MBA	Transection of pancreatic tail and large pseudocyst	Chance injury to L1/2 with spinal canal stenosis; Avulsion of L2-4 right transverse processes	Nil	III	Stable; FAST positive	Nil	CTAP; ERCP + Stent	DP and splenectomy, 1 mo form injury (delayed presentation)	Spinal stabilisation, lumbar fusion L1-2	39.0	Uncomplicated recovery
7	20M	MBA	Transection to tail of pancreas; Associated with MPD rupture and retroperitoneal haematoma	Grade IV/V left renal injury; Splenic hilum laceration; Left ulnar fracture and multiple ribs; Penetrating wound to right knee	Left renal artery transection	III	Stable; FAST positive	Nil	MRCP; ERCP + stent	DP and splenectomy, 4 d from injury	Removal of Meckel's diverticulum and appendicectomy; Left ulnar ORIF; Right knee wound washout and debridement	14.0	Uncomplicated recovery
8	17M	Sporting injury	Transected pancreatic neck and head; Associated with complete disruption of MPD	Liver laceration; Scaphoid fracture	Nil	IV	Stable	Nil	CTAP; ERCP	DP and splenectomy, 3 d from injury		12.0	
9	18M	Sporting injury	Transected pancreatic body; Associated with large retroperitoneal collection	Nil	Nil	III	Stable	Nil	CT 3Phase	DP and splenectomy, 3 d form injury	Nil	15.5	Postoperative pancreatitis; Intraabdominal collection requiring CT-guided drainage
10	21M	Sporting injury	Transected pancreatic body; Associated with large intraperitoneal and retroperitoneal haematoma	Splenic laceration and infarct	Nil	III	Unstable; FAST positive	1U pRBC	CTAP	DP and splenectomy; Initial CT imaging demonstrating isolated splenic injury	Left hemicolectomy; Re-look laparotomy and colonic anastomosis	7.7	
11	24M	Sporting injury	Transection at junction of pancreatic neck and body; Associated with complete disruption of MPD	Hepatic contusion	Nil	III	Stable; FAST negative	Nil	CTAP; MRCP; ERCP–Proceeded to laparotomy and DP	Subtotal pancreatectomy (spleen preserving), 3 d from injury; Missed ductal injury on initial CT	Nil	10.0	Uncomplicated recovery

AAST: American Association for the Surgery of Trauma; FAST: Focused assessment with sonography for trauma; MTP: Massive transfusion protocol; FFP: Fresh frozen plasma; Plt: Platelets; TXA: Tranexamic acid; Cryo:

Cryoprecipitate; ORIF: Open reduction internal fixation; MVA: Motor vehicle accident; MPD: Main pancreatic duct; pRBC: Packed red blood cells; FAST: Focused assessment with sonography in trauma; CTAP: Computed tomography abdomen and pelvis; ERCP: Endoscopic retrograde cholangiopancreatography; MRCP: Magnetic resonance cholangiopancreatography; PID: Post injury day; OT: Operating theatre; PD: Pancreaticoduodenectomy; DP: Distal pancreatectomy; LOS: Length of stay.

injuries associated with penetrating trauma is included in Table 3.

DISCUSSION

Fourteen trauma presentations proceeded to pancreatic resection over a 20-year period at our tertiary centre. Overall, there was a predominance of blunt aetiologies (11/14), with 7 patients sustaining AAST Grade III injuries and 7 sustaining Grades IV or V. Nine underwent DP and 5 proceeded to pancreatoduodenectomy.

Morbidity and mortality

Our morbidity and mortality rates are consistent with previous reports from the United Kingdom[14], Asia[15], and Australia[16]. This is likely due to the predominance of blunt injuries (11/14), with penetrating trauma comprising a minority of cases in this series (3/14). Motor vehicle accidents represented the prevailing mechanism of the blunt aetiologies (6/11), while penetrating pancreatic injuries were most frequently sustained by self-inflicted stabbings (2/3). Based on published data from American and South African centres, penetrating injuries are more common due to higher prevalence of shootings and stabbings[17-20], occurring in 48%–81% of cases in the US[21] and 53%-72% in South Africa[22,23].

For high-grade pancreatic injuries, morbidity and mortality rates have been reported to be as high as 40%[24,25] and 60%[26-28] respectively. Penetrating injuries are associated with higher mortality compared to blunt injuries, with comparable morbidity. The high mortality associated with penetrating injuries is due to concomitant vascular and solid organ injury; up to 90% of penetrating pancreatic injuries have associated intra-abdominal injury, most commonly involving the liver, large intestine, and major vessels[29]. In this series, 11/14 were associated with additional intra-abdominal injuries and 6/14 with vascular injury. We report one mortality following blunt abdominal trauma from multiorgan failure and none resulting from penetrating trauma.

Morbidity associated with pancreatic injury is attributed primarily to pancreas-specific complications, which are critically determined by the involvement of the main pancreatic duct. Pancreatic fistulae occur most frequently, with incidence rates of up to 50%. Other major complications include the formation of pseudocysts, peripancreatic collections and abscess, and post-traumatic pancreatitis[13,30]. In this series, major complications occurred in 7/14 of cases, which involved intraabdominal sepsis and pancreatic fistulae (Table 1).

Diagnostic challenges - Blunt trauma

In our series, 10/14 patients sustained blunt trauma and were haemodynamically stable at the time of their presentation. There are several challenges pertaining to the initial management in such cases.

Table 3 Summary of cases: Penetrating abdominal trauma resulting in high-grade pancreatic injuries

Patient	Mechanism	Pancreatic Injury	Associated injuries	Vascular injury	AAST Grade	Haemodynamic stability	Pre-operative transfusion requirements	Investigations prior to OT	Primary procedure, post-Injury day	Other	LOS	Post-operative course
1 32M	Gunshot	Devascularisation of head of Pancreas, 4 cm defect	CBD; Duodenum, Right kidney (Grade III)	IVC, IPDA	V	Stable; FAST scan negative	Nil	CTAP	PD, < 24 h from injury	Right nephrectomy, IVC repair, Extended right hemicolectomy	19.7	Uncomplicated recovery
2 51F	Stabbing	Transection of head of pancreas	Renal hilum	PV; SMV; Middle colic vein	IV	Unstable; FAST positive	2U pRBC; 2U FFP; MTP activated	None	PD, < 24 h from injury	Extended to thoracotomy	34.6	Intraabdominal sepsis, collections requiring CT-guided drainage
3 26F	Stabbing	Head and uncinate of pancreas	Duodenum, Gallbladder	IVC	V	Stable; FAST positive	Nil	CTAP; Mesenteric angiogram (+ Pancreaticoduodenal pseudoaneurysm embolization)	PD, < 24 h from injury	IVC repair; Cholecystectomy	40.4	Intraabdominal collections, Splenic infarct

AAST: American Association for the Surgery of Trauma; FAST: Focused assessment with sonography for trauma; MTP: Massive transfusion protocol; FFP: Fresh frozen plasma; CBD: Common bile duct; IVC: Inferior vena cava; IPDA: Inferior pancreaticoduodenal artery; SMV: Superior mesenteric vein; pRBC: Packed red blood cells; CTAP: Computed tomography abdomen and pelvis; PID: Post injury day; OT: Operating theatre; PD: Pancreaticoduodenectomy; DP: Distal pancreatectomy; LOS: Length of stay.

While helical CT imaging represents the best non-operative modality for the investigation of intraabdominal injuries, the ability to evaluate pancreatic injury is limited in the acute phase. Early radiological findings tend to be subtle and non-specific, such that up to 40% of initial CT scans for patients with pancreatic injuries have false negative results[31,32]. In our series, ductal injury was missed in 7/10 patients presenting with blunt trauma who underwent investigation with CT imaging. These were subsequently diagnosed on repeat CT or ERCP. Disruption to the main pancreatic duct is recognized as the most important prognostic factor in patients sustaining pancreatic trauma and is estimated to occur in over one third of cases[17,33]. A high index of suspicion should therefore be maintained; repeat imaging with CT or early use of MRCP or ERCP should be considered where there is clinical suspicion for ductal involvement, in the presence of persistent abdominal pain, serum hyperamylasemia, or when initial CT is equivocal[34].

Haemorrhage control - Penetrating trauma

All penetrating injuries in this series involved major vascular structures. Penetrating injuries to the pancreas are often complicated by concurrent injury to the abdominal aorta, inferior vena cava (IVC), and portal vein. The clinical presentation of such cases can be highly variable. Patients sustaining venous haemorrhage into the minimally distensible retroperitoneal space may be stable due to haematoma-induced tamponade at presentation[35,36], with no overt clinical signs or symptoms until a substantial amount of blood has been lost. These presentations should be cautioned for potential sudden

decompensation. In contrast, free intraperitoneal haemorrhage typically induces haemodynamic shock, necessitating urgent laparotomy for haemorrhage control.

Surgically, haemorrhage associated with pancreatic proximal injuries are harder to manage than those with the body and tail; the splenic artery and vein, coursing superiorly/posteriorly to the pancreatic body and tail, are readily accessed and controlled[37]. In contrast, combined pancreaticoduodenal injuries are often associated with damage to the portal vein, IVC, and mesenteric vessels, where haemorrhage control and stabilisation take precedence over resection or reconstructive attempts. In this series, the emerging role of endovascular technologies in haemorrhage control and resuscitation is evident. For 2 patients, angiographic embolization was employed to control intraabdominal haemorrhage resulting from injuries to the gastroduodenal and renal arteries respectively. In one earlier case, cross-clamping of the proximal aorta was performed at damage control laparotomy. Currently, resuscitative endovascular balloon occlusion provides a minimally invasive alternative in many centres for non-compressible truncal haemorrhage[38,39]. The endovascular approach may offer the advantage of expedient control without the need for extensive dissection to the aortic hiatus, which can be technically challenging. Its increasing use has been supported by evidence of improved survival outcomes over traditional approaches[40-42].

Staged vs immediate reconstruction – Complex proximal injuries

Overall, the evidence-base for decision making in the management of complex high-grade injuries is limited[1]. Controversy still surrounds PD in the trauma setting, with only a small number of single-centre retrospective studies published over the last two decades[43]. The emergency PD is performed in less than 1% of high-grade traumatic injuries, with previous studies reporting prohibitive mortality rates[44-46]. While immediate resection is typical for injuries to the pancreatic body and tail, resections for proximal injuries of the pancreatic head and duodenum are usually performed as part of damage control surgery with staged reconstruction. Within our series, all trauma patients proceeding to PD involved reconstruction at index laparotomy with favourable outcomes. Two of 5 cases were complicated by postoperative collections treated with drainage (Clavien-Dindo III) and there were no postoperative mortalities.

Our results contribute to the sparse literature on PD in the trauma setting. In a recent systematic review, de Carvalho *et al*[47] compared outcomes for two-staged *vs* one-staged approach to PD for high-grade trauma. Their review of the literature until 2020, comprising of data from 149 patients submitted to PD for AAST Grade IV and V pancreatoduodenal injuries, reported a mortality rate of 28.2%. Subgroup analysis comparing outcomes for staged and immediate reconstruction approaches based on haemodynamic status showed no significant difference in mortality for unstable patients, with rates of 38.7% and 34.2% respectively. For stable patients, one-stage PD was exclusively performed, and this was associated with a mortality rate of 14.6%.

While a staged approach has traditionally been favoured over immediate reconstruction for the critically injured and unstable patient, there is increasing evidence for the safety of one-staged PD in experienced centres[12,47]. In the largest single-centre cohort study to date, Krige *et al*[12] compared the outcomes of patients who underwent PD for complex pancreatic injuries (n = 14) to those who underwent an initial damage control operation prior to definitive surgery (n = 5). The results of this study suggest that PD may be safely achieved in the presence of specialist multidisciplinary hepato-pancreato-biliary care. Our experience has similarly demonstrated favourable outcomes in a cohort of 5 patients presenting with mixed aetiologies, of whom 2 were unstable at the time of presentation. It is well-established that delayed definitive management predisposes to increased morbidity; the development of pancreatic fistulae predisposes to pseudoaneurysms formation and secondary haemorrhage, peritonitis, intraabdominal collections, and sepsis[48]. Thus, where the clinical status of the patient and surgical expertise permits, immediate reconstruction should be considered for proximal pancreatic injuries.

Model of care

Conducted within one of the highest-volume hepato-pancreato-biliary surgical units in Australia, this study is uniquely placed to evaluate complex pancreatic resections in the trauma setting. In high-volume trauma centres, as in North America or South Africa, these presentations are typically managed by a dedicated team of trauma surgeons[49,50]. In low-volume trauma centres, multiple subspecialty teams are often involved, with one coordinating acute surgical care[51]. In such a centre, these results show that pancreatic can be safely managed with the support of surgical subspecialty, gastroenterology, and interventional radiology services. Patients presenting with high-grade trauma may therefore benefit from transfer to tertiary hepato-pancreato-biliary centres, either acutely or following their initial management by acute general surgical and trauma teams.

Strengths and limitations

Despite a modest sample size, this series captures the evolving practices in trauma management and the impact of concurrent advancements in surgical techniques over twenty years. Our cohort further represents a patient population that has been underrepresented in the literature. Several limitations are

inherent to its single-centre retrospective design, lack of data on long-term outcomes and bias to institutional practice. Finally, patient outcomes and interventions were not stratified by injury severity or by other coexisting injuries. Given the variability of pancreatic trauma presentations, prospective studies are needed to substantiate recommendations on management of high-grade pancreatic injuries.

CONCLUSION

This study presents a single-centre series of patients undergoing operative management for pancreatic trauma in Australia. Our experience provides locally relevant insights into the future management of penetrating and blunt pancreatic injuries. There is a growing role for minimally invasive techniques, including endovascular control of traumatic haemorrhage and interventional endoscopy in the diagnosis and management of pancreatic ductal disruption. Finally, in contrast to previous publications, we demonstrate that for high-grade pancreaticoduodenal injuries, with adequate expertise supported by modern techniques, resection and reconstruction can be safely achieved with favourable outcomes by high-volume specialist pancreatic surgeons.

ARTICLE HIGHLIGHTS

Research background

The management of high-grade pancreatic trauma is controversial.

Research motivation

The literature consists predominantly of studies conducted in regions such as North America and South Africa, where penetrating abdominal trauma occur with high prevalence. However, blunt abdominal trauma is more common than penetrating trauma in Australasian centres, and are underrepresented in the literature. While pancreatic injuries are estimated to occur in 20%-30% of penetrating abdominal trauma, they are observed in less than 2% of blunt trauma cases worldwide[13]. Furthermore, trauma services are not centralised in Australian healthcare settings. These regional differences are likely to have important implications for patient management and outcomes.

Research objectives

This study reviews the experience of an Australian tertiary referral center, with the aim of providing locally relevant insights into the management of high-grade pancreatic injuries.

Research methods

A retrospective review of records was performed on all patients undergoing surgical intervention for high-grade pancreatic injuries [American Association for the Surgery of Trauma (AAST) Grade III or greater] at a single Australian centre between January 2001 and December 2022.

Research results

Over a twenty-year period, 14 patients underwent pancreatic resection for high-grade injuries. Seven patients sustained AAST Grade III injuries and 7 were classified as Grades IV or V. Nine underwent distal pancreatectomy and 5 underwent pancreaticoduodenectomy (PD). Overall, there was a predominance of blunt aetiologies (11/14). Concomitant intra-abdominal injuries were observed in 11 patients and traumatic haemorrhage in 6 patients. Three patients developed clinically relevant pancreatic fistulas and there was one in-hospital mortality secondary to multi-organ failure. Among stable presentations, pancreatic ductal injuries were missed in two-thirds of cases (7/12) on initial computed tomography imaging and subsequently diagnosed on repeat imaging or endoscopic retrograde cholangiopancreatography. All patients who sustained complex pancreaticoduodenal trauma underwent PD without mortality.

Research conclusions

Penetrating and blunt trauma presentations are associated with varied patterns of injury. The management of pancreatic trauma is evolving; there is a growing role for endovascular and endoscopic techniques in the contemporary management of pancreatic trauma. Pancreatic resections including PD may be indicated and safely performed with appropriate specialist surgical, gastroenterology, and interventional radiology support in tertiary centres.

Research perspectives

We advocate that high-grade pancreatic trauma should be managed in high-volume hepato-pancreato-biliary specialty surgical units.

FOOTNOTES

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Surgical management of hydatid cyst disease of the liver: An improvement from our previous experience?

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Abstract

BACKGROUND

Hydatid liver disease remains an important issue in endemic areas, which may require immediate surgery. Although laparoscopic surgery is on the rise, the presence of certain complications may require conversion to the open approach.

AIM

To compare the results of laparoscopic treatment and the open approach in the context of a 12-year single institution experience, and to perform a further comparison between results from the current study and those from a previous study.

METHODS

Between January 2009 and December 2020, 247 patients underwent surgery for hydatic disease of the liver in our department. Of the 247 patients, 70 underwent laparoscopic treatment. A retrospective analysis between the two groups was performed, as well as a comparison between current and previous laparoscopic experience (1999-2008).

RESULTS

There were statistically significant differences between the laparoscopic and open approaches regarding the cyst dimension, location, and presence of cystobiliary fistula. There were no intraoperative complications in the laparoscopic group. The cutoff value for the cyst size regarding the presence of cystobiliary fistula was 6.85 cm (P = 0.001).

CONCLUSION

Laparoscopic surgery still plays an important role in the treatment of hydatid disease of the liver, with an increase in its usage over the course of years that has shown benefits regarding the postoperative recovery with a decreased rate of intraoperative complications. Although experienced surgeons can perform laparoscopic surgery in the most difficult conditions, there are some selection criteria that need to be maintained for higher quality results.

Key Words: Follow-up; Cystobilliary communication; Conversion; Postoperative complications; Imaging

Core Tip: Laparoscopic surgery for the treatment of liver hydatid disease has grown significantly in the last decade, due to increased accessibility and better training. Although, some limits were reported on previously regarding the cyst size, location, and presence of complications such as cystobiliary fistulas. This article discusses our experience over 12 years in the surgical treatment of hydatid liver disease, highlighting key aspects of surgical timing as well as differences between the open approach and laparoscopic approach in terms of case selection, comorbidities, and postoperative management.

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INTRODUCTION

Hydatid disease is a parasitic disease that is widespread across the world, with endemic areas in Central Asia, the Mediterranean Region, Northern and Central Africa, and South America, especially in rural areas where animals are raised. *Echinococcus granulosis* and *Echinococcus multilocularis* are the primary agents of the disease, with the liver being the most affected organ, followed by the lungs and spleen[1]. Despite being considered a benign disease, it can have a considerable socioeconomic impact, with important comorbidities and a mortality rate of 1%-4%[2]. Although in some cases, spontaneous healing can occur through the parasite's death and calcification, treatment remains mandatory, especially in symptomatic and/or viable cysts. Anthelmintic treatment is mandatory; however, it should not be used as a standalone treatment, as most published studies suggest that radical surgery is a better option than conservative treatment[3].

Despite surgery remaining the treatment of choice, there has been an increased interest in non-surgical techniques in the current literature. Since open procedures present a higher risk of morbidity, the laparoscopic approach has grown in popularity; although, the benefits that laparoscopy provides and the risk of recurrence remain debatable[4,5]. Even though robotic surgery is on the rise, the importance of laparoscopy should not be understated since the former technique is less accessible in underdeveloped centers, due to its high cost. In addition, recent developments in the laparoscopic technique as well as its cost-effectiveness have made the procedure much more accessible for less experienced as well as veteran surgeons.

This retrospective study evaluated results from the laparoscopic treatment of hydatic disease of the liver compared to those from the open approach in the context of a 12-year single institution experience and in terms of the morphological characteristics of the cysts and the perioperative parameters. Furthermore, this study compared the results with previous 10-year experience from 1999 to 2008 regarding laparoscopic treatment, in terms of case selection, duration, case volume, postoperative complications, and recurrence rate. The objective of the study was to highlight the possible selection criteria regarding the surgical treatment of choice.

MATERIALS AND METHODS

Between January 2009 and December 2020, 258 patients underwent surgery for hydatic disease of the liver in our surgical department. Patients were reviewed retrospectively. The primary inclusion criteria were patients who underwent surgery for hydatid disease of the liver, were over 18 years of age, and provided written informed consent. The exclusion criteria were patients with incomplete records, not providing written informed consent, who had experienced spontaneous rupture, who underwent conversion to open surgery, or who underwent percutaneous treatment. There were no exclusion criteria regarding cyst location, cyst size, or number of cysts. Data from all eligible patients were collected from an electronic database, and the earlier cases were collected from the medical archives of the hospital.

All patients received antiparasitic medical treatment 14 d prior to surgery. All patients were evaluated *via* ultrasound or contrast computed tomography (CT), which was used to classify the cysts as well (according to Gharbi classification). Magnetic resonance cholangiopancreatography (MRCP) was used preoperatively for patients with dilated biliary ducts, elevated liver enzymes, or hydatid elements in the bile ducts associated with jaundice. Preoperatively, all patients underwent treatment with albendazole (10 mg/kg), 7 to 14 d before surgery. Treatment was continued for 30 d postoperatively. Of the 268 patients, 77 underwent laparoscopic treatment, among which 7 required conversions to open surgery. Eleven cases presented with spontaneous rupture of the cyst and ten had incomplete data, and thus were excluded. Therefore, two groups were created: The first group (group A) comprised 70 patients who underwent laparoscopic treatment, and the second group (group B) comprised 170 patients who underwent open surgery. In both groups, there were 73 patients with cystobiliary communication. Associated cholecystectomy was performed in 62 of the cases. The groups were analyzed based on their demographic, preoperative and postoperative parameters, and cyst parameters, as well as follow-up and morbidity.

Recurrence in hydatid disease is considered when new cysts are discovered after therapy. This can mean reappearance and growth at the previously treated site, or appearance of other cysts at another site due to spillage. Our study defined recurrence as visible lesions *via* ultrasound or CT, with or without elevated eosinophils and liver enzymes over the follow-up duration. Follow-up was routinely performed every 6 mo, for a minimum duration of 18 mo. A minimum of three/four controls were performed for each patient. The study was approved by the Ethics Committee of the Regional Institute of Gastroenterology and Hepatology "O. Fodor", Cluj-Napoca.

Surgical technique for the laparoscopic group

The main aspects regarding the possible surgical approach are in terms of selecting whether a lagrot (partial) pericystectomy or a total pericystectomy is performed. Partial pericystectomy involves resection of the externalized pericyst at the border of the liver parenchyma, followed by aspiration of the contents with the residual cavity staying in place, thus requiring extra drainage or closure of the residual cavity; whereas, total pericystectomy involves removing the cyst in its entirety with the adjacent parenchyma and without spilling its contents.

There were no significant changes in the laparoscopic surgical technique from our previous study. We inserted a 10-mm supraumbilical port, through which a 30-degree telescope was inserted. The abdominal cavity was insufflated with carbon dioxide to create adequate working space. Afterwards, the remainder of the telescopes were inserted in a camera-guided manner, as follows: A 10-mm port was inserted in the epigastric area as near as possible to the cyst, to be used as a working channel, and then two 5-mm ports were inserted based on the cyst location. Furthermore, any adhesions between the cysts and the nearby organs were cauterized. After exposing and isolating the hydatid lesions from the rest of the peritoneal cavity (through wicks soaked in an inactivation solution - metronidazole or hypertonic saline solution), the cysts were punctured with the vacuum cannula and aspiration of the cystic cavity was performed. If there was certainty of the absence of any cystobiliary communication, inactivation solution could be injected in the cystic cavity. Another vacuum cannula was inserted through another port, which was permanently maintained near the puncture to prevent hydatid spillage.

After the entire content was aspirated, cystostomy was performed and the content was extracted in an endo-bag. After the parasite was inactivated and then removed, the surgical treatment for the residual cavity was applied. In the case of a cystobiliary fistula, application of metal clips or an "X" suture was performed. One or two drains were placed (especially in the lagrot pericystectomy). Preoperative endoscopic retrograde cholangiopancreatography (ERCP) was performed in cases of intrabiliary rupture to minimize the risk of cholangitis. Postoperatively, ERCP was performed to decrease the pressure in the biliary tract, if necessary.

Laparoscopic total pericystectomy was performed without puncturing the cyst wall during the procedure ("closed" technique), using ligation devices for resection through the healthy adjacent parenchyma. Hemostasis was performed and afterwards, a close inspection for cystobiliary communication or biliary leaks was performed. The specimen was then extracted into an endo-bag through the epigastric port. If required, the incision for the epigastric port could be enlarged. Injection of methylene blue to evaluate the biliary involvement of large cysts was not routinely performed;

however, in cases where the existence of a cystobiliary communication was certain but could not be adequately identified, this method was used.

Surgical technique for the open group

For the open surgical approach, we used a supraumbilical midline incision or a subcostal incision. Any adhesion between the cysts and the neighboring organs was lysed. To prevent any hydatid spillage, the peritoneal cavity was isolated with wicks soaked in 20% hypertonic saline solution before any maneuver on the hydatid cyst was performed. Parasite inactivation was performed by injecting 20% hypertonic saline solution. After 5 min, the hydatid content was aspirated. Starting from the puncture site, cystotomy was performed, with extraction of the germinal membrane and daughter vesicles. Afterwards, surgical treatment for the residual cavity was applied. Open total pericystectomy was performed in a similar manner as the laparoscopic technique, with a much easier extraction of the specimen, *via* the laparotomy incision.

Statistical analysis

All the statistical tests were made using the IBM SPSS v26.0 program (IBM Corp., Armonk, NY, United States). Comparisons between the two groups were performed. Categorical values and qualitative variables were analyzed using Pearson's chi-squared test. When accounting for quantitative variables such as surgery duration, estimated blood loss, and cyst diameter, normality tests were used to verify the data distribution (using Kolmogorov-Smirnov and Shapiro-Wilk tests). Thus, non-normal distributed data were evaluated by comparing median values using Mann-Whitney *U* tests, and normal distributed data were evaluated by comparing mean values using the *t*-test for independent variables (mean age). To determine the value of the cyst diameter from which there is an elevated risk of cystobiliary fistula, a receiver operating characteristic curve (ROC) curve was generated to determine the cutoff point, as was the area under the curve (AUC), with an AUC value of over 0.7 being an acceptable estimator. The value for statistical significance was $P < 0.05$. To minimize the potential sources of bias, additional related parameters were compared to verify the potential differences between the two groups as well as to control the potential confounding variables.

RESULTS

Demographic data, frequency of symptoms, and concurrent comorbidities

The demographic data regarding the age, sex, environment, symptoms at presentation, and comorbidities are detailed in Table 1. Both groups were relatively similar in terms of age, sex, frequency of symptoms, comorbidities, and preoperative risk profile [American Society of Anesthesiologists (ASA) classification]. The mean age of the laparoscopic group was lower than that of the open approach group (39.87 years *vs* 44.36 years, $P = 0.03$). Although the relative frequency of the obese patients was higher in the open group than in the laparoscopic group, there were no statistically significant differences between the groups (8.57% *vs* 11.9%, $P = 0.43$). The most frequently reported symptom was pain in the right-upper quadrant (71.42% *vs* 70.1%). When addressing the median alanine transaminase and aspartate transaminase values, no statistically significant differences were recorded. In total, 6 of 70 patients (8.57%) presented with hydatid elements in the common bile duct compared to 19 patients in the open group (11.17%); although, the difference was not statistically significant ($P = 0.34$).

Characteristics of the cysts and intraoperative parameters

The pathological characteristics of the cysts and the surgical treatment are presented in Table 2. The median size of the liver hydatid cyst in the laparoscopic group was 6.5 cm (range: 2-17 cm). Compared with the open approach group, in which the median size was 7.5 (range: 2-20 cm), the difference was statistically significant ($P = 0.001$). Although both groups were relatively similar in the lobe distribution of the cysts and the number of cysts involved, as well as the distribution of the cysts regarding the size, there were statistically significant differences in the involvement of segments 7 and 8 (28.57% *vs* 43.47%, $P = 0.03$ and 21.42% *vs* 35.86%, $P = 0.027$ respectively). Conversion to open surgery was required in 7 cases, with the reasons listed in Table 3.

The median operative time was 75 min (range: 50-110) in the laparoscopic group and 100 min (range: 55-280 min) in the open approach group ($P < 0.001$). Median blood loss was 35 mL (range: 0-100 mL) for the laparoscopic group, and 90 mL (rang: 0-400 mL) for the open approach group ($P < 0.001$). The mortality rate was 0% in both groups. The intraoperative complication rate in the laparoscopic group was significantly lower in the laparoscopic group (0% *vs* 4.89%, $P = 0.04$). Of the 73 cases that presented with cystobiliary fistula, 13 were found in the laparoscopic group and 60 in the open approach group, with a statistically significant difference (18.57% *vs* 32.60%, $P = 0.02$).

Regarding the postoperative complications (Table 4), although there was no statistically significant difference in the overall postoperative complications (5.7% *vs* 7.06%, $P = 0.76$), there was a significant difference regarding the abdominal wound complications between the groups (0% *vs* 4.7%, $P = 0.04$). In

Table 1 Demographic data and concurrent comorbidities in the patient population

Parameter		Laparoscopic, *n* = 70 (%)	Open approach, *n* = 170 (%)	*P* value
Age	Mean age	39.87 ± 14.4	44.36 ± 15.99	0.03
Sex	Male	29 (41.42)	80 (47.28)	0.4
	Female	41 (58.58)	90 (52.72)	
Environment	Urban	29 (41.42)	65 (38.04)	0.61
	Rural	41 (58.58)	105 (61.96)	
Symptoms	Pain in the RUQ	50 (71.42)	119 (70.1)	0.83
	Biliary dispeptic syndrome	12 (17.14)	40 (23.36)	0.28
	Cutaneous eruption	0 (0)	4 (2.71)	0.16
	Hepatomegalia w/palpable mass	1 (1.42)	7 (4.3)	0.46
Comorbidities	Hypertension	9 (12.85)	32 (19.02)	0.24
	Ischemic cardiopathy	2 (2.85)	14 (8.15)	0.13
	Type II diabetes	4 (5.71)	12 (7.06)	0.78
	Obesity	6 (8.57)	20 (11.9)	0.43
ASA	1 or 2	37 (52.85)	90 (53.2)	0.36
	3	29 (41.42)	68 (40.2)	0.97
	4	4 (5.71)	12 (6.5)	0.95
Hydatid elements in the CBD		6 (8.57)	19 (11.17)	0.34
Median ALT value		45 (25-180)	42 (25-220)	0.88
Median AST value		40 (25-190)	45 (20-225)	0.76

RUQ: Right upper quadrant; CBD: Cannabidiol; ASA: American Society of Anesthesiologists; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

the laparoscopic group, there were 3 cases of liver abscesses of the residual cavities that were laparoscopically drained. One case developed an external fistula that was treated conservatively. Most of the postoperative complications in the open approach group were comprised of the abdominal wound complications (suppuration, seromas, and infection), which required a longer hospitalization stay and daily antiseptic treatment and/or collection evacuation, presenting a good prognosis. One case developed an external fistula, which was adequately drained with complete closure in 7 d.

To assess the risk of developing cystobiliary fistula based on cyst dimension, an ROC curve was generated to determine whether the cyst size is a good predictor of developing cystobiliary fistula (Figure 1A). Thus, a cutoff point of 6.85 cm was determined with an AUC of 0.71 (moderate to good predictor, $P = 0.001$). Therefore, cysts larger than 6.85 cm present a higher risk of developing cystobiliary fistula for which MRCP is required for a full assessment. ROC curves were used to determine if the cyst size is a good predictor based on surgery type (Figure 1B). Thus, cyst size in the laparoscopic group was considered a poor predictor with an AUC of 0.52 ($P = 0.67$, cutoff value of 5.7 cm). In the open surgery group, cyst size was considered a poor to moderate predictor (AUC = 0.69, $P = 0.007$, cutoff value of 7.4 cm).

Hospital stays and evidence of hydatid recurrence

The median hospital stay was 4 d (range: 2-11 d) in the laparoscopic group and 6 d (range: 3-21 d) in the open approach group, with the stay being significantly longer for the second group ($P = 0.01$). There were no differences regarding the median follow-up period (24 mo *vs* 26 mo, $P = 0.35$). The recurrence rate for the laparoscopic approach group was lower than that for the open approach group, although the difference was not statistically significant (4.2% *vs* 5.2%, $P = 0.63$). These elements are showcased in Table 5.

Comparison between previous (1999-2008) and current laparoscopic experience (2009-2020)

A comparison of the general preoperative and postoperative parameters as well as the surgical technique between the two groups was performed, as listed in Table 6. The frequency of the laparoscopic approach was significantly higher in the current laparoscopic group (27.55% *vs* 17.71%, $P = 0.005$), with slightly higher conversion rate (8.10% *vs* 4.80%, $P = 0.17$) and median hospitalization (4 d *vs*

Table 2 Characteristics of the cysts and intraoperative parameters

Parameter		Laparoscopic, *n* = 70 (%)	Open approach, *n* = 170 (%)	*P* value
Liver segments	II-IV	27 (38.5)	41 (24.11)	0.04
	V-VI	28 (40)	48 (28.23)	0.14
	VII	20 (28.57)	63 (37.05)	0.03
	VIII	15 (21.42)	54 (31.24)	0.02
	I	1 (1.42)	11 (6.47)	0.06
Distribution	Right lobe	44 (62.85)	105 (61.95)	0.89
	Left lobe	18 (25.72)	31 (18.48)	0.2
	Both lobes	8 (11.43)	34 (20)	0.14
Number of cysts	Unique cysts	59 (84.28)	134 (72.82)	0.04
	Multiple cysts	11 (15.72)	50 (27.18)	
Dimension of cysts	Smaller than 5 cm	17 (24.28)	37 (20.13)	0.41
	5-10 cm	47 (67.14)	113 (61.42)	0.38
	Larger	6 (8.57)	34 (18.45)	0.06
	Median diameter (cm)	6.5 (2-17)	7.5 (2-20)	0.001
	No cystobiliary communication (cm)	5.5 (2-17)	7 (2-17)	0.02
	With cystobiliary communication (cm)	6 (4-10)	8 (3-20)	0.01
Type of cyst	Pure clear fluid cyst	16 (22.85)	39 (22.82)	0.93
	Hydatid daughter cyst	33 (47.14)	70 (41.3)	0.86
	Calcified cyst	9 (12.85)	33 (19.56)	0.43
	Avital hydatid cyst	6 (8.57)	5 (2.92)	0.07
	Secondarily infected cyst	6 (8.57)	23 (13.58)	0.22
Type of surgery	Lagrot percystectorny	56 (80)	118 (69.56)	0.26
	Total percystectomy	8 (11.45)	33 (20.1)	0.14
	Hepatic resection	6 (9.55)	19 (11.34)	0.67
Surgical parameters	Intraoperative complications	0 (0)	9 (4.89)	0.04
	Postoperative complications	4 (5.7)	13 (7.06)	0.76
	Presence of cysto-biliary fistula	13 (18.57)	56 (32.9)	0.01
	Median operative time (min)	75 (50-110)	100 (55-280)	0.001
	Median blood loss (mL)	35 (0-120)	90 (0-400)	0.001
Postoperative mortality		0 (0)	0 (0)	1

6 d, $P = 0.001$). Regarding the surgical technique, there were no differences in lagrot pericystectomy and total pericystectomy (80% *vs* 91.52%, $P = 0.11$ and 11.45% *vs* 8.48%, $P = 0.79$ respectively). There were 6 cases of laparoscopic liver resection, and the difference was statistically significant (9.55% *vs* 0%, $P = 0.001$). No other statistically significant difference in the median operative time, mean cyst size, or postoperative morbidity was recorded.

DISCUSSION

Although the risk of complications in the laparoscopic treatment of hydatid disease of the liver has not been fully evaluated, there has been a continuous increase in its usage during the last decade[6]. The important steps in this surgery remain removal of the cyst contents with as minimum risk of spillage as possible, sterilization of the cyst cavity, and closure of the remaining cavity. Moreover, even though surgery remains one of the main choices of treatment in hydatid disease of the liver, there is still a debate regarding the optimal choice of surgical treatment. A meta-analysis performed by Sokouti *et al*[7]

Table 3 Reasons for conversion to open surgery

Reasons for conversion to open surgery	
Unable to find the cyst based on the imaging	2
Difficult access	2
Unable to suture the cystobiliary fistula	1
Unable to provide adequate haemostasis	1
Difficulty in mobilizing the liver	1
Total	7

Table 4 Postoperative complications

Complications	Laparoscopic, *n* = 70 (%)	Open approach, *n* = 170 (%)	*P* value
Postoperative complications	4 (5.7)	13 (7.06)	0.76
Abdominal wound complications	0 (0)	8 (4.7)	0.04
External fistulas	1 (1.4)	1 (0.58)	0.93
Liver abscesses	3 (4.28)	4 (2.35)	0.21

Table 5 Postoperative parameters

Postoperative parameter	Laparoscopic, *n* = 70 (%)	Open approach, *n* = 170 (%)	*P* value
Recurrence rate	3 (4.2)	9 (5.2)	0.63
Median hospital stay	4 (2-11)	6 (3-21)	0.01
Median follow-up period	24 (9-48)	26 (648)	0.35

Table 6 Comparison of the current and previous laparoscopic groups

Postoperative parameter		Cument laparoscopic group, *n* = 70 (%)	Previous laparoscopic group, *n* = 59 (%)	*P* value
Surgery type	Lagrot pericystectomy	56 (80)	54 (91.52)	0.11
	Total pericystectorny	8 (11.45)	5 (8.48)	0.79
	Hepatic resection	6 (9.55)	0 (0)	0.04
Postoperative morbidity		4 (5.71)	6 (10.16)	0.11
Frequency (%)		28.34	17.71	0.005
Median cyst size		6.5 (2-17)	6.4 (2-15)	0.28
Median duration (min)		75 (50-110)	72 (45-130)	0.41
Conversion rate (%)		8.10	4.80	0.17
Median hospital stay (d)		4 (2-11)	6 (1-28)	0.001

highlighted the advantages of the minimally invasive puncture, aspiration, injection, and respiration technique in uncomplicated cysts, such as being more cost-effective with minimal risks; however, it is usually recommended for patients who cannot benefit from surgery due to various reasons (comorbidities and refusal of treatment) and it is contraindicated in patients with cystobiliary communication, while also having a higher recurrence rate. The indication of cholecystectomy was either elective, due to the presence of gallstones, which would pose a high risk of migration, or tactical to obtain adequate access to the cysts. In addition, in cases where ERCP associated with sphincterectomy or stenting for biliary decompression is needed, cholecystectomy is mandatory.

Compared to our previous article, this study had less exclusion criteria, which allowed us to showcase the differences between the previous and the current 10 years of laparoscopic surgery in the treatment of hydatid disease of the liver. Our previous series of 231 patients (59 laparoscopic approach

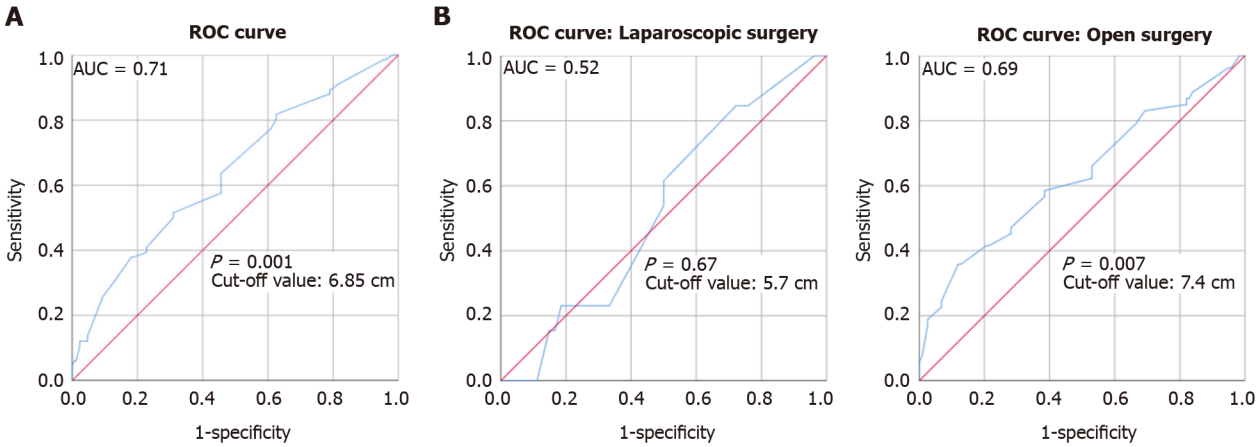

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Figure 1 Determining the cutoff point for the cystobiliary fistula and based on groups (receiver operating characteristic curve). A: Cystobiliary fistula; B: Based on groups (laparoscopic surgery and open surgery). ROC: Receiver operating characteristic curve.

vs 172 open approach) remains one of the largest series in the literature[8], with the current series showcasing a significant volume as well. One of the major differences between our two series resides in a slightly higher conversion rate and a lower hospitalization duration. The increase of conversion rate, although not statistically significant, can reflect the lack of selection criteria.

Regarding the demographic parameters, a statistically significant difference between the mean age of the two groups was recorded. This mean difference gap of 4.49 years could highlight the tendency for a minimally invasive approach in younger patients due to their better health condition; however, more reports are required in that regard. There were no statistically significant differences regarding sex, environment, symptoms at presentation, comorbidities, or ASA score. Although our previous study reported differences related to the patient's body mass index regarding the surgical approach, there were no statistically significant differences highlighted by our current study.

We did not use the cyst location as an exclusion criterion, although the differences between the laparoscopic approach and the open approach were statistically significant for the 7th segment. A statistically significant difference between the two groups regarding the cyst diameter was recorded, which could indicate a tendency towards open approach in cysts over 10 cm in diameter, although a reasonable number of cases with cysts of over 10 cm in diameter were treated laparoscopically. There is a constant change regarding the indications for the laparoscopic approach; however, due to improved imaging and better training, most of the contraindications regarding cyst diameter, cyst location, and cystobiliary fistula are in direct proportion with the surgeon's skill. Thus, the biggest limitation remains the surgeon's personal experience in hepatic surgery. However, some selection criteria need to be maintained, especially regarding the less accessible liver segments and for less experienced surgeons. Therefore, caution must be maintained when selecting cases in the posterior segments and in the caudate lobe as candidates for laparoscopic surgery.

There were statistically significant differences regarding the intraoperative parameters between the two groups, such as mean duration, blood loss, and presence of intraoperative complications. A lower mean duration in the laparoscopic approach can be explained by the fact that the more difficult cases are reserved for the open approach, thus taking longer to be resolved. Net duration of the open procedures was compared, although a slight bias might exist regarding the reporting of net duration (excluding the time from accessing and exiting the abdominal cavity) due to a shift to the electronic database which occurred in the late 2000s. Compared to our previous study, although not significant, there was a median difference of 3 min recorded between our current and previous studies, which can be further explained by the increasing complexity of the laparoscopically treated cases in our current group. The most frequent reasons for conversion to open surgery were in terms of difficult access and incompatibility of the diagnosis based on imaging. Establishing the diagnosis of hydatid cyst of the liver *via* imaging methods can sometimes prove to be a difficult task; therefore, such inconsistencies are reported in the literature[9,10].

One of the major advantages of the laparoscopic approach remains the magnified imaging of the cyst. Being able to insert the camera into the cystic cavity can permit a thorough inspection, allowing early detection of cystobiliary communications or remnant membranes. Thirteen cases presented with biliocystic fistula, which underwent the laparoscopic approach. The biliocystic communication was closed by either clipping or placing a laparoscopic suture, depending on the size and the surgeon's experience, although this method can sometimes prove difficult to be achieved laparoscopically, thus supporting the observed statistically significant difference between the laparoscopic and open approaches regarding the presence of cystobiliary fistula. However, due to the improved imaging and

the possibility of postoperative ERCP for lowering the biliary pressure or in case of the presence of biliary fistulas, the laparoscopic approach is more widely considered, even in the presence of biliocystic communication, with more studies supporting this statement[11-13].

Although the usage of MRCP in our study was limited, due to its low accessibility in the earlier cases, it can pose a selection bias, since cases evaluated *via* MRCP might be more carefully selected, with easier cases benefitting from laparoscopic surgery and thus improving the postoperative parameters. However, it is important to assess the size of the biliocystic communication through various methods (*e.g.*, intraoperative cholangiography or preoperative MRCP) to establish the viability of laparoscopic closure of the fistula. Our study encountered two external fistulas that were resolved conservatively. Although MRCP was not routinely performed, we recommend based on our findings that MRCP should routinely be performed for cysts over 6.5 cm to evaluate the presence of cystobiliary communication.

There were no statistically significant differences regarding the postoperative morbidity between the open and laparoscopic approach groups, nor between the current and previous laparoscopic approach groups. There were no fatalities registered. The median hospital stay was significantly shorter for the laparoscopic group, and compared to our previous study, there was a lower hospitalization duration for the current laparoscopic group (4 d *vs* 6 d). There were no differences regarding the recurrence rate between the laparoscopic and open approaches; however, we encountered a slightly higher recurrence rate compared to our previous study. Compared to similar studies, the recurrence rate was relatively similar, ranging from 1% to 20%[1,2,6].

There were no statistically significant differences in the type of the cyst or the type of surgery between the two groups. In contrast to our previous experience, 6 cases underwent laparoscopic resection on cases in which the cysts would occupy more than 70% of one segment with the presence of cystobiliary communication, in peripheric segments, developing no postoperative complications or comorbidities. Although this is a radical method, laparoscopic liver resection in the hydatid disease of the liver can be considered an alternative, feasible method of surgical treatment, with an increase in popularity in the last decade, showcased by recent studies[14,15]. However, the lack of a statistically significant difference between the techniques highlights the fact that the surgical approach is specifically based on each patient.

Recent practices exemplify the emergence of robotic surgery in the treatment of hydatid cysts. Robotic surgery is known for its superiority in terms of maneuverability, a better fine dissection which can allow removal of deeper intraparenchimatous cysts, as well as maintaining a similar rate of complication and recurrence in comparison with laparoscopic surgery[16-18]. However, one of the major disadvantages of robotic surgery consists of its cost effectiveness, which can be a deterrent for some tertiary centers. Therefore, robotic surgery is currently practiced by a select number of high-volume centers.

Our study has some limitations. First, being a retrospective study, the data completed in both electronic databases and medical archives might have errors in completion, which was one of the main reasons for excluding patients with incomplete data. Second, as a retrospective analysis, the choice for open or laparoscopy surgery can be purely subjective based on the surgeon's experience, which in a retrospective setting cannot be adequately quantified. One of the main reasons for comparing the current laparoscopic experience with the one from our previous study was to diminish this limit, highlighting a significant improvement with a broadened case selection, improved postoperative recovery as well as maintaining intraoperative parameters. Finally, compared to the current literature, our results showcase similar findings in terms of effectiveness of the laparoscopic procedure with relative changes in the management of the patients which can be explained by the current setting of our tertiary center. Some of these results might be difficult to reproduce in smaller-volume centers.

The laparoscopic treatment of hydatid cysts of the liver has been continuously evolving over the course of the last decade, due to improvements in diagnostic techniques, imaging, and instrumentation. Therefore, the barrier was constantly pushed in terms of cyst diameter, cyst location, the presence of cystobiliary communications, the presence of comorbidities, and the cyst type. An increasing number of studies have shown improving results regarding all characteristics mentioned above. There are currently no randomized clinical trials to compare the treatment modalities. However, taking all of these issues into consideration, the rapid postoperative recovery with improved aesthetic results, minimal scarring, and a low recurrence rate with minimal comorbidities should be taken into consideration when advocating for a laparoscopic treatment for hydatid disease of the liver.

CONCLUSION

Based on our current experience, laparoscopic surgery remains a safe approach for the treatment of hydatid disease of the liver, with minimal to no regard towards the comorbidities, preoperative complications, and constant increase in cyst dimension. Although some selection criteria need to be maintained, especially regarding cyst location, laparoscopic surgery can provide benefits regarding a broadened case selection, improved surgical timing, and a shorter postoperative stay. Compared with our previous laparoscopic experience, an increase in the difficulty of cases, as well as a tendency for improvement, which trends along with the surgeon's learning curve, some selection criteria need to be

maintained to minimize the risk of conversion and achieve a better outcome.

ARTICLE HIGHLIGHTS

Research background

Hydatid disease of the liver is a prevalent problem in endemic areas, and surgery plays an important role in resolution. Although laparoscopic treatment is on the rise due to its increased accessibility, there are some limits that need to be addressed.

Research motivation

This study highlighted our experience in terms of the laparoscopic approach over the last 12 years, as well as the differences between the current laparoscopic experience and the previous one. Our aim was to showcase the improvements of the laparoscopic approach as well as its current limits.

Research objectives

This retrospective study compared the differences between open and laparoscopic approaches in terms of demographic data, preoperative assessment, intraoperative characteristics, and postoperative parameters, as well as follow-up, morbidity, and mortality, thus highlighting key aspects, differences, and the pearls and pitfalls of the laparoscopic approach in the treatment of this disease.

Research methods

In this retrospective cohort study, patients were divided into two groups, for which the differences were showcased based on the inclusion and exclusion criteria. The database consisted of all patients who had received surgical treatment for hydatid disease of the liver over an experience of 12 years.

Research results

Despite the fact that some of the exclusion criteria were dropped, there are still some issues regarding cyst location and cyst size that impose careful selection criteria. These selection criteria should be taken into account by inexperienced surgeons. Furthermore, some imaging criteria need to be instated in larger cysts.

Research conclusions

Based on our experience, the laparoscopic approach remains a safe, feasible approach which can be implemented in smaller volume centers, as long as some selection criteria are maintained. These selection criteria can be broadened; thus, more patients can benefit from this procedure, which accounts for better postoperative parameters, shorter postoperative hospitalization, and comparable morbidities and risks of recurrence with the open procedure.

Research perspectives

Based on our experience, the laparoscopic approach remains a safe, feasible approach which can be implemented in smaller volume centers, as long as some selection criteria are maintained. These selection criteria can be broadened; thus, more patients can benefit from this procedure, which accounts for better postoperative parameters, shorter postoperative hospitalization, and comparable morbidities and risks of recurrence with the open procedure.

FOOTNOTES

Author contributions: Zaharie F designed the original report; Vălean D and Zaharie R contributed to data collection and analyses; Popa C, Schlanger D, Fetti A, and Ciocan A reviewed the literature; Moiș E and Zdrehuș C contributed to revising the manuscript; Zaharie F and Al-Hajjar N reviewed and approved the final manuscript; and all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Influence of liver function after laparoscopy-assisted *vs* totally laparoscopic gastrectomy

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Abstract

BACKGROUND

Previously, some studies have proposed that total laparoscopic gastrectomy (TLG) is superior to laparoscopic-assisted gastrectomy (LAG) in terms of safety and feasibility based on the related intraoperative operative parameters and incidence of postoperative complications. However, there are still few studies on the changes in postoperative liver function in patients undergoing LG. The present study compared the postoperative liver function of patients with TLG and LAG, aiming to explore whether there is a difference in the influence of TLG and LAG on the liver function of patients.

AIM

To investigate whether there is a difference in the influence of TLG and LAG on the liver function of patients.

METHODS

The present study collected 80 patients who underwent LG from 2020 to 2021 at the Digestive Center (including the Department of Gastrointestinal Surgery and the Department of General Surgery) of Zhongshan Hospital affiliated with Xiamen University, including 40 patients who underwent TLG and 40 patients who underwent LAG. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyltransferase (GGLT), total bilirubin (TBIL), direct bilirubin (DBIL) and indirect bilirubin (IBIL), and other liver function-related test indices were compared between the 2 groups before surgery and on the 1st, 3rd, and 5th d after surgery.

RESULTS

The levels of ALT and AST in the 2 groups were significantly increased on the 1st to 2nd postoperative days compared with those before the operation. The levels of ALT and AST in the TLG group were within the normal range, while the levels of ALT and AST in the LAG group were twice as high as those in the TLG group ($P < 0.05$). The levels of ALT and AST in the 2 groups showed a downward trend at 3-4 d and 5-7 d after the operation and gradually decreased to the normal range ($P < 0.05$). The GGLT level in the LAG group was higher than that in the TLG group on postoperative days 1-2, the ALP level in the TLG group was higher than that in the LAG group on postoperative days 3-4, and the TBIL, DBIL and IBIL levels in the TLG group were higher than those in the LAG group on postoperative days 5-7 ($P < 0.05$). No significant difference was observed at other time points ($P > 0.05$).

CONCLUSION

Both TLG and LAG can affect liver function, but the effect of LAG is more serious. The influence of both surgical approaches on liver function is transient and reversible. Although TLG is more difficult to perform, it may be a better choice for patients with gastric cancer combined with liver insufficiency.

Key Words: Totally laparoscopic gastrectomy; Laparoscopy-assisted gastrectomy; Liver function; Alanine aminotransferase; Aspartate aminotransferase

Core Tip: Previously, some studies have proposed that total laparoscopic gastrectomy (TLG) and laparoscopic-assisted gastrectomy (LAG) in terms of safety and feasibility based on the related intraoperative operative parameters and incidence of postoperative complications. However, there are still few studies on the changes in postoperative liver function in patients undergoing LG. The present study compared the postoperative liver function of patients with TLG and LAG, aiming to explore the influence of liver function after LAG *vs* TLG.

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INTRODUCTION

As a common tumor of the digestive system, gastric cancer (GC) has high morbidity and mortality rates. According to statistics from the International Agency for Research on Cancer (IARC), GC ranked fifth in incidence and fourth in mortality among new cancer patients worldwide in 2020[1].

Surgery is an indispensable part of the comprehensive treatment of GC. Total or distal gastrectomy (DG) with D2 lymphadenectomy is recommended for GC[2]. The commonly used radical gastrectomy for GC includes open gastrectomy (OG) and laparoscopic gastrectomy (LG). Compared with OG, LG is becoming more available in clinical practice, and it can be subdivided into total laparoscopic gastrectomy (TLG) and laparoscopic-assisted gastrectomy (LAG).

Previously, some studies have proposed that TLG is superior to LAG in terms of safety and feasibility based on the related intraoperative operative parameters and incidence of postoperative complications [3]. However, there are still few studies on the changes in postoperative liver function in patients undergoing LG. The present study compared the postoperative liver function of patients with TLG and LAG, aiming to explore whether there is a difference in the influence of TLG and LAG on the liver function of patients.

MATERIALS AND METHODS

Patients

The present study collected 80 patients who underwent LG from 2020 to 2021 at the Digestive Center (including the Department of Gastrointestinal Surgery and the Department of General Surgery) of Zhongshan Hospital affiliated with Xiamen University, including 40 patients who underwent TLG and

40 patients who underwent LAG.

The inclusion criteria were as follows: Patients were diagnosed with gastric carcinoma for the first time; patients had surgical indications for LG without obvious surgical contraindications; and the postoperative pathology was consistent with gastric carcinoma.

The exclusion criteria included patients with hepatitis B, hepatitis C, fatty liver, cirrhosis, and other related basic diseases; patients with liver disease who underwent liver surgery; and patients with gallbladder and biliary tract diseases who underwent biliary system surgery[4].

Operative methods

After anesthesia, a conventional disinfection cloth was applied, and a trocar was placed in the 1 cm transverse incision below the umbilical region to establish pneumoperitoneum (12-15 mmHg). Laparoscopy was performed, and a trocar was placed in the left and right upper abdomen under direct vision to explore the entire abdominal cavity and determine the surgical method. The left liver was suspended with a fine line, and to release the greater omentum, part of the intestine and mesangium, the adhesion of the abdominal wall was observed. Surgical site dissociation and D2 lymph node dissection were performed with an ultrasonic scalpel and noninvasive forceps. A 60 mm cutting closure device was used in surgery.

TLG: The digestive tract was reconstructed in the lumen. The specimen was removed with a small incision of 4 cm in the umbilical section (Figure 1A and B).

ALG: Another 7 cm longitudinal incision was made in the middle of the lower abdomen of the xiphoid process. The left liver was pulled externally with an S-type retractor to expose the field of vision. Digestive tract reconstruction was completed under direct vision (Figure 1C).

Observations

The levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyltransferase (GGLT), total bilirubin (TBIL), direct bilirubin (DBIL) and indirect bilirubin (IBIL) in the 2 groups were recorded before the operation, 1-2 d after the operation, 3-4 d after the operation, and 5-7 d after the operation. The normal range of the above test indices is as follows: ALT, 9-50 U/L; AST, 15-40 U/L; ALP, 45-125 U/L; GGLT, 10-60 U/L; TBIL, 5-21 μmol/L; DBIL, 0-4 μmol/L; and IBIL, 0-17 μmol/L.

Statistical analysis

SPSS 26.0 was used for statistical analysis to compare whether the liver function-related indicators of the two groups before and after surgery were significantly different. Continuous data are expressed as mean ± SD and were analyzed by the independent *t* test. Categorical data are expressed as percentages and were analyzed by the chi-square test. A P value < 0.05 was considered statistically significant.

RESULTS

General

Among the 40 patients who underwent TLG, there were 27 males and 13 females; 13 patients underwent total gastrectomy (TG), and 27 underwent DG, with an age of 64.63 year ± 8.40 year and a body mass index (BMI) of 22.45 kg/m^2 ± 3.90 kg/m^2. Among the 40 patients who underwent LAG, there were 26 males and 14 females, 19 patients who underwent TG and 21 patients who underwent DG, with an age of 64.78 year ± 9.50 year and BMI of 22.47 kg/m^2 ± 2.89 kg/m^2. There were no significant differences in sex, age, BMI or surgical resection extent between the 2 groups (P > 0.05) (Table 1).

Transaminase

The levels of preoperative ALT and AST were approximately the same in the 2 groups, both within the normal range; moreover, there was no significant difference in preoperative transaminase levels between the 2 groups (P > 0.05) (Table 2, Figure 2).

There were increases in the levels of ALT and AST from the preoperative value in the 2 groups on the 1st to 2nd d after the operation, and the increase was more significant in the LAG group, that is, approximately twice that of the TLG group. The ALT and AST levels in the TLG group were within the normal range, while the ALT and AST levels in the LAG group were beyond the normal range. There was a difference in transaminase levels between the 2 groups on the 1st to 2nd d after the operation (P < 0.05) (Table 2, Figure 2).

The ALT and AST levels in the 2 groups decreased on days 3-4 after surgery compared with days 1-2 after surgery, among which the levels in the TLG group had decreased to approximately the preoperative level and those in the LAG group had decreased to the normal value. There was a significant difference in the transaminase levels in the 2 groups on days 3-4 after surgery (P < 0.05) (Table 2, Figure 2).

Table 1 Comparison of the general situation in each group

Variable	TLG group (*n* = 40)	ALG group (*n* = 40)	*t* value	*P* value
Age (yr)	64.63 ± 8.40	64.78 ± 9.50	0.075	0.941^{Nonsig}
BMI (kg/m^2)	22.45 ± 3.90	22.47 ± 2.89	0.020	0.984^{Nonsig}
M/F (case)	27/13	26/14	0.056	0.813^{Nonsig}
TG/GG (case)	13/27	19/21	1.875	0.171^{Nonsig}

TLG: Totally laparoscopic gastrectomy; ALG: Another 7 cm longitudinal incision; BMI: Body mass index; TG: Total gastrectomy.

Table 2 Comparison of transaminase levels in each group

Variable	TLG group (*n* = 40)	ALG group (*n* = 40)	*t* value	*P* value
ALT (U/L)				
BO	17.98 ± 11.44	16.28 ± 8.24	0.763	0.448^{Nonsig}
AO				
1-2 d	33.54 ± 15.28	72.49 ± 58.70	4.061	< 0.001^{Sig}
3-4 d	19.02 ± 8.18	32.03 ± 25.27	3.099	0.003^{Sig}
5-7 d	21.18 ± 10.13	28.90 ± 17.20	2.447	0.017^{Sig}
AST (U/L)				
BO	20.47 ± 5.88	20.56 ± 5.97	0.068	0.946^{Nonsig}
AO				
1-2 d	39.02 ± 14.67	85.27 ± 79.95	3.598	0.001^{Sig}
3-4 d	17.99 ± 8.38	26.94 ± 19.35	2.684	0.010^{Sig}
5-7 d	20.59 ± 8.64	26.16 ± 14.52	2.084	0.040^{Sig}

TLG: Totally laparoscopic gastrectomy; ALG: Another 7 cm longitudinal incision; BO: Before the operation; AO: After the operation; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

The ALT and AST levels in the 2 groups showed little change on the 5th to 7th d after surgery compared with the 3rd to 4th d after surgery, presenting a general downward trend, both within the normal range, and there was a difference in the transaminase levels between the 2 groups on the 5th to 7th d after the operation ($P < 0.05$) (Table 2, Figure 2).

The 2 groups were further stratified according to TG or DG; that is, total laparoscopic TG (TLTG) was compared with laparoscopic-assisted TG (LATG), and total laparoscopic distal gastrectomy (TLGG) was compared with laparoscopic-assisted distal gastrectomy (LAGG). The overall change trend of transaminases between the TLTG group and the LATG, TLGG, and LAGG groups was approximately the same as that between the TLG and LAG groups. The preoperative transaminase levels in the TLTG group, LATG group, TLGG group and LAGG group were all within the normal range. The transaminase levels in the TLTG group, LATG group, TLGG group and LAGG group were increased 1-2 d after the operation, even beyond the normal range, and the increase was more significant in the LATG group and LAGG group. Transaminase levels in the TLTG group, LATG group, TLGG group and LAGG group showed a declining trend on postoperative days 3-4 and 5-7 and gradually decreased to the preoperative level. At the same time, it was found that the transaminase levels in the TLTG group increased significantly compared with those in the TLGG group, and the transaminase levels increased significantly in the LATG group compared with the LAGG group. There were significant differences in transaminase levels between the TLTG group and the LATG group at 1-2 d after surgery and between the TLGG group and the LAGG group at 1-2 d after surgery, 3-4 d after surgery, and 5-7 d after surgery ($P < 0.05$), while there were no other significant differences ($P > 0.05$) (Table 3, Figure 3).

Bilirubin

The levels of TBIL, DBIL, and IBIL were roughly the same between the 2 groups before surgery and on day 1-2 after the operation, and all were within the normal range. There was no significant difference in bilirubin levels between the 2 groups before surgery and on day 1-2 after the operation ($P > 0.05$)

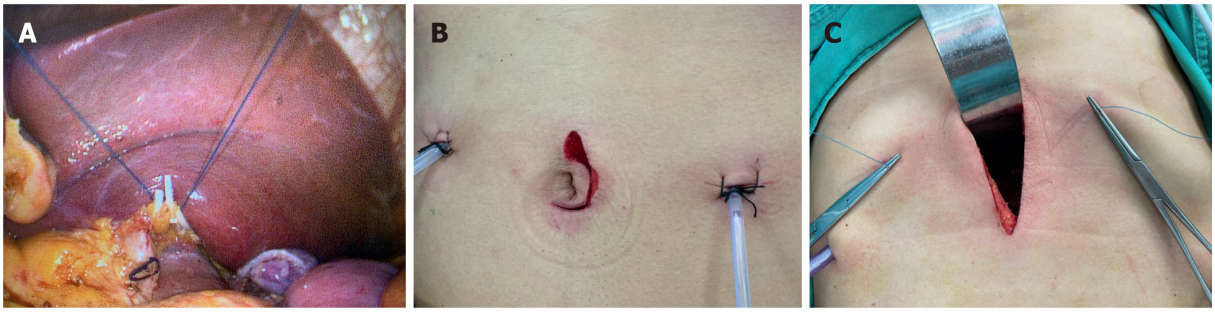

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Figure 1 Liver traction. A: Liver traction by a fine line; B: Abdominal incision in the totally laparoscopic gastrectomy group; C: Liver traction by an S-type retractor and Abdominal incision in another 7 cm longitudinal incision group.

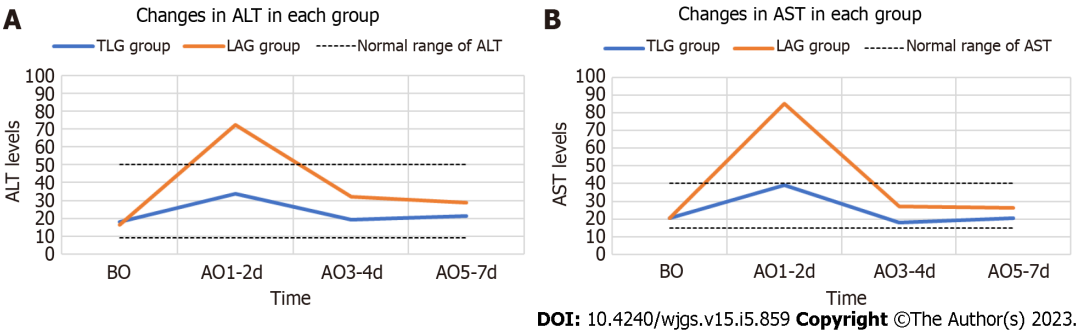

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Figure 2 Comparison of transaminase levels in each group. A: Changes in alanine aminotransferase in each group; B: Changes in aspartate aminotransferase in each group. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BO: Before the operation; AO: After the operation.

(Table 4, Figure 4).

The levels of TBIL, DBIL, and IBIL on the 3rd to 4th d after the operation and IBIL on the 5th to 7th d after the operation in both groups were within the normal range, and the TLG group had higher levels than the LAG group. There were significant differences in bilirubin levels on the 3rd to 4th d after the operation and in the IBIL levels on the 5th to 7th d after the operation between the 2 groups ($P < 0.05$). There were no significant differences in the levels of TBIL and DBIL between the 2 groups on the 5th to 7th d after surgery ($P > 0.05$) (Table 4, Figure 4).

The 2 groups were further stratified according to TG or DG; that is, TLTG was compared with LATG, and TLGG was compared with LAGG. The overall change trend of bilirubin between the TLTG group and the LATG, TLGG and LAGG groups was roughly the same as that between the TLG and LAG groups. The bilirubin levels at all time points in each group were within the normal range. There were significant differences in bilirubin levels between the TLGG group and LAGG group 3-4 d after surgery, in the indirect bilirubin levels between the TLGG group and LAGG group 5-7 d after surgery, and in the indirect bilirubin levels between the TLTG group and LATG group 3-4 d after surgery ($P < 0.05$). The bilirubin levels in the TLTG group and TLGG group increased significantly, while there were no other significant differences ($P > 0.05$) (Table 5).

Alkaline phosphatase and γ-glutamyltransferase

The levels of ALP and GGLT in the 2 groups were approximately the same before surgery and 5-7 d after surgery, both within the normal range, with no significant difference ($P > 0.05$) (Table 6, Figure 5).

The ALP level on postoperative days 3-4 and the GGLT level on postoperative days 1-2 in the 2 groups were within the normal range. ALP in the TLG group was higher than that in the LAG group, and GGLT was higher than that in the TLG group, with significant differences ($P < 0.05$). There were no differences in ALP levels on the 1st to 2nd postoperative days or in the GGLT levels on the 3rd to 4th postoperative days between the 2 groups ($P > 0.05$) (Table 6, Figure 5).

The 2 groups were further stratified according to TG or DG; that is, TLTG was compared with LATG, and TLGG was compared with LAGG. The overall change trend of ALP and GGLT between the TLTG group and LATG group and between the TLGG group and LAGG group was roughly the same as that between the TLG group and LAG group. The ALP and GGLT levels at each time point in each group were within the normal range. There were significant differences in GGLT levels 1-2 d after the operation and in the ALP levels 3-4 d after the operation between the TLTG group and the LATG group ($P < 0.05$). The former levels were higher in the TLTG group, while the latter levels were higher in the

Table 3 Hierarchical comparison of transaminases in each group

Variable	TLTG group (*n* = 13)	LATG group (*n* = 19)	TLGG group (*n* = 27)	LAGG group (*n* = 21)	*P* value
ALT (U/L)					
BO	17.50 ± 8.85	13.94 ± 6.47	18.21 ± 12.65	18.39 ± 9.21	0.198[1,Nonsig], 0.956[2,Nonsig]
AO					
1-2 d	39.60 ± 16.03	93.41 ± 77.54	30.63 ± 14.31	53.57 ± 22.72	0.008[1,Sig], < 0.001[2,Sig]
3-4 d	20.93 ± 10.11	36.93 ± 31.96	18.10 ± 7.10	27.60 ± 16.80	0.092[1,Nonsig], 0.023[2,Sig]
5-7 d	24.82 ± 11.65	28.99 ± 15.59	19.42 ± 9.03	28.81 ± 18.91	0.419[1,Nonsig], 0.045[2,Sig]
AST (U/L)					
BO	20.52 ± 5.96	20.13 ± 7.21	20.44 ± 5.96	20.94 ± 4.72	0.874[1,Nonsig], 0.754[2,Nonsig]
AO					
1-2 d	48.78 ± 13.56	112.37 ± 104.91	34.33 ± 12.94	60.74 ± 35.04	0.017[1,Sig], 0.003[2,Sig]
3-4 d	20.44 ± 10.63	24.96 ± 13.41	16.81 ± 6.99	28.74 ± 23.70	0.318[1,Nonsig], 0.036[2,Sig]
5-7 d	24.43 ± 8.54	24.49 ± 9.71	18.74 ± 8.20	27.66 ± 17.92	0.986[1,Nonsig], 0.044[2,Sig]

[1]Total laparoscopic total gastrectomy group compared with the laparoscopic-assisted total gastrectomy group;
[2]Total laparoscopic distal gastrectomy group compared with the laparoscopic-assisted distal gastrectomy group.
TLTG: Total laparoscopic total gastrectomy; LATG: Laparoscopic-assisted total gastrectomy; LAGG: Laparoscopic-assisted distal gastrectomy; BO: Before the operation; AO: After the operation; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

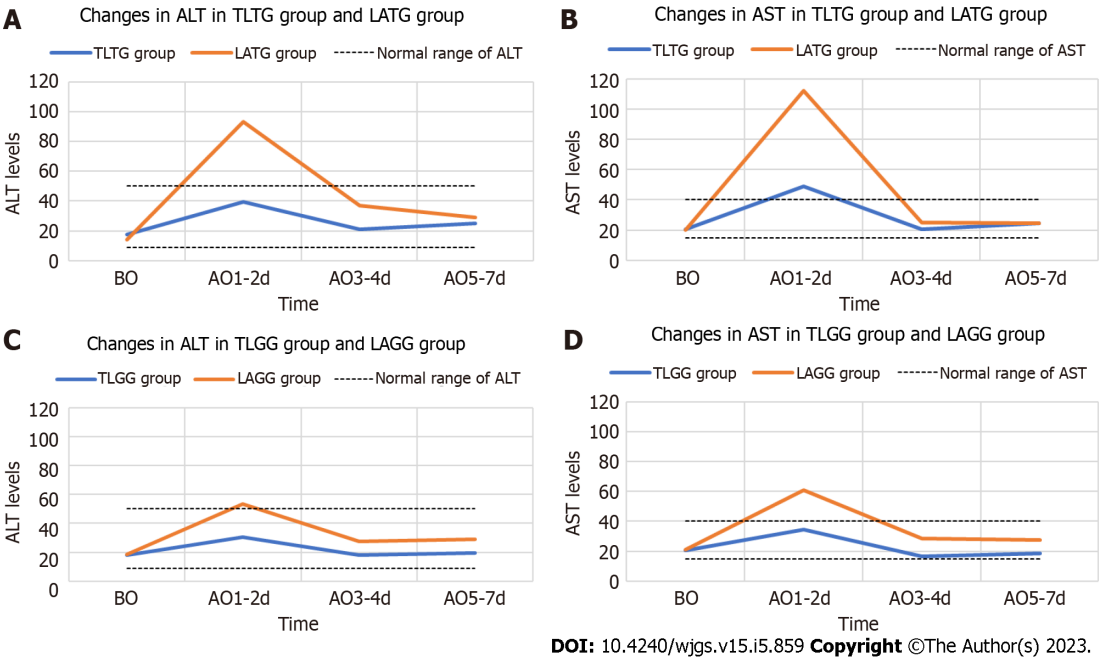

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Figure 3 Hierarchical comparison of transaminases in each group. A: Changes in alanine aminotransferase (ALT) in total laparoscopic total gastrectomy (TLTG) group and laparoscopic-assisted total gastrectomy (LATG) group; B: Changes in aspartate aminotransferase (AST) in TLTG group and LATG group; C: Changes in ALT in total laparoscopic distal gastrectomy (TLGG) group and laparoscopic-assisted distal gastrectomy (LAGG) group; D: Changes in AST in TLGG group and ALGG group. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TLTG: Total laparoscopic total gastrectomy; LATG: Laparoscopic-assisted total gastrectomy; TLGG: Total laparoscopic distal gastrectomy; LAGG: Laparoscopic-assisted distal gastrectomy; BO: Before the operation; AO: After the operation.

LATG group, and there were no significant differences in the other groups ($P > 0.05$) (Table 7).

Table 4 Comparison of bilirubin in each group

Variable	TLG group (*n* = 40)	ALG group (*n* = 40)	*t* value	*P* value
TBIL (μmol/L)				
BO	13.44 ± 6.57	11.62 ± 4.85	1.409	0.163^{Nonsig}
AO				
1-2 d	15.05 ± 7.10	15.11 ± 7.27	0.042	0.967^{Nonsig}
3-4 d	17.38 ± 8.44	11.65 ± 6.72	3.358	0.001^{Sig}
5-7 d	15.26 ± 5.91	12.82 ± 6.70	1.728	0.088^{Nonsig}
DBIL (μmol/L)				
BO	2.40 ± 1.05	2.15 ± 0.99	1.074	0.286^{Nonsig}
AO				
1-2 d	3.74 ± 1.73	3.79 ± 2.05	0.112	0.911^{Nonsig}
3-4 d	4.63 ± 3.32	3.22 ± 2.03	2.286	0.025^{Sig}
5-7 d	4.17 ± 2.31	4.05 ± 4.09	0.155	0.877^{Nonsig}
IBIL (μmol/L)				
BO	10.93 ± 5.58	9.47 ± 3.93	1.355	0.179^{Nonsig}
AO				
1-2 d	11.36 ± 5.68	11.33 ± 5.45	0.020	0.984^{Nonsig}
3-4 d	12.75 ± 5.90	8.43 ± 5.02	3.530	0.001^{Sig}
5-7 d	11.21 ± 4.17	8.77 ± 3.54	2.819	0.006^{Sig}

TLG: Totally laparoscopic gastrectomy; ALG: Another 7 cm longitudinal incision; TBIL: Total bilirubin; DBIL: Direct bilirubin; IBIL: Indirect bilirubin; BO: Before the operation; AO: After the operation.

DISCUSSION

Currently, studies have pointed out that LG has survival benefits similar to those of OG[5,6]. With the development of laparoscopic technology and the update and progress of surgical instruments, LG is becoming increasingly common in the clinic. However, TLG and LAG are still not clearly preferred in the clinic. Although relevant studies[7-11] have reported that TLG has advantages in many aspects, such as intraoperative dissection and postoperative recovery, the small incision in LAG also limits the intraoperative field of vision and operating space. However, TLG has higher requirements for surgical technique and operation coordination.

Comparative studies on the short-term therapeutic effect and long-term quality of life resulting from the 2 surgical methods have been completed, but there is still a lack of research on the postoperative liver function of patients receiving either of the 2 surgical methods. In this study, we found that in terms of transaminases, ALT and AST levels in the TLG group and the LAG group increased significantly after surgery; peaked on the 1st to 2nd d after surgery; gradually decreased, returning to the normal range on approximately the 3rd to 4th d after surgery; and then returned to the preoperative level on the 5th to 7th d after surgery. Among these values, the levels of ALT and AST in patients with LAG were significantly increased and beyond the normal range, and even the ALT and AST levels in patients with ALG were more than twice as high as those in patients with TLG on the 1st to 2nd d after surgery. Previous studies [12-15] have pointed out that CO_2 pneumoperitoneum reduces portal vein blood flow through intra-abdominal pressure and hypercapnia, thus causing liver function injury. In addition, both the TLG group and the LAG group underwent the operation of exposing the field of vision with liver traction by a fine line, and both groups underwent the operation of blocking the possible left vagal hepatic artery, which was the reason why the ALT and AST levels in the TLG group and the LAG group were higher than those before surgery. However, in this study, under the same CO_2 pneumoperitoneum conditions, the TLG group needed to complete all surgical steps under endoscopy, while the LAG group could complete digestive tract reconstruction under open conditions; that is, the effect of CO_2 pneumoperitoneum in the TLG group lasted longer than that in the LAG group. However, the ALT and AST levels in the LAG group were higher than those in the TLG group; in other words, the postoperative liver function injury in the LAG group was higher than that in the TLG group, so the effect of CO_2 pneumoperitoneum was not considered the reason for the difference between the 2 groups. At the same

Table 5 Hierarchical comparison of bilirubin in each group

Variable	TLTG group (*n* = 13)	LATG group (*n* = 19)	TLGG group (*n* = 27)	LAGG group (*n* = 21)	*P* value
TBIL (μmol/L)					
BO	16.65 ± 9.40	11.77 ± 5.85	11.90 ± 4.04	11.49 ± 3.89	0.080[1,Nonsig], 0.726[2,Nonsig]
AO					
1-2 d	16.53 ± 7.32	15.17 ± 9.32	14.33 ± 7.01	15.06 ± 4.98	0.662[1,Nonsig], 0.687[2,Nonsig]
3-4 d	19.62 ± 11.28	12.67 ± 8.17	16.30 ± 6.66	10.73 ± 5.11	0.052[1,Nonsig], 0.003[2,Sig]
5-7 d	16.69 ± 6.58	13.75 ± 8.33	14.57 ± 5.56	11.98 ± 4.84	0.295[1,Nonsig], 0.097[2,Nonsig]
DBIL (μmol/L)					
BO	2.83 ± 1.42	2.12 ± 1.44	2.19 ± 0.76	2.18 ± 0.86	0.131[1,Nonsig], 0.969[2,Nonsig]
AO					
1-2 d	3.97 ± 1.67	3.69 ± 2.44	3.63 ± 1.77	3.87 ± 1.67	0.722[1,Nonsig], 0.628[2,Nonsig]
3-4 d	4.78 ± 2.56	3.70 ± 2.46	4.56 ± 3.67	2.80 ± 1.48	0.237[1,Nonsig], 0.044[2,Sig]
5-7 d	4.65 ± 1.51	4.63 ± 5.38	3.93 ± 2.60	3.53 ± 2.44	0.987[1,Nonsig], 0.587[2,Nonsig]
IBIL (μmol/L)					
BO	13.48 ± 8.09	9.65 ± 4.76	9.70 ± 3.42	9.30 ± 3.09	0.102[1,Nonsig], 0.678[2,Nonsig]
AO					
1-2 d	12.56 ± 5.83	11.48 ± 7.10	10.78 ± 5.62	11.20 ± 3.54	0.454[1,Nonsig], 0.765[2,Nonsig]
3-4 d	14.83 ± 8.88	8.97 ± 6.07	11.75 ± 3.57	7.94 ± 3.94	0.034[1,Sig], 0.001[2,Sig]
5-7 d	12.38 ± 5.33	9.12 ± 4.33	10.64 ± 3.46	8.45 ± 2.71	0.066[1,Nonsig], 0.021[2,Sig]

[1]Total laparoscopic total gastrectomy group compared with the laparoscopic-assisted total gastrectomy group;
[2]Total laparoscopic distal gastrectomy group compared with the laparoscopic-assisted distal gastrectomy group.
TLTG: Total laparoscopic total gastrectomy; LATG: Laparoscopic-assisted total gastrectomy; TLGG: Total laparoscopic distal gastrectomy; LAGG: Laparoscopic-assisted distal gastrectomy; TBIL: Total bilirubin; DBIL: Direct bilirubin; IBIL: Indirect bilirubin; BO: Before the operation; AO: After the operation.

baseline in this study, the difference between the TLG group and the LAG group was only due to differences in surgical methods. In the LAG group, a 7 cm longitudinal incision was made in the middle of the lower xiphoid, and the left liver was continuously pulled externally with the help of an S-type retractor to expose the field of vision during digestive tract reconstruction. Therefore, we considered that the operation of continuous squeezing and pulling of the liver with an S-type retractor was the main factor leading to the higher postoperative ALT and AST levels in the LAG group than in the TLG group. In addition, the 2 groups were further stratified according to TG or DG; that is, TLTG was compared with LATG, and TLGG was compared with LAGG. We found that the ALT and AST levels in the TLTG group were higher than those in the TLGG group, and the ALT and AST levels in the LATG group were higher than those in the LAGG group. Compared with DG, TG requires a more fully exposed field of vision for reconstruction of the digestive tract; that is, there is a higher degree of continuous squeezing and pulling of the left liver, which also confirms that continuous squeezing and pulling of the liver with an S-type retractor is the main factor leading to the difference in ALT and AST levels after surgery. Therefore, we considered that the higher postoperative transaminase level in the LAG group compared with the TLG group was caused by the different surgical methods; that is, the damage to liver function in the LAG group was greater than that in the TLG group. However, the levels of ALT and AST in the 2 groups recovered to the normal range approximately 3-4 d after surgery and returned to the preoperative level 5-7 d after surgery, indicating that the liver function injury was transient and reversible.

In this study, TBIL, DBIL, IBIL, ALP and GGLT levels at each time point in the 2 groups were all within the normal range. Between the 2 surgical methods, only the bilirubin levels on postoperative days 3-4, the indirect bilirubin levels on postoperative days 5-7, the ALP levels on postoperative days 3-4, and the GGLT levels on postoperative days 1-2 were significantly different, while the changes in TBIL, DBIL, IBIL, ALP, GGLT, and other indicators showed no obvious regularity. Among them, the GGLT level in the TLG group was higher than that in the LAG group on the 1st to 2nd d after the operation, which was similar to the changes in postoperative transaminase in the 2 groups. Although the ALP level in the LAG group was higher than that in the TLG group 3-4 d after surgery, the

Table 6 Comparison of other liver function indicators in each group

Variable	TLG group (*n* = 40)	ALG group (*n* = 40)	*t* value	*P* value
ALP (U/L)				
BO	78.78 ± 16.73	76.10 ± 20.28	0.644	0.521[Nonsig]
AO				
1-2 d	60.59 ± 14.26	59.86 ± 13.99	0.231	0.818[Nonsig]
3-4 d	65.40 ± 15.58	57.06 ± 13.76	2.539	0.013[Sig]
5-7 d	73.97 ± 17.62	64.77 ± 26.06	1.850	0.068[Nonsig]
GGLT (U/L)				
BO	28.06 ± 32.63	31.70 ± 28.05	0.536	0.593[Nonsig]
AO				
1-2 d	20.46 ± 25.74	34.07 ± 26.10	2.347	0.021[Sig]
3-4 d	28.47 ± 29.22	24.11 ± 16.19	0.825	0.413[Nonsig]
5-7 d	50.66 ± 37.38	54.33 ± 39.28	0.428	0.670[Nonsig]

TLG: Totally laparoscopic gastrectomy; ALG: Another 7 cm longitudinal incision; GGLT: γ-glutamyltransferase; ALP: Alkaline phosphatase; BO: Before the operation; AO: After the operation.

Table 7 Hierarchical comparison of the other liver function indicators in each group

Variable	TLTG group (*n* = 13)	LATG group (*n* = 19)	TLGG group (*n* = 27)	LAGG group (*n* = 21)	*P* value
ALP (U/L)					
BO	83.63 ± 13.24	76.36 ± 25.15	76.44 ± 17.92	75.87 ± 15.27	0.348[1,Nonsig], 0.907[2,Nonsig]
AO					
1-2 d	59.95 ± 9.59	57.47 ± 15.06	60.89 ± 16.19	62.01 ± 12.93	0.604[1,Nonsig], 0.796[2,Nonsig]
3-4 d	68.39 ± 15.53	56.44 ± 15.68	63.96 ± 15.70	57.61 ± 12.12	0.042[1,Sig], 0.133[2,Nonsig]
5-7 d	83.56 ± 19.69	66.68 ± 31.49	69.35 ± 14.78	63.04 ± 20.63	0.097[1,Nonsig], 0.223[2,Nonsig]
GGLT (U/L)					
BO	27.42 ± 30.31	33.03 ± 32.33	28.36 ± 34.25	30.50 ± 24.29	0.625[1,Nonsig], 0.809[2,Nonsig]
AO					
1-2 d	19.15 ± 19.42	37.11 ± 28.46	21.09 ± 28.61	31.32 ± 24.15	0.042[1,Sig], 0.196[2,Nonsig]
3-4 d	34.22 ± 36.82	26.34 ± 19.69	25.70 ± 25.12	22.10 ± 12.39	0.490[1,Nonsig], 0.500[2,Nonsig]
5-7 d	59.74 ± 34.97	56.77 ± 44.02	46.29 ± 38.34	52.13 ± 35.42	0.840[1,Nonsig], 0.592[2,Nonsig]

[1]Total laparoscopic total gastrectomy group compared with the laparoscopic-assisted total gastrectomy group;
[2]Total laparoscopic distal gastrectomy group compared with the laparoscopic-assisted distal gastrectomy group.
TLTG: Total laparoscopic total gastrectomy; LATG: Laparoscopic-assisted total gastrectomy; TLGG: Total laparoscopic distal gastrectomy; LAGG: Laparoscopic-assisted distal gastrectomy; TLG: Totally laparoscopic gastrectomy; ALG: Another 7 cm longitudinal incision; GGLT: γ-glutamyltransferase; ALP: Alkaline phosphatase; BO: Before the operation; AO: After the operation.

postoperative ALP level in the 2 groups remained unchanged or decreased compared with the preoperative ALP level, which was similar to the results of Singal *et al*[16] in comparing liver function after laparoscopic cholecystectomy and open cholecystectomy. In addition, the levels of bilirubin in the TLG group on days 3-4 after surgery and the levels of indirect bilirubin in the TLG group on days 5-7 after surgery were higher than those in the LAG group. Relevant studies by Zhang *et al*[3] have pointed out that TLG patients exhaust for the first time earlier than LAG patients; therefore, we believed that TLG enables exhaust earlier than LAG does and restores intestinal function faster, thus opening the enterohepatic circulation, and bilirubin circulates into the blood through the portal vein. As a result, the postoperative bilirubin level in the TLG group was higher than that in the LAG group. Certainly, further clinical studies are required to confirm these findings.

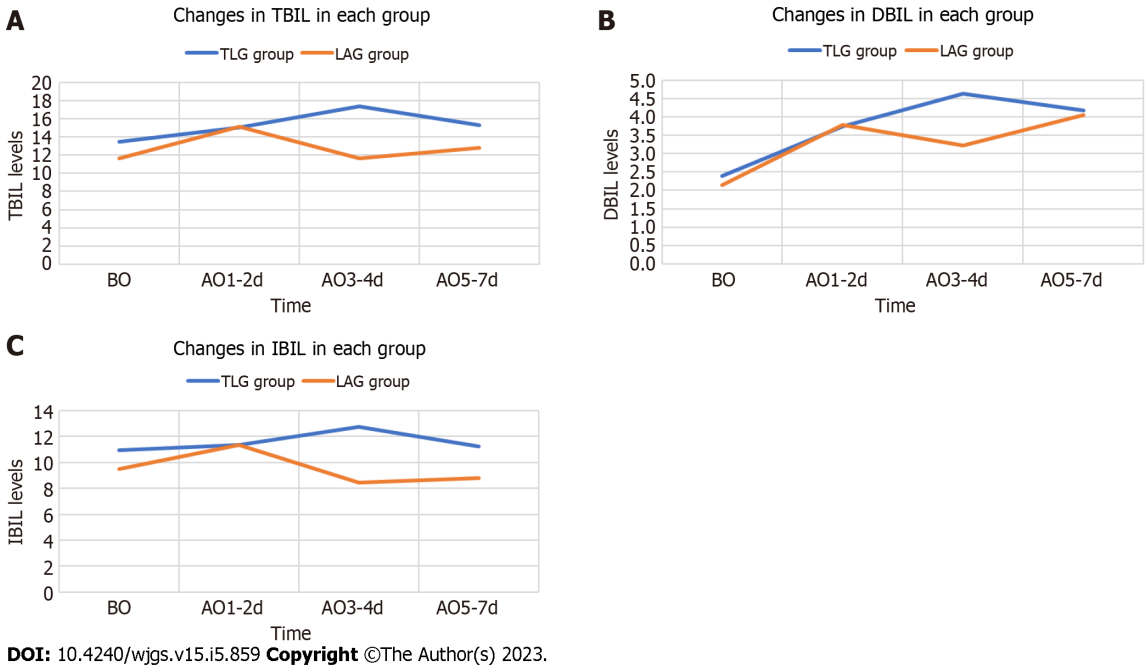

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Figure 4 Comparison of bilirubin in each group. A: Changes in total bilirubin in each group; B: Changes in direct bilirubin in each group; C: Changes in indirect bilirubin in each group. TBIL: Total bilirubin; DBIL: Direct bilirubin; IBIL: Indirect bilirubin; BO: Before the operation; AO: After the operation.

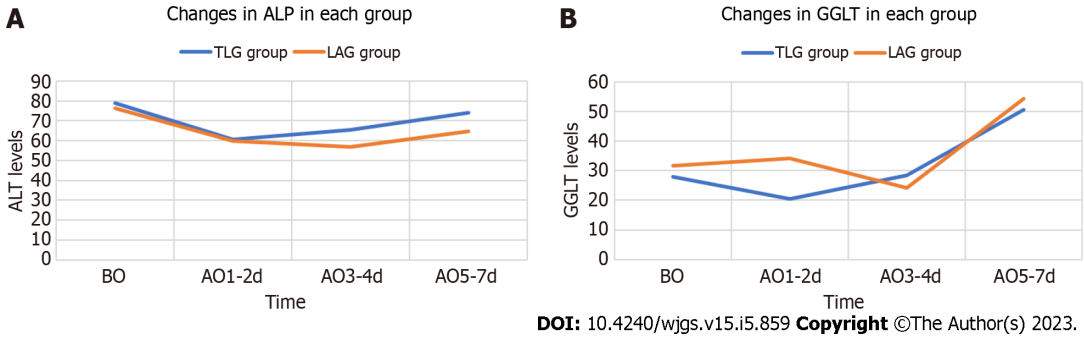

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Figure 5 Comparison of other liver function indicators in each group. A: Changes in alkaline phosphatase in each group; B: Changes in γ-glutamyltransferase in each group. ALP: Alkaline phosphatase; GGLT: γ-glutamyltransferase; BO: Before the operation; AO: After the operation.

The limitation of this retrospective study lies in the fact that the digestive center of Zhongshan Hospital Affiliated to Xiamen University included gastrointestinal surgery and general surgery. Therefore, the 40 patients with TLG and 40 patients with LAG in this retrospective study may be from different surgical treatment groups, which means that there are deviations in the surgical process caused by the difference in operational level of the operators. In addition, different surgical groups may also lead to certain differences in the diagnosis and treatment protocols adopted after surgery. For example, patients undergoing TLG resume enteral nutrition path earlier, enterohepatic circulation is opened, bilirubin circulates into the blood through the portal vein, and postoperative transient increase of bilirubin. This may also be the reason why the level of bilirubin on days 3-4 after surgery and indirect bilirubin on days 5-7 after surgery are both higher in the patients undergoing TLG.

CONCLUSION

In conclusion, both TLG and LAG can affect liver function, and this effect is transient and reversible. The effect of LAG on liver function is more serious. TLG is not only superior to LAG in terms of short-term efficacy and long-term quality of life but also in terms of liver function protection. Although TLG is more difficult to perform, it may be a better choice in radical gastrectomy.

ARTICLE HIGHLIGHTS

Research background

Previously, some studies have proposed that totally laparoscopic gastrectomy (TLG) is superior to laparoscopy-assisted gastrectomy (LAG) in terms of safety and feasibility based on the related intraoperative operative parameters and incidence of postoperative complications. However, there are still few studies on the changes in postoperative liver function in patients undergoing LG. The present study compared the postoperative liver function of patients with TLG and LAG, aiming to explore whether there is a difference in the influence of TLG and LAG on the liver function of patients.

Research motivation

To compare the postoperative liver function of patients with TLG and LAG.

Research objectives

To investigate whether there is a difference in the influence of TLG and LAG on the liver function of patients.

Research methods

The present study collected 80 patients who underwent LG from 2020 to 2021 at the Digestive Center (including the Department of Gastrointestinal Surgery and the Department of General Surgery) of Zhongshan Hospital affiliated with Xiamen University, including 40 patients who underwent TLG and 40 patients who underwent LAG. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyltransferase (GGLT), total bilirubin (TBIL), direct bilirubin (DBIL), and indirect bilirubin (IBIL), and other liver function-related test indices were compared between the 2 groups before surgery and on the 1st, 3rd, and 5th d after surgery.

Research results

The levels of ALT and AST in the 2 groups were significantly increased on the 1st to 2nd postoperative days compared with those before the operation. The levels of ALT and AST in the TLG group were within the normal range, while the levels of ALT and AST in the LAG group were twice as high as those in the TLG group ($P < 0.05$). The levels of ALT and AST in the 2 groups showed a downward trend at 3-4 d and 5-7 d after the operation and gradually decreased to the normal range ($P < 0.05$). The GGLT level in the LAG group was higher than that in the TLG group on postoperative days 1-2, the ALP level in the TLG group was higher than that in the LAG group on postoperative days 3-4, and the TBIL, DBIL and IBIL levels in the TLG group were higher than those in the LAG group on postoperative days 5-7 ($P < 0.05$). No significant difference was observed at other time points ($P > 0.05$).

Research conclusions

Both TLG and LAG can affect liver function, but the effect of LAG is more serious. The influence of both surgical approaches on liver function is transient and reversible. Although TLG is more difficult to perform, it may be a better choice for patients with gastric cancer combined with liver insufficiency.

Research perspectives

In conclusion, both TLG and LAG can affect liver function, and this effect is transient and reversible. The effect of LAG on liver function is more serious. TLG is not only superior to LAG in terms of short-term efficacy and long-term quality of life but also in terms of liver function protection. Although TLG is more difficult to perform, it may be a better choice in radical gastrectomy.

FOOTNOTES

Author contributions: Xiao F contributed significantly to analysis and manuscript preparation; Qiu XF contributed to the conception of the study; You CW, Xie FP, and Cai YY helped perform the analysis with constructive discussions.

Institutional review board statement: The study was reviewed and approved by the Institutional review board of Zhongshan Hospital Xiamen University (approval No. 2022-257).

Informed consent statement: The informed consent was waived from the patients.

Conflict-of-interest statement: We declare that we have no conflict of interest.

Data sharing statement: The data that support the findings of this study are available on request from the corresponding author.

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ORIGINAL ARTICLE

Retrospective Study

Rikkunshito increases appetite by enhancing gastrointestinal and incretin hormone levels in patients who underwent pylorus-preserving pancreaticoduodenectomy: A retrospective study

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Abstract

BACKGROUND

Rikkunshito (TJ-43) relieves gastrointestinal disturbance by increases in the levels of acylated ghrelin.

AIM

To investigate the effects of TJ-43 in patients undergoing pancreatic surgery.

METHODS

Forty-one patients undergoing pylorus-preserving pancreaticoduodenectomy (PpPD) were divided into two groups; patients took daily doses of TJ-43 after surgery or after postoperative day (POD) 21. The plasma levels of acylated and desacylated ghrelin, cholecystokinin (CCK), peptide YY (PYY), gastric inhibitory peptide (GIP), and active glucagon-like peptide (GLP)-1 were evaluated. Oral calorie intake was assessed at POD 21 in both groups. The primary endpoint of this study was the total food intake after PpPD.

RESULTS

The levels of acylated ghrelin were significantly greater in patients treated with TJ-43 than those in patients without TJ-43 administration at POD 21, and oral intake was significantly increased in patients treated with TJ-43. The CCK and PYY levels were significantly greater in patients treated with TJ-43 than those in patients without TJ-43 treatment. Furthermore, the GIP and active GLP-1 levels increased and values at POD 21 were significantly greater in patients treated with TJ-43 than those in patients without TJ-43 administration. Insulin secretion tended to increase in patients treated with TJ-43.

CONCLUSION
TJ-43 may have advantages for oral food intake in patients in the early phase after pancreatic surgery. Further investigation is needed to clarify the effects of TJ-43 on incretin hormones.

Key Words: Gastrointestinal hormone; Japanese traditional herbal medicine; Ghrelin; Incretin; Pancreatic surgery

Core Tip: This study investigated the effects of a Japanese herbal medicine, namely rikkunshito (TJ-43), on patients who underwent pancreatic surgery. TJ-43 may promote oral food intake in patients in the early phase after pancreatic surgery because TJ-43 increases appetite by enhancing gastrointestinal and incretin hormone levels.

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INTRODUCTION

The Japanese traditional herbal medicine known as rikkunshito (TJ-43) is an extract of eight crude herbal medicines. 10-dehydrogingerdin, glycycoumarin, 10-gingerdion, 8-gingerol, hesperidin, hesperetin, heptamethoxyflavone, isoliquiritigenin, liquiritigenin, naringenin, nobiletin, tangeretin, 8-shogaol, and 10-shogaol, are typical components of TJ-43.

TJ-43 increases peripheral acylated-ghrelin levels secreted from the stomach[1]. It is well known that acylated ghrelin has an appetite-enhancing effect, in addition to a growth hormone secretion-promoting effect[2,3]. Furthermore, acylated ghrelin is the only hormone that exhibits an appetite-promoting effect following intravenous administration[4]. Moreover, it has various actions, including gastric acid secretion[5], growth hormone secretion, and a positive energy balance induction[6]. The blood levels of acylated ghrelin correlated with gastrointestinal disturbances. Hence, ghrelin is used to treat gastrointestinal disturbance due to anorexia[7-9]; however, the repeated intravenous treatment of ghrelin has shown a considerable burden.

TJ-43 is often used to treat upper gastrointestinal disturbance[10-12]. Rats treated with TJ-43 exhibited enhanced gastric emptying[13]. In addition, the combined administration of TJ-43 and an anti-emetic drug for breast cancer patients alleviated emesis and anorexia that occur as an adverse complication to chemotherapy[14]. Thus, TJ-43 promotes mobility and motility of the stomach. It was previously reported that decreases in plasma acylated-ghrelin levels induced by cisplatin administration and oral food intake is mediated by 5-HT2B/2C receptors and suppressed by flavonoids in TJ-43 in animal models[15,16]. Hence, an important effect of TJ-43 is an increase in acylated ghrelin.

To improve delayed gastric emptying (DGE) after pylorus-preserving pancreaticoduodenectomy (PpPD), we previously treated patients with TJ-43 from the 21st postoperative day (POD) after beginning meal consumption as a conventional method in our hospital; however, this treatment did not allow for adequate food intake in the early postoperative phase, which is important for recovery from surgical stress. Therefore, to resolve the previous results of TJ-43 treatment for oral intake, the treatment protocol was changed to the new method. In this study, the TJ-43 treatment was started in the early post-operative phase, and oral intake was compared with the conventional treatment. Moreover, there are several appetite-suppression gastrointestinal hormones other than ghrelin, and TJ-43 may influence these gastrointestinal hormones, which can also affect gastrointestinal motility and mobility; however, the effects of TJ-43 on other gastrointestinal hormones remain unclear. The levels of incretin hormones, which are related to the blood insulin levels, were also investigated in this study because insulin secretion is particularly important in patients who undergo PpPD.

This study aimed to investigate a new clinical treatment protocol for TJ-43 and evaluate its effects on acylated-ghrelin levels and appetite in patients after pancreatic surgery. In addition to acylated-ghrelin levels, we investigated the effects of TJ-43 on other gastrointestinal hormones that affect gastrointestinal physiology and incretin hormones, including gastric inhibitory peptide (GIP, also known as a glucose-dependent insulinotropic polypeptide) and active glucagon-like peptide (GLP)-1.

MATERIALS AND METHODS

Patients and sample collection

This was a retrospective observational study. Blood samples were obtained from 41 patients who underwent PpPD at the University Hospital between 2015 and 2018 because of pancreato-biliary malignant tumors (Table 1). The Ethics Committee (Chief, Prof. Zentaro Yamagata; No. 820) approved this study. The study was conducted following the ethical standards outlined in the Declaration of Helsinki. On admission, informed consent was obtained from all patients. Furthermore, the tumor stage was evaluated according to the Union for International Cancer Control classification[17]. Moreover, the histological and pathological diagnoses of the specimens were confirmed using the World Health Organization classification criteria.

TJ-43 is a mixture of eight herbal ingredients[18] and is often used in the treatment of patients undergoing gastrointestinal surgery, including pancreatic surgery[18]. The patients were preoperatively enrolled into the two groups based on treatments of TJ-43; the TJ-43(-) group (n = 20) was treated from POD 21 with TJ-43 (7.5 g/d) using an enteral feeding catheter or by oral administration, which was a conventional treatment, and the TJ-43(+) group (n = 21) was treated daily with TJ-43 (7.5 g/d) from the 1st POD, which was the modified new treatment (Figure 1). Enteral feeding of 900 kilocalories per day was started from the 1st POD and continued throughout this study period. The postoperative diet was started at POD 7 in all cases. Furthermore, the total oral calorie intake was evaluated in both groups at 3 wk after surgery. The primary endpoint of this study was the total calorie intake.

For the definition of complications, DGE was defined based on international criteria[19]. Postoperative pancreatic fistula (POPF) was classified into grades based on the guidelines established by the International Study Group on Pancreatic Fistula in 2005[20] and revised in 2016[21]. Grade A POPF is called a biochemical fistula and has no clinical impact on the normal postoperative pathway. Clinically significant POPFs are classified as grades B and C. Grade B POPF requires one of the following conditions: An endoscopic or radiological intervention, a drain in situ for > 3 wk, clinical symptoms without organ failure, or a clinically relevant change in POPF management. Whenever a major change in clinical management or deviation from the normal clinical pathway is required or organ failure occurs, the fistula shifts to grade C POPF[21].

Blood samples

Blood samples were obtained before surgery (as the control samples before TJ-43 treatment in each case) and on POD 7, 14, and 21 at the time of the standard postoperative clinical blood examination, in the hospital. All samples were collected before breakfast (from 6 to 7 a.m.) and kept on ice. Immediately after blood collection, centrifugation was performed. Furthermore, EDTA-2Na and aprotinin were added to centrifuge blood samples at final concentrations of 1 mg/mL and 500 KIU, respectively. Then, DPP-IV inhibitor was added at 20 μl/mL to 1 mL of plasma, and the samples were stored at −80 °C until further analysis.

For the determination of peripheral acylated and desacylated ghrelin levels, the plasma samples were promptly centrifuged at 4 °C, and the supernatant was acidified with 1 mol/L HCl (1/10 volume)[22].

Immunoreactive insulin levels

Immunoreactive insulin (IRI) was assessed by clinical laboratory analysis. IRI levels were measured using the Lumipulse G1200 immunoassay instrument (FUJIREBIO Inc., Tokyo, Japan). Lumipulse® G Insulin-N Immunoreaction cartridges for *in vitro* diagnostic were used in the Lumipulse G system for the quantitative measurement of insulin in serum or plasma. The assay results were available in less than 35 min.

Evaluation of ghrelin and gastrointestinal hormones

Plasma levels of acylated and desacylated ghrelin were evaluated by enzyme-linked immunosorbent assay (ELISA) kits (Iwai Chemicals Co., Tokyo, Japan).

Plasma levels of cholecystokinin (CCK) (LifeSpan BioSciences), peptide YY (PYY) (LifeSpan BioSciences), GIP (RayBiotech Life Inc., Peachtree Corners, GA), and active GLP-1 (Invitrogen, Waltham, MA) were evaluated by ELISA.

Statistical analysis

Statistical analyses were performed using EZR software (Saitama Medical Center, Saitama, Japan), which is using the R programming language (The R Foundation for Statistical Computing, Vienna, Austria)[23].

The power calculation was performed as follows: The number of samples required for statistical analysis was 20 in each group. Data are expressed as the mean ± standard error of the mean. The paired t-test or ANOVA with Bonferroni's *post-hoc* test was used for comparisons between the two groups. $P < 0.05$ was considered significantly different.

Table 1 Clinicopathological characteristics

Variable		TJ-43(−), *n* = 20	TJ-43(+), *n* = 21	*P* value
Age in yr		67 ± 7.0	66 ± 7.7	0.962
Sex, *n* (%)	Male	10 (50)	14 (67)	0.199
	Female	10 (50)	7 (33)	
Disease, *n* (%)	Pancreas Ca. (Ph)	7 (35)	8 (38)	
	IPMC	2 (10)	2 (10)	
	IPMA	2 (10)	1 (5)	
	CBD Ca.	5 (25)	5 (24)	
	Vater Ca.	3 (15)	4 (19)	
	Panaceas-NET	1 (5)	0 (0)	
	GB Ca.	0 (0)	1 (5)	
UICC Tumor stage: Pancreas Ca. (0/I/IIA/IIB); Other Ca. (0/I/II/III)	Pancreas Ca. (Ph)	(0/0/1/6)	(0/0/3/5)	
	IPMC	(1/0/1/0)	(0/0/1/1)	
	IPMA	N/A	N/A	
	CBD Ca.	(0/1/4/0)	(0/3/2/0)	
	Vater Ca.	(0/1/2/0)	(0/2/2/0)	
	P-NET	(0/1/0/0)	N/A	
	GB Ca.	N/A	(0/0/1/0)	
Tumor differentiation (well/mod/poor)	Pancreas Ca. (Ph)	(3/2/2)	(1/6/1)	
	IPMC	(0/2/0)	(1/0/1)	
	IPMA	N/A	N/A	
	CBD Ca.	(0/5/0)	(2/2/1)	
	Vater Ca.	(2/1/0)	(1/3/0)	
	P-NET	N/A	N/A	
	GB Ca.	N/A	(0/1/0)	
Time of operation in min		500 ± 56	509 ± 0.72	0.299
Blood loss in mL		692 ± 0.54	959 ± 0.66	0.182
HbA1c, %		5.6 ± 2.2	5.7 ± 2.3	0.892
Tumor markers	CEA in ng/mL	3.1 ± 1.3	3.7 ± 1.1	0.872
	CA19-9 in U/mL	455 ± 23	451 ± 29	
DGE, %		25	19	0.773
POPF, *n* (%)	Grade A	15 (75)	16 (76)	
	Grades B and C	5 (25)	5 (24)	0.886
Post-operative pneumonia, *n* (%)		1 (5)	1 (4.8)	0.889

UICC: Union for International Cancer Control; Ph: Pancreas head; IPMC: Intraductal papillary mucinous carcinoma; IPMA: Intraductal papillary mucinous adenoma; CBD: Common bile duct; Ca: carcinoma; NET: Neuroendocrine tumor; GB: Gall bladder; Hb: Hemoglobin; DGE: Delayed gastric empty; POPF: Post-operative pancreatic fistula; TJ-43: Rikkunshito; TJ-43(-): Patients without TJ-43 treatment; TJ-43(+): Patients with TJ-43 treatment; N/A: No application.

RESULTS

TJ-43 administration after pancreatico-duodenectomy

Adverse events were not observed in patients treated with TJ-43. Furthermore, no significant differences in the clinical features were observed in both groups (Table 1).

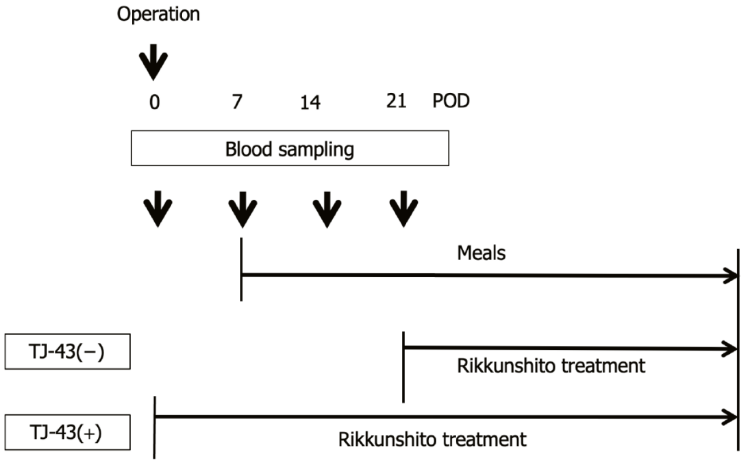

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Figure 1 Study protocol. TJ-43: Rikkunshito; TJ-43(-): Patients without TJ-43 treatment; TJ-43(+): Patients with TJ-43 treatment; POD: Postoperative day.

Effect of TJ-43 on plasma acylated-ghrelin levels

Acylated ghrelin was detected in plasma collected from patients before the operation (Figure 2A). The levels of acylated ghrelin did not significantly change after the operation in patients without TJ-43 treatment; however, the levels gradually increased after the operation in patients treated with TJ-43, compared with their levels before the operation. There were significant differences in levels of acylated ghrelin at POD 21 between the TJ-43(-) and TJ-43(+) groups ($P < 0.05$).

The plasma desacylated-ghrelin levels were not markedly changed in either group after the operation, compared with their levels before the operation (Figure 2B).

Effects of TJ-43 on meal intake

Consistent with the analysis of acylated ghrelin, total food consumption was more significant in patients treated with TJ-43 compared with patients without TJ-43 administration (patients treated with TJ-43, 491.5 ± 59.2 Kcal; and patients without TJ-43 treatment, 317.5 ± 52.3 Kcal, respectively). In addition, dietary intake from staple food was significantly greater in patients treated with TJ-43 compared with patients without TJ-43 treatment (patients treated with TJ-43, 375.3 ± 62.3 Kcal; and patients without TJ-43 treatment, 236.9 ± 49.7 Kcal, respectively) ($P < 0.05$) (Figure 3).

Effects of TJ-43 on plasma gastrointestinal hormone levels

CCK and PYY were detected in plasma harvested before the operation (Figure 4). The levels of gastrointestinal hormones did not markedly change after the operation in patients without TJ-43 treatment; however, these levels were significantly increased at POD 21 in patients treated with TJ-43, compared with their levels before surgery ($P < 0.05$).

Effects of TJ-43 on plasma incretin hormones

The plasma GIP and active GLP-1 Levels were not significantly changed after the operation in the TJ-43(-) group, compared with those before the operation. In contrast, these levels were significantly greater at POD 21 in the TJ-43(+) group, compared with those before the operation ($P < 0.05$) (Figure 5). These increases were significantly greater for the values of GIP than those of active GLP-1 ($P < 0.05$).

Effects of TJ-43 on IRI levels

IRI levels were assessed at POD 21. Although no significant differences were observed in the IRI levels between the groups, levels in patients treated with TJ-43 were greater than those in patients without TJ-43 administration (Figure 6).

Blood glucose levels were 116.3 ± 18.5 in the TJ-43(-) group and 107.2 ± 15.3 in the TJ-43(+) group, 1 h after the meal. There were no significant differences between the two groups.

DISCUSSION

TJ-43 improves oral food intake by increasing the peripheral level of acylated ghrelin after PpPD. This study found that oral food intake in the TJ-43(+) group was significantly higher than that in the TJ-43(–) group after PpPD. Furthermore, the acyl ghrelin level in the TJ-43(+) group was significantly higher than that in the TJ-43(–) group at the same time points.

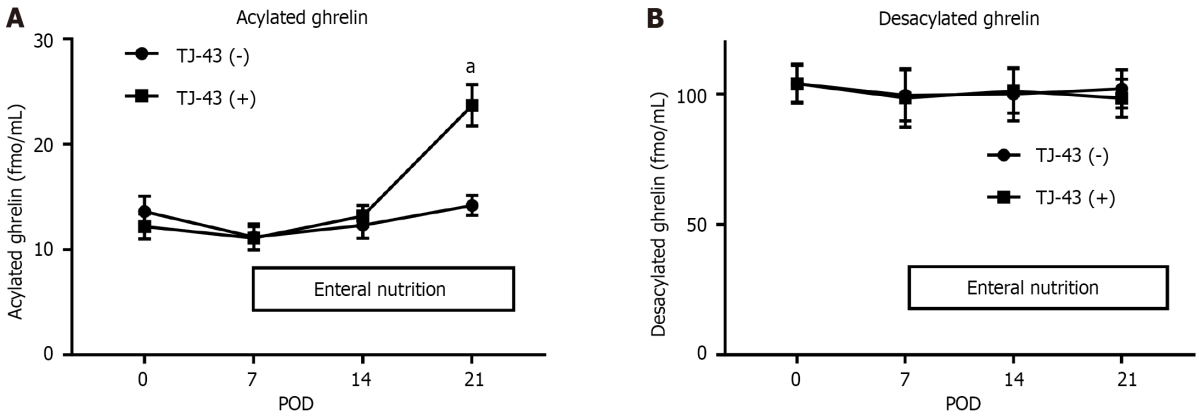

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Figure 2 Plasma acylated and desacylated ghrelin levels. A: Plasma levels of acylated ghrelin; B: Plasma levels of desacylated ghrelin. Plasma levels of acylated and desacylated ghrelin were measured by ELISA. $^{a}P < 0.05$ compared with the Tj-43(-) group by ANOVA with Bonferroni's *post-hoc* test. TJ-43: Rikkunshito; TJ-43(-): Patients without TJ-43 treatment; TJ-43(+): Patients with TJ-43 treatment; POD: Postoperative day.

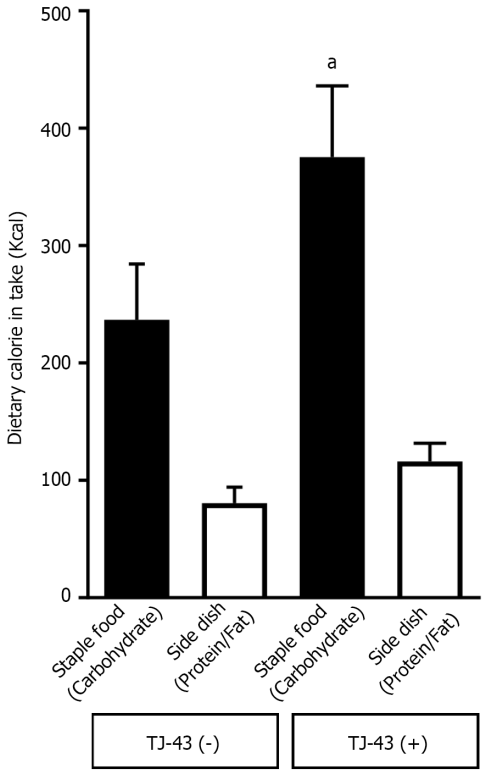

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Figure 3 Oral dietary intake after pancreatic surgery. After starting meals, the amount of oral dietary intake of each meal was scored from 0 to 100% (staple food and side dishes), and the average oral intake for 7 d (postoperative day 21) was calculated and analyzed in the two groups. $^{a}P < 0.05$ compared with carbohydrate intake in the TJ-43(-) group by ANOVA with Bonferroni's *post-hoc* test. TJ-43: Rikkunshito; TJ-43(-): Patients without TJ-43 treatment; TJ-43(+): Patients with TJ-43 treatment.

Patients undergoing PpPD with the reconstruction of the gastrointestinal tract have lower food intake in the early postoperative period. Reasons for this include vagal denervation and shrinkage of the residual stomach. Regarding the relationship between postoperative complications and oral food intake, DGE, POPF, and postoperative pneumonia are critical factors[24]. These complications may lead to loss of appetite. In this study, these complications were observed in both groups, without significant differences (Table 1).

Furthermore, levels of acylated ghrelin increased in patients treated with TJ-43 group compared with patients without TJ-43 administration after the operation (Figure 3). Since the only difference between the two groups was the start time of TJ-43 treatment, the reason for the increased acylated-ghrelin levels was most likely the early treatment with TJ-43, as reported previously[25]. Notably, oral meal

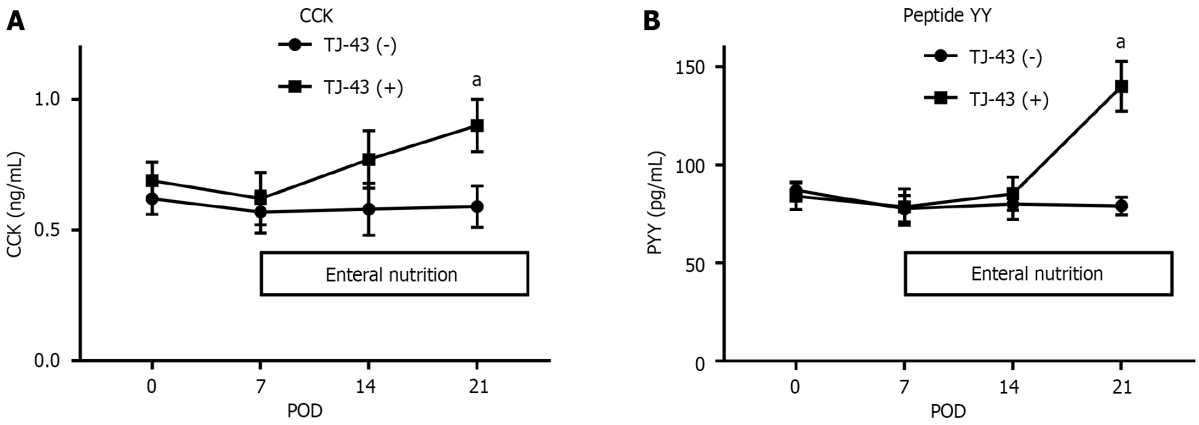

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Figure 4 Plasma cholecystokinin and peptide YY levels. A: Plasma levels of cholecystokinin (CCK); B: Plasma levels of peptide YY (PYY). Plasma levels of CCK and PYY were measured by ELISA. $^{a}P < 0.05$ compared with the TJ-43(-) group by ANOVA with Bonferroni's *post-hoc* test. TJ-43: Rikkunshito; TJ-43(-): Patients without TJ-43 treatment; TJ-43(+): Patients with TJ-43 treatment; CCK: Cholecystokinin; PYY: Peptide YY; POD: Postoperative day.

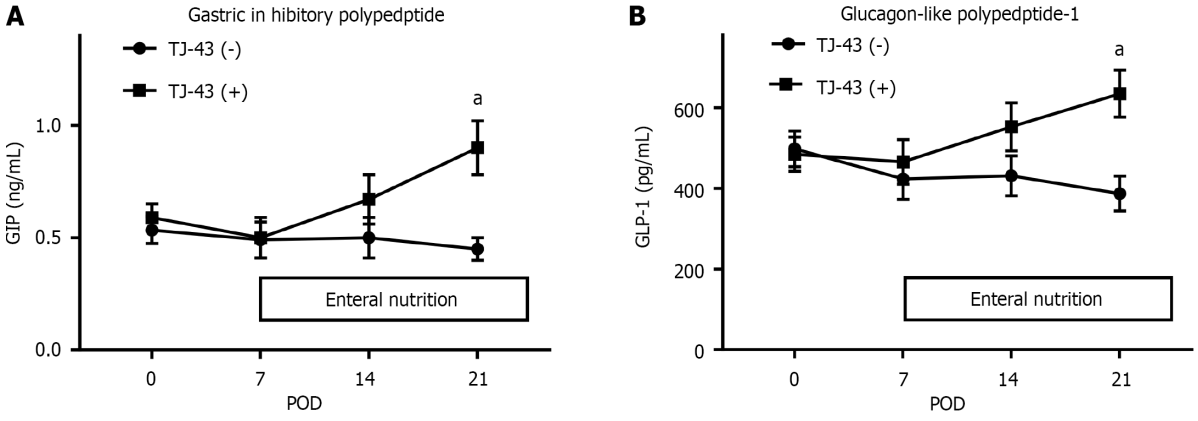

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Figure 5 Plasma incretin levels. A: Plasma levels of gastric inhibitory peptide; B: Plasma levels of glucagon-like polypeptide-1. Plasma levels of gastric inhibitory peptide and glucagon-like peptide-1 were measured by ELISA. $^{a}P < 0.05$ compared with the TJ-43(-) group by ANOVA with Bonferroni's *post-hoc* test. TJ-43: Rikkunshito; TJ-43(-): Patients without TJ-43 treatment; TJ-43(+): Patients with TJ-43 treatment; GIP: Gastric inhibitory peptide; active GLP-1: Glucagon-like polypeptide-1; POD: Postoperative day.

consumption significantly increased in patients treated with TJ-43 than those in patients without TJ-43 treatment after the operation (Figure 2). Hence, TJ-43 increases acylated-ghrelin levels and improves food intake, mainly by promoting motility and mobility of the remnant stomach[7,18,26,27].

In addition to the enhancement of acylated-ghrelin levels by TJ-43[25], several other mechanisms contribute to the effects of TJ-43 on gastrointestinal function such as enhancement of gastric emptying, motility, and adaptive relaxation[28,29] The improvement in food consumption that was observed in this study may be mediated by these pathways, as well as ghrelin signaling, and thus, multiple actions of TJ-43 may improve oral food intake after PpPD. Moreover, in addition to acylated-ghrelin, TJ-43 increases plasma CCK, PYY, GIP, and GLP-1 after PpPD (Figures 2, 4 and 5). It has been reported that PYY and CCK cause DGE[30], which is opposite to the effects of acylated ghrelin. These results suggest that the body's response involves constant feedback mechanisms. Regarding appetite, acylated ghrelin contradicts CCK, PYY, and GLP-1. Furthermore, regarding gastric emptying, acylated ghrelin contradicts CCK and GLP-1. In this study, the ratio (POD 21/POD 0) for the change in the levels of acylated ghrelin, CCK, PYY, GIP, and GLP-1 was 2.14, 1.45, 1.61, and 1.37, respectively. Thus, the increase in acylated ghrelin was greater than that of CCK, PYY, GIP, and GLP-1. This result may support the effect of TJ-43 on an increase in food intake. Additionally, the effects of TJ-43 on acylated ghrelin may be more significant in the early period of TJ-43 treatment.

Moreover, gastrointestinal polypeptide hormone incretins secreted after meal intake[31] induce insulin secretion from the pancreas in a blood sugar-dependent manner, suggesting that hypoglycemia is unlikely to induce in the absence of food intake. Furthermore, it inhibits gastric acid secretion but does not affect gastric emptying[31]. The GIP is secreted from the K cells in the upper intestine and activates the islet β-cells. Furthermore, GLP-1 is secreted from the L cells in the lower intestine. Thus,

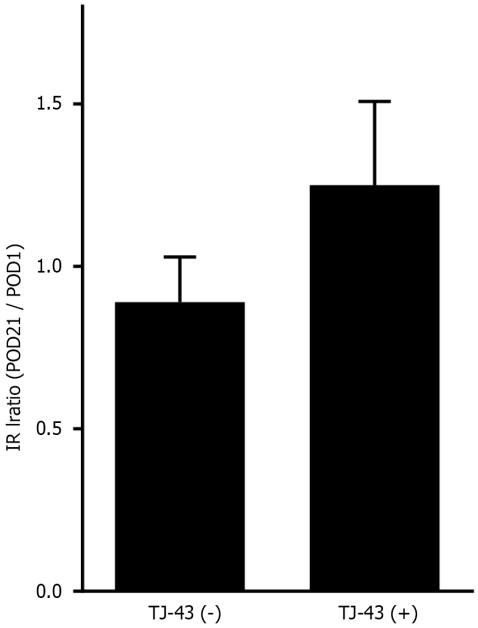

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Figure 6 Effect of rikkunshito on insulin secretion. Immunoreactive insulin levels are shown. TJ-43: Rikkunshito; TJ-43(-): Patients without TJ-43 treatment; TJ-43(+): Patients with TJ-43 treatment; IRI: Immunoreactive insulin.

incretin hormones are attracting interest for their application in clinical diabetes treatments. One new drug that has become recently available is a DPP-4 inhibitor. Collectively, these new drugs are called incretin-related drugs. By suppressing the action of this enzyme, incretin is less likely to be destroyed and blood glucose levels after eating are reduced. It was reported that herbal medicines can stimulate incretin secretion and regulate blood glucose in mice[32]. Furthermore, TJ-43 enhances insulin secretion after meals in humans[33]. In the present study, TJ-43 increased GIP and active GLP-1 Levels in patients who underwent PpPD. GIP and GLP-1 hormones can improve glucose tolerance and their effects are additive. GIP appears to quantitatively be the most important, particularly regarding insulin secretion, whereas the action of GLP-1 is mainly related to the inhibition of glucagon secretion[34]. The ratio of the change in GIP was greater than that of active GLP-1. These results may indicate that the effect of TJ-43 on the increase in GIP is more predominant than that in GLP-1.

Plasma levels of incretin hormones were increased by TJ-43 administration (Figure 4). In this study, insulin secretion tended to increase by TJ-43 administration (Figure 2), however, there were also no significant differences in blood glucose levels after a meal between the two groups (data not shown). Since undergoing PpPD involves reconstruction of the gastrointestinal tract, the effects also need to be investigated under normal physiological conditions. Considering that the increases in incretin hormone and IRI levels are most likely due to increases in oral food intake in the TJ-43(+) group, an animal study is necessary to resolve the clinical questions. Therefore, studies using animal models are currently underway. In one pilot study, the plasma and gastrointestinal expressions of incretin hormones significantly increased, and the expression of insulin in the pancreas was significantly enhanced by intragastric administration of TJ-43 for 28 d (unpublished data). Furthermore, activation of the islet cells increased with TJ-43 treatment. Thus, TJ-43 increases the incretin hormone levels in the blood after continuous intragastric administration and increases the expression of insulin in the pancreatic islet cells. Moreover, the administration of TJ-43 inhibits increased blood glucose levels during oral glucose tolerance tests in rats. These pilot studies in the animal model indicate that TJ-43 may increase insulin secretion after pancreatic surgery. Therefore, TJ-43 may benefit patients who undergo pancreatic resection.

CONCLUSION

In this study, TJ-43 increased the peripheral levels of acylated ghrelin and postoperative oral food intake. The findings indicate that TJ-43 may improve oral food intake by increasing the plasma acylated-ghrelin levels after PpPD. However, this study was small and non-randomized. A multicenter, randomized, placebo-controlled study is required to validate these findings. Furthermore, the effects of TJ-43 on incretin hormones need to be clarified in future studies.

ARTICLE HIGHLIGHTS

Research background

Rikkunshito (TJ-43) improves gastrointestinal disturbances.

Research motivation

The effects of TJ-43 in patients undergoing pancreatic surgery have not been elucidated.

Research objectives

This study investigated the effects of TJ-43 in patients undergoing pylorus-preserving pancreaticoduodenectomy (PpPD).

Research methods

Forty-one patients who underwent PpPD were divided into two groups; patients treated with daily doses of TJ-43 after surgery [TJ-43(+) group] or just on postoperative day (POD) 21 [TJ-43(-) group]. Plasma levels of acylated and desacylated ghrelin, cholecystokinin (CCK), peptide YY (PYY), gastric inhibitory peptide (GIP), and active glucagon-like peptide (GLP)-1 were evaluated. Oral calorie intake was assessed at POD 21 in both groups. The primary endpoint of this study was the total food intake after PpPD.

Research results

The acylated-ghrelin levels were significantly greater in patients treated with TJ-43 than those in patients without TJ-43 treatment at POD 21. Similarly, oral intake significantly increased in the TJ-43(+) group. The levels of CCK and PYY were significantly greater in patients treated with TJ-43 than those in patients without TJ-43 administration. Furthermore, the GIP and active GLP-1 levels increased and the values at POD 21 were significantly greater in patients treated with TJ-43 than those in patients without TJ-43 treatment. Insulin secretion tended to increase in patients treated with TJ-43.

Research conclusions

TJ-43 may improve oral food intake in patients in the early phase after pancreatic surgery.

Research perspectives

Further investigation is needed to clarify the effects of TJ-43 on incretin hormones.

FOOTNOTES

Author contributions: Kono H conducted and organized this experiment; Hosomura N Amemiya H and Akaike H made an assessment of samples; Shoda K, Furuya S and Kawaguchi Y analyzed the data; Kawaida H collected the samples; Ichikawa D provided suggestions for this experiment.

Institutional review board statement: This study was approved by University of Yamanashi Hospital Institutional Review Board (Chief of the committee Zentaro Yamagata; and Approval number: 820) and was performed following the ethical standards outlined in the Declaration of Helsinki and its later amendments. Informed consent was obtained from all patients and/or donors of clinical samples, including blood or tissues, where necessary, at the time of admission.

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

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ORIGINAL ARTICLE

Retrospective Study

Diagnostic performance of texture analysis in the differential diagnosis of perianal fistulising Crohn's disease and glandular anal fistula

Xin Zhu, Dan-Dan Ye, Jian-Hua Wang, Jing Li, Shao-Wei Liu

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Abstract

BACKGROUND

Perianal fistulising Crohn's disease (PFCD) and glandular anal fistula have many similarities on conventional magnetic resonance imaging. However, many patients with PFCD show concomitant active proctitis, but only few patients with glandular anal fistula have active proctitis.

AIM

To explore the value of differential diagnosis of PFCD and glandular anal fistula by comparing the textural feature parameters of the rectum and anal canal in fat suppression T2-weighted imaging (FS-T2WI).

METHODS

Patients with rectal water sac implantation were screened from the first part of this study (48 patients with PFCD and 22 patients with glandular anal fistula). Open-source software ITK-SNAP (Version 3.6.0, http://www.itksnap.org/) was used to delineate the region of interest (ROI) of the entire rectum and anal canal wall on every axial section, and then the ROIs were input in the Analysis Kit software (version V3.0.0.R, GE Healthcare) to calculate the textural feature parameters. Textural feature parameter differences of the rectum and anal canal wall between the PFCD group *vs* the glandular anal fistula group were analyzed using Mann-Whitney U test. The redundant textural parameters were screened by bivariate Spearman correlation analysis, and binary logistic regression analysis was used to establish the model of textural feature parameters. Finally, diagnostic accuracy was assessed by receiver operating characteristic-area under the curve (AUC) analysis.

RESULTS

In all, 385 textural parameters were obtained, including 37 parameters with statistically significant differences between the PFCD and glandular anal fistula groups. Then, 16 texture feature parameters remained after bivariate Spearman correlation analysis, including one histogram parameter (Histogram energy); four grey level co-occurrence matrix (GLCM) parameters (GLCM energy_all direction_offset1_SD, GLCM entropy_all direction_ offset4_SD, GLCM entropy_all direction_offset7_SD, and Haralick correlation_all direction_ offset7_SD); four texture parameters (Correlation_all direction_offset1_SD, cluster prominence _angle 90_offset4, Inertia_all direction_offset7_SD, and cluster shade_angle 45_offset7); five grey level run-length matrix parameters (grey level nonuniformity_angle 90_offset1, grey level nonuniformity_all direction_offset4_SD, long run high grey level emphasis_all direction_offset1_SD, long run emphasis_all direction_ offset4_ SD, and long run high grey level emphasis_all direction_offset4_SD); and two form factor parameters (surface area and maximum 3D diameter). The AUC, sensitivity, and specificity of the model of textural feature parameters were 0.917, 85.42%, and 86.36%, respectively.

CONCLUSION

The model of textural feature parameters showed good diagnostic performance for PFCD. The texture feature parameters of the rectum and anal canal in FS-T2WI are helpful to distinguish PFCD from glandular anal fistula.

Key Words: Anal fistula; Crohn's diseases; Magnetic resonance imaging; Texture analysis; Differential diagnosis

Core Tip: Crohn's disease (CD) is a localized, segmental chronic granulomatous inflammation that can affect the digestive tract from the oral cavity to the anus, and its pathophysiology is non-caseous necrotic granuloma. Nearly 10% of patients with CD have an anal fistula before presenting gastrointestinal symptoms. At the same time, perianal fistulising CD (PFCD) and glandular anal fistula have many similarities on conventional magnetic resonance imaging (MRI); therefore, it is difficult to differentiate between these conditions in the early stages with conventional MRI. Texture analysis based on conventional MRI images can quantitatively analyze image pixel information and reflect the internal heterogeneity and pathological characteristics of the lesion. Currently, this approach is widely used to distinguish between benign and malignant tumors, predict tumor stage, and evaluate treatment efficacy. In addition to the application of texture analysis in the study of tumors or substantial organs, some studies have applied texture analysis to hollow organs such as the intestine. Many patients with PFCD show concomitant active proctitis, but only few patients with glandular anal fistula have active proctitis. Based on this theory, we analyzed the texture of the rectum and anal canal wall in the PFCD group and glandular anal fistula group in this study to explore whether the texture feature parameters are valuable in identifying and differentiating these two lesions.

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INTRODUCTION

Crohn's disease (CD) is a localized, segmental chronic granulomatous inflammation that can affect the digestive tract from the oral cavity to the anus, and its pathophysiology is non-caseous necrotic granuloma[1]. Nearly 10% patients with CD have an anal fistula before presenting with gastrointestinal symptoms. At the same time, perianal fistulising CD (PFCD) and glandular anal fistula have many similarities on conventional magnetic resonance imaging (MRI); therefore, it is difficult to differentiate these conditions in the early stages with conventional MRI[2]. Texture analysis based on conventional MRI images can quantitatively analyze image pixel information and reflect the internal heterogeneity and pathological characteristics of the lesion[3]. Currently, this approach is widely used to distinguish between benign and malignant tumors, predict tumor stage, and evaluate treatment efficacy[4-7]. In

addition to the application of texture analysis in the study of tumors or substantial organs, some studies have applied texture analysis to hollow organs such as the intestine[8,9]. Many patients with PFCD show concomitant active proctitis, but only few patients with glandular anal fistula have active proctitis. Based on this theory, we analyzed the texture of the rectum and anal canal wall in the PFCD group and glandular anal fistula group in this study to explore whether the texture feature parameters are valuable in identifying and differentiating these two lesions.

MATERIALS AND METHODS

General data

This study was approved by the institutional review board of the Affiliated Hospital of Nanjing University of Chinese Medicine; informed consent was waived owing to the retrospective nature of the study. This study was conducted in two parts through a search of our medical records. In the first part, we conducted screening for rectal water sac implantation in the existing cohort of PFCD and glandular anal fistula patients; those with an air sac or water sac were included and those without, were excluded. The flow chart of patient inclusion and exclusion is shown in Figure 1. Finally, 48 PFCD patients [41 male and 7 female; mean age: 28.60 ± 10.77 (13–61) years] with rectal water sac implantation were screened. Of these, 22 patients [19 male and 3 female; mean age: 34.95 ± 12.71 (15–62) years] had glandular anal fistula with rectal water sac implantation. This study was approved by the Ethics Review Committee of our hospital. Considering the retrospective nature of the study, the need for informed consent was waived.

MRI examination method

Before MRI examination of the rectum, the patient was required to perform cleansing enema, and a water sac (approximately 150 mL of normal saline, fully expanded) was inserted into the rectal cavity by the clinician. All MRI exams were performed using a Siemens Magnetom Aera 1.5 T scanner, and the body phased array coil was used for scanning. The patient was in the supine position, and the scanning range was from the level of the anterior superior iliac spine to the level of the upper femur. The horizontal scanning line was perpendicular to the anal canal, while the coronal and sagittal scanning lines were parallel to the anal canal. The scanning sequence and specific parameters were the same as in the first part of the study.

Region of interest delineation method

The patient's imaging files including T2-weighted imaging (T2WI) were accessed using the open-source software ITK-SNAP (Version 3.6.0, http://www.itksnap.org/). A radiologist with 3 years diagnostic experience in anal fistula manually drew the region of interest (ROI) on the fat suppression T2WI axial position along the rectal and anal canal wall opened by the water sac (Figure 2). The scope of the sketch covered the entire rectal and anal canal wall. If there was any doubt about the sketch, another senior doctor was consulted to reach consensus. The sketched ROI and original image were imported into the Analysis Kit software (version V3.0.0.R, GE Healthcare), which automatically analyzed and calculated the texture feature parameter table of the drawn ROI.

Statistical analysis

The SPSS 22.0 software was used to perform all statistical analysis on the obtained textural feature parameters and detect the normal distribution of the parameters. For normally distributed data, two-tailed independent sample *t*-test was used. For non-normally distributed data, Mann–Whitney U test was used for comparison. $P < 0.05$ was considered to indicate statistical significance. Bivariate Spearman's correlation analysis was conducted on indicators with statistical differences to calculate the redundancy between the textural feature parameters; those with a redundancy threshold > 0.9 were screened out. The receiver operating characteristic (ROC) curve analysis was used to calculate the diagnostic efficacy of each index selected by area under the curve (AUC) comparison, following which the Youden index, specificity, sensitivity, positive likelihood ratio, and negative likelihood ratio of each index were calculated. Finally, binary logistic regression analysis was carried out to identify indicators with statistical differences to establish the logistic regression model of textural feature parameters and calculate the corresponding statistical indicators.

RESULTS

A total of 385 textural feature parameters of the final drawn ROI were calculated by the Analysis Kit software. Of these, 37 parameters showed statistically significant differences in the PFCD group and glandular anal fistula group. Through bivariate Spearman correlation analysis, the redundancy between the feature parameters was calculated, the indicators with a redundancy threshold > 0.9 were filtered

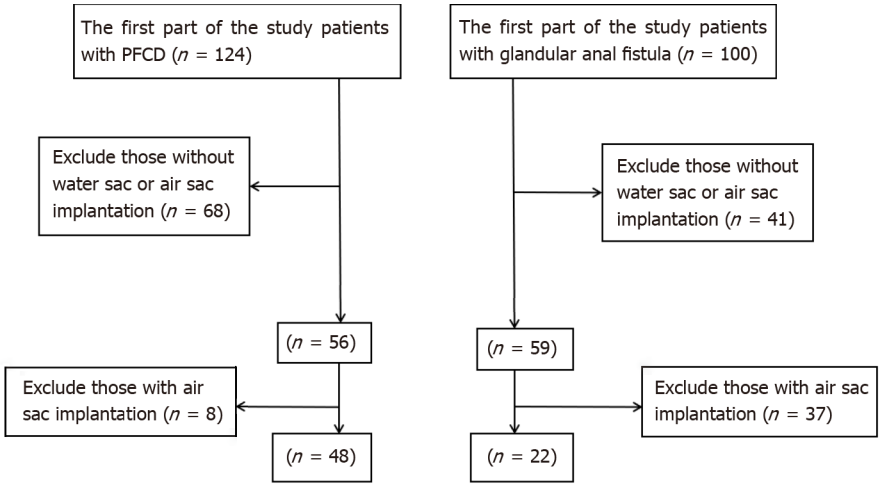

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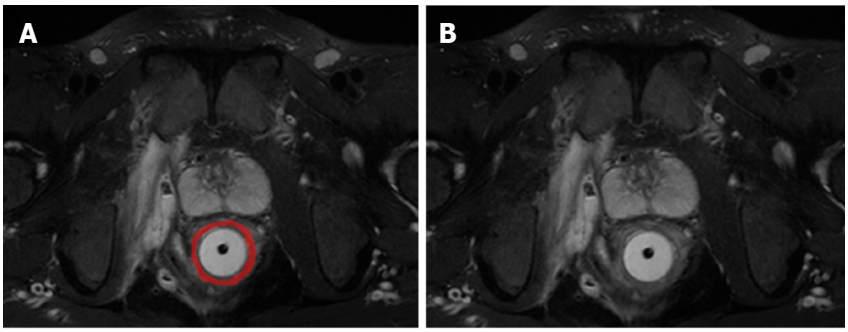
Figure 1 Flow chart of patient inclusion and exclusion. PFCD: Perianal fistulising Crohn's disease.



DOI: 10.4240/wjgs.v15.i5.882 **Copyright** ©The Author(s) 2023.

Figure 2 Region of interest sketch diagram. A: The horizontal axis of fat suppression T2-weighted (FS-T2WI) image. The red part is the outlined region of interest. B: The horizontal axis of FS-T2WI image, on the same layer as figure panel A.

out. Finally, 16 textural feature parameters were obtained, including one histogram parameter (histogram-energy); four grey level co-occurrence matrix (GLCM) parameters (GLCM energy_all direction_offset1_SD, GLCM entropy_all direction_offset4_SD, GLCM entropy_all direction_offset7_SD, and Haralick correlation_all direction_offset7_SD); four texture parameters (Correlation_all direction_offset1_SD, cluster prominence_angle 90_offset4, inertia_all direction_offset7_SD, and cluster shade_angle 45_ offset7); five grey level run-length matrix (RLM) parameters (Grey level nonuniformity_ angle 90_offset1, long run emphasis_all direction_offset4_SD, long run high grey level emphasis_all direction _offset1_SD, long run high grey level emphasis_all direction_ offset4_SD, and long run high grey level emphasis_all direction_offset4_SD); and two form factor parameters (surface area and maximum 3D diameter). ROC analysis was carried out for the above texture feature parameters. The AUC of each parameter and its corresponding Youden index, sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio are shown in Table 1. Through binary logistic regression analysis, a logistic regression model of textural feature parameters was established (Table 2). The AUC of the textural feature parameter model was 0.917, and its sensitivity and specificity were 85.42% and 86.36%, respectively. The AUC, sensitivity, and specificity were higher than any individual texture feature parameters (Figure 3, Table 3).

DISCUSSION

The textural feature parameters calculated by the Analysis Kit software were divided into the following six categories: Histogram parameters, texture parameters, form factor parameters, GLCM parameters, grey level RLM parameters, and gray-scale area matrix parameters. Among the 16 parameter indices obtained by statistical analysis in the PFCD group and the glandular anal fistula group, there were two form factor parameters, one histogram parameter, four GLCM parameters, four texture parameters, and five grey level RLM parameters.

Table 1 Receiver operating characteristic curve analysis results of 16 textural feature parameters

Textural feature parameters	AUC	Asymptotic significance level	95%CI	Z statistics	Youden index	Sensitivity	Specificity	+LR	-LR
Histogram parameter									
Histogram-energy	0.670	0.0226	0.547-0.777	2.280	0.3068	62.50	68.18	1.96	0.55
Gray-scale co-occurrence matrix parameters									
GLCM energy_all direction_offset1_SD	0.683	0.0085	0.561-0.789	2.630	0.3087	85.42	45.45	1.57	0.32
GLCM entropy_all direction_offset4_SD	0.664	0.0185	0.541-0.772	2.354	0.3390	52.08	81.82	2.86	0.59
GLCM entropy_all direction_ offset7_SD	0.648	0.0500	0.524-0.758	1.960	0.2992	70.83	59.09	1.73	0.49
Haralick correlation_all direction_offset7 _SD	0.702	0.0027	0.580-0.805	3.005	0.3598	54.17	81.82	2.98	0.56
Texture parameters									
Correlation_all direction_offset1_SD	0.673	0.0126	0.551-0.781	2.496	0.3598	54.17	81.82	2.98	0.56
Cluster prominence_angle 90_offset4	0.648	0.0300	0.524-0.758	2.171	0.3807	56.25	81.82	3.09	0.53
Inertia_all direction_offset7_SD	0.654	0.0397	0.531-0.764	2.057	0.3864	75.00	63.64	2.06	0.39
Cluster shade_angle 45_ offset7	0.648	0.0230	0.524-0.758	2.274	0.3883	47.92	90.91	5.27	0.57
Grey level run-length matrix (RLM) parameters									
Grey level nonuniformity_ angle 90_offset1	0.671	0.0144	0.549-0.779	2.446	0.3598	54.17	81.82	2.98	0.56
Grey level nonuniformity_all direction_offset4_ SD	0.657	0.0243	0.534-0.767	2.253	0.3125	81.25	50.00	0.38	0.62
Long run high grey level emphasis_all direction _offset1_SD	0.728	0.0003	0.609-0.828	3.618	0.3864	75.00	63.64	2.06	0.39
Long run emphasis_all direction_offset4_SD	0.722	0.0013	0.602-0.822	3.222	0.3883	47.92	90.91	5.27	0.57
Long run high grey level emphasis_all direction_ offset4_SD	0.652	0.0391	0.529-0.762	2.063	0.2803	91.67	36.36	1.44	0.23
Form factor parameters									
Surface area	0.728	0.0003	0.609-0.828	3.640	0.3883	47.92	90.91	5.27	0.57
Maximum 3D diameter	0.739	0.0001	0.620-0.836	4.024	0.4337	47.92	95.45	10.54	0.55

AUC: Area under the receiver operating characteristic curve; +LR: Positive likelihood ratio; -LR: Negative likelihood ratio.

The significance of textural feature parameters

Histogram parameters: The histogram represents the properties of a single pixel and describes the distribution of voxel intensity. The first-order statistics included 20 indicators such as energy, entropy, skewness, kurtosis, maximum intensity, minimum intensity, and mean. Among them, energy is a measure of the uniformity of the intensity level distribution, wherein a higher value represents a more uniform intensity level distribution. Entropy is a measure of the randomness of the distribution of coefficient values at intensity levels. A higher entropy value indicates more intense levels of image distribution. That is, the simpler the image, the lower the entropy value, and the more complex the image, the higher the entropy value.

Texture parameters: The texture represents the appearance of the surface and the distribution of its elements, which helps to predict the surface appearance as being either smooth or rough from the image. Correlation refers to the similarity of the gray level of adjacent pixels, indicating the correlation of pixels with their adjacent pixels in the entire image, ranging from -1 to 1. Inertia reflects the clarity and clarity of the image. The degree of depression of the texture can better distinguish the complexity of the grayscale spatial distribution of the lesion area. Cluster prominence reflects the abrupt situation of the image texture: The greater the contrast between the textures, the greater the value. Cluster shade represents the correlation between texture smoothness and symmetry: The higher the value, the less

Table 2 Analysis results of logistic regression model of textural feature parameters

	β coefficient	SE	χ^2 value	Significance	OR	95%CI	
						Lower limit	Upper limit
Inertia_all direction_offset7_SD	-0.004	0.002	3.699	0.054	0.996	0.993	1.000
Cluster shade_angle 45_ offset7	0.000	0.000	7.194	0.007	1.000	1.000	1.000
Long run high grey level emphasis_all direction _offset1_SD	-0.145	0.069	4.351	0.037	0.865	0.755	0.991
Long run emphasis_all direction_offset4_SD	-98.665	56.394	3.061	0.080	0.000	0.000	142353.563
Surface area	0.000	0.000	3.973	0.046	1.000	1.000	1.001
Maximum 3D diameter	-0.121	0.040	8.963	0.003	0.886	0.819	0.959
Constant	9.412	3.758	6.273	0.012	12234.477	-	-

OR: Odds ratio.

Table 3 Receiver operating characteristic curve analysis results of logistic regression model of textural feature parameters

AUC	Asymptotic significance level	95%CI	Z statistics	Youden index	Sensitivity	Specificity	+LR	-LR
0.917	< 0.0001	0.826-0.969	12.645	0.7178	85.42	86.36	6.26	0.17

AUC: Area under the receiver operating characteristic curve; +LR: Positive likelihood ratio; -LR: Negative likelihood ratio.

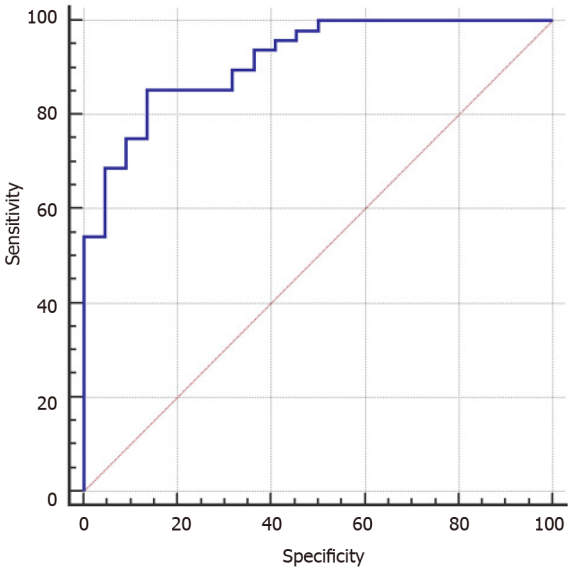


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Figure 3 Receiver operating characteristic curve of the logistic regression model of textural feature parameters.

smooth and more asymmetric the texture.

Gray level co-occurrence matrix parameters: GLCM represents the joint probability of certain pixels with a certain gray value. By changing the displacement vector between each pair of pixels, the number of joint occurrences of pixels of one gray value and those of another gray value are calculated. The advantage is that it can be spatially correlated in different directions according to the spatial relationship of distance and angle, to fully display the joint information of grayscale and position. Among them, the energy represents the square sum of the elements in GLCM, the range is 0–1, the energy of the unchanged image is 1; and Haralick correlation is to measure the similarity of the gray level of the image in the row or column direction, indicating the local gray correlation. The larger the value, the greater the correlation; the sum entropy can reflect the heterogeneity of the lesion. The greater the sum entropy, the greater the qualitative nature of the disease.

Grey level run-length matrix parameters: RLM is defined as the number and running length of gray scale pixels running in a given direction. The RLM parameters reflect the roughness or smoothness of the image. The larger the long-stroke advantage value, the smoother the image. On the contrary, the larger the short-stroke advantage value, the rougher the image.

Form factor parameters: These describe the three-dimensional size and shape of the ROI[10-12].

The value of textural feature parameters in distinguishing PFCD from glandular anal fistula

Texture analysis is based on image images by quantifying the roughness, regularity, and uniformity of the spatial distribution of pixel gray values in normal tissues and pathological tissues to evaluate the heterogeneity of image signals (including both the heterogeneity that the human eye can and cannot recognize)[3,13]. For MRI images, the gray-scale contrast, uniformity, and texture depth and thickness of the images are important features to distinguish images of lesions from non-lesions[14]. Existing studies have used MRI texture analysis for lesion detection, classification, treatment response evaluation, and prediction of various cancers such as breast cancer, brain tumors, and rectal cancer[15-18]. The statistically different texture feature parameters obtained in this study reflect the uniformity of the distribution of PFCD and glandular anal fistula in the grayscale value of the image, correlation of local gray-scale, roughness of the image, and differences in spatial heterogeneity.

Studies have found that most patients with PFCD are associated with active proctitis. Glandular anal fistula is mostly caused by infection or obstruction of the perianal glands, so it is rarely associated with active proctitis[19]. We conducted a study on the indirect signs of rectal involvement and proctitis in patients with PFCD through texture analysis of the rectal and anal canal wall in patients in the PFCD and glandular anal fistula groups. This study obtained 385 textural feature parameters from the Analysis Kit software, many of which were similar, and some features even had a negative effect on correct classification. The greater the number of features, the higher the complexity and the lower the classification speed, resulting in a reduction in classification accuracy and thus, poor universality[14]. The redundancy of each textural feature parameter was calculated by using the Spearman's correlation analysis and finally 16 textural feature parameters were obtained. The texture feature parameter regression model was obtained by binary logistic regression. The AUC was 0.917, and the calculated sensitivity and specificity was 85.42% and 86.36%, respectively, which was higher than the AUC, sensitivity and specificity of any individual texture feature parameter. We believed that the texture feature parameters had certain discrimination value for PFCD and glandular anal fistula. Although texture analysis is rarely applied to cavity organs such as the rectum or anal canal wall, it is also applied to the analysis of the intestinal wall of Crohn's disease. Makanyanga *et al*[20] applied MRI texture analysis to evaluate the activity of the small intestine in CD, and found that texture feature parameters were correlated with lesion activity. Bhatnagar *et al*[21] found that depending on the presence or absence of histological markers of hypoxia and angiogenesis, the textural feature parameters of the T1-weighted imaging-enhanced image of the small intestine in CD were different. Both local and international literature revealed that there are no studies on the application of image texture analysis to analyze the rectal and anal canal wall of PFCD and glandular anal fistula. Our results likely show that the texture feature parameters are of certain significance for the differential diagnosis of PFCD and glandular anal fistula.

Limitations and perspective

First, owing to the thin wall of the rectum and anal canal, it is difficult to delineate the ROI. In this study, filling the rectum and anal canal with water sacs was used to increase the contrast with the surrounding tissue to reduce the error. Second, because of the small sample size in this study, there was no separate verification set to validate the textural feature parameter model of this study. Further studies with larger sample size are needed to increase the stability of the textural feature parameter and verify the model. Meanwhile, the PFCD group included in this study contains a mix of patients with and without active proctitis. In the future, texture analysis should be used to further investigate whether there are differences between the two subgroups. Third, a primary issue with regard to the texture field is the decipherer of the texture features in a context, even though they were somehow validated[22].

CONCLUSION

In conclusion, the textural feature parameters obtained from the texture analysis of the rectal and anal canal wall in the PFCD group and glandular anal fistula group has some identification value for these two lesions, and can be used as a reference index for imaging specialists to identify and distinguish these two lesions.

ARTICLE HIGHLIGHTS

Research background

Perianal fistulising Crohn's disease (PFCD) and glandular anal fistula have many similarities on conventional magnetic resonance imaging (MRI); therefore, it is difficult to differentiate these conditions in the early stages with conventional MRI. Texture analysis based on conventional MRI images can quantitatively analyze image pixel information and reflect the internal heterogeneity and pathological characteristics of the lesion.

Research motivation

This study aimed to analyze the texture of the rectum and anal canal wall in the PFCD group and glandular anal fistula group to explore whether the texture feature parameters are valuable in identifying and differentiating these two lesions, which provides a non-invasive method for preoperatively differentiating these two entities.

Research objectives

Therefore, the purpose of this study is to differentiate PFCD from glandular anal fistula using MRI texture analysis.

Research methods

Patients with rectal water sac implantation were screened from the first part of this study (48 patients with PFCD and 22 patients with glandular anal fistula). Open-source software ITK-SNAP (Version 3.6.0, http://www.itksnap.org/) was used to delineate the region of interest (ROI) of the entire rectum and anal canal wall on every axial section, and then the ROIs were input in the Analysis Kit software (version V3.0.0.R, GE Healthcare) to calculate the textural feature parameters. Textural feature parameter differences were compared between the two groups and selected for further analysis.

Research results

In all, 385 textural parameters were obtained, including 37 parameters with statistically significant differences between the PFCD and glandular anal fistula groups. Then, 16 texture feature parameters remained after bivariate Spearman correlation analysis, including one histogram parameter; four grey level co-occurrence matrix (GLCM) parameters; four texture parameters; five grey level run-length matrix (RLM) parameters; and two form factor parameters. The AUC, sensitivity, and specificity of the model of textural feature parameters were 0.917, 85.42%, and 86.36%, respectively.

Research conclusions

The model of textural feature parameters showed good diagnostic performance for PFCD. The texture feature parameters of the rectum and anal canal in fat suppression T2-weighted imaging are helpful to distinguish PFCD from glandular anal fistula.

Research perspectives

This study provides a non-invasive method (MRI texture analysis) to preoperatively differentiate PFCD from glandular anal fistula, which has a profound clinical significance in guiding treatment strategy and predicting prognosis for patients with PFCD and anal fistula.

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FOOTNOTES

Author contributions: Zhu X designed the research study; Ye DD, Li J, and Liu SW performed the research; Zhu X and Wang JH analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript.

Institutional review board statement: This study was approved by the institutional review board of the Affiliated Hospital of Nanjing University of Chinese Medicine; informed consent was waived owing to the retrospective nature of the study.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: All datasets generated for this study are included in the manuscript and/or the

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ORIGINAL ARTICLE

Retrospective Study

Elderly patients over 80 years undergoing colorectal cancer resection: Development and validation of a predictive nomogram for survival

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Abstract

BACKGROUND

Surgery remains the primary treatment for localized colorectal cancer (CRC). Improving surgical decision-making for elderly CRC patients necessitates an accurate predictive tool.

AIM

To build a nomogram to predict the overall survival of elderly patients over 80 years undergoing CRC resection.

METHODS

Two hundred and ninety-five elderly CRC patients over 80 years undergoing surgery at Singapore General Hospital between 2018 and 2021 were identified from the American College of Surgeons – National Surgical Quality Improvement Program (ACS-NSQIP) database. Prognostic variables were selected using univariate Cox regression, and clinical feature selection was performed by the least absolute shrinkage and selection operator regression. A nomogram for 1- and 3-year overall survival was constructed based on 60% of the study cohort and tested on the remaining 40%. The performance of the nomogram was evaluated using the concordance index (C-index), area under the receiver operating characteristic curve (AUC), and calibration plots. Risk groups were stratified using the total risk

points derived from the nomogram and the optimal cut-off point. Survival curves were compared between the high- and low-risk groups.

RESULTS

Eight predictors: Age, Charlson comorbidity index, body mass index, serum albumin level, distant metastasis, emergency surgery, postoperative pneumonia, and postoperative myocardial infarction, were included in the nomogram. The AUC values for the 1-year survival were 0.843 and 0.826 for the training and validation cohorts, respectively. The AUC values for the 3-year survival were 0.788 and 0.750 for the training and validation cohorts, respectively. C-index values of the training cohort (0.845) and validation cohort (0.793) suggested the excellent discriminative ability of the nomogram. Calibration curves demonstrated a good consistency between the predictions and actual observations of overall survival in both training and validation cohorts. A significant difference in overall survival was seen between elderly patients stratified into low- and high-risk groups ($P < 0.001$).

CONCLUSION

We constructed and validated a nomogram predicting 1- and 3-year survival probability in elderly patients over 80 years undergoing CRC resection, thereby facilitating holistic and informed decision-making among these patients.

Key Words: Colorectal cancer; Elderly; Nomogram; Overall survival; Prognostic; Risk stratification

Core Tip: This is the first predictive nomogram evaluating the survival outcomes among elderly colorectal cancer patients over 80 years. This nomogram has incorporated age, Charlson comorbidity index, body mass index, serum albumin level, the presence of metastatic disease, emergency surgery, as well as postoperative pneumonia and myocardial infarction. Our study is the first to link these variables together in predicting overall survival in elderly colorectal cancer patients over 80 years. This novel nomogram that accurately predicts survival probabilities may facilitate preoperative treatment decisions in the advancing age group.

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DOI: https://dx.doi.org/10.4240/wjgs.v15.i5.892

INTRODUCTION

The world's population is rapidly aging, with currently over 84 million people aged 75 and above[1]. Population aging will impact cancer control, as around 50% of all cancers affect the older population[2]. Colorectal cancer (CRC) is the second most prevalent malignancy, with an incidence of 1.36 million cases yearly[3]. CRC is the third leading cause of cancer-related mortality, with 50% of new CRC diagnoses being made in patients aged over 70, and 20% in those over 80 years[4]. In Singapore, the incidence of CRC has risen over the last four decades and is now the most common malignancy in the country[5].

Surgery remains the primary treatment for localized CRC. With increasing life expectancy and advances in surgical techniques, there is a growing number of elderly patients over 80 years undergoing CRC resection nowadays[6]. Besides the technical considerations of surgical resectability of the primary CRC, elderly patients continue to pose challenges for the surgeon, as they often have significant comorbidities, such as cardiovascular or pulmonary diseases, which would increase operative risks and potentially lead to postoperative morbidity and mortality[6-8]. Other factors, such as emergency presentation[9] and poor nutritional status, may also result in adverse perioperative outcomes and overall survival (OS).

Therefore, for elderly CRC patients over 80 years, a more individualized approach is essential in the decision-making process, weighing the risks and benefits of surgery on a case-by-case basis[10,11]. Although some studies have suggested that advanced age is a risk factor following specific surgical procedures[12-14], certain results are procedure-specific and limited to the experiences of single centers.

Moreover, no study has fully established the impact of advanced age and clinical risk factors on the probability of survival at one year or longer among elderly patients undergoing CRC resection[15-17].

In this study, we developed and validated a predictive nomogram to quantify the probability of OS at one and three years among elderly CRC patients over 80 years, to enable patients, caregivers, and surgeons to make better-informed decisions.

MATERIALS AND METHODS

Patient selection

This study was approved by our institutional review board (IRB No. 2022/2438). Data from the American College of Surgeons–National Surgical Quality Improvement Program (ACS-NSQIP) Participant User File between 2018 and 2021 were analyzed. Colectomy and proctectomy procedures were identified by the current procedural terminology codes. A total of 295 elderly patients aged over 80 years with stage I-IV CRC who underwent surgery at Singapore General Hospital during the study period were included. Of these, 60% of cases were randomly selected into the training cohort to construct the nomogram. The remaining 40% of cases were used to validate the nomogram.

Clinical feature selection

Clinical variables from NSQIP database were: age, American Society of Anesthesiologists classification (ASA), body mass index (BMI), chronic disease history, preoperative medical conditions, serum albumin level, surgical information, tumor-node-metastasis (TNM) staging, postoperative complications, and 30-d mortality. Diagnosis information was collected from our electronic health record system (Sunrise Clinical Manager version 5.8, Eclipsys Corp., Atlanta, GA, United States). Charlson comorbidity index (CCI) was calculated based on a patient's diagnosis using the 10th revision of the International Statistical Classification of Diseases and Related Health Problems codes. The primary endpoint was OS, which was defined as the time from surgery completion to death of all causes or to the date of the last outpatient clinic follow-up in 2022. Patients who were alive at the time of the last follow-up were censored. Clinical features for constructing a nomogram were screened in three steps. Clinical perspective was the most critical consideration for variable screening. Based on our clinical experiences, we first selected those confirmed factors with a strong association with OS. Secondly, univariate Cox regression was used to identify variables statistically associated with OS. The list of candidate clinical features is presented in Supplementary Table 1. Variables with a P value < 0.20 of univariate analysis were selected. Lastly, the least absolute shrinkage and selection operator (LASSO) regression algorithm was employed to screen all selected features. The 10-fold cross-validation was used to confirm the significant clinical variables and optimal tuning parameter (λ) of LASSO Cox regression.

Nomogram construction and evaluation

The nomogram was constructed using clinically significant risk factors identified in the univariate and multivariate Cox proportional hazards analyses and important features recommended by LASSO. The 1- and 3-year OS probabilities were predicted by the nomogram. The performance of the nomogram was evaluated using the concordance index (C-index) and area under the receiver operating characteristic (ROC) curve (AUC)[18]. Similar to AUC, the C-index quantified the discrimination performance of the nomogram. C-index and AUC values ranged from 0 to 1, with 0.5 representing random chance and 1.0 indicating a perfect fit. Values greater than 0.7 suggested a reasonable and accurate model prediction. Calibration curves based on the bootstrap re-sampling method were used to assess the goodness-of-fit of the nomogram[19]. Calibration was determined by comparing the 1- and 3-year OS probabilities predicted by the nomogram to the observed OS probabilities.

Nomogram to predict OS and stratify risk groups

The total risk points for each elderly CRC patient were computed using the nomogram. The optimal cut-off risk point was determined by the "*survivalROC*" model using the Kaplan-Meier estimator[20]. A time-dependent survival ROC curve was plotted to evaluate the prediction of OS based on the total risk points. All elderly patients were stratified into low- and high-risk groups according to the optimal risk threshold. Survival curves of low- and high-risk groups were generated with a hazard ratio (HR) and the P value of the log-rank test.

Statistical analysis

All statistical calculations were performed using R programming language (version 4.2.1). Continuous variables were shown as median [interquartile range (IQR)]. Categorical variables were presented as frequency distributions (percentage). The Wilcoxon-Mann-Whitney and χ^2 or Fisher's exact tests were used to analyze continuous and categorical variables, respectively. P values of < 0.05 indicated statistical significance.

RESULTS

Clinical and surgical characteristics

The baseline demographic, clinicopathologic, and surgical characteristics of 295 elderly CRC patients are shown in Table 1. All patients were randomly divided into a training cohort (n = 177) and a validation cohort (n = 118) in a ratio of 6:4. The median duration of follow-up was 22.68 (IQR: 13.54-37.00) months for the entire cohort. In total, there were 135 male patients (45.8%) and 160 female patients (54.2%) with a median age of 83 (IQR: 81-86) years. Two hundred and sixty-nine patients (91.2%) were between 80 and 89 years old, whereas 26 (8.8%) were nonagenarians. The training and validation cohorts possessed nearly identical characteristics (P > 0.05), with the proportion of patients with significant comorbidities, including congestive heart failure and diabetes mellitus, similar between both groups. Within the entire study cohort, 206 patients (69.8%) underwent surgery on an elective basis. Minimally invasive approach (MIS) was used for 160 patients (54.2%), while the remaining 135 patients (45.8%) underwent open surgery. Right hemicolectomy was performed in 110 patients (37.3%), and anterior resection was performed in 138 patients (46.8%). No stoma formation was required in 205 patients (69.5%). The majority of patients in the study cohort had non-metastatic disease (94.2%, n = 278), with the largest proportion having stage III disease (43.7%, n = 129). None of the patients received adjuvant chemotherapy. In terms of perioperative outcome, 19 patients (6.4%) developed postoperative pneumonia, and 6 patients (2.0%) had an anastomotic leak. The perioperative 30-d mortality was 2.0%.

Nomogram feature selection

All candidate clinical features with their univariate Cox regression P values are listed in Supplementary Table 1. According to univariate analyses, 19 variables with P values < 0.20 were statistically associated with OS. CCI, serum albumin, TNM staging, postoperative pneumonia, and postoperative myocardial infarction were most significantly associated with OS (P < 0.001). All these 19 characteristics were then evaluated as potential predictors. A LASSO regression was employed to assess prognostic factors, and eight variables (age, CCI, BMI, priority of operation, serum albumin, TNM staging, postoperative pneumonia, and postoperative myocardial infarction) with nonzero coefficients were retained in the LASSO regression (Figure 1). The optimal tuning parameter log (λ) was 0.056 when the mean square error reached its smallest value. Table 2 shows the eight variables ultimately selected for the multivariate Cox model. Age (P = 0.002), BMI (< 18.5 kg/m^2, P = 0.038), serum albumin (< 2.5 g/dL, P = 0.002), CCI (P < 0.001), postoperative pneumonia (P = 0.004), and postoperative myocardial infarction (P = 0.012) were determined to be independent predictors of OS. Although every increase of one year in age was associated with a 10% increase in the risk of mortality [HR = 1.10, 95% confidence interval (CI): 1.04-1.17], there was no significant difference in OS between nonagenarians (90-99 years old) and those aged 80-89 years old (P = 0.470). Two additional variables, TNM staging (stage IV, P = 0.068) and priority of operation (emergency surgery, P = 0.278), were relevant clinical factors significantly associated with OS on univariate analyses and hence included in the nomogram construction.

Nomogram construction and validation

A nomogram applicable to all elderly CRC patients was created using eight selected predictors' point scales, with the sum of the eight variables' points defining the total number of points. Estimated 1- and 3-year OS probabilities could be obtained by drawing a vertical line from the "Total Points" axis down to the two-outcome probability axis (Figure 2). The AUC of the nomogram for predicting 1-year OS was 0.843 (95%CI: 0.827-0.935) in the training cohort and 0.826 (95%CI: 0.816-0.912) in the validation cohort, while AUC for predicting 3-year OS was 0.788 (95%CI: 0.762-0.889) in the training cohort and 0.750 (95%CI: 0.734-0.883) in the validation cohort (Figure 3). The C-index value was 0.845 (95%CI: 0.789-0.889) in the training cohort and 0.793 (95%CI: 0.754-0.887) in the validation cohort. Both AUC and C-index values indicated the constructed nomogram provided favorable discrimination. The calibration curves of the nomogram were evaluated by plotting the predicted 1- and 3-year OS against the observed 1- and 3-year OS. A 45-degree line would be obtained if the predictions were accurately calibrated. The 1- and 3-year calibration curves in both training and validation cohorts showed a good concordance between the predicted and observed OS probabilities (Figure 4).

Nomogram prediction of OS in risk-stratified elderly CRC patients

The total risk points of each elderly CRC patient were calculated based on the nomogram. The optimal risk cut-off point of 81 was determined using the Kaplan-Meier estimation[20]. On the nomogram, the risk threshold of 81 points approximately corresponded to the 1-year OS probability of 87% and the 3-year OS probability of 56%. A time-dependent 3-year survival ROC curve was generated for all patients using the total risk points computed by the nomogram (Figure 5A). The AUC of the total risk points (0.769, 95%CI: 0.724-0.883) indicated that the optimal risk threshold was adequate for risk stratification in elderly CRC patients. All patients were categorized into low-risk (total risk points < 81) or high-risk (total risk points ≥ 81) groups. The Kaplan-Meier curves accurately distinguished the low- and high-risk groups (Figure 5B). The 3-year OS probabilities of elderly CRC patients in the high-risk groups were

Table 1 Patient demographics, clinicopathologic, and surgical characteristics

Variable	Total, *n* (%)	Training cohort, *n* (%)	Validation cohort, *n* (%)	*P* value
Total case	295	177	118	
Follow-up period (mo)				
Median (IQR)	22.68 (13.54, 37.00)	23.43 (14.04, 37.00)	21.00 (12.93, 37.75)	0.798
Age (yr)				
Median (IQR)	83 (81, 86)	82 (81, 86)	83 (81, 86)	0.738
80-89	269 (91.19)	161 (90.96)	108 (91.53)	0.867
90-99	26 (8.81)	16 (9.04)	10 (8.47)	
Sex				
Male	135 (45.76)	81 (45.76)	54 (45.76)	0.998
Female	160 (54.24)	96 (54.24)	64 (54.24)	
Race				
Chinese	274 (92.88)	165 (93.22)	109 (92.37)	0.491
Malay	6 (2.03)	3 (1.69)	3 (2.54)	
Indian	9 (3.06)	4 (2.26)	5 (4.24)	
Others	6 (2.03)	5 (2.83)	1 (0.85)	
ASA classification				
1	2 (0.68)	1 (0.56)	1 (0.85)	0.599
2	90 (30.51)	52 (29.38)	38 (32.20)	
3	187 (63.39)	112 (63.28)	75 (63.56)	
4	16 (5.42)	12 (6.78)	4 (3.39)	
BMI (kg/m^2)				
Median (IQR)	22.43 (19.82, 25.68)	22.51 (20.08, 25.82)	22.23 (19.31, 25.19)	0.480
≥ 18.5	252 (85.42)	154 (87.01)	98 (83.05)	0.346
< 18.5	43 (14.58)	23 (12.99)	20 (16.95)	
Smoking				
No	281 (95.25)	170 (96.05)	111 (94.07)	0.434
Yes	14 (4.75)	7 (3.95)	7 (5.93)	
Congestive heart failure within 30 d				
No	289 (97.97)	174 (98.31)	115 (97.46)	0.686
Yes	6 (2.03)	3 (1.69)	3 (2.54)	
COPD				
No	291 (98.64)	174 (98.31)	117 (99.15)	0.652
Yes	4 (1.36)	3 (1.69)	1 (0.85)	
Diabetes mellitus				
No	217 (73.56)	133 (75.14)	84 (71.19)	0.451
Yes	78 (26.44)	44 (24.86)	34 (28.81)	
Preoperative dialysis dependent				
No	291 (98.64)	174 (98.31)	117 (99.15)	0.652
Yes	4 (1.36)	3 (1.69)	1 (0.85)	
CCI				
0	2 (0.68)	1 (0.56)	1 (0.85)	0.118

1-2	98 (33.22)	50 (28.25)	48 (40.68)	
3-4	62 (21.02)	40 (22.60)	22 (18.64)	
≥ 5	133 (45.08)	86 (48.59)	47 (39.83)	
Serum albumin (g/dL)				
Median (IQR)	3.6 (3.2, 3.9)	3.6 (3.1, 3.9)	3.6 (3.2, 3.9)	0.316
≥ 3.0	261 (88.48)	160 (90.40)	101 (85.59)	0.209
2.5-3.0	27 (9.15)	12 (6.78)	15 (12.71)	
< 2.5	7 (2.37)	5 (2.82)	2 (1.70)	
Priority of operation				
Elective	206 (69.83)	121 (68.36)	85 (72.03)	0.501
Emergency	89 (30.17)	56 (31.64)	33 (27.97)	
Method of operation				
Open	135 (45.76)	80 (45.20)	55 (46.61)	0.812
Minimally invasive surgery	160 (54.24)	97 (54.80)	63 (53.39)	
Type of operation				
Right hemicolectomy	110 (37.29)	65 (36.72)	45 (38.14)	0.942
Left hemicolectomy	8 (2.71)	5 (2.83)	3 (2.54)	
High anterior resection	86 (29.15)	51 (28.81)	35 (29.66)	
Low anterior resection	52 (17.63)	30 (16.95)	22 (18.64)	
Subtotal/total colectomy	13 (4.40)	10 (5.65)	3 (2.54)	
Abdominoperineal resection	12 (4.07)	7 (3.95)	5 (4.24)	
Hartmann's procedure	14 (4.75)	9 (5.09)	5 (4.24)	
Stoma				
No	205 (69.49)	123 (69.49)	82 (69.49)	0.529
Loop ileostomy	23 (7.80)	10 (5.65)	13 (11.02)	
End ileostomy	6 (2.03)	5 (2.82)	1 (0.85)	
Ileo-colostomy	8 (2.71)	5 (2.82)	3 (2.54)	
Loop colostomy	19 (6.44)	12 (6.78)	7 (5.93)	
End colostomy	34 (11.53)	22 (12.44)	12 (10.17)	
TNM staging				
I	61 (20.68)	40 (22.60)	21 (17.80)	0.274
II	88 (29.83)	50 (28.25)	38 (32.20)	
III	129 (43.73)	80 (45.20)	49 (41.53)	
IV	17 (5.76)	7 (3.95)	10 (8.47)	
Postoperative anastomotic leak				
No	289 (97.97)	173 (97.74)	116 (98.31)	0.999
Yes	6 (2.03)	4 (2.26)	2 (1.69)	
Postoperative pneumonia				
No	276 (93.56)	165 (93.22)	111 (94.07)	0.771
Yes	19 (6.44)	12 (6.78)	7 (5.93)	
Postoperative myocardial infarction				
No	288 (97.63)	172 (97.18)	116 (98.31)	0.706
Yes	7 (2.37)	5 (2.82)	2 (1.69)	

Postoperative 30-d readmission				
No	255 (86.44)	154 (87.01)	101 (85.59)	0.729
Yes	40 (13.56)	23 (12.99)	17 (14.41)	
Postoperative 30-d mortality				
No	289 (97.97)	175 (98.87)	114 (96.61)	0.222
Yes	6 (2.03)	2 (1.13)	4 (3.39)	
Postoperative 1-yr mortality				
No	206 (69.83)	124 (70.06)	82 (69.49)	0.918
Yes	89 (30.17)	53 (29.94)	36 (30.51)	

Continuous variables were presented as median (interquartile range). Categorical variables were presented as *n* (%). *P* values of categorical variables were calculated by χ^2 or Fisher's exact test; *P* values of continuous variables were calculated by the Wilcoxon-Mann-Whitney test. IQR: Interquartile range; ASA: American Society of Anaesthesiologists classification; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CCI: Charlson comorbidity index; TNM: Tumor-node-metastasis.

Table 2 Univariate and multivariate Cox regression on predictors for the overall survival of elderly colorectal cancer patients undergoing surgery

	Univariate		Multivariate	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age[1]	1.08 (1.02-1.14)	**0.005**	1.10 (1.04-1.17)	**< 0.001**
Age				
80-89	Reference			
90-99	1.31 (0.63-2.73)	0.470	-	-
BMI (kg/m^2)				
≥ 18.5	Reference		Reference	
< 18.5	1.93 (1.12-3.33)	**0.018**	1.93 (1.05-3.53)	**0.034**
Serum albumin (g/dL)				
≥ 3.0	Reference		Reference	
2.5-3.0	1.75 (0.90-3.44)	0.101	1.18 (0.55-2.54)	0.672
< 2.5	7.15 (2.82-18.2)	**< 0.001**	5.04 (1.82-13.9)	**0.002**
TNM staging				
I, II, and III	Reference		Reference	
IV	3.95 (2.07-7.55)	**< 0.001**	2.06 (0.95-4.49)	0.068
CCI[1]	1.34 (1.21-1.48)	**< 0.001**	1.41 (1.25-1.59)	**< 0.001**
Priority of operation				
Elective	Reference		Reference	
Emergency	1.81 (1.13-2.88)	**0.013**	1.35 (0.78-2.33)	0.278
Postoperative pneumonia				
No	Reference		Reference	
Yes	3.46 (1.77-6.78)	**< 0.001**	2.99 (1.43-6.23)	**0.004**
Postoperative myocardial infarction				
No	Reference		Reference	
Yes	6.01 (2.17-16.6)	**< 0.001**	4.09 (1.37-12.2)	**0.012**

[1]Continuous variables. Bold values indicate statistical significance at the $P < 0.05$ level. HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index; TNM: Tumor-node-metastasis; CCI: Charlson comorbidity index.

significantly lower (HR = 6.58, 95%CI: 4.06-10.7, $P < 0.001$).

DISCUSSION

Increasing age is a well-known risk factor for the development of CRC, with a majority of patients diagnosed after 70 years old[21]. Moreover, elderly patients tend to have a higher prevalence of frailty, comorbidities, and mortality risk from other causes[22]. Nevertheless, there is still significant heterogeneity in terms of physiological capacity and performance status among the elderly population. Considering the increased life expectancy of an aging population as well as new advances in surgical technology and perioperative care, it is, therefore, necessary to stratify the risk associated with elderly patients undergoing surgery. As the proportion of elderly CRC patients continues to rise, there is a greater need to comprehend the risks associated with surgical resection.

In the present study, we developed and validated a nomogram based on clinical risk factors predicting the probabilities of 1- and 3-year OS in elderly CRC patients over 80 years undergoing surgical resection using the ACS-NSQIP data. Although there are existing nomograms[23,24] predicting cancer-specific and OS among CRC patients, this is the first predictive nomogram evaluating the survival outcomes among elderly CRC patients over the age of 80. Our ACS-NSQIP dataset was comprehensive and well-organized, allowing us to obtain critical clinical data regarding the association between risk factors and OS after colorectal resection. We identified eight variables as independent prognostic factors based on clinical observations and LASSO regression, which efficiently processed demographic and clinical feature selection as a statistical strategy for high-dimensional data.

This nomogram incorporated age, CCI, BMI, serum albumin level, TNM staging, priority of surgery, postoperative pneumonia, and postoperative myocardial infarction. Some characteristics included in the nomogram construction have previously been reported to have a significant correlation with mortality and OS, but our study is the first to link them together in predicting OS in elderly CRC patients over 80 years. We found that every additional year of age beyond 80 was associated with a 10% increase in mortality risk. In terms of the comorbidity profile, an increase of one point in the CCI score was associated with a 41% increase in mortality risk. Of note, CCI has been reported as an independent prognostic factor in older CRC patients[25]. Elderly CRC patients with high CCI scores tended to have a lower OS[25]. In addition, surgical outcomes of the geriatric population have been stratified using frailty assessments involving age and CCI[26,27]. A systematic review revealed that frailty was associated with an increased incidence of postoperative complications, mortality, readmissions, reoperations, and prolonged hospital length of stay, but age by itself was not associated with any adverse outcomes[28]. Suboptimal nutritional status reflected by BMI < 18.5 kg/m^2 and serum albumin level < 2.5 g/dL were also independent risk factors for poorer OS. It has been reported that lower BMI and serum albumin levels were nutritional risk factors associated with shorter survival in cancer patients[29,30]. Lymph node metastasis is another risk factor for OS. It is well-known that lymph node metastasis is associated with worse outcomes in CRC patients with poor prognoses[31]. Emergency surgery was identified to be significantly associated with poorer OS in our elderly CRC cohort. Among the 17 elderly patients with stage IV disease who underwent CRC resection, 12 had surgery performed in an emergency setting. Some studies have highlighted the need for improved risk stratification based on emergency because surgeries performed urgently are more likely to have distinct morbidity and mortality rates than surgeries performed electively[32,33].

In this study, MIS was found to have a positive impact on OS in elderly CRC patients in the univariate Cox regression ($P = 0.01$). The LASSO regression, however, eliminated the method of operation, indicating that it was not a predictor of OS in CRC patients over 80 years undergoing surgery. The majority (90.6%) of the 160 elderly patients in the MIS group underwent laparoscopic surgery, whereas 15 patients (9.4%) underwent robotic surgery. Laparoscopic surgery for colon cancer has been shown to be associated with improved postoperative outcomes with similar long-term oncological outcomes in recent years[34,35]. It has been recommended as the preferred approach for elective surgery[36]. While the long-term oncological outcomes of laparoscopic rectal cancer surgery have yet to be conclusive, it does confer improved postoperative outcomes and has been included in society guidelines to be considered in centers with technical expertise and experience. Although laparoscopic surgery is associated with superior postoperative outcomes such as reduced wound pain and ileus, without compromising long-term oncological outcomes[37-39], its role among elderly patients remains unclear given the longer operating time and the effect of pneumoperitoneum on the cardiorespiratory system.

Elderly patients, after surgery, are at increased risk of postoperative complications such as surgical site infections, pneumonia, cardiac complications, and anastomotic leak. In our study cohort, primary

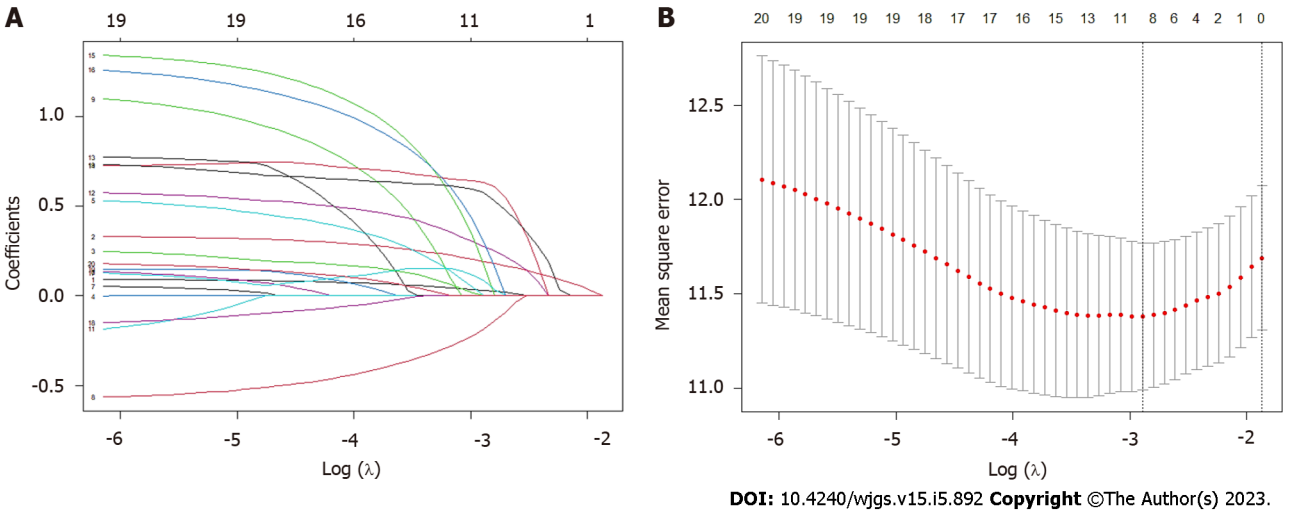

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Figure 1 Least absolute shrinkage and selection operator Cox regression for feature selection. A: The correlation between the clinical characteristics' coefficient and logarithm of *λ* in least absolute shrinkage and selection operator (LASSO) regression. Each coefficient was shown against the log (*λ*) sequence; B: The relationship between the log (*λ*) and mean square error in LASSO regression using the 10-fold cross-validation. The vertical dotted lines were placed at the optimal log (*λ*) values where clinical features were selected.

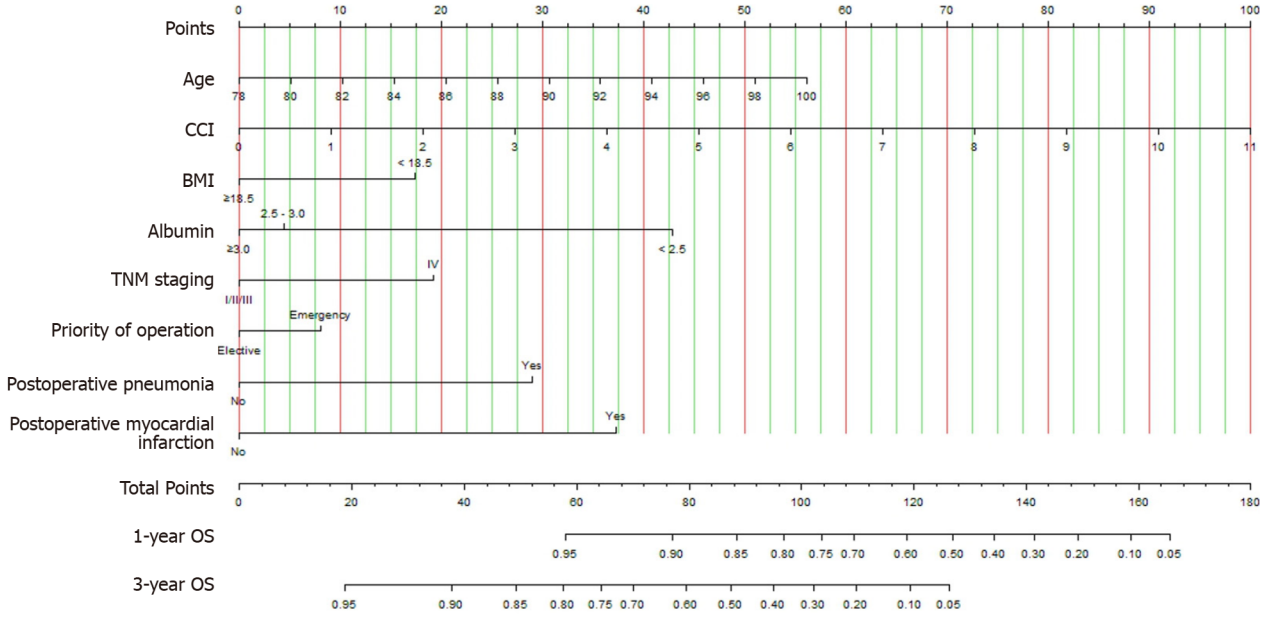

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Figure 2 Nomogram for predicting 1- and 3-yr overall survival following colorectal surgery in elderly cancer patients over 80 yr. Draw a vertical line from each variable value to the top "Points" axis, then sum all variables' points. The total points on the bottom scale corresponding to the 1- and 3-yr survival would be displayed. BMI: Body mass index; TNM: Tumor-node-metastasis; CCI: Charlson comorbidity index; OS: Overall survival.

anastomosis was performed in 69.5% of the patients. There were 6 cases (2.03%) had the postoperative anastomotic leak. These findings are consistent with other recent studies. Hashimoto *et al*[40] reported an anastomosis rate of 86.0% with a leak rate of 2.3%, while Zeng *et al*[41] reported an anastomosis rate of 62.9% with a leak rate of 2.1%. Furthermore, it has been estimated that a patient older than 80 years is more than five times as likely to suffer from postoperative pulmonary complications compared to a patient younger than 50 years[42]. Unsurprisingly, postoperative pneumonia and myocardial infarction were identified as prognostic factors of OS in elderly CRC patients. Therefore, the identification of elderly patients at risk of postoperative cardiopulmonary complications can facilitate the early involvement of the multidisciplinary team in pre-habilitation and postoperative care, including adequate pain control, chest physiotherapy, and early mobilization. In line with our predictive nomogram, the successful mitigation of postoperative pneumonia and myocardial infarction risks can result in higher probabilities of improved OS at one and three years among elderly patients undergoing CRC resection.

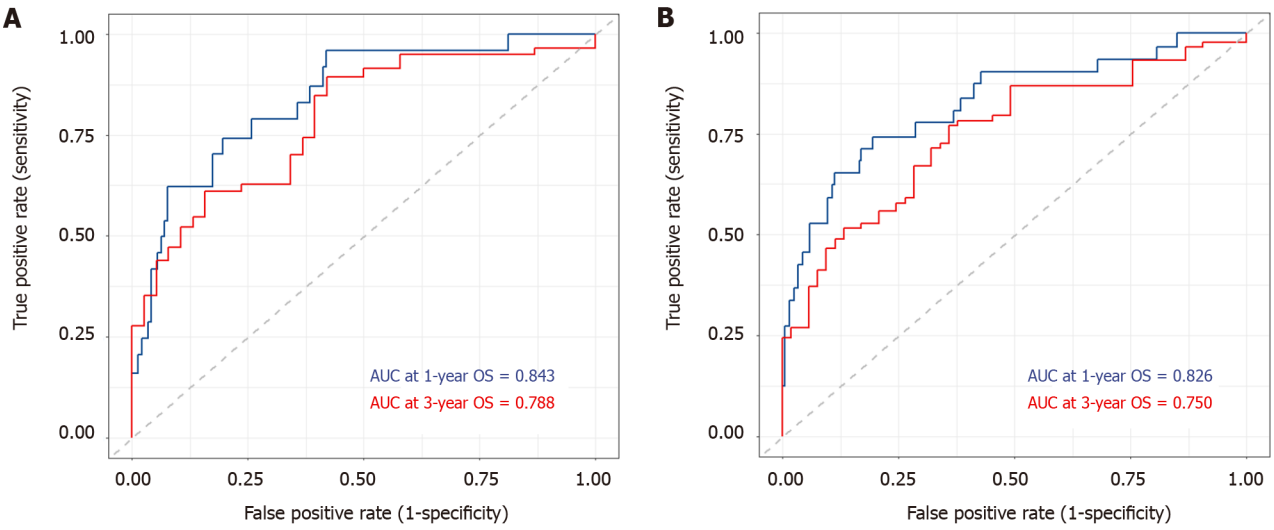

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Figure 3 Area under the receiver operating characteristic curve of the constructed nomogram to predict 1- and 3-yr overall survival of elderly colorectal cancer patients. A: Training cohort; B: Validation cohort. AUC: Area under the receiver operating characteristic curve; OS: Overall survival.

We consolidated the eight selected predictors into the nomogram and evaluated the performance using bootstrapping and cross-validation methods in calculating AUC, C-index, and calibration curves. Both AUC and C-index values were replicated well in the training and validation sets. The calibration curves of 1- and 3-year OS in both sets displayed favorable agreement between the predicted and observed survival probabilities. We further stratified elderly CRC patients into low- and high-risk groups according to their total risk points and optimal threshold values. The Kaplan-Meier method and Cox proportional hazards model revealed statistically significant differences between the two risk groups in terms of OS. Our results demonstrate that the nomogram accurately identifies the high-risk population and predicts OS, thereby facilitating appropriate clinical decision-making. It provides a distinct visual representation that enables information sharing between clinicians and patients. For example, it is clear that advanced age is not the only predictive factor influencing OS. In addition, an elderly patient in the high-risk group with multiple comorbidities and poor nutrition, may benefit from a period of pre-habilitation and optimization prior to CRC resection.

Our study has some limitations, including its retrospective nature and selection bias. First, elderly CRC patients who are physically fit are more likely to undergo surgery. In our study cohort, octogenarians comprised a more significant percentage (91.2%) than nonagenarians. Nevertheless, the primary data was complete with a median follow-up duration of 22.68 mo. Secondly, our data were limited in size and derived from a single institution, which may limit the generalizability of the nomogram. Despite these limitations, the ability of our constructed nomogram to accurately predict survival probability in elderly CRC patients over 80 years undergoing colorectal resection has substantial clinical implications. In this advancing age group, it is challenging to make management decisions in light of the risks associated with surgery. Therefore, the application of the nomogram lies in its capacity to guide the individualization of clinical decisions in complex scenarios.

CONCLUSION

In summary, colorectal surgery in elderly CRC patients is associated with a lower likelihood of survival. We used data from ACS-NSQIP to construct and validate an original nomogram for the postoperative survival of elderly CRC patients over 80 years. By accurately predicting 1- and 3-year survival probabilities, our novel nomogram, which incorporated age, CCI, BMI, serum albumin level, distant metastasis, emergency surgery, postoperative pneumonia, and postoperative myocardial infarction, may facilitate preoperative clinical decisions for patients, caregivers, and clinicians.

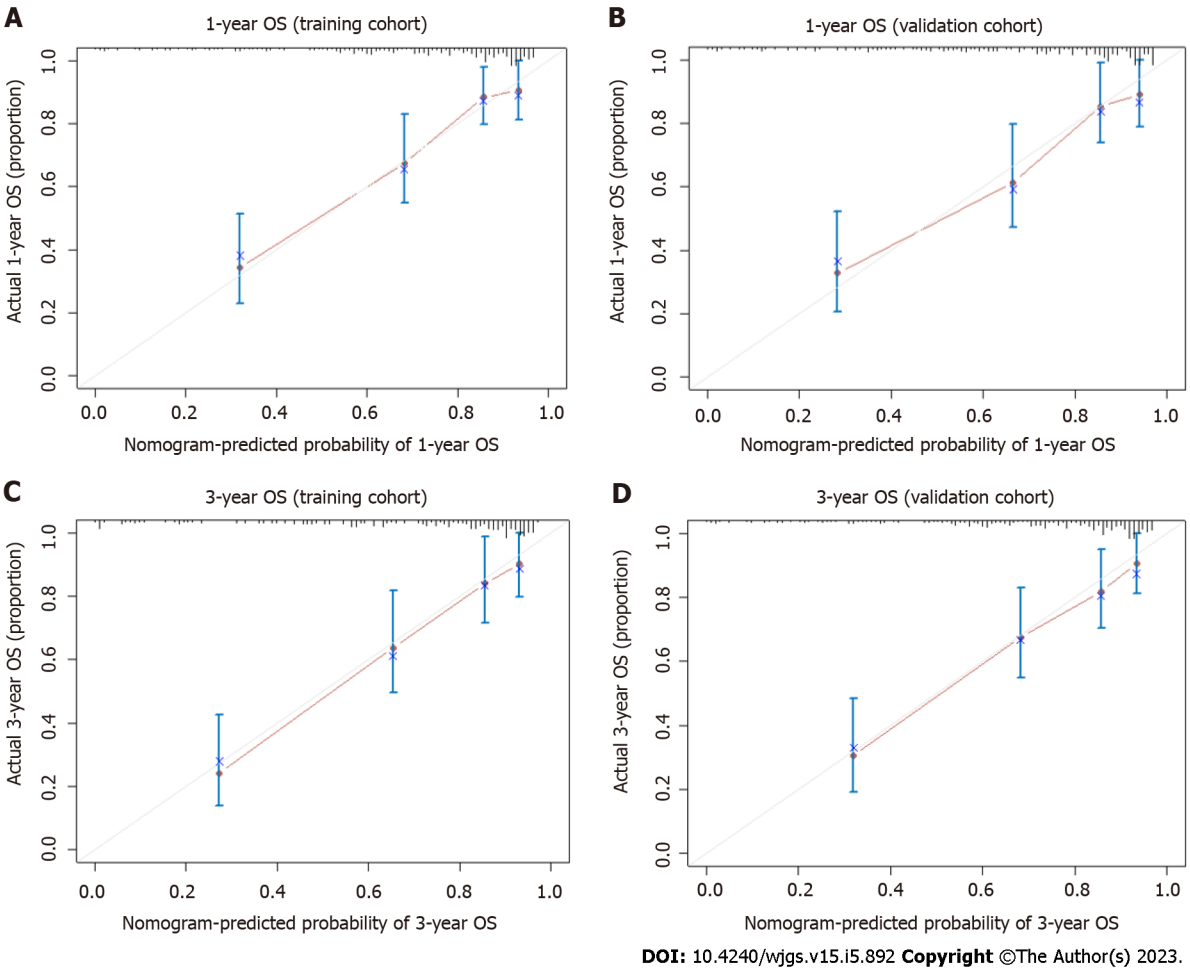

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Figure 4 Calibration curves of 1- and 3-yr overall survival for elderly colorectal cancer patients. A: 1-yr overall survival (OS) of the training cohort; B: 1-yr OS of the validation cohort; C: 3-yr OS of the training cohort; D: 3-yr OS of the validation cohort. The grey line represented the optimal reference line where the predicted survival probability corresponded to the observed OS rates. The red dots obtained by bootstrapping (re-sample size: 1000) represented the performance of the constructed nomogram. The greater the proximity of the solid red line to the grey line, the more precisely the nomogram model predicted the OS probability. OS: Overall survival.

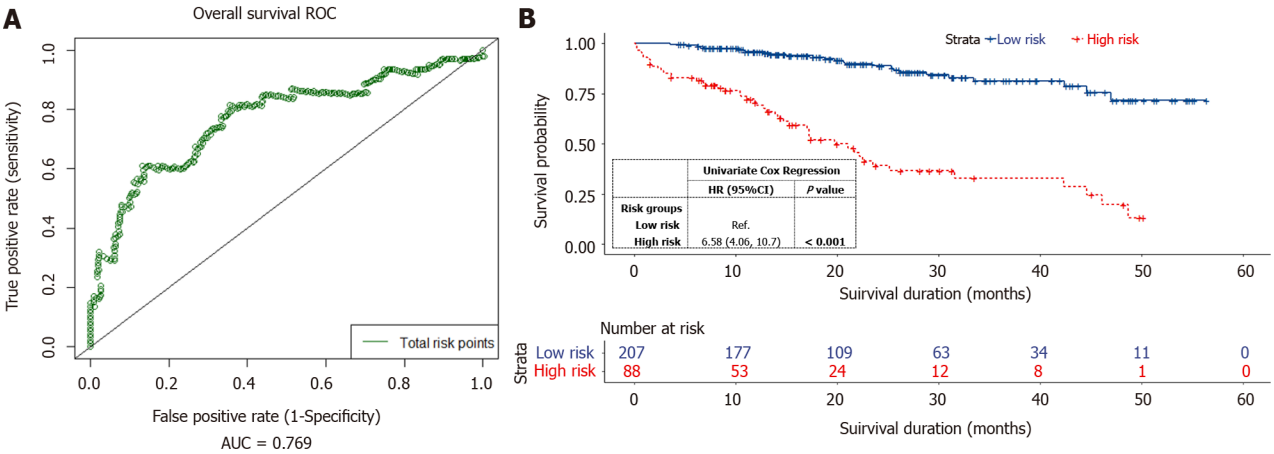

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Figure 5 Overall survival of elderly colorectal cancer patients stratified by the optimal risk threshold into low-risk and high-risk groups. A: A time-dependent survival receiver operating characteristic curve using the total risk points generated by the nomogram for all patients. The green line indicated an area under the receiver operating characteristic curve of 0.769; B: Kaplan-Meier curves for the overall survival of patients in low- and high-risk groups, based on the optimal cut-off risk point of 81. ROC: Receiver operating characteristic; AUC: Area under the receiver operating characteristic curve.

ARTICLE HIGHLIGHTS

Research background

Colorectal surgery is associated with a decreased probability of survival in elderly cancer patients. Several factors can affect the postoperative survival of elderly colorectal cancer (CRC) patients.

Research motivation

A precise predictive tool is required to enhance the decision-making process for elderly CRC patients undergoing colorectal resection.

Research objectives

To construct and validate a nomogram to predict the overall survival of elderly CRC patients over 80 years undergoing colorectal surgery.

Research methods

This retrospective study included 295 elderly CRC patients over 80 years undergoing colorectal resection. Variables were selected using regression methods, and a nomogram for 1- and 3-year overall survival was constructed from 60% of the cohort and validated on the remaining 40%. The performance of the nomogram was evaluated using various metrics, and the risk group was stratified based on the risk points of the nomogram.

Research results

The nomogram, which comprised age, comorbidities, body mass index, serum albumin level, distant metastasis, emergency surgery, postoperative pneumonia, and postoperative myocardial infarction, demonstrated excellent discriminative ability and consistency between predictions and actual observations. The risk group was stratified based on the nomogram's risk points, and a significant difference in overall survival was observed between low- and high-risk groups.

Research conclusions

This novel nomogram provides a valuable tool for informed decision-making in elderly CRC patients undergoing colorectal resection.

Research perspectives

We developed a nomogram using demographic and clinical variables to estimate the survival of elderly CRC patients undergoing colorectal surgery. This nomogram may guide treatment decisions, facilitate patient counseling, and enhance surgical outcomes.

FOOTNOTES

Author contributions: Chok AY designed the study and interpreted the data; Zhao Y performed the analysis and visualization; Chen HLR and Zhao Y performed the literature review; Tan IEH, Chew DHW, Au MKH collected the clinical data; Chok AY, Zhao Y, Chen HLR, and Zhao Y drafted the manuscript; Chok AY, Zhao Y and Tan EJKW edited the manuscript; Chok AY and Tan EJKW provided critical revision for final approval; all authors have read and approved the final version of the manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Retrospective efficacy analysis of olaparib combined with bevacizumab in the treatment of advanced colorectal cancer

Yi-Ling Jiang, Xue-Yuan Fu, Zhi-Hui Yin

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Abstract

BACKGROUND

Colorectal cancer (CRC) is a highly prevalent malignancy of the digestive tract worldwide, characterized by a significant morbidity and mortality rate and subtle initial symptoms. Diarrhea, local abdominal pain, and hematochezia occur with the development of cancer, while systemic symptoms such as anemia and weight loss occur in patients with advanced CRC. Without timely interventions, the disease can have fatal consequences within a short span. The current therapeutic options for colon cancer include olaparib and bevacizumab, which are widely utilized. This study intends to evaluate the clinical efficacy of olaparib combined with bevacizumab in the treatment of advanced CRC, hoping to provide insights into advanced CRC treatment.

AIM

To investigate the retrospective efficacy of olaparib combined with bevacizumab in the treatment of advanced CRC.

METHODS

A retrospective analysis was conducted on a cohort of 82 patients with advanced colon cancer who were admitted to the First Affiliated Hospital of the University of South China between January 2018 and October 2019. Among them, 43 patients subjected to the classical FOLFOX chemotherapy regimen were selected as the control group, and 39 patients undergoing treatment with olaparib combined with bevacizumab were selected as the observation group. Subsequent to different treatment regimens, the short-term efficacy, time to progression (TTP), and incidence rate of adverse reactions between the two groups were compared. Changes in serum-related indicators [vascular endothelial growth factor (VEGF),

matrix metalloprotein-9 (MMP-9), cyclooxygenase-2 (COX-2)] and tumor markers [human epididymis protein 4 (HE4), carbohydrate antigen 125 (CA125), carbohydrate antigen 199 (CA199)] levels before and after treatment were compared between the two groups at the same time.

RESULTS

The objective response rate was discovered to be 82.05%, and the disease control rate was 97.44% in the observation group, which were significantly higher than the respective rates of 58.14% and 83.72% in the control group ($P < 0.05$). The median TTP was 24 mo (95%CI: 19.987-28.005) in the control group and 37 mo (95%CI: 30.854-43.870) in the observation group. The TTP in the observation group was significantly better than that in the control group, and the difference held statistical significance (log-rank test value = 5.009, $P = 0.025$). Before treatment, no substantial difference was detected in serum VEGF, MMP-9, and COX-2 levels and tumor markers HE4, CA125, and CA199 levels between the two groups ($P > 0.05$). Following treatment with different regimens, the above indicators in the two groups were remarkably promoted ($P < 0.05$), VEGF, MMP-9, and COX-2 in the observation group were lower than those in the control group ($P < 0.05$), and HE4, CA125, and CA199 levels were also lower than those in the control group ($P < 0.05$). Vis-à-vis the control group, the total incidence of gastrointestinal reactions, thrombosis, bone marrow suppression, liver and kidney function injury, and other adverse reactions in the observation group was notably lowered, with the difference considered statistically significant ($P < 0.05$).

CONCLUSION

Olaparib combined with bevacizumab in the treatment of advanced CRC demonstrates a strong clinical effect of delaying disease progression and reducing the serum levels of VEGF, MMP-9, COX-2 and tumor markers HE4, CA125 and CA199. Moreover, given its fewer adverse reactions, it can be regarded as a safe and reliable treatment option.

Key Words: Olaparib; Bevacizumab; Advanced colorectal cancer; Efficacy

Core Tip: Colorectal cancer (CRC) presents insignificant symptoms in the early stage and is commonly diagnosed in the middle and advanced stages. Therefore, surgery is usually not viable because the best timing is missed, and chemotherapy, targeted therapies and other regimens are often utilized as interventions. Olaparib and bevacizumab are common targeted therapies with excellent therapeutic effects in a variety of solid tumors. This research collected the clinical data of 82 patients with advanced CRC, retrospectively investigated the clinical efficacy and safety of olaparib combined with bevacizumab in advanced CRC treatment, and analyzed the effect of this treatment regimen on the serum levels of vascular endothelial growth factor, matrix metalloprotein-9, cyclooxygenase-2, and related tumor markers.

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INTRODUCTION

Colorectal cancer (CRC), a malignant tumor disease of the digestive tract originating from the epithelial tissues of the colon or rectal mucosa, is the third most prevalent cancer worldwide and the fourth leading contributor to cancer-related death[1-3]. Epidemiological statistics show that as of 2018, approximately 1.8 million new CRC pathologies were reported worldwide, resulting in 881000 deaths, underscoring the considerable harmful consequences of this disease[4]. Over the past five decades, the incidence and mortality of colon cancer have increased year by year in young and middle-aged people (< 50 years old), with an annual increase of 2% in individuals < 50 years old since 1994, leading to a surge in CRC incidence in younger age groups[5]. According to different histological types, colon cancer can be classified into three categories: adenocarcinoma, mucinous adenocarcinoma, and undifferentiated carcinoma[6,7]. Early-stage colon cancer often lacks obvious clinical symptoms and is easily neglected. Progressing to the middle and later stages, the disease often demonstrates abdominal pain, abdominal distension, diarrhea, hematochezia, and other symptoms. Moreover, about 20%-50% of patients have developed distant organ metastasis to varying degrees at the time of diagnosis[8], which

seriously impacts patient survival and prognosis.

At present, colon cancer is predominantly treated with surgical resection, but this approach is not suitable for advanced metastatic colon cancer. Chemotherapeutic drugs such as 5-fluorouracil, oxaliplatin, and olaparib are used clinically for first-line targeted chemotherapy[9,10]. In addition, with the continuous improvement of targeted molecular therapies, treatment strategies targeting vascular endothelial growth factor (VEGF) as well as epidermal growth factor (EGF) receptors have been demonstrated to heighten the survival rate of patients with advanced colon cancer[11,12]. Bevacizumab, an anti-angiogenic targeted therapeutic agent with strong anti-tumor activities, has been applied in the clinical treatment of malignant solid tumors such as breast cancer, non-small cell lung cancer, and CRC, and has achieved certain results[13,14]. Nevertheless, the efficacy of olaparib combined with bevacizumab in the clinical treatment of patients with advanced colon cancer remains less well studied. Based on this, 82 cases of advanced CRC patients admitted to the First Affiliated Hospital of the University of South China were collected for retrospective analysis in this study so as to investigate the efficacy of olaparib combined with bevacizumab in advanced CRC treatment. It's expected to offer more effective data support for the clinical application of this treatment regimen in advanced CRC.

MATERIALS AND METHODS

General information

Eighty-two patients with advanced colon cancer admitted to the First Affiliated Hospital of the University of South China from January 2018 to October 2019 were enrolled as the subjects of this retrospective study. The control group consisted of 43 patients who received the classical FOLFOX chemotherapy regimen, while the observation group included 39 patients who received olaparib combined with bevacizumab. The control group was composed of 24 males and 19 females, with age ranging from 22 to 71 years (average age: 46.02 ± 7.28 years), while the observation group encompassed 19 males and 20 females aged between 21-73 years (mean age: 48.37 ± 6.41 years). There was no remarkable statistical difference in gender, age, body mass index, histological type, and tumor-node-metastasis stage between the two groups ($P > 0.05$), as shown in Table 1, indicating the comparability of the two groups.

Inclusion and exclusion criteria

Inclusion criteria: Participants were aged 18 years or older; diagnosed with advanced colon cancer by magnetic resonance imaging, computed tomography, and other imaging examinations combined with pathological section, cytological examination, and clinical diagnosis; and were at stage III-IV according to the eighth edition of the American Joint Committee on Cancer Staging Manual[15]. Additionally, patients were required to have at least one objective measurable tumor lesion, blood routine, electrocardiogram, and other biochemical tests before treatment. Participants with no history of drug allergy and complete clinical data were included in the study.

Exclusion criteria: Patients with liver cancer, gastric cancer, and other malignant tumor diseases; patients with blood diseases or autoimmune diseases; patients with heart, liver and kidney, and other vital organ dysfunction; patients who received radiotherapy or other regimens of chemotherapy before enrollment; patients with hypertension, diabetes, heart disease, and other underlying diseases; patients with mental disorders, Alzheimer's disease or other cognitive impairment; patients during pregnancy and lactation; an expected survival of fewer than 3 mo.

Treatment regimen

The control group (43 patients) received classical FOLFOX chemotherapy, which consisted of oxaliplatin (Zhejiang Hisun Pharmaceutical Co., Ltd.; approval number: GYZZ H20093487) administered intravenously at a dose of 135 mg/m^2 for 2 h on day 1, calcium folinate (Jiangsu Hengrui Medicine Co., Ltd.; approval number: GYZZ H20000418) administered at 200 mg/m^2 for 2 h on days 1-3, and 5-fluorouracil (Hainan Zhuotai Pharmaceutical Co., Ltd.; approval number: GYZZ H20051626) given continuously by an intravenous pump at a dose of 2600 mg/m^2 for 46-48 h, every 3 weeks for a total of 6 cycles of chemotherapy.

The observation group (39 patients) underwent the treatment of olaparib combined with bevacizumab. To wit, olaparib (AstraZeneca; registration certificate number: H20180049) was taken orally at a dose of 200 mg twice daily- once in the morning and once in the evening; bevacizumab injection (Shanghai Roche Pharmaceutical Co., Ltd.; approval No.: S20120068) was intravenously injected at 15 mg/kg for 0.5-1 h on day 1, every three weeks for a total of six cycles of chemotherapy.

Clinical assay items

Short-term efficacy: As per the iRECIST response evaluation criteria for cancer immunotherapy [16], the efficacy of both patient groups was assessed at the conclusion of treatment. Short-term efficacy was categorized into immune complete response (iCR), immune partial response (iPR), immune stable

Table 1 Comparison of general data between the two groups

General information	Control group (n = 43)	Observation group (n = 39)	t/χ^2	P value
Gender (n)			0.413	0.521
Male	24	19		
Female	19	20		
Age (yr), mean ± SD	46.02 ± 7.28	48.37 ± 6.41	1.545	0.126
BMI (kg/m^2), mean ± SD	22.45 ± 3.46	23.01 ± 2.98	0.781	0.437
Histological classification (n)			0.427	0.808
Adenocarcinoma	27	22		
Mucinous cancer	12	12		
Undifferentiated carcinoma	4	5		
TNM stage (n)			2.201	0.138
III	12	17		
IV	31	22		

BMI: Body mass index; TNM: Tumor-node-metastasis.

disease (iSD) and immune progressive disease (iPD). Among them, iCR was identified as tumor changes disappeared and clinical symptoms improved; iPR was recognized upon lessened tumor volume and no detection of new tumor metastasis or lesion; iSD was identified when the tumor volume was reduced (degree of reduction less than 25%), and no new metastasis or lesion occurred; iPD was recognized when the tumor volume barely changed, and the number of distant metastasis and lesion increased instead. Objective response rate (ORR) = (iCR + iPR)/total number of patients > 100%, disease control rate (DCR) = (iCR + iPR + iSD)/total number of patients > 100%.

Time to progression (TTP): The time required from grouping to objective tumor progression was observed and counted for both groups during the follow-up period. Non-progression and survivors were considered censored data following the conclusion of the follow-up.

Serum-related parameters: Before treatment and after six treatment cycles, 5 mL fasting venous blood was harvested from each patient in both groups. The serum was separated after high-speed centrifugation and stored in an ultra-low temperature freezer at -80 ℃ for later use. Serum levels of VEGF, MMP-9, and COX-2 were determined using an enzyme-linked immunosorbent assay[17]. VEGF kits were purchased from Beijing Zhongshan Biotechnology Co., Ltd., MMP-9 kits were bought from Anhui Anke Biological Co., Ltd., and COX-2 kits were purchased from Shanghai Kaibo Biochemical Reagent Co., Ltd. All procedures were performed in strict accordance with the kit instructions.

Tumor markers: Prior to treatment and subsequent to six treatment cycles, 5 mL fasting venous blood was collected from each patient in the two groups. The serum was separated after high-speed centrifugation and stored in an ultra-low temperature freezer at -80 ℃ for later use. The levels of tumor markers HE4, CA125, and CA199 in serum samples were confirmed through enzyme-linked immunosorbent assay [18] with the assistance of an ST-360 automatic enzyme-linked immunosorbent assay analyzer (Shanghai Kehua Experimental Instrument Co., Ltd.). The kits were purchased from Shanghai Youkewei Biotechnology Co., Ltd. All operations were conducted in strict accordance with the kit instructions.

Adverse reactions: Gastrointestinal reactions, thrombosis, bone marrow suppression, and liver and kidney function injury, and other adverse reactions and symptoms were closely observed, recorded, and analyzed in both groups, and the incidence was calculated.

Statistical analysis

All data in this study were processed and analyzed using SPSS 22.0 software. Measurement data were presented as mean ± SD, and t-test was applied for analysis. Enumeration data were represented as percentages, and χ^2 test was used for analysis. The Kaplan-Meier method was utilized to calculate the TTP. When $P < 0.05$, statistical significance was determined.

RESULTS

Comparison of short-term efficacy between the two groups

Following distinct treatment strategies, a comparative evaluation of short-term efficacy was conducted between the two groups. The results showed that ORR attained 82.05%, while DCR was 97.44% in the observation group, which were higher than the respective rates of 58.14% and 83.72% in the control group. As highlighted in Table 2, there was a notable difference in the short-term efficacy between the two groups ($P < 0.05$).

Comparison of time to disease progression between the two groups

The Kaplan-Meier analysis displayed that the median TTP was 24 mo (95%CI: 19.987-28.005) in the control group and 37 mo (95%CI: 30.854-43.870) in the observation group, which was better than that in the control group (Figure 1). The difference was statistically meaningful (log-rank test value = 5.009, $P = 0.025$).

Comparison of serum-related index levels between the two groups

Prior to treatment, no substantial difference was observed in serum VEGF, MMP-9, and COX-2 levels between the two groups ($P > 0.05$). After the adoption of different treatment methods, the above indicators were improved in both groups ($P < 0.05$). VEGF, MMP-9, and COX-2 in the observation group were 294.81 ± 20.63 pg/mL, 200.43 ± 15.02 mg/L, and 311.36 ± 22.14 ng/L, respectively. In contrast, the control group exhibited higher levels of these indicators (375.60 ± 22.05 pg/mL, 256.78 ± 17.62 mg/L, and 523.41 ± 27.48 ng/L, respectively), as presented in Table 3. The difference held statistical significance ($P < 0.05$).

Comparison of tumor marker levels between the two groups

Prior to treatment, there was no discernible difference in the levels of tumor markers HE4, CA125, and CA199 between the two groups ($P > 0.05$). After distinct treatment strategies, the above indicators in the two groups were vigorously bolstered ($P < 0.05$). HE4, CA125 and CA199 in the observation group were 121.36 ± 19.48 pmol/L, 35.61 ± 4.25 ng/mL and 56.37 ± 7.41 U/mL, respectively. On the contrary, the control group had higher levels of the above indicators (184.65 ± 22.34 pmol/L, 58.56 ± 6.08 ng/mL, and 82.84 ± 9.28 U/mL, respectively), as displayed in Table 4. The difference held statistical significance ($P < 0.05$).

Comparison of the incidence of adverse reactions between the two groups

The total incidence rate of adverse reactions, including gastrointestinal reactions, thrombosis, bone marrow suppression, and liver and kidney function injury, was significantly lower in the observation group (5.12%) compared to the control group (20.94%), as indicated in Table 5. The difference was statistically significant ($P < 0.05$). Timely symptomatic treatment ameliorated the adverse reactions for patients in both groups and had no substantial impact on the implementation of this treatment plan.

DISCUSSION

According to global cancer incidence and mortality statistics, colon cancer has emerged as the second most common cancer worldwide, surpassed only by lung cancer, with an incidence rate as high as 10.2% and a mortality rate of 9.2%[19]. CRC exhibits no evident specific symptoms in the early stage and is mostly screened out during routine health examinations. However, patients are typically diagnosed when they seek medical treatment for hematochezia, diarrhea, abdominal pain, weight loss, anemia, and weight loss, at which point they are usually in the middle or advanced stage. Tumor lesions and metastases can severely impair the patient's physical condition, and invasive surgical resection or treatment methods with greater toxicity and side effects may not be suitable for advanced patients[20,21]. Therefore, it is of paramount significance to explore effective treatment plans for advanced CRC that prolong the patient's life cycle and improve their quality of life.

The primary treatment for early-stage colon cancer is surgical resection of the tumor lesion. However, for advanced colon cancer, the high degree of malignancy and strong metastasis pose significant clinical challenges[22,23]. In a survey of 7786 patients who underwent resection of colon cancer, Moghadamyeghaneh *et al*[24] reported that approximately 10.8% of patients developed metastases at the time of surgery, and patients with metastatic colon cancer displayed higher postoperative morbidity and mortality than those with localized colon cancer. At present, for the treatment of advanced colon cancer, cytotoxic drugs such as 5-fluorouracil, oxaliplatin, capecitabine, and irinotecan combined with biological agents such as cetuximab, panitumumab, and bevacizumab are mainly used for chemotherapy, with good clinical efficacy in improving progression-free survival and overall survival rates[25-27]. Based on previous studies, this study compared the short-term efficacy, time to progression, incidence of adverse reactions, and changes in serum VEGF, MMP-9, COX-2 levels and

Table 2 Comparison of short-term efficacy between the two groups, *n* (%)

Group	iCR	iPR	iSD	iPD	ORR	DCR
Control group (n = 43)	9 (20.93)	16 (37.21)	11 (25.58)	7 (16.28)	25 (58.14)	36 (83.72)
Observation group (n = 39)	20 (51.28)	12 (30.77)	6 (15.38)	1 (2.56)	32 (82.05)	38 (97.44)
χ^2					5.518	4.369
P value					0.019	0.037

ORR: Objective response rate; DCR: Disease control rate; iCR: Immune complete response; iPR: Immune partial response; iSD: Immune stable disease; iPD: Immune progressive disease.

Table 3 Comparison of serum-related index levels between the two groups

Group	VEGF (pg/mL)		MMP-9 (mg/L)		COX-2 (ng/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n = 43), mean ± SD	421.38 ± 36.41	375.60 ± 22.05[a]	301.25 ± 26.73	256.78 ± 17.62[a]	711.39 ± 54.43	523.41 ± 27.48[a]
Observation group (n = 39), mean ± SD	427.91 ± 37.23	294.81 ± 20.63[a]	308.43 ± 22.08	200.43 ± 15.02[a]	718.43 ± 49.26	311.36 ± 22.14[a]
t	0.802	17.083	1.318	15.504	0.612	38.227
P value	0.425	< 0.001	0.191	< 0.001	0.542	< 0.001

[a]P < 0.05 *vs* before treatment in the same group. VEGF: Vascular endothelial growth factor; MMP-9: Matrix metalloprotein-9; COX-2: Cyclooxygenase-2.

Table 4 Comparison of tumor marker levels between the two groups

Group	HE4 (pmol/L)		CA125 (ng/mL)		CA199 (U/mL)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n = 43), mean ± SD	343.75 ± 51.26	184.65 ± 22.34[a]	82.43 ± 11.27	58.56 ± 6.08[a]	119.60 ± 15.62	82.84 ± 9.28[a]
Observation group (n = 39), mean ± SD	349.81 ± 45.79	121.36 ± 19.48[a]	83.26 ± 10.33	35.61 ± 4.25[a]	121.03 ± 19.85	56.37 ± 7.41[a]
t	0.562	13.610	0.346	19.618	0.364	14.177
P value	0.576	< 0.001	0.730	< 0.001	0.717	< 0.001

[a]P < 0.05 *vs* before treatment in the same group. HE4: Human epididymis protein 4; CA125: Carbohydrate antigen 125; CA199: Carbohydrate antigen 199.

Table 5 Comparison of incidence rate of adverse reactions between the two groups, *n* (%)

Group	Gastrointestinal reactions	Thrombus	Myelosuppression	Hepatic and renal impairment	Total incidence
Control group (n = 43)	4 (9.30)	1 (2.33)	3 (6.98)	1 (2.33)	9 (20.94)
Observation group (n = 39)	1 (2.56)	0 (0)	0 (0)	1 (2.56)	2 (5.12)
χ^2					4.397
P value					0.036

tumor markers HE4, CA125, and CA199 levels before and after treatment in advanced colon cancer patients treated with the standard FOLFOX chemotherapy of 5-fluorouracil, oxaliplatin, and Calcium Folinate combination, as well as the chemotherapy using olaparib combined with bevacizumab.

In this study, 43 patients in the control group treated with standard FOLFOX chemotherapy and 39 patients in the observation group treated with olaparib combined with bevacizumab chemotherapy

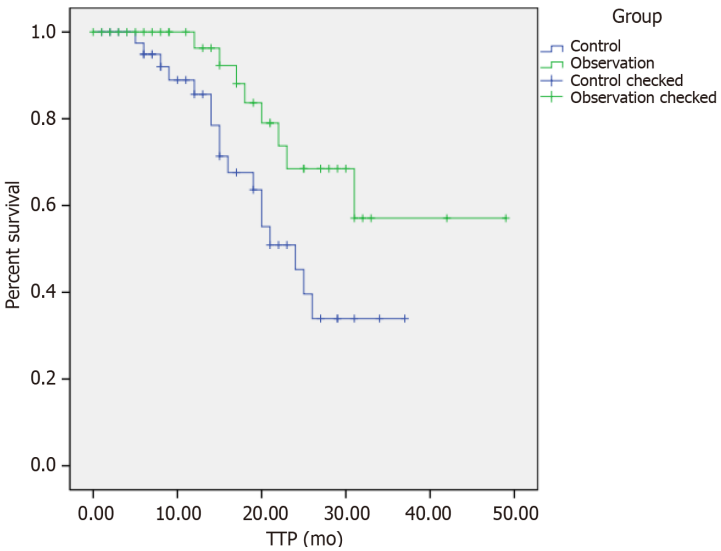

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Figure 1 Comparison of time to disease progression between control group and observation group. TTP: Time to progression.

were retrospectively analyzed to compare the clinical efficacy, disease progression time and adverse reactions between the two strategies during advanced CRC treatment. The outcomes demonstrated that ORR and DCR in the observation group were higher than those in the control group, the disease progression time was longer than that in the control group, while the total incidence of adverse reactions was lower than that in the control group, indicating that olaparib combined with bevacizumab in the treatment of advanced CRC not only had excellent short-term efficacy, but also prolonged the disease progression of patients, and had smaller toxic and side effects. As compared with the classical FOLFOX chemotherapy, it was safer and more reliable, with better clinical efficacy. FOLFOX chemotherapy is a widely used approach for the clinical management of CRC. Nonetheless, its clinical application may result in bone marrow suppression, digestive system disorders, and nervous system reactions, resulting in significant adverse effects on the patients [28]. Furthermore, studies have reported that approximately 60% of patients with CRC do not respond adequately to FOLFOX chemotherapy [29]. Kim *et al*[30] have pointed out that in patients with unresectable or metastatic CRC, the use of drugs such as olaparib or bevacizumab specifically targets proteins that promote cancer cell proliferation, with fewer toxic effects than FOLFOX chemotherapy. This study's results were consistent with previous reports, demonstrating that olaparib combined with bevacizumab was more effective than oxaliplatin, calcium folinate, and 5-fluorouracil chemotherapy for treating advanced CRC. Specifically, this therapy suppressed the homologous recombination defect of tumor genes by repressing PARP protein and tumor angiogenesis, effectively adopted cytotoxic therapy to increase cell killing, improved the efficiency of killing mutant cancer cells[31], and also effectively delayed tumor angiogenesis. For patients with small tumor masses requiring fewer chemotherapy cycles, it dampened the chance of inducing drug resistance, lowered the possibility of CRC cells becoming resistant to olaparib and bevacizumab, enhanced the immune activity after the resection of large tumors, bettered the clinical efficacy from multiple aspects[32], prolonged the patient's life cycle, and also lessened the damage done to the patient's body by the toxic and side effects of chemotherapeutic drugs[33,34]. This treatment method is relatively safer and more efficient.

Furthermore, this study compared the serum-associated indicators and tumor markers between the two groups subjected to different treatment regimens. The findings revealed no remarkable difference in various indicators between the two groups before treatment, while all indicators were effectively boosted subsequent to distinct treatment regimens. Serum VEGF, MMP-9, and COX-2 levels were significantly reduced in the observation group receiving olaparib combined with bevacizumab compared to the control group. Moreover, a more substantial decrease was observed in tumor markers, including HE4, CA125, and CA199 levels, in the observation group compared to the control group. These results provided evidence that olaparib combined with bevacizumab could effectively dampen tumor neovascularization, kill tumor cells, and assist in reducing tumor burden in patients diagnosed with advanced CRC. VEGF, MMP-9, and COX-2 are critical regulators of tumor angiogenesis, cell migration, as well as extracellular matrix degradation, and are typically present at high levels in advanced CRC[35,36]. HE4, an acidic protein tumor marker mainly expressed in epididymis and vas deferens epithelial cells, has been extensively applied in the diagnosis and prognostic evaluation of cancers such as endometrial cancer, ovarian cancer and lung cancer. The latest studies have also found it abnormally elevated in digestive system tumors [37]. CA125 is a heterogeneous mucin-like glycoprotein widely distributed in the mesothelial cell group and is dramatically heightened in patients with ovarian,

cervical, liver, lung, as well as CRC progression[38]. CA199, a glycolipid substance on the cell membrane, belongs to oligosaccharide tumor-correlated antigens and is widely believed to be highly expressed in patients with cholangiocarcinoma, gastric cancer, liver cancer, as well as colon cancer[39]. Here, bevacizumab was harnessed to block VEGF binding to its receptor to impede tumor neovascularization and suppress the formation of type IV collagen and integral membrane-bound protease[40]. Meanwhile, olaparib functioned in blocking base excision repair, specifically killing cancer cells while also repairing DNA damage after chemotherapy to some extent[41], hence impeding serum VEGF, MMP-9, and COX-2 levels and effectively attenuating the profiles of tumor-related markers HE4, CA125 and CA199 in serum[42].

Nonetheless, this study has some limitations that should be acknowledged. Firstly, the retrospective design of the study may have introduced inherent biases. Additionally, all enrolled cases were from the same hospital, and the research outcomes may be affected by the unique practice of the unit. As such, further prospective studies are recommended to validate these findings and fill the gaps.

CONCLUSION

In summary, the combination of olaparib and bevacizumab has superior clinical efficacy compared to the conventional FOLFOX chemotherapy regimen for treating patients with advanced CRC. Specifically, the combination therapy was found to significantly delay disease progression and reduce serum VEGF, MMP-9, and COX-2 levels, as well as tumor marker HE4, CA125, and CA199 levels, while also exhibiting fewer adverse reactions and a high level of safety and reliability. These findings provide valuable insights for targeted therapies in the context of advanced rectal cancer and have significant clinical implications.

ARTICLE HIGHLIGHTS

Research background

Olaparib and bevacizumab are well-established targeted drugs utilized in the treatment of solid tumors in clinical settings. They can exert anti-tumor effects by inhibiting PARP and tumor neovascularization. Advanced colorectal cancer (CRC) has a high degree of malignancy, and conventional surgical treatment and chemotherapy are effective. However, there is a pressing need to identify safe and effective treatments for patients with advanced CRC.

Research motivation

Olaparib combined with bevacizumab in the treatment of advanced CRC has an ideal clinical efficacy.

Research objectives

This study aims to investigate the short-term efficacy, time to progression, safety, and their effects on the serum parameters of olaparib combined with bevacizumab in advanced CRC treatment.

Research methods

Comparisons were made for the assessment of the short-term efficacy, time to progression (TTP), the incidence of adverse reactions, serum-related parameters [vascular endothelial growth factor (VEGF), matrix metalloprotein-9 (MMP-9), cyclooxygenase-2 (COX-2)], and tumor markers [human epididymis protein 4 (HE4), carbohydrate antigen 125 (CA125), carbohydrate antigen 199 (CA199)] levels in patients with advanced CRC treated with classical FOLFOX chemotherapy and olaparib combined with bevacizumab chemotherapy.

Research results

The objective response rate and disease control rate in the observation group were significantly higher than those in the control group, and the median TTP in the observation group was better than that in the control group. After treatment, the serum levels of VEGF, MMP-9, COX-2, HE4, CA125, and CA199 in the observation group were lower than those in the control group, and the total incidence of adverse reactions in the observation group was also lower than that in the control group.

Research conclusions

Olaparib combined with bevacizumab in the treatment of advanced CRC has a remarkable clinical effect. Specifically, the combination can delay the disease and reduce serum VEGF, MMP-9, and COX-2 levels and tumor markers HE4, CA125, and CA199 levels, with a high degree of safety and reliability.

Research perspectives

The mechanism of olaparib combined with bevacizumab in the treatment of advanced CRC can be further investigated so as to enable a better understanding of its target and provide a comprehensive theoretical basis and data support for the clinical application of this treatment modality in patients with advanced CRC.

FOOTNOTES

Author contributions: Jiang YL drafted the manuscript; Jiang YL and Fu XY collected and analyzed the clinical data; Yin ZH designed the study, reviewed and revised the manuscript; and all authors have read and approved the final manuscript.

Institutional review board statement: The study was approved by the Ethics Committee of The First Affiliated Hospital, Hengyang Medical School, University of South China.

Informed consent statement: The data used in this study were not involved in the patients' private information, so the informed consent was waived by the Ethics Committee of The First Affiliated Hospital, Hengyang Medical School, University of South China. All patient data obtained, recorded and managed are only used for this study, and all patient information is strictly confidential, without any harm to the patient.

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ORIGINAL ARTICLE

Observational Study

CD4+CD25+ regulatory T cells decreased future liver remnant after associating liver partition and portal vein ligation for staged hepatectomy

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Abstract

BACKGROUND

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is an innovative surgical approach for the treatment of massive hepatocellular carcinoma (HCC), the key to successful planned stage 2 ALPPS is future liver remnant (FLR) volume growth, but the exact mechanism has not been elucidated. The correlation between regulatory T cells (Tregs) and postoperative FLR regeneration has not been reported.

AIM

To investigate the effect of $CD4^+CD25^+$ Tregs on FLR regeneration after ALPPS.

METHODS

Clinical data and specimens were collected from 37 patients who developed massive HCC treated with ALPPS. Flow cytometry was performed to detect changes in the proportion of $CD4^+CD25^+$ Tregs to $CD4^+$ T cells in peripheral blood

before and after ALPPS. To analyze the relationship between peripheral blood $CD4^+CD25^+$ Treg proportion and clinicopathological information and liver volume.

RESULTS

The postoperative $CD4^+CD25^+$ Treg proportion in stage 1 ALPPS was negatively correlated with the amount of proliferation volume, proliferation rate, and kinetic growth rate (KGR) of the FLR after stage 1 ALPPS. Patients with low Treg proportion had significantly higher KGR than those with high Treg proportion (P = 0.006); patients with high Treg proportion had more severe postoperative pathological liver fibrosis than those with low Treg proportion (P = 0.043). The area under the receiver operating characteristic curve between the percentage of Tregs and proliferation volume, proliferation rate, and KGR were all greater than 0.70.

CONCLUSION

$CD4^+CD25^+$ Tregs in the peripheral blood of patients with massive HCC at stage 1 ALPPS were negatively correlated with indicators of FLR regeneration after stage 1 ALPPS and may influence the degree of fibrosis in patients' livers. Treg percentage was highly accurate in predicting the FLR regeneration after stage 1 ALPPS.

Key Words: Associating liver partition and portal vein ligation for staged hepatectomy; Regulatory T cells; Future liver remnant

Core Tip: To investigate the mechanisms affecting future liver remnant (FLR) after stage 1 associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), this study was conducted by analyzing clinical data and peripheral blood specimens collected from hepatocellular carcinoma patients treated with ALPPS. The results showed that $CD4^+CD25^+$ regulatory T cells (Tregs) in peripheral blood after stage 1 ALPPS was negatively correlated with the index of FLR regeneration after stage 1 ALPPS and may influence the extent of liver fibrosis in patients. The percentage of Tregs was highly accurate in predicting FLR regeneration after stage 1 ALPPS.

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INTRODUCTION

Primary liver cancer is a common malignant tumor of the digestive system, with approximately 906000 new cases and 830000 deaths worldwide each year, making it an important health threat to the nation [1]. Surgical treatment of primary liver cancer is an important tool for the long-term survival of patients. For patients with primary liver cancer who are able to obtain radical resection, the 5-year survival rate can reach 60%-80%[2]. Due to the insidious onset of primary liver cancer, many patients are at an advanced stage at the time of initial diagnosis. Posthepatectomy liver failure (PHLF) may occur in massive hepatocellular carcinoma (HCC) due to the large size of the tumor and the lack of volume of the future liver remnant (FLR) after direct resection. PHLF is a common postoperative complication and an important factor in the rate of liver resection, and is one of the leading causes of death after hepatectomy due to the lack of targeted and effective treatment[3]. FLR volume is a key factor in determining the safe performance of hepatectomy[4]. The emergence and development of portal vein embolization (PVE) has expanded the indications for hepatectomy in the treatment of massive HCC with insufficient FLR volume. PVE can increase FLR volume augmentation by blocking portal vein flow[5]. However, PVE promotes slow growth of the FLR, with postoperative complications reaching up to 20% and more than 20% of patients eventually unable to undergo reoperation[6]. In addition, the long waiting interval for PVE accelerates tumor progression[7].

To further accelerate the regeneration of the FLR and improve the surgical resection rate of massive HCC. German scholars reported in 2007 and in 2012 officially named and summarized an innovative hepatectomy, associating liver partition and portal vein ligation (PVL) for staged hepatectomy (ALPPS) [8]. Stage 1 ALPPS ligates the portal branches of the liver on the tumor side, whereas the right and left

hemispheric parenchyma are separated and the hepatic artery and bile ducts are preserved. Once the FLR has reached a safe threshold, a right hemicolectomy or an enlarged right hemicolectomy is performed in stage 2 ALPPS. The technical approach to ALPPS is still being discussed and improved today, whereas research into the mechanisms of FLR regeneration in ALPPS is gradually increasing. An important feature of ALPPS is the rapid growth of the FLR in the stage 1 ALPPS, and the mechanisms behind this regeneration pattern are still unclear.

Natural regulatory T cells (Tregs) express surface CD4 and CD25, contain intracellular forkhead box P3 (FOXP3), and inhibit the proliferation of other cells in a contact-dependent manner[9]. It was first reported by Asano *et al*[10] that most mouse natural Tregs migrate out of the thymus on the 3rd day after birth; therefore, thymectomy on the 3rd day induces an autoinflammatory state that predisposes to autoimmune disease. With the discovery of Tregs and the understanding of their immunosuppressive effects, evidence has accumulated that this cell population is decisively involved in the pathogenesis of various diseases, such as chronic viral and autoimmune liver disease and HCC[11]. In particular, $CD4^+$ $CD25^+$ Tregs are thought to be responsible for the impaired immune response during chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. Patients with chronic HBV infection are characterized by an increased proportion of $CD4^+CD25^+$ Tregs in the peripheral blood, which aggregate significantly in the liver, with a positive correlation between their frequency and serum HBV DNA load [12]. Similarly, in patients with persistent HCV infection, an increased frequency of $CD4^+CD25^+$ Tregs in the blood and liver has been reported[13].

In recent years, the role of Tregs in tissue and organ repair and regeneration has received much attention. Many studies have confirmed the use of Tregs in tissue and organ repair and regeneration [14]. As the liver is one of the organs that can be regenerated in the human body, the study of regeneration of the FLR in HCC patients after surgery has become a hot topic in hepatobiliary surgery. However, most of the studies at home and abroad have focused on the changes of $CD4^+CD25^+$ Tregs in peripheral blood and tumor in the development of HCC and their mechanisms of action. Studies on Tregs affecting FLR regeneration after hepatectomy have not been reported.

This study focused on the correlation between peripheral blood $CD4^+CD25^+$ Tregs and FLR regeneration after stage 1 ALPPS in patients with HCC.

MATERIALS AND METHODS

Patient selection

This study reviewed basic clinical data of patients with massive HCC treated with ALPPS at our medical center from March 2018 to September 2021. This study followed the Declaration of Helsinki and was approved by the Ethics Committee of our medical center [No. 2018 (KY-E-079)]. Inclusion and exclusion criteria for this study were as follows: (1) FLR/standard liver volume (SLV) < 30%-50%, treatment strategy based on the degree of liver fibrosis, willingness to treat, preoperative liver function status, and patients already receiving ALPPS; (2) Preoperative liver function Child grade A or B; (3) All patients had pathologically confirmed HCC after surgical resection; and (4) All patients had not undergone any targeted drug therapy, kinase drug therapy, or immunotherapy preoperatively.

Exclusion criteria were: Preoperative diagnosis of non-B viral HCC or autoimmune HCC; postoperative pathological diagnosis of bile duct cell carcinoma or benign findings; incomplete clinical case information and clinical specimens; and use of any targeted drug therapy, kinase drug therapy, and immunotherapy in the perioperative period.

Experimental methods

Evaluation of liver volume and surgical procedure: In combination with computed tomography (CT) images, preoperative and postoperative liver volumes as well as FLR volumes were measured, calculated, and recorded for each patient with liver cancer undergoing ALPPS surgery using the digital software of intelligent/interactive qualitative and quantitative analyses (IQQA-Liver; EDDA Technology Inc., Princeton, NJ, United States). The formula for calculating SLV was: SLV = -794.41 + 1267.28 × body surface area (M2)[15]. Kinetic growth rate (KGR) was calculated according to the method in a previous study[16]. All patients were operated by the same surgical team. Stage 1 ALPPS was performed using an anterior approach combined with selective PVL and liver parenchymal compartment[16]. After stage 1 ALPPS, CT was reviewed periodically to assess the regeneration of the FLR. Stage 2 ALPPS is accepted after meeting the following safety criteria[17]: FLR/SLV ≥ 50% with severe fibrosis or cirrhosis, FLR/SLV ≥ 40% with mild/moderate fibrosis, and FLR/SLV ≥ 30% without liver fibrosis or cirrhosis.

Flow cytometry: Patients undergoing ALPPS had 1 mL heparin-anticoagulated venous blood drawn early in the morning on an empty stomach, and the main procedure was to isolate a suspension of peripheral blood mononuclear cells (PBMCs) by Ficoll density gradient centrifugation. Then 1 mL whole blood was taken and three times the volume of erythrocyte lysate was added. The solution was mixed well and lysed on ice for 15 min, followed by centrifugation at 450 × g for 10 min at 4 °C. The

supernatant was discarded, and the precipitate was resuspended by adding two times the volume of red blood cell lysate, followed by centrifugation at 450 × g for 10 min at 4 °C. The supernatant was discarded, and after resuspending the cells in 1 mL flow cytometry staining buffer, the cell suspension was filtered through a flow tube and the filtrate was placed on ice. Then 100 μL cell suspension was aspirated and 0.625 μL fluorescein isothiocyanate-labeled mouse anti-human CD4 monoclonal antibody, 0.5 μL pulmonary embolism-labeled mouse anti-human CD25, and the corresponding isotype antibody immunoglobulin G1 in the same volume were added. The solution was incubated for 45 min in the dark, followed by the addition of 400 μL flow cytometry staining buffer and centrifugation at 300 × g for 5 min. The supernatant was discarded and the cells were resuspended by adding 500 μL flow cytometry staining buffer. A combination of CD4 and CD25 was used to stain cells to count the percentage of $CD4^+$ $CD25^+$ Tregs. Data were obtained and analyzed with Cell Quest software.

Statistical analyses

SPSS 20.0 statistical software was used for statistical analyses and GraphPad Prism 8.0 software for plotting. Comparisons between two groups were made using *t*-tests for measurement data; repeated measures data were compared using repeated measures analysis of variance (ANOVA); and correlations were analyzed using Spearman's rank correlation test. The receiver operating characteristic curve (ROC) was used to assess the predictive effect. $P < 0.05$ was considered statistically significant.

RESULTS

Preoperative data and intraoperative and postoperative conditions of ALPPS stage 1 and 2

From March 2018 to September 2020, a total of 37 patients with HCC undergoing ALPPS were included according to the screening criteria. There were 34 males and 3 females. The mean age was 45 ± 11 years. All patients had hepatitis B-associated HCC. The mean tumor diameter was 9.5 ± 4.2 cm. The preoperative FLR volume was (364.3 ± 74.5) cm^3; preoperative FLR/SLV was 35.1% ± 7.0%; and preoperative liver volume/body mass ratio was 0.60% ± 0.13% (Tables 1 and 2).

Proportion of $CD4^+CD25^+$ Tregs to $CD4^+$ T cells in PBMCs in peripheral blood by flow cytometry

The results of flow cytometry showed that the proportion of $CD4^+CD25^+$ Tregs showed a progressive increase in the postoperative period in stage 1 and stage 2 ALPPS (Figure 1). After repeated measures ANOVA, the differences were statistically significant ($P < 0.05$) on days 1, 3, 5, 7, and 10 after stage 1 and stage 2 ALPPS compared to preoperatively (Table 3). The difference was statistically significant ($F = 6.962$, $P < 0.001$) when comparing the trend of $CD4^+CD25^+$ Treg percentage preoperatively and postoperatively in stage 1 ALPPS and was statistically significant ($F = 4.726$, $P = 0.011$) when comparing the trend of $CD4^+CD25^+$ Treg percentage preoperatively and postoperatively in stage 2 ALPPS.

Assessment of liver volume after ALPPS

The median increase in FLR volume between stage 1 ALPPS and stage 2 ALPPS stages was 64.5% (22.3%-221.9%). The absolute and relative KGR of the FLR were 17.4 cm^3/d (range = 0.45-36.6 cm^3/d) and 5.0%/d (range = 0.1%-18.5%/d), respectively. The FLR volume in stage 2 ALPPS was significantly greater than the FLR volume in stage 1 ALPPS, with a statistically significant difference ($P < 0.001$) (Figure 2 and Table 4).

Correlation between the proportion of $CD4^+CD25^+$ Tregs and the FLR regeneration after stage 1 ALPPS

Through Spearman's rank correlation analysis, we found that on the 3rd day after stage 1 ALPPS, the proportion of $CD4^+CD25^+$ Tregs was significantly negatively correlated with liver regeneration. The correlation coefficient between the proportion of Tregs and the hyperplasia volume between stage 1 and 2 ALPPS was $r = -0.442$ ($P = 0.009$), that between the proportion of Tregs and the hyperplasia rate was $r = -0.469$ ($P = 0.005$), and that between the proportion of Tregs and KGR was $r = -0.511$ ($P = 0.001$) (Figure 3).

The proportion of $CD4^+CD25^+$ Tregs on the 3rd day after stage 1 ALPPS was categorized as high or low according to the median. The median KGR of patients with low and high Treg proportions was 13.3 (6.1-24.9 cm^3/d) and 7.5 (0.67-22.35 cm^3/d), respectively. The results showed that the proliferation volume, proliferation rate, and KGR were significantly higher in patients with low Treg proportion than in those with a high Treg proportion ($P < 0.05$; Figure 4).

Validation of the accuracy of $CD4^+CD25^+$ Treg proportion in predicting FLR regeneration after stage 1 ALPPS

The ROC method was used to verify the accuracy of the $CD4^+CD25^+$ Treg percentage in predicting FLR regeneration after stage 1 ALPPS. The results showed that the area under the curve (AUC) between

Table 1 Baseline index data of hepatocellular carcinoma patients undergoing association liver partition and portal vein ligation for staged hepatectomy

Variable	ALPPS, *n* = 37
Age, yr	45 (26-75)
Sex, women/man, *n* (%)	3 (8.1)/34 (91.9)
BMI, kg/m^2	22.2 (17.99-30.09)
AFP, ≥ 400 ng/mL/< 400 ng/mL, *n* (%)	19 (51.4)/18 (48.6)
Degree of liver fibrosis, *n*	
No fibrosis	7
Mild fibrosis	2
Moderate fibrosis/fibrosis	8
Cirrhosis, *n* (%)	20 (54.1)
MELD score	5.12 (0.75-11.00)
ICGR15, %	5.3 (1.3-18.8)
Child-Pugh class, A/B/C, *n*	36/1/0
BCLC staging, A/B/C, *n*	10/7/20

AFP: Alpha-fetoprotein; ALPPS: Association liver partition and portal vein ligation for staged hepatectomy; BCLC: Barcelona Clinic Liver Cancer; BMI: Body mass index; ICGR15: Indocyanine green retention rate at 15 min; MELD: Model for end-stage liver disease.

Table 2 Intraoperative and postoperative conditions of association liver partition and portal vein ligation for staged hepatectomy - stage 1 and 2

Variable	ALPPS - stage 1	ALPPS - stage 2
Operative time, min	341 (229-496)	300 (167-483)
Blood loss, mL	328 (50-2600)	792 (200-6000)
Blood transfusion, mL	300 (0-900)	250 (0-2150)
Postoperative bile leakage, *n*		
No	36	27
Yes	1	3
Clavien-Dindo classification, *n*		
I	20	12
II	14	14
III	3	4
IV	0	0
ISGLS classification, *n*		
A	21	9
B	16	18
C	0	1
Ishak fibrosis score	/	3 (1-6)
Ishak inflammation score	/	5 (2-12)

ALPPS: Association liver partition and portal vein ligation for staged hepatectomy; ISGLS: International Study Group of Liver Surgery.

Table 3 The proportion of CD4⁺CD25⁺ regulatory T cells to CD4⁺ T cells before and after the association liver partition and portal vein ligation for staged hepatectomy - stage 1 and 2

ALPPS	PRE	POD1	POD3	POD5	POD7	POD10	F	*P* value
ALPPS-1	1.69 ± 1.32	1.79 ± 1.42	2.29 ± 1.34	2.41 ± 1.49	2.62 ± 1.72	2.64 ± 1.64	6.962	0.001
ALPPS-2	1.69 ± 1.32	2.19 ± 1.26	2.28 ± 1.63	2.73 ± 2.05	2.21 ± 1.49	2.34 ± 1.35	4.726	0.011

ALPPS: Association liver partition and portal vein ligation for staged hepatectomy; POD: Postoperative day; PRE: Preoperative.

Table 4 Data related to liver volume, including standard liver volume, future liver remnant, future liver remnant/standard liver volume ratio, and future liver remnant increase

Variable	ALPPS stage 1 and 2
SLV, cm^3	1034.0 (851.9-1300.7)
Preoperation of ALPPS-1	
FLR, cm^3	1043.3 (851.8-1358.2)
FLR/SLV, %	35.1 (18.9-47.4)
Preoperation of ALPPS-2	
FLR, cm^3	548.4 (378.1-823.0)
FLR/SLV, %	53.2 (33.8-78.3)

ALPPS: Association liver partition and portal vein ligation for staged hepatectomy; FLR: Future liver remnant; SLV: Standard liver volume.

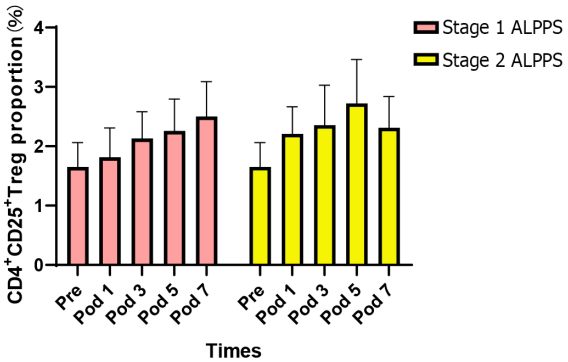

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Figure 1 Changes in the proportion of CD4⁺CD25⁺ Tregs to CD4⁺ T cells in peripheral blood before and after surgery for stage 1 ALPPS and stage 2 ALPPS. ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; Pre: Preoperation; Pod: Postoperative; Tregs: Regulatory T cells.

postoperative CD4⁺CD25⁺ Treg percentage and proliferation was 0.7197 (0.5400-0.8994; P = 0.029), the AUC between CD4⁺CD25⁺ Treg percentage and proliferation rate was 0.7474 (0.5806-0.9142; P = 0.014), and the area under the ROC curve with KGR was 0.7785 (0.6172-0.9399; P = 0.006) (Figure 5).

The relationship between the proportion of CD4⁺CD25⁺ Tregs and postoperative pathological liver fibrosis

To analyze the relationship between the preoperative proportion of CD4⁺CD25⁺ Tregs in peripheral blood and postoperative pathological liver fibrosis, we divided the preoperative CD4⁺CD25⁺ Treg results into high- and low-Treg proportion groups according to the median. The degree of pathological liver fibrosis was significantly higher in patients with a high Treg proportion than in patients with a low Treg proportion, and the difference was statistically significant (P = 0.043).

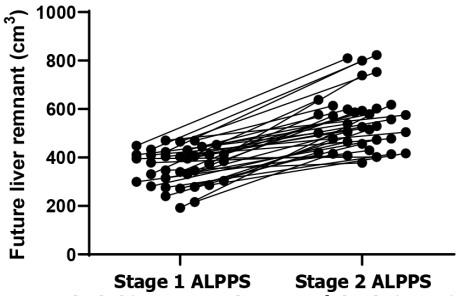

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Figure 2 Trends in future liver remnant volume between stage 1 ALPPS and stage 2 ALPPS. ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy.

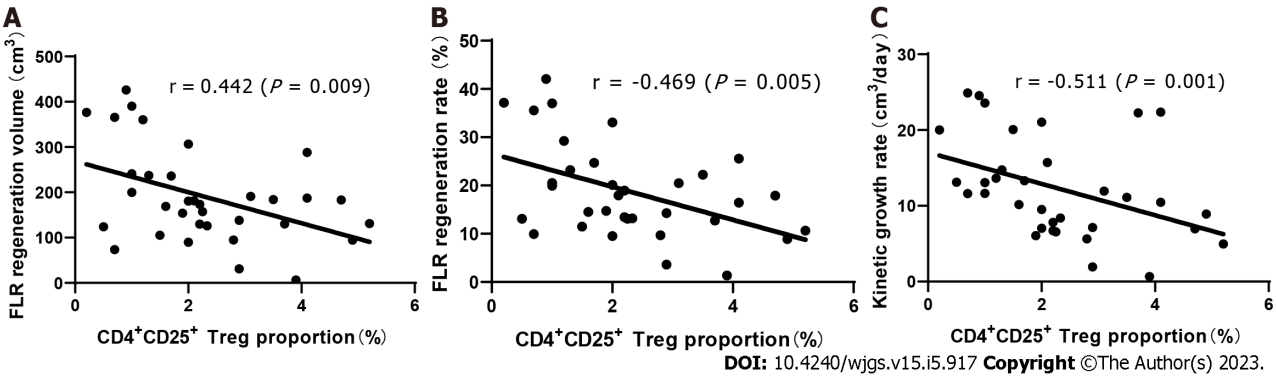

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Figure 3 Relationship between the proportion of CD4$^+$CD25$^+$ Tregs in peripheral blood and future liver remnant regeneration indexes after stage 1 ALPPS. A: Proliferative volume, r = -0.442 (P = 0.009); B: Proliferation rate, r = -0.469 (P = 0.005); C: Kinetic growth rate, r = -0.511 (P = 0.001). ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy. FLR: Future liver remnant; Tregs: Regulatory T cells.

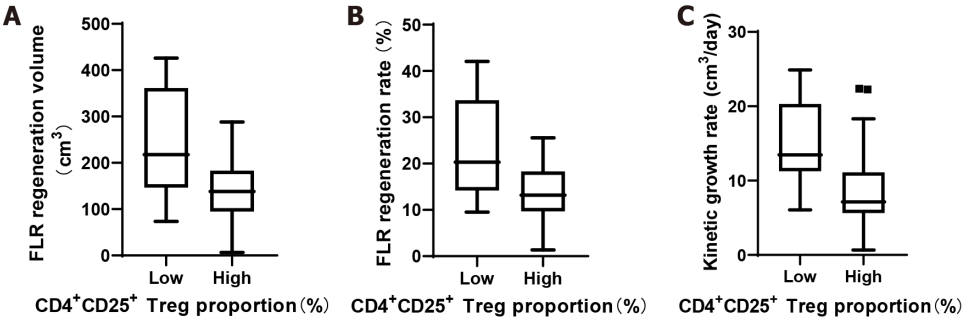

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Figure 4 Relationship between the proportion of CD4$^+$CD25$^+$ Tregs after stage 1 ALPPS and the index of future liver remnant regeneration after stage 1 ALPPS. A: Proliferative volume (P < 0.05); B: Proliferation rate (P < 0.05); C: Kinetic growth rate (P < 0.05). ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy. FLR: Future liver remnant; Tregs: Regulatory T cells.

DISCUSSION

The liver is considered an "immune" organ, housing a variety of resident immune cells that play a key role in maintaining organ homeostasis[18]. Resident innate immune cells consisting of macrophages or Kupffer cells, natural killer cells, natural killer T cells, and dendritic cells are considered to be the primary sentinels in the liver[19]. Tregs are a subset of T lymphocytes that regulate the immune response by suppressing the proliferation of effector T lymphocytes and the production of cytokines [20]. In 2003, the forkhead box transcription factor FOXP3 was identified as a specific marker for Tregs and its expression is thought to be essential for their suppressive activity[21]. Tregs arise from the thymus and constitutively express high levels of interleukin (IL)-2 receptor alpha chain, cytotoxic T lymphocyte associated antigen-4, and glucocorticoid-induced tumor necrosis factor receptor. Tregs account for 5% to 10% of peripheral CD4$^+$ T cells[22]. Early studies have demonstrated that the

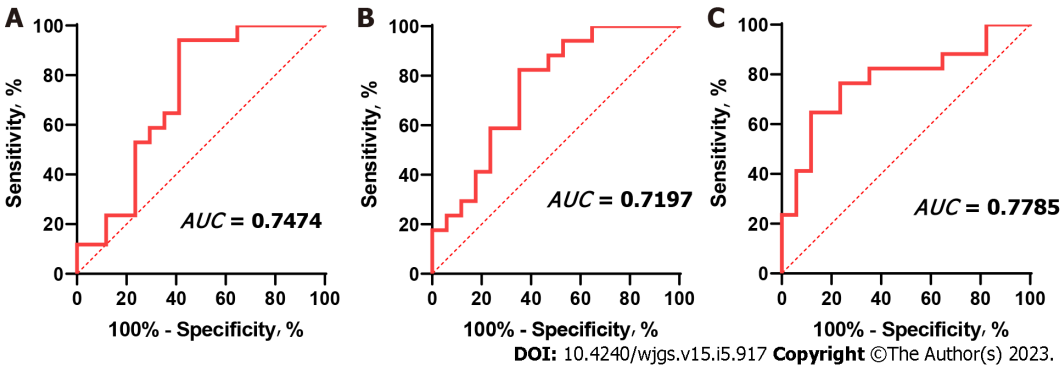

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Figure 5 Receiver operating characteristic curve of CD4$^+$CD25$^+$ Tregs after stage 1 ALPPS and the index of future liver remnant regeneration after stage 1 ALPPS. The AUC between CD4$^+$CD25$^+$ Tregs percentage and proliferative volume was 0.7197 (0.5400-0.8994; P = 0.029), the AUC between CD4$^+$CD25$^+$ Tregs percentage and proliferative rate was 0.7474 (0.5806-0.9142; P = 0.014), and the AUC between CD4$^+$CD25$^+$ Tregs percentage and Kinetic growth rate was 0.7785 (0.6172-0.9399; P = 0.006). ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy. FLR: Future liver remnant; Tregs: Regulatory T cells. AUC: Area under the curve.

suppressive effect of Tregs *in vivo* is mainly achieved through the production of suppressive cytokines such as IL-10, transforming growth factor (TGF)-β1, and IL-35[23]. Recent studies have demonstrated that immunosuppressive CD4$^+$CD25$^+$ Tregs represent a unique T cell lineage that is functionally and developmentally distinct from other T cells, with CD4$^+$CD25$^+$ Tregs involved in regulating the immune response/immune tolerance in an "active" manner. Their main function is to suppress the function of self-reactive T cells and multiple immune cells, inhibit the proliferation of CD4$^+$ T cells and CD8$^+$ T cells, perform immune homeostatic functions, and maintain immune tolerance and immune homeostasis[24].

The role of Tregs in tissue and organ repair and regeneration has received much attention in recent years[25]. Burzyn *et al*[26] showed that Treg populations with different phenotypes and functions rapidly accumulate during acute injury in mouse skeletal muscle, changing from a pro-inflammatory to a pro-regenerative state. Preferential induction of Tregs with hyperexcitable anti-CD28 monoclonal antibody increases Treg infiltration into the myocardium after myocardial infarction. Higher numbers of Tregs promote macrophage polarization towards the M2 phenotype in the healing myocardium and reduce ventricular rupture, leading to improved myocardial survival[27]. Tiemessen *et al*[28] found that secretion of IL-10, IL-4, and IL-13 by Tregs induce the polarization of M1 pro-inflammatory macrophages into M2 anti-inflammatory macrophages, which promotes the proliferation and differentiation of muscle satellite cells and secretes chemokines to promote muscle regeneration. Depletion of Tregs after treatment of FOXP3DTR mice with diphtheria toxin after skin injury resulted in significantly reduced wound closure with increased tissue granulation and superficial scabbing, indicating that Tregs promote skin wound healing[29]. Epithelial cell proliferation during lung recovery was found to be significantly impaired after specific elimination of Tregs from FOXP3DTR mice treated with diphtheria toxin in an acute lung injury or partial lung resection model[30]. Shi *et al*[31] found that Treg-derived bone bridge proteins act through integrin receptors on microglia to enhance the repair activity of microglia, thereby promoting oligodendrocyte production and white matter repair. IL-33 has been found to promote the recruitment of Tregs in damaged tissues and facilitate recovery after central nervous system (CNS) injury. In addition, mice lacking IL-33 had impaired recovery after CNS injury, which was associated with reduced infiltration of myeloid cells at the site of injury and reduced induction of M2 homologous genes[32].

As the liver is a regenerative organ, the mechanism of regeneration of the FLR after liver cancer surgery is of great interest. FLR volume is an important limiting factor in the safe performance of hepatectomy[4]. For giant HCC with a small FLR volume, resection rates can be improved by compensatory augmentation of the FLR. Reported by German surgeon Schnitzbauer *et al*[8] and summarized and named in 2012 as an innovative hepatectomy – ALPPS. When the volume of the FLR after stage 1 ALPPS meets safety criteria, a second-stage resection can be performed, which creates the opportunity for radical resection of the tumor in some patients with liver cancer who cannot undergo direct hepatectomy. Preoperative assessment and screening is particularly important prior to treatment with ALPPS, which has more stringent screening criteria. These include preoperative liver fibrosis and cirrhosis, tumor staging and grading, and most critically, accurate assessment of liver reserve. For accurate preoperative assessment of liver reserve there are several methods to assess safety after hepatectomy, such as the Child-Pugh score of liver function, measurement of indocyanine green retention test, and preoperative estimation of postoperative liver remnants by a three-dimensional imaging system[33,34]. In some patients with rigorously screened liver cancer, these risks are consistent with conventional hepatectomy and increase the rate of resection for giant liver cancer[35]. The results of our team's study on ALPPS in patients with isolated giant HCC that cannot be resected in one stage suggest that ALPPS is a viable treatment option for patients with HCC that cannot be resected in one

stage[16].

In the development of ALPPS, numerous studies have confirmed that the regenerative effect of ALPPS is significantly better than that of PVL[36,37]. The majority of patients undergoing ALPPS in Europe and the United States have metastatic liver cancer without a background of cirrhosis, unlike patients undergoing ALPPS in China, where the majority of patients have primary liver cancer and approximately 85% have post-hepatitis cirrhosis[38]. After these patients have undergone stage 1 ALPPS, 30%-40% of them still have FLR dysplasia, resulting in delayed planned stage 2 surgery or the inability to undergo a radical stage 2 resection. The mechanisms involved in the promotion of FLR regeneration by ALPPS have been the focus of research, but the exact mechanisms have not been elucidated. The possible mechanisms are now thought to be twofold: (1) After PVL of the liver, the portal blood flow in the FLR increases and the portal pressure rises, promoting rapid proliferation of the FLR; and (2) PVL of the liver on the tumor side leads to an ischemic state of the tumor, which in combination with the separation of the liver parenchyma, releases a large amount of inflammatory factors or complement that may also be associated with rapid proliferation of the liver[39,40]. Tregs, as emerging regeneration-associated target cells, have never been reported in studies of liver regeneration. Therefore, we offer speculation on how Tregs might affect FLR regeneration after ALPPS and explore the role of $CD4^+CD25^+$ Tregs in ALPPS-associated FLR regeneration and the regenerative mechanisms involved.

Flow cytometry was used to detect changes in the proportion of $CD4^+CD25^+$ Tregs to $CD4^+$ T cells in the peripheral blood of patients after stage 1 ALPPS and to correlate with indicators of residual postoperative liver regeneration. The results showed that the $CD4^+CD25^+$ Treg proportion showed a gradual increase after stage 1 ALPPS, and in addition the $CD4^+CD25^+$ Treg proportion after stage 1 ALPPS showed a significant negative correlation with the FLR regeneration indicators (proliferation volume, proliferation rate, and KGR). This suggests that Tregs may inhibit the regeneration of the FLR after ALPPS in patients with liver cancer. To verify the reliability of the results of the relationship between peripheral blood Tregs and FLR regeneration, we performed ROC analysis, which showed that the area under the ROC curve between Treg percentage and proliferation volume and proliferation rate and KGR were > 0.70 ($P < 0.05$), indicating that Treg percentage is highly accurate in predicting FLR regeneration after stage 1 ALPPS.

During the recovery period after stage 1 ALPPS, the body's immune function is disrupted for a short period of time due to the high surgical trauma, and immune homeostasis is disrupted, causing Tregs to be elevated to some extent. The high expression of Tregs suggests the establishment of immune tolerance and the high secretion of the suppressive cytokines TGF-β1 and IL-10, which significantly inhibit the development of the inflammatory response. Imbalance in the tumor microenvironment, which disrupts the regenerative microenvironmental homeostasis of the FLR, ultimately leading to poor regeneration of the FLR after surgery (Figure 6). The presence of tumor cells can induce rapid and sustained proliferation of Tregs, a process that may be interrupted immediately when the tumor is removed and lead to a significant reduction in the expression of tumor-associated Tregs in peripheral blood in the early postoperative period[41]. About 1 wk after radical resection of the tumor, sustained organismal stress effects may lead to the upregulation of $CD4^+CD25^+FOXP3^+$ Treg expression in peripheral blood. This finding was validated in the present study, where Treg numbers continued to show an increasing trend in the first 4 d postoperatively and began to show a decrease on postoperative day 5 after resection of stage 2 ALPPS stage liver tumors.

It has been reported that the number of $CD4^+CD25^+$ Tregs detected in peripheral blood, localized tumor, tumor-infiltrating lymph nodes, and draining lymph nodes of patients with HCC tumors is negatively correlated with disease progression and prognosis[42]. Increased numbers of Tregs in peripheral blood may be associated with impaired immune response, high mortality, and shortened survival in patients with liver cancer[43]. In this study, we divided the postoperative $CD4^+CD25^+$ Tregs into two groups: high and low. By comparing the results between the two groups, we showed that the patients with a low Treg percentage had a statistically significant higher KGR than those with a high Treg percentage ($P = 0.006$). The patients with a high Treg percentage had a statistically significant higher degree of postoperative pathological liver fibrosis than those with a low Treg percentage ($P = 0.043$). There are many factors affecting poor FLR regeneration such as hepatic arteriovenous-portal fistula, portal hyperperfusion, and liver fibrosis. Our group's latest clinical study reported that hepatic arteriovenous-portal fistulas after stage 1 ALPPS resulted in poor regeneration of the FLR[44]. Huang *et al*[45] analyzed patients with massive HCC in a post-hepatitis B cirrhotic background and showed that the FLR could still proliferate after ALPPS in patients with severe liver fibrosis, but less efficiently than in patients with mild to moderate liver fibrosis. In Chia *et al*[46], it was shown that liver fibrosis negatively affects the growth of the FLR after ALPPS. The results of this study showed that patients with a higher percentage of Tregs in their peripheral blood had more severe liver fibrosis. In this case, the rate of regeneration of the FLR after stage 1 ALPPS is reduced and the regeneration of the FLR is limited. Therefore, Tregs may be one of the factors affecting the regeneration of the FLR after stage 1 ALPPS.

Advances and developments in ALPPS technology have made radical treatment available for HCC with small FLR volumes, but HCC with insufficient FLR is mostly intermediate and advanced and is also often associated with adverse factors affecting liver regeneration such as hepatitis B cirrhosis, and

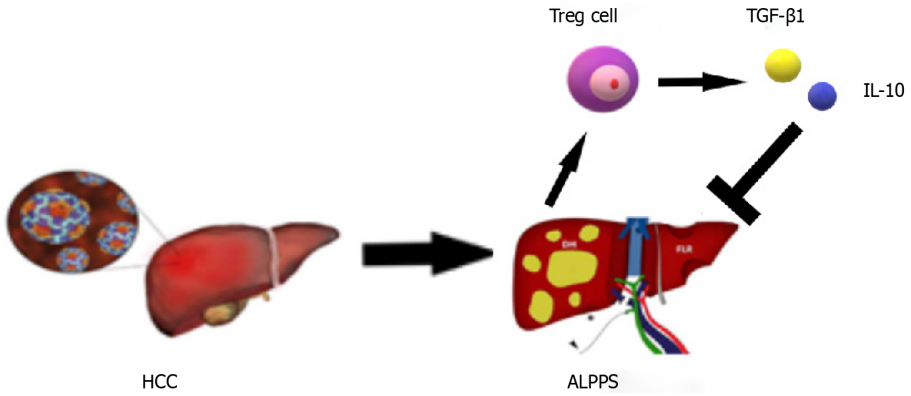

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Figure 6 Schematic diagram of the immune mechanism that regulatory T cells may participate in after ALPPS. ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; HCC: Hepatocellular carcinoma; IL: Interleukin; TGF: Transforming growth factor; Tregs: Regulatory T cells.

still leaves a proportion of patients unable to meet the demand for ALPPS surgery. In the present study, we found that Tregs, as immune-negative regulatory cells, played a role in the postoperative FLRs of liver cancer patients who underwent ALPPS surgery, as well as in the postoperative FLRs of the rat ALPPS model, potentially inhibiting the regeneration of the FLRs. In short, attenuating or knocking down Tregs in the tumor microenvironment of HCC after effective Treg immunotherapy following stage 1 ALPPS may promote regeneration of the FLR. For example, Beyer *et al*[47] found that fludarabine treatment resulted in a significant reduction in Treg numbers and a concomitant reduction in function, and that fludarabine also promoted apoptosis of Tregs. Dannull *et al*[48] found that IL-2 diphtheria toxin coupling significantly reduced the amount of Tregs present in the peripheral blood of patients with metastatic renal cell carcinoma and eliminated Treg-mediated immunosuppressive activity *in vivo*, enabling effective antitumor immunity with therapeutic impact by combining Treg depletion strategies. Therefore, there is an urgent need to explore drugs that target the abnormal increase in Tregs after HCC surgery to increase the rate of regeneration of the FLR after ALPPS, reduce the waiting time between ALPPS surgeries in patients and improve the quality of life of HCC patients.

CONCLUSION

$CD4^+CD25^+$ Tregs in the peripheral blood of patients with massive HCC at stage 1 ALPPS were negatively correlated with indicators of FLR regeneration after stage 1 ALPPS and may influence the degree of fibrosis in patients' livers. Treg percentage was highly accurate in predicting the FLR regeneration after stage 1 ALPPS.

ARTICLE HIGHLIGHTS

Research background

The mechanism of regeneration of the future liver remnant (FLR) after associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is a hot research topic in the field of hepatobiliary surgery, but the definitive mechanism of regeneration has not yet been fully elucidated.

Research motivation

Regulatory T cells (Tregs) are closely associated with tissue and organ regeneration in a number of studies, but no studies have been reported on their association with liver regeneration.

Research objectives

This study explored the correlation between $CD4^+CD25^+$ Tregs and FLR regeneration after ALPPS from the perspectives of FLR regeneration volume, FLR regeneration rate, kinetic growth rate (KGR), and liver fibrosis score.

Research methods

Collection of clinical data and peripheral blood samples from hepatocellular carcinoma (HCC) patients treated with ALPPS. Flow cytometry was performed to detect changes in the proportion of $CD4^+CD25^+$ Tregs to $CD4^+$ T cells in peripheral blood before and after ALPPS. To analyze the relationship between

peripheral blood $CD4^+CD25^+$ Treg proportion and clinicopathological information and FLR.

Research results

The postoperative $CD4^+CD25^+$ Treg proportion in stage 1 ALPPS was negatively correlated with the amount of proliferation volume, proliferation rate, and KGR of the FLR after stage 1 ALPPS. Patients with a high Treg proportion had a lower postoperative KGR as well as a more severe degree of fibrosis. Also, Treg proportion was a good predictor of in postoperative proliferation volume, proliferation rate and KGR.

Research conclusions

$CD4^+CD25^+$ Tregs in the peripheral blood of patients with HCC at stage 1 ALPPS were negatively correlated with indicators of FLR regeneration after stage 1 ALPPS and may influence the degree of fibrosis in patients' livers. Treg percentage was highly accurate in predicting the FLR regeneration after stage 1 ALPPS.

Research perspectives

Research on the mechanism of FLR regeneration after ALPPS is still being explored. In future studies, this report provides certain strong evidence to explore the regeneration mechanism, which will provide positive reference value to further improve the regeneration rate of FLR after ALPPS, reduce the waiting time of patients for ALPPS surgery and improve the survival rate of HCC patients.

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FOOTNOTES

Author contributions: Wang W and Ye CH are equal coauthors of this article; Wang W, Ye CH, Deng ZF, Wang JL, Bao L, and Zhang L contributed to the study design; Wen Z and Guo Y provided administrative support; Wang W, Ye CH, and Wen Z provided study materials and/or patients; Wang W, Ye CH, Xu BH, Zhu H, Guo Y, and Wen Z contributed to data collection and assembly; Wang W and Ye CH contributed to data analysis and interpretation; and all authors contributed to manuscript writing and final approval.

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

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The data presented in this study are available upon request to the corresponding author.

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ORIGINAL ARTICLE

Observational Study

Diagnostic value of matrix metalloproteinases 2, 7 and 9 in urine for early detection of colorectal cancer

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Abstract

BACKGROUND

A noninvasive biomarker with high diagnostic performance is urgently needed for the early diagnosis of colorectal cancer (CRC).

AIM

To evaluate the diagnostic value of matrix metalloproteinases (MMPs) 2, 7 and 9 in urine for CRC.

METHODS

Of 59 healthy controls, 47 patients with colon polyps and 82 patients with CRC were included in this study. Carcinoembryonic antigen (CEA) in serum and MMP2, MMP7, and MMP9 in urine were detected. The combined diagnostic model of the indicators was established by binary logistic regression. The receiver operating characteristic curve (ROC) of the subjects was used to evaluate the independent and combined diagnostic value of the indicators.

RESULTS

The MMP2, MMP7, MMP9, and CEA levels in the CRC group differed significantly from levels in the healthy controls ($P < 0.05$). The levels of MMP7, MMP9, and CEA also differed significantly between the CRC group and the colon polyps group ($P < 0.05$). The area under the curve (AUC) distinguishing between the healthy control and the CRC patients using the joint model with CEA, MMP2, MMP7 and MMP9 was 0.977, and the sensitivity and specificity were 95.10% and 91.50%, respectively. For early-stage CRC, the AUC was 0.975, and the sensitivity and specificity were 94.30% and 98.30%, respectively. For advanced stage CRC,

the AUC was 0.979, and the sensitivity and specificity were 95.70% and 91.50%, respectively. Using CEA, MMP7 and MMP9 to jointly established a model distinguishing the colorectal polyp group from the CRC group, the AUC was 0.849, and the sensitivity and specificity were 84.10% and 70.20%, respectively. For early-stage CRC, the AUC was 0.818, and the sensitivity and specificity were 76.30% and 72.30%, respectively. For advanced stage CRC, the AUC was 0.875, and the sensitivity and specificity were 81.80% and 72.30%, respectively.

CONCLUSION
MMP2, MMP7 and MMP 9 may exhibit diagnostic value for the early detection of CRC and may serve as auxiliary diagnostic markers for CRC.

Key Words: Colorectal cancer; Early detection; Matrix metalloproteinases; Urine; Biomarker

Core Tip: Colorectal cancer (CRC) is one of the most common cancers. Early diagnosis and early treatment have become the consensus of CRC diagnosis and treatment. Matrix metalloproteinases (MMPs), as a group of zinc-dependent endopeptidases, participate in the degradation of the extracellular matrix and are secreted and activated outside the cell. We aimed to evaluate the MMP2, MMP7 and MMP9 diagnostic value for early detection of CRC.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers. Although detection and treatment have improved, the incidence and mortality of CRC are on the rise[1]. A large number of clinical studies have confirmed that early diagnosis of CRC can significantly prolong survival, but at present, only approximately 30% to 40% of patients are diagnosed at an early stage. Early diagnosis and early treatment have become the consensus of CRC diagnosis and treatment[2]. At present, the commonly used clinical tests include invasive colonoscopy, noninvasive fecal occult blood testing, fecal DNA testing, carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199) levels, and Septin 9 methylation levels, but such tests are limited by their complexity and diagnostic performance[3]. A noninvasive biomarker with high diagnostic performance is urgently needed for the early diagnosis of clinical CRC[4].

Research has demonstrated that cytokines can be used as potential biomarkers for cancer detection and treatment response[5]. Cytokines are soluble peptides that play an important role in inflammation and immune cells signaling as well as in the multistep process of carcinogenesis. Cytokines can bind to their receptor and trigger the production of additional cytokines, leading to high concentrations in blood or other body fluids[6]. Compared with blood or stool, urine represents a better source because of its simple collection method, high patient acceptance and ability to collect repeated samples. Many urine biomarkers for CRC have been studied and have demonstrated potential diagnostic value[7-9]. Matrix metalloproteinases (MMPs), as a group of zinc-dependent endopeptidases, participate in the degradation of the extracellular matrix and are secreted and activated outside the cell. The overexpression of MMPs in the development and progression of CRC has been confirmed, and the use of MMPs as a potential serum marker for the early diagnosis of CRC has been previously reported[10-13]. Tumors represent multistage and multigene diseases. At present, the necessity of using multiple markers for cancer diagnosis has become accepted and can effectively improve the diagnostic value of a single marker. We aimed to evaluate the diagnostic value of serum CEA and CA199 and urine MMP2, MMP7 and MMP9 in distinguishing among healthy controls, colon polyps and CRC patients to establish an auxiliary diagnostic method for early CRC.

MATERIALS AND METHODS

Clinical samples

The study was approved by the Ethics Committee of Peking University Cancer Hospital & Institute and

provided their informed consent. Serum and urine samples were collected from 59 healthy controls, 47 patients with colon polyps and 82 patients with CRC. The age and sex of the healthy control group, colon polyp group and CRC group were matched. Among the 82 patients with CRC, there were 10, 28, 20, and 24 Duke A, B, C and D stage cancers, respectively. The were 38 cases of early CRC and 44 cases of late CRC. The inclusion criteria for the colon polyps and colon cancer groups were as follows: No prior treatment (*e.g.*, surgery, chemotherapy or radiotherapy), histopathological confirmation, no other gastrointestinal diseases and no other major diseases. The age-matched healthy controls all had negative blood biomarker, X-ray, ultrasound, computed tomography (CT), and fecal occult blood tests, and diagnosis was further confirmed by histopathological analysis. CRC sites included the cecum, ascending colon, descending colon, transverse colon, sigmoid colon and rectum. CRC was staged in accordance with Dukes staging criteria. Dukes stage A and B cancers represent early CRC, and Dukes stage C and D cancers represent late CRC. The clinical characteristics of the subjects are presented in Table 1.

Biomarker detection

Fasting peripheral blood was collected from all subjects included in this study in the morning and centrifuged at 3000 rpm for 10 min, and the supernatants were collected and labeled. All urine samples were collected from the middle section of the second morning urine (10 mL) and centrifuged at 1500 rpm for 10 min; the supernatant was collected, labeled, and stored at -80 °C. CEA and CA199 were detected by chemiluminescence, and a Roche E170 automatic immune analyzer was used for detection. The fasting peripheral blood of the subjects was collected using vacuum collecting tubes, and the serum was separated after centrifugation. CEA and CA199 were detected after the instrument was calibrated using standards. Urine MMP2, MMP7, and MMP9 were detected by a modular collection rapid detection system and using the antigen-antibody combination luminescence principle, which can detect trace MMP9 levels.

Statistical analysis

The data of this study were analyzed using SPSS 20.0. The CEA, CA199, MMP2, MMP7, and MMP9 levels are expressed as medians (25%, 75%). Differences in marker levels among the healthy control group, colon polyp group and CRC group were tested using one-way ANOVA for significance. The combined diagnostic model of the three indicators was established using binary logistic regression. The receiver operating characteristic curve (ROC) was used to evaluate the independent and combined diagnostic value of the indicators. $P < 0.05$ was defined as a significant difference.

RESULTS

Comparison of MMP2, MMP7, MMP9 and CEA levels among healthy control, colon polyp and CRC groups

The MMP2, MMP7 MMP9, and CEA levels in the three groups were detected and compared. As shown in Table 1, MMP2, MMP7 MMP9, and CEA levels in the healthy controls were 2128.42 (1635.60, 3119.34), 2612.71 (2087.86, 3110.04) and 8153.00 (5170.05, 11732.83), respectively. In the colon polyp group, the MMP2, MMP7 MMP9, and CEA levels were 15459.62 (12244.16, 18777.56), 3237.57 (2513.33, 3915.02), 14288.33 (8711.57, 17994.25), and 3.05 (1.55, 7.82). In the CRC group, the MMP2, MMP7 MMP9, and CEA levels were 15396.14 (6571.35, 20006.06), 4173.63 (3023.82, 6327.17), 8324.22 (4005.56, 11932.17), and 6.84 (1.86, 14.43), respectively. The MMP2, MMP7, MMP9, and CEA levels in the CRC group differed significantly from those in the healthy control group ($P < 0.05$). The MMP7, MMP9, and CEA levels in the CRC group differed significantly from the levels in the colon polyp group ($P < 0.05$). MMP2 levels did not differ significantly between the colon polyp and CRC groups.

Evaluation of the diagnostic value of CEA, MMP2, MMP7 and MMP9 in distinguishing healthy controls from CRC patients

CEA, MMP2, MMP7 and MMP9 were separately used to distinguish the 59 healthy controls from the 82 CRC patients; the results are presented in Figure 1 and Table 2, respectively. The area under the curve (AUC) of urine MMP2 was the highest, 0.875 [95% confidence interval (CI): 0.815-0.935], followed by MMP7, CEA, and MMP9. The AUCs were 0.786 (95%CI: 0.711-0.862), 0.779 (95%CI: 0.704-0.853) and 0.748 (95%CI: 0.667-0.830), respectively. As shown in Figure 2, when CEA, MMP2, MMP7 and MMP9 levels were combined to established a model to distinguish the 59 healthy controls and 82 CRC patients, the AUC was 0.977 (95%CI: 0.957-0.998), and the sensitivity and specificity were 95.10% and 91.50%, respectively. When this combined model was used to distinguish 59 healthy controls and 38 patients with early CRC, the AUC was 0.975 (95%CI: 0.940-1.000), and the sensitivity and specificity were 94.30% and 98.30%, respectively. When used to distinguish 59 healthy controls and 47 patients with advanced CRC, the AUC was 0.979 (95%CI: 0.956-1.000), and the sensitivity and specificity were 95.70% and 91.50%, respectively.

Table 1 Comparison of matrix metalloproteinases 2, 7, 9 and carcinoembryonic antigen contents in healthy controls, colon polyps and colorectal cancer groups

Group	Healthy control	Colon polyps	Colorectal cancer
MMP2	2128.42 (1635.60, 3119.34)	15459.62 (12244.16, 18777.56)	15396.14 (6571.35, 20006.06)
MMP7	2612.71 (2087.86, 3110.04)	3237.57 (2513.33, 3915.02)	4173.63 (3023.82, 6327.17)
MMP9	8153.00 (5170.05, 11732.83)	14288.33 (8711.57, 17994.25)	10324.22 (6005.56, 14932.17)
CEA	1.52 (0.79, 2.26)	3.05 (1.55, 7.82)	6.84 (1.86, 14.43)

MMP: Matrix metalloproteinase; CEA: Carcinoembryonic antigen.

Table 2 Diagnostic value of matrix metalloproteinases 2, 7, 9 and carcinoembryonic antigen for distinguishing healthy control group from colorectal cancer group

	AUC	Standard error	*P* value	95%CI	
				Lower	Upper
MMP2	0.875	0.031	< 0.001	0.815	0.935
MMP7	0.786	0.039	< 0.001	0.711	0.862
MMP9	0.748	0.042	< 0.001	0.667	0.830
CEA	0.779	0.038	< 0.001	0.704	0.853

MMP: Matrix metalloproteinase; CEA: Carcinoembryonic antigen; AUC: Area under the curve; CI: Confidence interval.

Evaluation of the diagnostic value of CEA, MMP7 and MMP9 in distinguishing patients with colorectal polyps from CRC patients

CEA, MMP7 and MMP9 were separately used to distinguish the 47 patients with colorectal polyps from the 82 CRC patients; the results are presented in Figure 3 and Table 3. The AUC of urine MMP7 was the highest, 0.769 (95%CI: 0.688-0.851), followed by MMP9 and CEA. The AUCs for MMP9 and CEA were 0.737 (95%CI: 0.647-0.827) and 0.626 (95%CI: 0.528-0.723), respectively. As shown in Figure 4, when CEA, MMP7 and MMP9 were combined to establish a model to distinguish the 47 colorectal polyp patients from the 82 CRC patients, the AUC was 0.849 (95%CI: 0.781-0.916), and the sensitivity and specificity were 84.10% and 70.20%, respectively. When this combined model was used to distinguish the 47 colorectal polyp patients and 38 patients with early CRC, the AUC was 0.818 (95%CI: 0.730-906), and the sensitivity and specificity were 76.30% and 72.30%, respectively. When used to distinguish 47 colorectal polyp patients and 47 patients with advanced CRC, the AUC was 0.875 (95%CI: 0.806-944), and the sensitivity and specificity were 81.80% and 72.30%, respectively.

DISCUSSION

CRC is one of the most common cancers worldwide and a leading cause of death. Detection of CRC at an early stage can significantly reduce CRC mortality. Early diagnosis is particularly important for improving the survival and quality of life of CRC patients[14]. Colonoscopy is recognized as the gold standard for CRC screening due to its high sensitivity and specificity[15]. However, colonoscopy requires experienced endoscopic doctors and patient cooperation. With the development of molecular biotechnology, the detection and treatment of tumors has improved. At present, protein, DNA (mutation and methylation), RNA (primarily microRNA), volatile organic compounds, and intestinal microflora have been identified as potential early diagnostic markers of CRC[16-18]; however, there remain some limitations for their use in the early diagnosis of CRC[19]. A highly sensitive and specific, easily collected, and noninvasive or minimally invasive method is urgently needed for the early diagnosis of CRC.

CEA has been used in diagnosis, disease monitoring and treatment response of various gastrointestinal tumors, and patients with positive and negative serum CEA expression prior surgery exhibit significant differences in the incidence of lymph node metastasis, nerve invasion and TNM staging[20]. The rates of CEA positivity were 24%, 44%, 56% and 87% in patients stage I to IV CRC patients, respectively. Measurements of serum CEA levels can predict the disease status of CRC[21],

Table 3 Diagnostic value of matrix metalloproteinases 2, 7, 9 and carcinoembryonic antigen for distinguishing colorectal polyp from colorectal cancer group

Indicator	AUC	Standard error	*P* value	95%CI	
				Lower	Upper
MMP2	0.532	0.050	0.550	0.433	0.630
MMP7	0.769	0.042	< 0.001	0.688	0.851
MMP9	0.737	0.046	< 0.001	0.647	0.827
CEA	0.626	0.050	0.018	0.528	0.723

MMP: Matrix metalloproteinase; CEA: Carcinoembryonic antigen; AUC: Area under the curve; CI: Confidence interval.

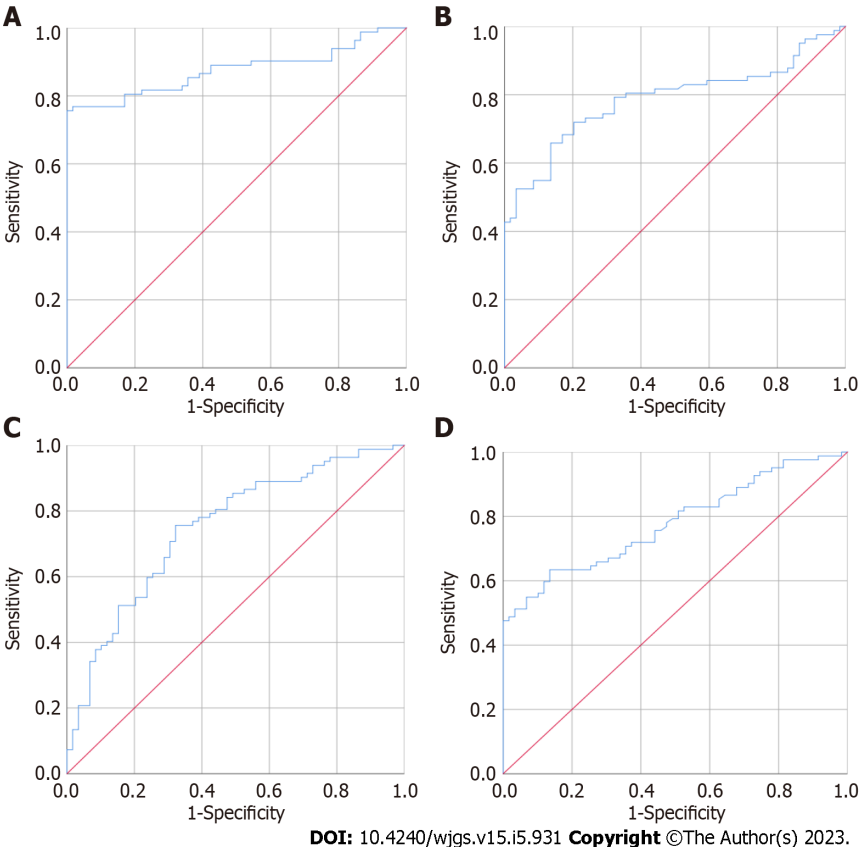

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Figure 1 Receiver operating characteristic curve of matrix metalloproteinases 2, 7, 9 and carcinoembryonic antigen alone for distinguishing healthy control group from colorectal cancer group. A: Matrix metalloproteinase (MMP) 2; B: MMP7; C: MMP9; D: Carcinoembryonic antigen.

including the tumor stage and presence of lymph node metastasis, and can provide guidance for clinical treatment and prognosis. In addition, CEA, as a common marker of CRC, can be used in combination with multiple indicators to improve the detection of CRC[22]. In this study, CEA levels in CRC increased significantly, which demonstrates its diagnostic value for CRC.

MMP9 is upregulated in macrophages of various types of tumors, primarily in the subpopulations of macrophages located at the edge of tumors, indicating that the specific expression of MMP9 in macrophages is directly related to cancer invasion. In addition, MMP9 has been reportedly linked to the development and progression of cancer, including but not limited to cancer invasion, metastasis and angiogenesis[23]. Furthermore, the value of MMP9 for tumor diagnosis, treatment response and disease progression has been studied in a variety of tumors[24,25]. When MMP9 is used alone as a biomarker, it may lack sufficient specificity for clinical application. The combination of biomarkers can improve the specificity of biomarkers. To achieve high specificity, MMP9 can be used in combination with other cancer biomarkers. With the development of statistical methods, bioinformatics and interdisciplinary research, a variety of multiparameter diagnostic models have been widely used in clinical diagnosis

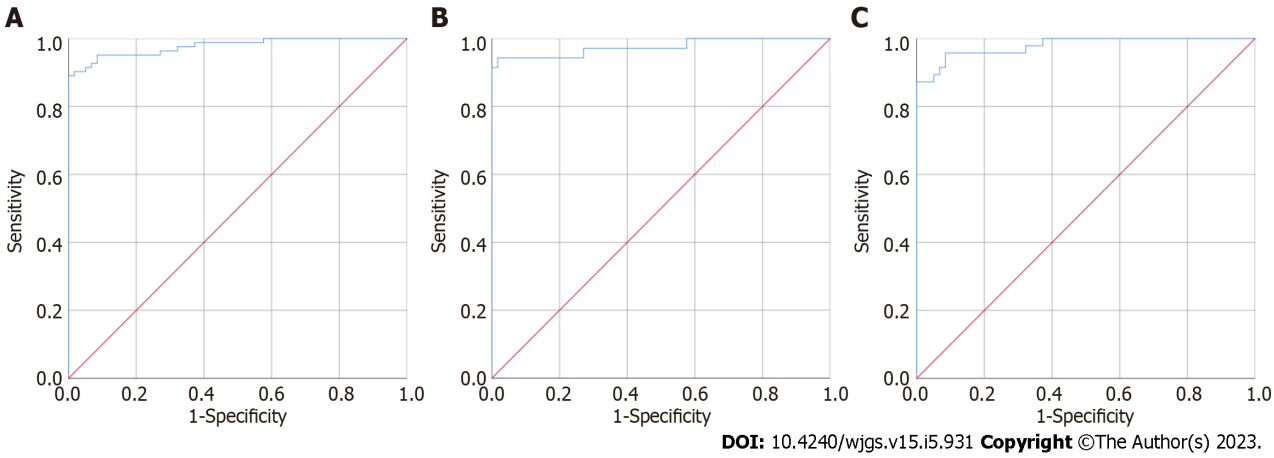

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Figure 2 Receiver operating characteristic curve of matrix metalloproteinases 2, 7, 9 and carcinoembryonic antigen joint for distinguishing healthy control group from colorectal cancer group. A: Healthy control group *vs* colorectal cancer group; B: Healthy control group *vs* early stage of colorectal cancer group; C: Healthy control group *vs* advanced stage of colorectal cancer group.

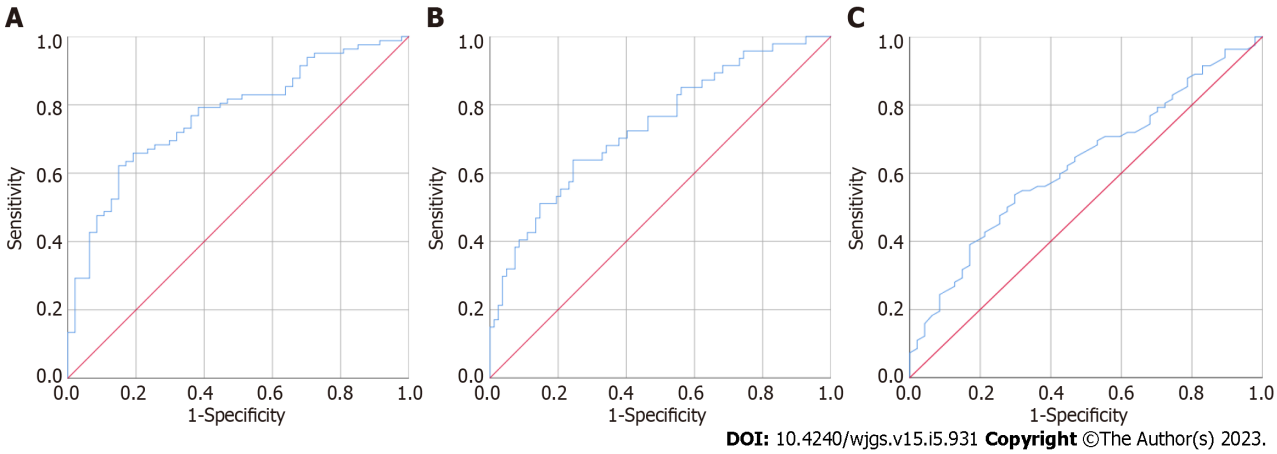

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Figure 3 Receiver operating characteristic curve of matrix metalloproteinases 7, 9 and carcinoembryonic antigen alone for distinguishing colorectal polyp group from colorectal cancer group. A: Matrix metalloproteinase (MMP) 7; B: MMP9; C: Carcinoembryonic antigen.

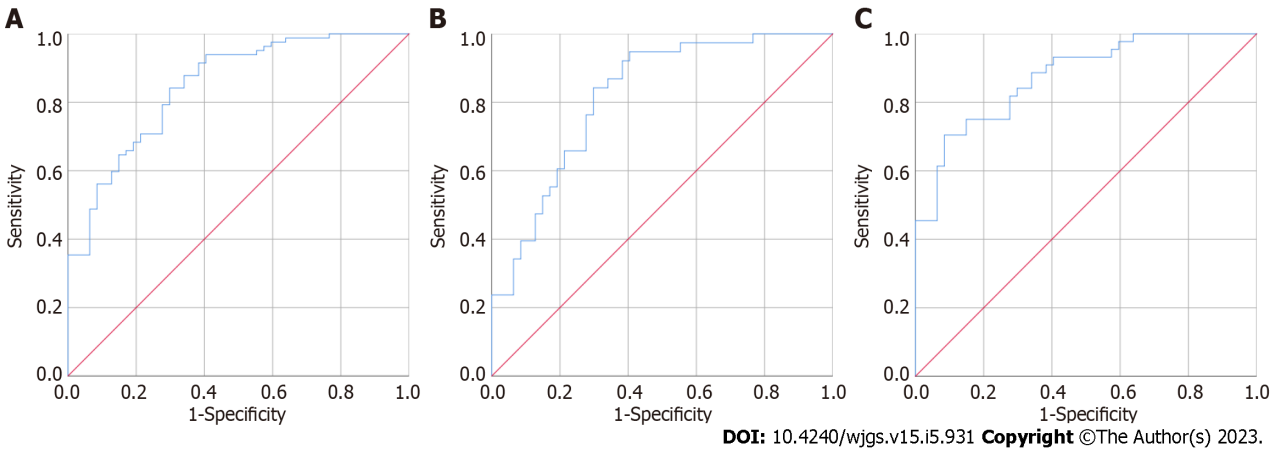

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Figure 4 Receiver operating characteristic curve of matrix metalloproteinases 2, 7, 9 and carcinoembryonic antigen joint for distinguishing colorectal polyp from colorectal cancer group. A: Colorectal polyp group *vs* colorectal cancer group; B: Colorectal polyp group *vs* early stage of colorectal cancer group; C: Colorectal polyp group *vs* advanced stage of colorectal cancer group.

[26], and their diagnostic efficiency is superior to that of single indicator detection[27].

This study has limitations. First, our research team evaluated the diagnostic value of serum MMP9 for the detection of early-stage CRC. Compared with urine MMP, serum MMP9 exhibits less diagnostic value for early CRC, and the relationship between serum and urine MMP9 requires further study. Second, although a diagnostic model based on three indicators has been established, the model has not yet been verified using a large sample size. Third, although the diagnostic value of this model is superior to the conventional indicators CEA or CA199, our model may be combined with other potential biomarkers or artificial intelligence to establish a multi-indicator model with improved diagnostic value.

CONCLUSION

Compared with the commonly used indicator CEA, the diagnostic performance of a model combining CEA, MMP2, MMP7 and MMP9 levels was significantly improved and can be used as a potential diagnostic method for CRC.

ARTICLE HIGHLIGHTS

Research background

Early diagnosis and early treatment are critical to improved colorectal cancer (CRC) diagnosis and treatment.

Research motivation

A noninvasive biomarker with high diagnostic performance is urgently needed for the early clinical diagnosis of CRC.

Research objectives

To evaluate the diagnostic value of matrix metalloproteinases (MMPs) 2, 7 and 9 for the early detection of CRC.

Research methods

Serum carcinoembryonic antigen (CEA) and urine MMP2, MMP7, and MMP9 levels were measured in 59 healthy controls, 47 patients with colon polyps and 82 patients with CRC. The independent and combined diagnostic values of the indicators for the detection of CRC were compared.

Research results

A model for CRC detection using CEA, MMP2, MMP7 and MMP9 exhibited an area under the curve (AUC) of 0.977. For early-stage and advanced-stage CRC, the model AUCs were 0.975 and 0.979, respectively. To distinguish the colorectal polyp patients from the CRC patients, the model using CEA, MMP7 and MMP9 levels produced an AUC of 0.849. For early-stage and advanced-stage CRC, the AUCs were 0.818 and 0.875, respectively.

Research conclusions

Compared with CEA alone, the diagnostic performance of a model combining CEA, MMP2, MMP7 and MMP9 established in this study was significantly improved.

Research perspectives

Validation of the model built in our study using a larger sample size should be performed.

FOOTNOTES

Author contributions: Peng L, Jiang T and Zhang PJ designed the study; Peng L, Zhang X performed the research; Peng L, Jiang T, Zhang ML and Zhang PJ analyzed the date; Peng L wrote the paper; Jiang T and Zhang PJ revised the manuscript for final submission; Peng L and Zhang X contributed equally to this study; Jiang T and Zhang PJ are the co-corresponding authors.

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SYSTEMATIC REVIEWS

How far is the endoscopist to blame for a percutaneous endoscopic gastrostomy complication?

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Abstract

BACKGROUND

Percutaneous endoscopic gastrostomy (PEG) is a well-established, minimally invasive, and easy to perform procedure for nutrition delivery, applied to individuals unable to swallow for various reasons. PEG has a high technical success rate of insertion between 95% and 100% in experienced hands, but varying complication rates ranging from 0.4% to 22.5% of cases.

AIM

To discuss the existing evidence of major procedural complications in PEG, mainly focusing on those that could probably have been avoided, had the endoscopist been more experienced, or less self-confident in relation to the basic safety rules for PEG performance.

METHODS

After a thorough research of the international literature of a period of more than 30 years of published "case reports" concerning such complications, we critically analyzed only those complications which were considered - after assessment by two experts in PEG performance working separately - to be directly related to a form of malpractice by the endoscopist.

RESULTS

Malpractice by the endoscopist were considered cases of: Gastrostomy tubes passed through the colon or though the left lateral liver lobe, bleeding after puncture injury of large vessels of the stomach or the peritoneum, peritonitis after viscera damage, and injuries of the esophagus, spleen, and pancreas.

CONCLUSION
For a safe PEG insertion, the overfilling of the stomach and small bowel with air should be avoided, the clinician should check thoroughly for the proper trans-illumination of the light source of the endoscope through the abdominal wall and ensure endoscopically visible imprint of finger palpation on the skin at the center of the site of maximum illumination, and finally, the physician should be more alert with obese patients and those with previous abdominal surgery.

Key Words: Percutaneous endoscopic gastrostomy; Complications; Doctor responsibility

Core Tip: For a safe percutaneous endoscopic gastrostomy insertion, the physician should avoid overfilling the stomach and small bowel with air, check thoroughly for the proper trans-illumination of the light source of the endoscope through the abdominal wall, ensure endoscopically visible imprint of finger palpation on the skin at the center of the site of maximum illumination, and be more alert with obese patients and those with previous abdominal surgery.

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INTRODUCTION

Percutaneous endoscopic gastrostomy (PEG) was introduced into clinical practice by Gauderer *et al*[1] in 1980. Nowadays it is a widely used, minimally invasive procedure-a flexible feeding tube placed endoscopically through the mouth into the stomach and exiting *via* the abdominal wall-to administer enteral nutrition, fluids, and drugs to individuals unable to swallow for various reasons[2,3]. It is a well-established method for nutrition delivery with a high technical success rate of insertion between 95% and 100% in experienced hands[4,5].

However, there still exists a complication rate, varying from 0.4% to 22.5% of cases[6-9]. For teaching and communication purposes, the complications are classified as major and minor, depending on the severity of resulting illness; severe bleeding due to injury of visceral vessels or liver damage, perforation of hollow viscera, as well as cardiopulmonary events and aspiration pneumonia, although rare, are generally severe or even fatal, and thus categorized as major complications, which happen at a rate of 1.0%-2.4% with a mortality of 0.8%. Minor complications include, among others, peristomal infection, peristomal leakage, tube dislodgment, pneumo-peritoneum, gastric outlet obstruction, and buried bumper syndrome. An alternative classification is based on the time elapsing after PEG performance: Early and late complications, but, for no reason should a "late" complication be considered as "minor" [3,8,10-15].

For the present commentary review, we decided to focus on those complications that could have been avoided if the endoscopist had been more experienced or less self-confident and therefore less casual about the basic safety rules for PEG performance. Gastrostomy tubes passed through the colon or though the left lateral liver lobe, bleeding after puncture injury of large vessels of the stomach or the peritoneum, peritonitis after viscera damage and injuries of the esophagus, spleen, and pancreas are critically discussed in relation to who should assume the responsibility.

MATERIALS AND METHODS

Data collection

An electronic literature search of PubMed databases from their inception in 1980 to 2022 was performed to detect all published case reports or case series pertinent to a complication after PEG tube insertion. An ultimate check of databases was carried out on November 15, 2022.

For literature search purposes, the subject heading "percutaneous endoscopic gastrostomy" combined with "complications", with AND as Boolean term, was applied to retrieve data related to the objectives of this study. The inclusion criteria were: (1) Either a "case report" or "case series"; (2) Full-text available; and (3) Human cases only. No language restriction was applied, except for Chinese.

The titles and abstracts of all publications identified were first screened and assessed and those obviously irrelevant were discarded. If eligibility could not be ascertained from the title or abstract, the full text of the article was examined. Papers deemed suitable were then reviewed by two independent reviewers to exclude, manually, all cases related to PEG tube malfunction or peristomal wound care, peristomal infections/leakage, buried bumper syndrome, and accidental dislodgement of the tube, as well as those related to sedation itself (aspiration, cardiac arrest, and similar). The references in the remaining papers were then scrutinized for additional cases, in a further effort to ensure that relevant publications were not missed.

Grouping complication cases

Two qualified endoscopists (EE and KK), working independently of each other, thoroughly studied all the remaining articles describing major complications: Vascular injuries-intra/retroperitoneal bleeding, colon injuries, liver injuries, and splanchnic organ injuries. For each article that they studied, they asked themselves: "Was this complication preventable?" and "what was the wrong maneuver on the part of the endoscopist which resulted in this complication?" Based on their 35+ years' experience each and the large number of procedures that they had performed, they separately judged and then discussed and agreed which of the complications could have been avoided had the endoscopist strictly followed the guidelines for a gastrostomy insertion.

RESULTS

A total of 88 complications out of the 575 cases screened were identified, *i.e.*, those which both endoscopists agreed could have been avoided (Figure 1). They were classified according to the organ/anatomical structure injured, as follows (Table 1).

Colon injuries (n = 50)

There were a total of 50 reports on transverse colon accidental penetration by the gastrostomy tube before it entered the stomach. In detail, 29 patients remained for between 6 wk and 4 years with a PEG tube in their stomach, after it had passed through the colon; this complication was recognized only during the process of changing the gastrostomy tube, when the new one failed to be inserted into the stomach and remained in the colon. Mainly diarrhea and fecal odor sent the patient to hospital for investigation. Another 11 cases of a similar complication were recognized early, from 25 h to 2.5 mo, mainly due to fecal material exiting from the tube and/or around the gastrostomy tube (Table 2). The same complication occurred in 4 patients with previous abdominal surgery: Two cases with a history of surgical jejunostomy[16] and an exploratory laparotomy[17], with diagnosis only occurring upon gastrostomy tube replacement; in one case[18] with a right hemicolectomy in the past and difficulties in transillumination, the PEG tube was inserted through the colon and 1 wk later the internal bumper had moved within the colon lumen. A poly-trauma patient previously subjected to splenectomy[19] received a PEG inserted through the splenic flexure, recognized 2 years later within the colon lumen due to fecal odor. Two infants presented with fecal emesis 2 to 3 mo after a PEG, which was passed from the skin, through the colon, into the posterior stomach wall[20]. Finally, there were 4 more cases: One presenting 10 d later with rectal bleeding[21]; one presenting a year after PEG insertion, when the tube was obstructed[22]; one presented 3 d after PEG with abdominal distention, with the bumper being in the splenic flexure[23]; and, the last case, presenting with diarrhea 15 d after PEG placement, was found to have a colo-jejuno-gastric communication after the PEG tube had passed through the colon and jejunum before entering the stomach[24].

Liver injuries (n = 14)

In the cases where the PEG tube penetrated the liver prior to insertion into the stomach without causing severe bleeding, patients experienced pain either a few hours later, upon feeding induction[25], or within a week (5 cases)[26-29], or after 2 wk in the case of a patient having total colectomy and ileostomy[30]. In 3 patients, the liver injury was only recognized later as a liver abscess, after the gastrostomy internal bumper accidentally moved out of the stomach[31-33]. In another patient, during the process of changing gastrostomy tube, the new one failed to be inserted into the stomach and remained in the liver, thus becoming symptomatic[34]. Finally, it is of interest to separately mention the unfortunate case of an obese patient scheduled for gastrostomy by means of radiology. The presence of a colonic loop anterior to the stomach caused the radiologic procedure to be aborted and endoscopic gastrostomy was thus decided on and performed uneventfully. On day 3 post-procedure, a computed tomography scan was performed to totally exclude the possibility of colon injury - this revealed that the gastrostomy tube had traversed hepatic segment 3, making a large adjacent hematoma, resulting in the patient's death a few days later[35].

Additionally, there were 4 cases in which the passage of the gastrostomy tube through the left hepatic lobe parenchyma caused severe hemorrhage (hemoperitoneum), requiring surgical intervention[29,36-38].

Table 1 Classification according to the organ/anatomical structure injured

Classification of complications
Colonic injuries
Liver injuries
Vascular injuries/bleeding
R. gastric artery
L. gastric artery
Splenic artery
Gastroepiploic artery
Portal vein
Splenic artery and pancreas
Sup. pancreatic branch of SMA and pancreas
Lesser curvate small vessels
Gastroepiploic artery pseudoaneurysm
L. gastric artery pseudoaneurysm
Gastroduodenal artery pseudoaneurysm
Gastric wall intramural hematoma
Visceral injuries
Esophagus
Posterior gastric wall
Jejunum
Spleen
Peritonitis

SMA: Superior mesenteric artery.

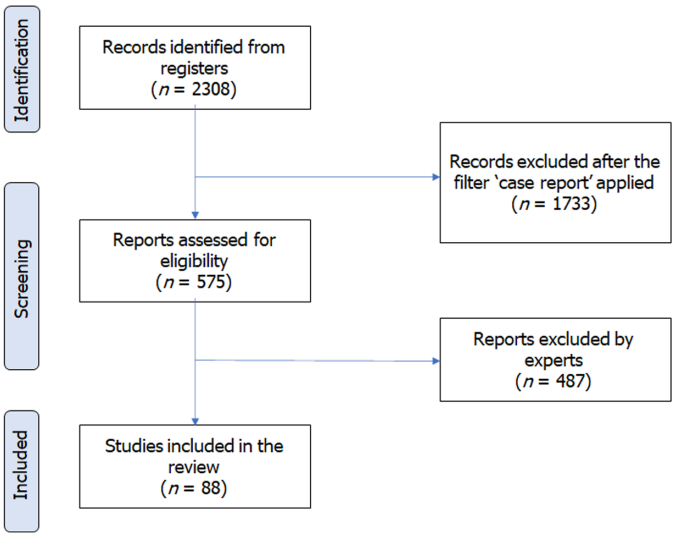

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Figure 1 Identification of studies *via* databases and registers.

Vascular injuries/bleeding (n = 12)

Ectopic insertion of the needle in the anatomical area of the major gastric curvature caused injury of the gastric artery (2 cases)[15], or its left branch[39], of the splenic artery[40], and of the gastro-epiploic

Table 2 Publications including the 50 cases of colonic injuries

Ref.	Cited	Clinical signs
Aschl *et al*[72]	*Z Gastroenterol* 2010; 48: 760-762	Diarrhea and fecal odor
Bertolini *et al*[18]	*World J Gastroenterol* 2014; 20: 11439-11442	Diarrhea and fecal odor
Brown *et al*[73]	*Pediatr Radiol* 2007; 37: 229-231	Fecal material exiting from the tube
Burke *et al*[74]	*Diagn Ther Endosc* 2011; 2011: 849460	Fecal material exiting from the tube
Chime *et al*[75]	*Gastrointest Med* 2020	Fecal material exiting from the tube
Diéguez Castillo *et al*[76]	*Gastroenterología y Hepatología (English Edition)* 2019; 42: 39-40	Fecal material exiting from the tube
Fernandes *et al*[77]	*Gastrointestinal endoscopy* 1988; 34: 368-369	Diarrhea and fecal odor
Friedmann *et al*[78]	*Parenter Enteral Nutr* 2007; 31: 469-476	Diarrhea and fecal odor
Guloglu *et al*[79]	*J Laparoendosc Adv Surg Tech A* 2003; 13: 69-72	Fecal material exiting from the tube
Heuss *et al*[80]	*Dtsch Med Wochenschr* 2012; 137: 2043-2046	Diarrhea and fecal odor
Huang *et al*[81]	*AJR Am J Roentgenol* 2005; 184: S65-66.	Fecal material exiting from the tube
Hwang *et al*[82]	*Clin Endosc* 2012; 45: 95-98	Fecal material exiting from the tube
Kim *et al*[83]	*Intest Res* 2014; 12: 251-255	Diarrhea and fecal odor
Kuriyama *et al*[84]	*Intern Med* 2016; 55: 3549	Fecal material exiting from the tube
Lee *et al*[85]	*Korean J Gastroenterol* 2014; 63: 120-4	Diarrhea and fecal odor
Lee *et al*[86]	*Clin Endosc* 2018; 51:196-200	Fecal material exiting from the tube
Lenzen *et al*[19]	*Journal of Gastroenterology and Hepatology* 2012; 27: 1254	Diarrhea and fecal odor
Lohiya *et al*[87]	*J Am Board Fam Med* 2010; 23: 681-684	Fecal material exiting from the tube
Murphy *et al*[16]	*J Am Geriatr Soc* 1991; 39: 532-533	Diarrhea and fecal odor
Nunes *et al*[88]	*Turk J Gastroenterol* 2019; 30:761-763	Diarrhea and fecal odor
Nunes *et al*[89]	*GE Port J Gastroenterol* 2019; 26:441-447	Diarrhea and fecal odor
Okutani *et al*[90]	*Acta Med Okayama* 2008; 62: 135-138	Diarrhea and fecal odor
Pitsinis *et al*[91]	*Eur J Clin Nutr* 2003; 57: 876-878	Diarrhea and fecal odor
Saltzberg *et al*[92]	*JPEN J Parenter Enteral Nutr* 1987; 11: 86-87	Diarrhea and fecal odor
Smyth *et al*[93]	*Nutrition* 2003; 19: 905-906	Diarrhea and fecal odor
Taheri *et al*[94]	*JPEN J Parenter Enteral Nutr* 2011; 35: 56-60	Diarrhea and fecal odor
Tong *et al*[95]	*Endoscopy* 2007; 39 Suppl 1: E69	Diarrhea and fecal odor
van Gossum *et al*[96]	*Endoscopy* 1988; 20: 161	Diarrhea and fecal odor
Jiménez Varo *et al*[97]	*Nutricion hospitalaria* 2014; 29: 460-463	Diarrhea and fecal odor
Winder *et al*[17]	*Gastrointest Endosc* 2016; 83: 1290-1291	Fecal material exiting from the tube
Yamazaki *et al*[98]	*Surg Endosc* 1999; 13:280-282	Diarrhea and fecal odor

artery (2 cases)[41,42]. Needle puncture at the lesser curvature led to: A huge retroperitoneal hemorrhage due to rupture of the splenic and superior mesenteric veins near the confluence to the portal vein[38] and severe injury to the splenic artery and pancreas[42], both occurring in previous cholecystectomy patients; massive hemoperitoneum after injury of small vessels on the lesser curvature, probably related to a first failed attempt to insert the needle into the stomach, followed by a second attempt[43]; and severe injury to the pancreas and the pancreatic branch of the superior mesenteric artery after needle insertion from the anterior stomach wall and penetration of the posterior wall towards the pancreas being just behind[44].

The formation of a pseudo-aneurysm after puncture of the gastro-epiploic artery[45]; of the left gastric artery[45,46]; and of the gastro-duodenal artery[47] was also reported. An intra-mural hematoma of the gastric wall also developed in a patient with platelet dysfunction and on a low dose of aspirin[48].

Splanchnic injuries (n = 12)

Two cases of esophageal catastrophic damage related to PEG placement were reported. In a 3-mo-old

boy weighing 3.7 kg, the pulling of a 18CH gastrostomy tube immediately led to esophageal intussusception towards the stomach and thus complete esophageal transection[49]. The other case was an obese, multi-trauma patient, on whom PEG procedure was difficult[50]. Without the help of transillumination, and only using finger pressure, 3 attempts, at a 45° angle, were made to insert the needle into the stomach. The patient became tachycardic, hypotensive, and progressively febrile, with upper abdominal tenderness, mediastinitis, thickening of the pericardium, and bilateral pleural effusions, leading, finally, on day 14 to an urgent left lateral-posterior thoracotomy which revealed a small hole on the anterior esophageal wall at the esophagogastric junction, covered by omentum. Additionally, the PEG was dislocated in the subcutaneous adipose tissue.

A case of gastric volvulus was reported in a 10-mo-old infant; PEG was performed at the age of 1 mo, under general anaesthesia. Unfortunately, the gastrostomy tube passed between the gastric curvature and the transverse colon to be inserted finally into the posterior gastric wall, causing the stomach to twist along its organo-axis and compromising the gastric outlet[51].

Four cases of PEG tube passage through the jejunal lumen prior to entering the stomach were also found. These cases remained silent from 8.5 to 24 mo, and were only discovered by symptoms occurring upon tube replacement[52-55].

Microbial peritonitis occurred in 3 cases: One following PEG on the posterior gastric wall[15] and another two after penetration of the jejunum[15] and transverse colon[40], both being between the abdominal and the gastric wall. Finally, there were two cases of severe spleen injuries[48,56] in patients with previous surgeries.

DISCUSSION

Critical analysis of events

The PEG procedure is a well-established method for safe creation of a gastrostomy, without surgery, and in most cases, without general anaesthesia. The goal of PEG is to endoscopically insert a flexible gastrostomy catheter *via* the mouth-esophagus-stomach route - by pulling it from the outside - to be externalized in the mid-abdomen, which allows easy delivery of commercially available liquid nutrients to the patient. While most PEG procedures have yielded positive long-term outcomes, there are substantial adverse events associated with their performance; some of them, directly related to the technical part of the operation itself, would have been avoided if the manipulations for tube implantation had been carried out in accordance with the generally accepted guidelines[2-4,6-9]. In our opinion, only an inexperienced or super-experienced endoscopist would dare to ignore these rules: The former from ignorance of danger and of basic rules and the latter from excessive self-confidence or arrogance.

In the present study, we decided to review and comment on the adverse events reported in the literature, irrespective of their being either major or minor, early or late, after two experienced endoscopists, each with almost 40 years of experience in performing PEG, were tasked to critically examine the literature and identify those complications that could have been prevented.

Colonic injuries

The displacement of the transverse colon in close proximity to or over the anterior gastric wall, due mainly to stomach and small bowel overinflation at the beginning of the procedure, can predispose the patient to colonic injury during the needle puncture for PEG placement[8,10,24,57-59]. The endoscopist must take into consideration that the laxity of the colonic mesentery is more common among elderly patients[23] and that both chronic constipation and previous abdominal surgery are serious parameters which further increase the risk of colon penetration if the colon interposes between the abdominal wall and the stomach, creating colo-gastric communication[60,61]. Although colon perforation is considered a severe trauma needing emergency treatment due to incipient fecal peritonitis, in most cases it is totally asymptomatic. Some transient episodes of fever or ileus may occur in a few patients, the diagnosis of which is often difficult, given the problems in communication due to underlying altered mental status [3]. In most cases, colon compression between the external and internal bumpers of the gastrostomy tube partially closes the opening and thus minimizes the leakage, while the artificial liquid enteral formulas given for feeding further minimize the existence of colon over-distension due to a bulk mass of feces.

On the other hand, when the PEG is removed for replacement or accidentally pulled back a little, it is almost impossible to reinsert the replacement tube through the colon, into the stomach; for this reason, the technique of exchanging the tube over a guidewire can prove a safe solution. Once feeding restarts, diarrhea occurs, due to the acceleration of increased motility of the colon and thus the rapid passage of undigested food to the anus, this being the most common symptom for referral of the patient to the treating physician, leading to recognition of the complication. In a few cases, leakage of feces through the cutaneous opening helps diagnosis, while in the case of total removal of the tube a colo-cutaneous fistula is created[8,11,61].

Liver injuries

Passage of the gastrostomy tube through the liver may happen in a similar way to that occurring with the colon, when the left lateral liver lobe interposes between the abdominal wall and the stomach. Although such an injury, which is puncture of the "bloody" liver and passage of the PEG tube through into the stomach, would be expected to be associated with severe intraperitoneal bleeding, most of the cases have no prominent hemorrhage, probably because of liver compression between the internal and external bumpers of the gastrostomy tube. However, bleeding occurs both at the time of PEG tube removal for replacement, and more extensively as the endoscopist tries to insert and inflate the balloon of a new tube[8,10,11,57,61].

The main reason for this complication is the violation of standard rules: (1) When liver tissue exists between the abdominal wall and the stomach, it is impossible to identify an area of maximum trans-illumination on the abdominal wall, since there is only a rather diffuse light, only visible in thin individuals; (2) Even more distinctly, the finger imprint from the outside palpation is not clearly identifiable as a "point" but rather only as an extra-lumen pressure moving the anterior wall of the stomach; (3) Regarding the "safe tract" technique - that is the technique involving constant aspiration while advancing the needle - it is our personal opinion that it proves more reliable when performed in such cases. In case the needle enters the liver accidentally, it is much easier to aspirate blood and be aware of the complication. On the contrary, if the needle enters the colon, fecal matter may not be aspirated, making the endoscopist unaware of the complication until it is possibly too late; and (4) Finally, liver hilum palpation is a good practice, totally forgotten nowadays[3,11,62].

Bleeding

Significant bleeding happens when the needle "blindly" punctures the underlying tissues; large or small arteries of the great and lesser gastric curvature or the gastric insisura may occasionally - and easily - be found on the route of the needle. Of course, just below the epigastrium is located the anterior gastric wall, which does not have large vessels; when excess air volume over-inflates the stomach, it can be twisted either clockwise or counterclockwise along its organ axis, thus exposing the great or the lesser curvature and their vessels, and more extremely, perhaps the posterior gastric wall - there were at least 5 cases of PEG performed in the posterior gastric wall[15,20,44,51]. This stomach rotation has been fully documented by Croaker *et al*[63], who inserted a laparoscopic camera into the abdomen in order to study the movement of the viscera when inflated[58,64].

Another dangerous condition for bleeding is the previously operated abdomen. Thick adhesion bundles, sometimes containing a large vessel, pull and rotate the stomach and the gut, changing their orientation in the abdominal cavity. Characteristic are the cases of previous cholecystectomy patients, in whom shrinkage of the area between the liver, duodenum, and gastric insisura led to severe needle-induced splenic artery and pancreatic tissue injury[38,42]. Much more dangerous is the situation after a previous colectomy or gastrectomy of any type, pancreatic surgery, or aortic surgery[60]. However, in these cases there is the surgical incision scar to warn the operator that some anatomical alterations may exist in the abdominal cavity - they must, however, notice it.

Finally, there are reported injuries of the splenic artery, the mesenteric veins, and even the aorta, all leading to hemo-peritoneum and/or retro-peritoneal hematomas. Additionally, but of less seriousness, are injuries to abdominal wall vessels and the rectus sheath, which, fortunately, are immediately recognizable and therefore, generally, stopped by applying constant pressure for a few minutes between the internal and external gastrostomy bumpers and over the abdominal wound[3,8]. A negative paradigm is if the operator, despite recognizing a large intramural hematoma in progress, stops the procedure. The expansion of the hematoma would be controlled if it was immediately compressed by the bumpers after finishing PEG insertion[48].

On the other hand, although there are detailed guidelines and strict warnings to stop some antiplatelet drugs, there are cases where these are not heeded. When the endoscopist decides to perform the PEG simply at the request of the treating physician, despite the European Society of Gastrointestinal Endoscopy (ESGE) recommendations on anti-coagulant use[4,65,66], the responsibility rests entirely with the endoscopist. There is no case for an urgent endoscopic gastrostomy.

Splanchnic viscera injuries

Among the described injuries to the small bowel and colon causing peritonitis, as well as to the spleen and pancreas due to over-inflation of the stomach followed by rotation along the organ axis, three cases of great importance need to be noted[8,58,59]. The first is an esophageal intussusception and then transection in a 3-mo-old boy, weighing 3.7 kg, to whom insertion of an adult gastrostomy tube of 18Ch was attempted[49]. The second case is a gastric volvulus, following insertion of the PEG into the posterior gastric wall, due to stomach over-inflation, finally causing compromised gastric emptying[51]. The third is the case of an obese, multi-trauma patient; without trans-illumination, 3 puncture attempts at a 45° angle, resulted in a gastrostomy placement but also an esophageal perforation which were fortunately recognized after 14 d of suffering mediastinitis[50].

Further comments

It is common sense that PEG-procedure-related complications are undoubtedly associated with the endoscopist's skill and adherence to the basic principles of good practice; both an inexperienced and a super-expert endoscopist, based on the one hand on lack of skill and the other on an excess of confidence, are likely to be implicated in an iatrogenic injury. While the inexperienced practitioner would probably persist longer, possibly resulting in a serious complication, likely to remain temporarily unrecognized, an expert might consider that he could rush the rules, because of his skill, and thus also involve the patient in severe complications, only recognized much later.

But what is the meaning of 'inexperienced' and 'super-expert' in relation to the endoscopist? Practically, an experienced practitioner is somebody well-trained in the past, who continuously renews his skills and maintains his competence by means of frequent, repetitive practice over the years. Officially, there is no standard curriculum for endoscopy training in performing PEG, as with many other much newer interventional techniques. The latest curricula, from 2019 thereafter, issued by the ESGE are those for training in performing endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound, and electrostatic discharge (ESD), which highly recommend a minimum, non-interrupted training period of 12 mo in a high volume, qualified, training center and involving the performance of more than 300 ERCPs. As a foundation, the endoscopist should have previously achieved competence in upper gastrointestinal endoscopy, through personal experience of at least 300 gastroscopies, followed by at least a further year, and ideally 3 years, of dedicated training that is likely required to reach competence. For ESD, initial experience of at least 20 procedures in animal or *ex vivo* models is highly recommended, and in order to maintain proficiency, ESGE recommends a minimum case load of 25 ESD procedures per year to demonstrate maintenance of competence. The attainment of competence in interventional or therapeutic endoscopy is not a single event, but a career-long process - meaning that endoscopists should be continually performing such procedures[67-69].

In this commentary review, we discuss the existing evidence of major procedural complications after a PEG insertion, while focusing on the exact cause of malpractice, as documented by cases meticulously collected from the literature over a period of more than 35 years. In other words, we have tried to find and underline the errors in the manipulations made which result in each specific complication.

Initially we note that the serious complications may occur related mainly to the type and location of the needle puncture[35,36]. However, to the best of our knowledge, few reports have addressed the relationship between PEG site and complications. Lee *et al*[13] found by a multivariate analysis that PEG tube insertion in the upper body of the stomach was a significant risk factor for complication occurrence, with the most obvious reason being the relatively long distance between the gastric and abdominal walls in the upper body as compared with the lower gastric body; this distance produces stronger tension between the abdominal and gastric walls during stomach contraction, inducing slow or incomplete adherence and thus fistula formation[64].

An experienced endoscopist, prior to performing the PEG procedure, lays the patient in a reverse or anti-Trendelemburg position, so that viscera moves downward to the pelvis. He/she also avoids overfilling the stomach and small bowel with air, which may 'lift' the transverse colon and increase the probability of colon, or even intestinal injury. He/she then checks thoroughly for the proper trans-illumination through the abdominal wall of the light source of the distal tip of the endoscope, and ensures the endoscopically visible imprint of his finger palpation on the patient's skin, at the center of the site of maximum illumination[7,57,62,70,71]. He/she is also extra cautious in the case of previous abdominal surgery, which remains a relative contra-indication for the young and inexperienced endoscopist[60], as is also obesity. In every case, he is careful to insert the needle strictly at a 90° angle to the skin, to ensure both the shortest route of the tube within the body and, mainly, so the abdominal opening is in line with the gastric opening, both of which will facilitate the proper adhesion between the stomach and abdominal walls. When the two openings are not aligned, the tension is likely to lead to tube dislodgement and peritonitis. Finally, he/she avoids multiple needle punctures - failure means that there is a violation of rules of trans-illumination and finger palpation, and even one additional puncture may be the cause of peritonitis or severe bleeding.

When transillumination or visible imprint or both are not clear, the endoscopist must understand that he/she violates the standard requirements and take full responsibility for any subsequent complications. Phrases such as "I have the feeling the stomach is just behind the xiphoid" are absolutely inappropriate, indeed wrong, and a bad example for younger endoscopists. The same applies to the use of the "safe tract" technique, which is endoscopic visualization of the needle and simultaneous return of air into the fluid-filled[57]. Return of fluid or gas prior to endoscopic visualization of the tip of the needle in the stomach lumen when it is inserted under continuous suction, means that the needle has passed through another organ interposed between the stomach and the abdominal wall, although a negative test does not provide a hundred percent certainty of no viscera in-between[17].

CONCLUSION

As a conclusion, we have to accept that complications will continue to occur, even in high volume

centers with well qualified practitioners; however, both young and experienced endoscopists must understand and deeply believe that they will not be blamed for stopping a PEG procedure in the case of obscure trans-illumination and an unsatisfactory palpation test, and much more in the case of a previously operated abdomen. On the contrary, they will and should be blamed in the case of a preventable injury, which may finally cost even the life of an albeit high risk patient.

ARTICLE HIGHLIGHTS

Research background

This study was carried out by specialists who are involved on a daily basis both in the performance of gastrostomies and in the management of their complications, which often have disastrous consequences. This study aimed to identify the problems internationally and to find possible methods of preventing them.

Research motivation

Trying to figure out and analyze the percutaneous endoscopic gastrostomy (PEG) tubes' complications, and focus on those that could be predicted and furthermore avoided.

Research objectives

To investigate the international literature in order to clarify the importance and the severity of these complications, and the possible ways of avoiding them.

Research methods

A 30-year database research was carried out, investigating the literature on PubMed, using the terms "percutaneous endoscopic gastrostomy" AND "complications", and all the case reports or case series were included, with the only language restriction being Chinese.

Research results

We identified 2308 articles. Only 575 were included according to the research criteria placed. After expertise investigation, 88 articles were in the final selection.

Research conclusions

The complications that can arise from the potentially simple technique of the PEG are of great concern to the international scientific community.

Research perspectives

Complications of PEG tube placement should be avoided.

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FOOTNOTES

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META-ANALYSIS

Nutritional status efficacy of early nutritional support in gastrointestinal care: A systematic review and meta-analysis

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Abstract

BACKGROUND

Gastrointestinal surgery is a complicated process used to treat many gastrointestinal diseases, and it is associated with a large trauma: Most patients often have different degrees of malnutrition and immune dysfunction before surgery and are prone to various infectious complications during postoperative recovery, thus affecting the efficacy of surgical treatment. Therefore, early postoperative nutritional support can provide essential nutritional supply, restore the intestinal barrier and reduce complication occurrence. However, different studies have shown different conclusions.

AIM

To assess whether early postoperative nutritional support can improve the nutritional status of patients based on literature search and meta-analysis.

METHODS

Articles comparing the effect of early nutritional support and delayed nutritional support were retrieved from PubMed, EMBASE, Springer Link, Ovid, China National Knowledge Infrastructure, China Biology Medicine databases. Notably, only randomized controlled trial articles were retrieved from the databases (from establishment date to October 2022). The risk of bias of the included articles was determined using Cochrane Risk of Bias V2.0. The outcome indicators, such as albumin, prealbumin, and total protein, after statistical intervention were

combined.

RESULTS

Fourteen literatures with 2145 adult patients undergoing gastrointestinal surgery (1138 patients (53.1%) receiving early postoperative nutritional support and 1007 patients (46.9%) receiving traditional nutritional support or delayed nutritional support) were included in this study. Seven of the 14 studies assessed early enteral nutrition while the other seven studies assessed early oral feeding. Furthermore, six literatures had "some risk of bias," and eight literatures had "low risk". The overall quality of the included studies was good. Meta-analysis showed that patients receiving early nutritional support had slightly higher serum albumin levels, than patients receiving delayed nutritional support [MD (mean difference) = 3.51, 95%CI: -0.05 to 7.07, Z = 1.93, P = 0.05]. Also, patients receiving early nutritional support had shorter hospital stay (MD = -2.29, 95%CI: -2.89 to -1.69), Z = -7.46, P < 0.0001) shorter first defecation time (MD = -1.00, 95%CI: -1.37 to -0.64), Z = -5.42, P < 0.0001), and fewer complications (Odd ratio = 0.61, 95%CI: 0.50 to 0.76, Z = -4.52, P < 0.0001) than patients receiving delayed nutritional support.

CONCLUSION

Early enteral nutritional support can slightly shorten the defecation time and overall hospital stay, reduce complication incidence, and accelerate the rehabilitation process of patients undergoing gastrointestinal surgery.

Key Words: Early nutritional support; Gastrointestinal care; Nutritional status; Gastrointestinal surgery; Gastrointestinal diseases

Core Tip: Gastrointestinal tract surgery is a complex process, with a wide range of operations and large trauma. It is easy to have various infectious complications in postoperative recovery, which affects the efficacy of surgical treatment. Early postoperative nutritional support can provide necessary nutrition, restore intestinal barrier, and reduce complications. However, whether early postoperative nutritional support can significantly improve the nutritional status of patients, different studies have reached different conclusions. This study used literature retrieval and Meta analysis to conduct quantitative analysis. It was found that early enteral nutrition support could shorten the defecation time after gastrointestinal surgery, the overall hospital stay, reduce the incidence of complications, and speed up the rehabilitation process. However, the improvement of nutritional status was not significant.

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INTRODUCTION

Gastrointestinal diseases (especially tumors) are becoming common yearly, thus seriously threatening the health and quality of life of many patients and burdening families and the whole society[1,2]. Gastrointestinal surgery is a complicated process used to treat many gastrointestinal diseases and is associated with large trauma. Patients have different degrees of malnutrition and immune dysfunction before surgery and are prone to various infectious complications during postoperative recovery, affecting the efficacy of surgical treatment[3]. However, nutritional support therapy can improve the above problems. Perioperative enteral or parenteral nutritional support provides the necessary nutritional supply and energy demand, thus improving the nutritional status of the patients and promoting early recovery of normal physiological function, especially gastrointestinal function. As a result, nutritional support therapy has received great clinical attention in recent years[4]. Parenteral nutrition (PN) and enteral nutrition (EN) are the most commonly used nutritional support methods. PN is mostly used in the early stage after gastrointestinal surgery in clinical practice[5]. However, PN can cause metabolic and functional complications by affecting intestinal mucosal metabolism and function, leading to impairment of the intestinal mucosal barrier, bacterial and endotoxin translocation, and increasing the incidence of enterogenous infections[6]. The rapid development of fast-track surgical nutrition in recent years can improve postoperative small intestinal peristalsis, digestion, and

absorption function after a few hours of abdominal surgery, thus promoting the rapid development of early postoperative EN and early EN support[7]. Jordan *et al*[8] indicated that early EN can improve the reconstruction of the immune barrier, accelerate postoperative recovery, reduce complication incidence, and shorten the length of hospital stay. Besides, early EN is simpler, economical, and free of serious complications. However, no meta-analysis has studied the effect of early EN on nutritional status. Das *et al*[9] showed that early EN support cannot significantly improve the nutritional status of patients compared with traditional nutritional support. This study aimed to quantitatively investigate the effect of early nutritional support on nutritional status of patients undergoing gastrointestinal surgery based on meta-analysis.

MATERIALS AND METHODS

Database

All articles published before October 2022 were retrieved from PubMed, EMBASE, Scopus, Web of Science, China National Knowledge Infrastructure, and Chinese BioMedical Literature Database, regardless of the language. The clinical study registration website (Clinicaltrials.org) was also checked to avoid missing unpublished literature.

Search strategy

The following keywords were used for literature search: ("early"[All Fields] AND ("nutritional support"[MeSH Terms] OR ("nutritional"[All Fields] AND "support"[All Fields]) OR "nutritional support"[All Fields]) AND ("digestive system surgical procedures"[MeSH Terms] OR ("digestive"[All Fields] AND "system"[All Fields] AND "surgical"[All Fields] AND "procedures"[All Fields]) OR "digestive system surgical procedures"[All Fields] OR ("gastrointestinal"[All Fields] AND "surgery"[All Fields]) OR "gastrointestinal surgery"[All Fields])) AND (randomized controlled trial[Filter]).

Inclusion and exclusion criteria

Inclusion criteria: (1) Only single or multi-center randomized controlled trials (RCTs); (2) Patients undergoing gastrointestinal surgery, including esophageal cancer resection, gastric cancer resection, pancreatic cancer resection, acute pancreatitis, colorectal cancer resection and other types of surgery, excluding patients intolerant to early EN support; (3) Good quality studies based on implementation process (randomization process, data deviation, and data measurement). The patients were divided into the experimental group (observation group) and the control group. The possibility of deviation from the established intervention in the study quality was evacuated if there were differences in the basic data, such as age, type, tumor grade, and surgical classification between the two groups. Patients in the two groups underwent surgery *via* the same surgical methods, preoperative preparation, and infection control. However, patients in the experimental group began to receive nutritional support in the early postoperative period, while those in the control group received traditional nutritional support or delayed nutritional support. Early nutritional support was performed 1-3 d after surgery (enteral nutritional support, oral feeding of liquid diet, PN, or a mixture of multiple nutritional support methods), while conventional nutritional support was given using indwelling intestinal nasal tube, conventional intravenous infusion. The patients were gradually given clear water, liquid food, semi-liquid food after the first defecation; and (4) The primary outcome indicators included nutritional status indicators, serum albumin indicators, serum prealbumin indicators, and serum total protein indicators after the intervention, while the secondary outcome indicators included length of hospital stay, first defecation time, and incidence of postoperative complications.

Exclusion criteria: (1) Non-RCT studies (descriptive literature, observational studies, meeting minutes, review studies); (2) Studies with stroke patients, joint replacement patients, and other patients undergoing non-gastrointestinal surgery; (3) Studies with no nutritional status outcome indicators, or where data on outcome indicators could not be obtained; and (4) Studies comparing different nutritional formulations, or studies comparing EN with PN.

Literature quality evaluation

The quality of the included RCTs was conducted using Cochrane Risk of Bias V2.0[10]. This process involved five domains (randomization process, implementation bias, data bias, data measurement bias, and selection bias) and 1 overall bias assessment. Three evaluations ("low risk", "some concerns of risk" and "high risk") were used for each domain (or overall bias).

Outcome indicators

No other nutritional indicators, such as postoperative weight loss, muscle loss, hemoglobin, serum sodium, and potassium, were included in this study according to the actual retrieved literature.

Literatures screening

Two researchers screened the retrieved literatures, read the abstract, obtained the remaining literatures after preliminary screening according to the inclusion and exclusion criteria, read the full text and further screened the RCTs, and removed the studies with serious bias and low quality after quality evaluation.

Data extraction and transformation

Data, such as interventions, total number of people, grouping, characteristics of study subjects, and outcome indicators, were extracted and entered Excel sheets. A uniform unit was used to represent the data. For example, g/dL was converted to g/L, 1 g/dL = 10 g/L and hour (h) was converted to day (d).

Statistical analysis

Continuous data (serum albumin, serum prealbumin, serum total protein, length of hospital stay, first defecation time after intervention) were expressed using combined mean difference (MD) and 95%CI as effect size, while discrete data (complication rate) were expressed using odd ratio (OR) as effect size. The combined results were presented as a forest plot using random effects model with $P < 0.05$ considered statistically significant. Tau values were calculated using Q test to ensure literature heterogeneity ($P < 0.05$ indicated heterogeneity). Subgroup analysis and one-by-one exclusion were used to calculate the contribution of each study to the results in case of heterogeneity between the articles. Publication bias was quantified using Egger' test and presented using trim-filled funnel plots.

RESULTS

Literature screening process and results

Literature search and screening (identification, screening involving the three main processes) followed The Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendation. The flow chart is shown in Figure 1. A total of 693 literatures were initially retrieved, and only 14 literatures were included in the final study after de-duplication and screening (Table 1).

Basic characteristics and patient characteristics of included literatures

Fourteen studies with 2145 adult patients (1138 patients (53.1%) who received early postoperative nutritional support and 1007 patients (46.9%) who received traditional nutritional support or delayed nutritional support) were included in this analysis. Seven of the 14 studies adopted early EN, while the other seven studies adopted early oral feeding (Table 1).

Literature bias and quality assessment

Three of the 14 articles (21.4%)[18-19,23] were retrospective controlled studies and had "some risk of bias" in terms of deviations from established interventions, data measurement bias, while four articles (28.6%)[11,16,18,19] had "some risk of bias" in terms of data measurement. Six articles had "some risk of bias" overall while eight articles had "low risk". All articles had good overall quality. The details of the assessment using Cochrane Risk of Bias V2.0 are shown in Figure 2A and Table 2.

Meta-quantitative analysis results of outcome indicators

Albumin (g/L): Six literatures reported albumin levels after nutritional support intervention in the two groups. The heterogeneity among the literatures was statistically significant ($\chi^2 = 46.55$, $I^2 = 89\%$, $P < 0.01$), including 402 patients who received early nutritional support and 385 patients who received traditional nutritional support. A random-effects model showed that serum albumin levels were slightly higher in patients receiving early nutritional support than in patients receiving traditional nutritional support (MD = 3.51, 95%CI: -0.05 to 7.07, $Z = 1.93$, $P = 0.05$, Figure 2A).

Prealbumin and total serum protein (g/L): Only two literatures reported prealbumin and serum total protein levels (Table 3).

Length of stay (d): Twelve literatures compared the length of hospital stay between the two groups. The heterogeneity among the literatures was statistically significant ($\chi^2 = 37.10$, $I^2 = 70\%$, $P < 0.01$) (1011 patients who received early nutritional support and 994 patients who received traditional nutritional support). A random-effects model showed that patients receiving early nutritional support spent significantly less time in the hospital than patients receiving traditional nutritional support (MD = -2.29, 95%CI: -2.89 to -1.69, $Z = -7.46$, $P < 0.0001$, Figure 2B).

Time to first defecation: Sevan literatures compared the first defecation time between the two groups. The heterogeneity among the literatures was statistically significant (Chi^2=46.80, I^2=87%, $P < 0.01$) (750 patients receiving early nutritional support and 733 patients receiving traditional nutritional support). A random-effects model showed that patients receiving early nutritional support took a significantly

Table 1 Basic characteristics, patient characteristics, and outcome indicators of the included literatures

Ref.	Year	Design	Intention-to-treat total	Sample (E/D)	Surgery type	Age (yr)	Nutrition support mode	Outcomes
Sun *et al*[11]	2017	A prospective, randomized, single-blinded, controlled study	107	53/54	Major abdominal surgery	56 ± 10	Oral feeding	e, f
Pragatheeswarane *et al*[12]	2014	A randomized controlled study	120	60/60	Elective open bowel surgeries	46.5 ± 17.2	Oral feeding	d, e, f
Dag *et al*[13]	2011	A randomized controlled study	199	99/100	Elective open colorectal cancer surgery	62 (35-85)	Oral feeding	d, e, f
Fujii *et al*[14]	2014	A controlled study	120	62/58	Elective colorectal resection surgery	67.4 ± 11.7	Oral feeding	a, d, e, f
Liao *et al*[15]	2020	A randomized controlled study	41	21/20	Esophageal carcinoma surgery	57.2 ± 8.2	Enteral nutrition	d, f
Mi *et al*[16]	2012	A randomized controlled study	60	30/30	Gastrectomy	57.2 ± 9.5	Oral feeding	a, b, d, f
Mahmoodzadeh *et al*[17]	2015	A randomized controlled study	109	54/55	Gastrointestinal surgeries	64.2 ± 8.2	Oral feeding	d, f
Wang *et al*[18]	2005	A retrospective comparative study	454	227/227	Colorectal cancer resection surgery	63.5 ± 11.3	Enteral nutrition	d, e, f
Qiu *et al*[19]	2020	A retrospective comparative study	26	13/13	Severe acute pancreatitis treatment	33.4 ± 5.7	Enteral nutrition	a, c, d
Wang *et al*[20]	2015	A randomized controlled study	188	101/87	Esophagectomy	59.5 ± 8.4	Enteral nutrition	a, c, d, e, f
Klappenbach *et al*[21]	2013	A randomized controlled study	295	148/147	Abdominal elective surgery	37.3 ± 18.1	Oral feeding	d, e, f
Li *et al*[22]	2015	A randomized controlled study	300	150/150	Gastric cancer surgery	59.2 ± 9.7	Enteral nutrition	a, b, d, f
Zou *et al*[23]	2014	A retrospective comparative study	93	46/47	Severe acute pancreatitis treatment	46.5 (34.6-59.3)	Enteral nutrition	a, d, f
Barlow *et al*[24]	2011	A randomized controlled study	121	64/57	Upper gastrointestinal cancer surgery	64.0 ± 15.0	Eternal feeding	f

a: Albumin (g/L); b: Prealbumin (g/L); c: Total serum protein (g/L); d: Length of stay (d); e: Time to first defecation (h); f: Complications rate; E/D: Early/delayed.

shorter time to first defecation than patients receiving traditional nutritional support (MD = -1.00, 95%CI: -1.37 to -0.64, Z = -5.42, P < 0.0001, Figure 2C).

Complication rate: Thirteen literatures compared the incidence of complications between the two groups. There was no statistically significant heterogeneity among the literatures (χ^2 = 18.74, I^2 = 36%, P = 0.09). A fixed effect model showed that the incidence rate of complications was significantly lower in patients receiving early nutritional support than in patients receiving traditional nutritional support (OR = 0.61, 95%CI: 0.50 to 0.76, Z = -4.52, P < 0.0001, Figure 2D).

Heterogeneity investigation: Twelve literatures were divided into two subgroups based on different methods of early nutritional support to analyze the source of literature heterogeneity. Subgroup analysis showed that there was no significant difference between the two groups (P = 0.55), indicating that early nutritional support method was not the source of literature heterogeneity (Figure 3).

Influence analysis: The influence analysis on the outcome indicators of postoperative hospital stay was performed by removing the literatures one by one. The results did not find any significant differences, indicating that the overall results were stable and there was no variability in the study results (Figure 4).

Publication bias analysis: Publication bias in the combined results of postoperative hospital stay outcome indicators was measured using Egger' test (t = -0.78, P = 0.4551). The P value was > 0.05, indicating that there was no publication bias. The funnel plot after trim-filled is shown in Figure 5.

Table 2 Risk of bias and quality assessment based on Cochrane Risk of Bias V2.0

Ref.	Randomization Process	Bias from defined interventions	Data missing bias	Data measurement offset	Optional reporting	Overall bias	Weight (%)
Sun *et al*[11]	Low	Low	Low	Some concerns	Low	Some concerns	8
Sun *et al*[11]	Low	Low	Low	Low	Low	Low	8
Pragatheeswarane *et al*[12]	Low	Low	Low	Low	Low	Low	8
Dag *et al*[13]	Low	Low	Low	Low	Low	Low	8
Fujii *et al*[14]	Low	Low	Low	Low	Low	Low	8
Liao *et al*[15]	Low	Low	Low	Some concerns	Low	Some concerns	8
Mi *et al*[16]	Low	Low	Low	Low	Low	Some concerns	8
Mahmoodzadeh *et al*[17]	Low	Some concerns	Low	Some concerns	Low	Some concerns	8
Wang *et al*[18]	Low	Some concerns	Low	Some concerns	Low	Some concerns	8
Qiu *et al*[19]	Low	Low	Low	Low	Low	Low	8
Wang *et al*[20]	Low	Low	Low	Low	Low	Low	8
Klappenbach *et al*[21]	Low	Low	Low	Low	Low	Low	8
Li *et al*[22]	Low	Some concerns	Low	Low	Low	Some concerns	8
Zou *et al*[23]	Low	Low	Low	Low	Low	Low	8
Barlow *et al*[24]	Low	Some concerns	Low	Some concerns	Low	Some concerns	8
Klappenbach *et al*[21]	Low	Low	Low	Low	Low	Low	8
Li *et al*[22]	Low	Low	Low	Low	Low	Low	8
Zou *et al*[23]	Low	Some concerns	Low	Low	Low	Some concerns	8
Barlow *et al*[24]	Low	Low	Low	Low	Low	Low	8
Klappenbach *et al*[21]	Low	Low	Low	Low	Low	Low	8

Table 3 Meta-analysis results of other nutritional indicators

Outcomes	Literature number	Analysis mode	*P* value	Effect size	Pooling value	Z, *P* value
Prealbumin	2	Fixed effect mode	0.22	mean difference	12.4776 (9.1231, 15.8320)	7.29, < 0.0001
Serum total protein	2	Random effect mode	0.0002	mean difference	5.2401 (-5.1833, 15.6635)	0.99, 0.3245

DISCUSSION

Gastrointestinal surgery can lead to many pathophysiological changes in the human body (acute phase reactions), especially after larger operations, causing significant and persistent metabolic alterations characterized by hypercatabolism and declining total somatic cell counts[25]. Yuan *et al*[26] suggested that early EN may mitigate this endocrine and metabolic response. The recovery of intestinal function takes about three days after abdominal surgery due to anesthesia and surgical trauma, and most recovery markers are anal excretions. However, postoperative gastrointestinal paralysis mainly occurs in the stomach and colon. Besides, most small intestines with normal preoperative function recover from peristalsis a few hours after surgery and thus can absorb nutrients for about 12 h, thus providing a theoretical basis for the implementation of EN in the early postoperative period[27].

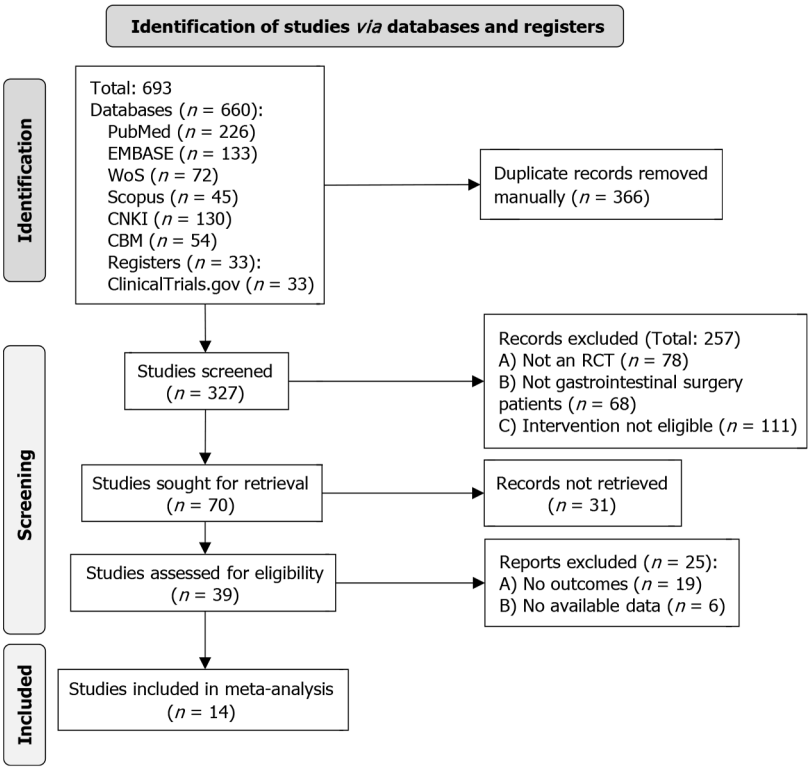

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Figure 1 PRISMA based literature selection. WoS: Web of Science; CNKI: China National Knowledge Infrastructure; CBM: Chinese BioMedical Literature Database; RCT: Randomized controlled trial.

In this study, serum prealbumin levels were significantly higher in the early nutritional support group than in the traditional nutritional support. However, albumin level and serum total protein levels were not significantly different between the two groups, suggesting that early nutritional support does not significantly improve nutritional status of patients. Also, the combined results showed that early nutritional support shortened the first defecation time and hospital stay, reduced complications (infection), and accelerated postoperative rehabilitation of patients. Postoperative gastrointestinal paralysis only occurs in the stomach and colon. The small intestine can quickly restore peristalsis and absorption function. The intestinal mucosa with intraluminal nutrition is the main way to obtain energy when the body is hungry, fasting, disease process, surgical trauma, and other circumstances. However, the intestinal mucosa cannot obtain the nutritional substrates required for its energy supply from the intestinal lumen. Intestinal mucosal barrier and immune barrier damage may lead to intestinal flora imbalance, intestinal failure, resulting in poor prognosis. Partial nutrient supplementation can promote early recovery of intestinal physiological function after surgery, protect the barrier function of intestinal mucosa, and prevent postoperative infectious complications[28]. In addition, early EN support ensures the energy supply of immune cells and normal operation of immune cell function while providing nutrients for the intestinal mucosa, thereby promoting the recovery of immune function after surgery and effectively inhibiting the inflammatory response[29]. In this study, early nutritional support was consistent with the nutritional formula adopted for delayed nutritional support. The effect of the two nutritional support regimens on patient nutrition was not significantly different. Besides, no theoretical support has indicated whether early nutritional intervention after surgery can improve the nutritional status of patients. The improvement of the nutritional status of patients is mainly determined by the patient's physical condition and the formulation of nutritional preparations. Nonetheless, the clinical value of early nutritional intervention for a better prognosis should not be ignored.

In this meta-analysis, Boscarino *et al*[30] concluded that EN can improve intestinal mucosal circulation, facilitate epithelial cells to take energy directly from the intestine and improve microecological environment, prevent translocation of intestinal flora, protect intestinal mucosal barrier, reduce bacterial infection, and promote intestinal peristalsis in postoperative patients compared with PN. However, this meta-analysis did not focus on the type of nutritional support.

Early postoperative nutritional support cannot be as early as possible. Notably, EN may only increase the burden of body metabolism when the respiratory, circulatory, water electrolyte, and acid-base balance of critically ill patients are not stable. In addition, EN may cause diarrhea, abdominal distension, vomiting, and other symptoms when intestinal function has not been resuscitated, thus aggravating the physiological dysfunction. Therefore, special attention should be paid to indications when early postoperative enteral nutritional support is applied. Early nutritional support should be discontinued

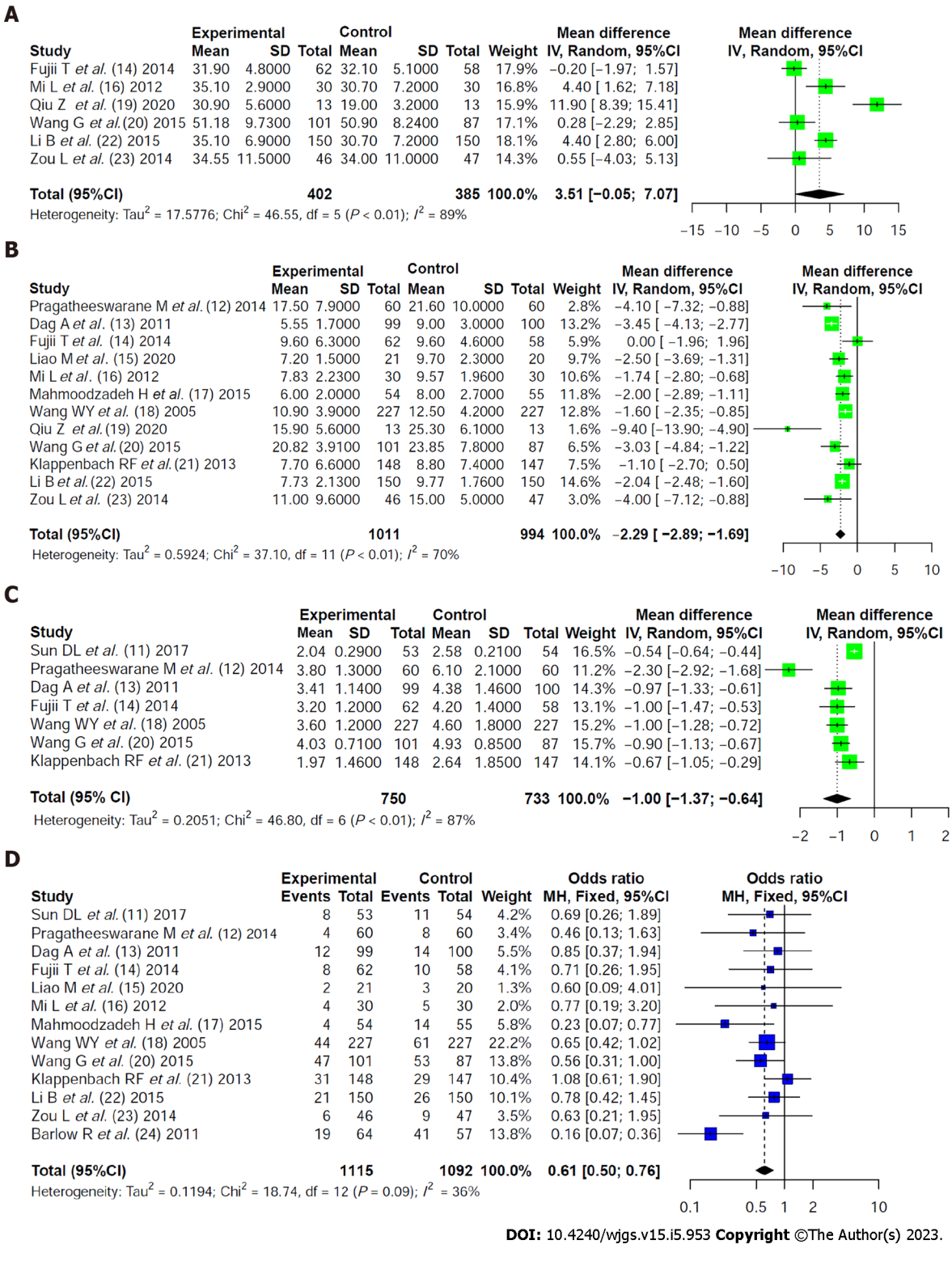

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Figure 2 Effect of early nutrition support and delayed nutrition support on postoperative albumin level, postoperative hospital stay, postoperative time to first defecation, and postoperative complication rate. A: Effect of early nutrition support and delayed nutrition support on postoperative albumin level; B: Effect of early nutrition support and delayed nutrition support on postoperative hospital stay; C: Effect of early nutrition support and delayed nutrition support on postoperative time to first defecation; D: Effect of early nutrition support and delayed nutrition support on postoperative complication rate. IV: Inverse variance; SD: Standard difference.

and changed to PN once a patient develops intolerance[31].

Furthermore, although heterogeneity was significant among literatures, heterogeneity was not detected within subgroups after subgroup analysis according to factors (nutritional support route) that can cause heterogeneity among literatures, suggesting that the source of heterogeneity was independent of nutritional support route. Therefore, the heterogeneity could have been caused by sample characteristics of subjects in different studies.

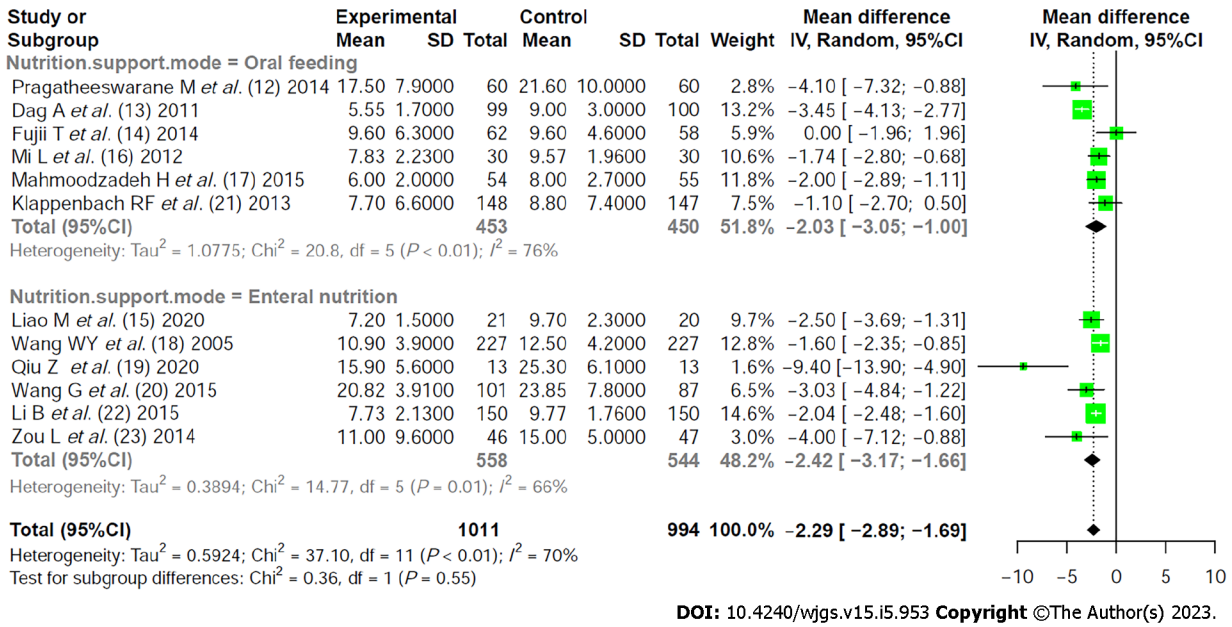


Figure 3 Subgroup analysis. IV: Inverse variance; SD: Standard difference.

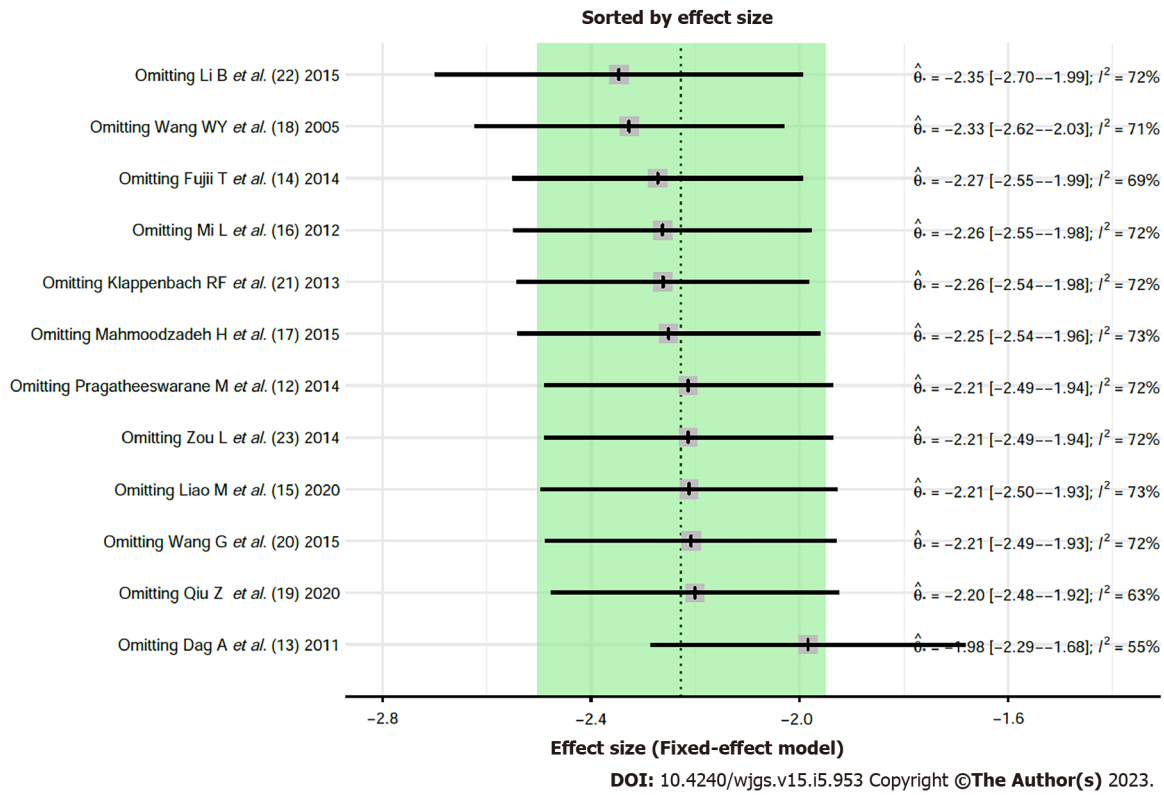
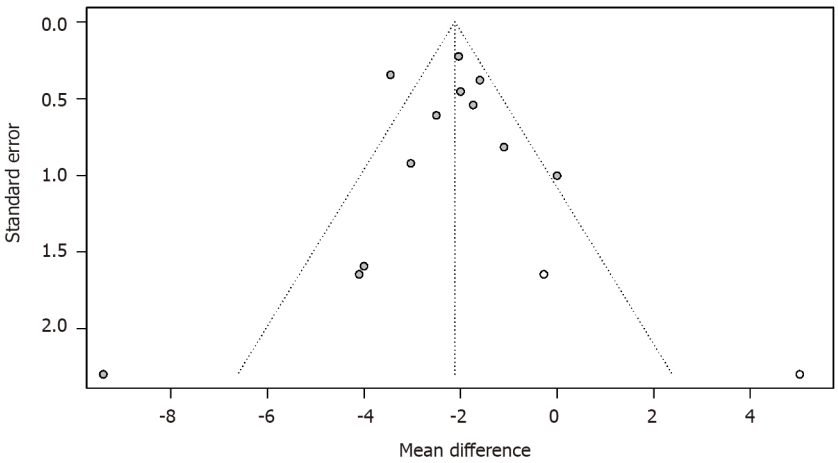


Figure 4 Influence analysis.

Although seven literatures had "some concerns of risk", the overall quality of the literatures was good, the results were stable, and there was no publication bias. However, only six literatures reported albumin of nutritional indicators, while only two literatures reported preprotein and total protein indicators, indicating that the effect of early nutritional support on the improvement of nutritional status should be further studied. Furthermore, very few reports had analyzed the key nutritional indicators, such as potassium, sodium, hemoglobin, and weight loss in such RCT studies, and thus a meta-analysis synthesis could not be performed. Therefore, more studies of better quality are needed for in-depth analysis of different indicators from different perspectives.



DOI: 10.4240/wjgs.v15.i5.953

Figure 5 Trim-filled funnel plots.

CONCLUSION

Although this study showed that early EN support can shorten the postoperative defecation time, overall hospital stay, reduce the incidence of complications, and accelerate the rehabilitation process in patients undergoing gastrointestinal surgery, the improvement of nutritional status was not significant. Also, this study included a few articles and thus lacked an in-depth analysis for some important nutritional indicators. Therefore, more clinical multicenter, large-sample, high-quality studies are needed to further evaluate the effect of early EN support on patient's nutritional status.

ARTICLE HIGHLIGHTS

Research background

Gastrointestinal tract surgery is a complex process, with a wide range of operations and large trauma. It is easy to have various infectious complications in postoperative recovery, which affects the efficacy of surgical treatment.

Research motivation

Early postoperative nutritional support can provide necessary nutrition, restore intestinal barrier, and reduce complications.

Research objectives

This study aimed to assess whether early postoperative nutritional support can improve the nutritional status of patients based on literature search and meta-analysis.

Research methods

This study used literature retrieval and meta-analysis to conduct quantitative analysis.

Research results

It was found that early enteral nutrition (EN) support could shorten the defecation time after gastrointestinal surgery, the overall hospital stay, reduce the incidence of complications, and speed up the rehabilitation process.

Research conclusions

Early enteral nutritional support can slightly shorten the defecation time and overall hospital stay, reduce complication incidence, and accelerate the rehabilitation process of patients undergoing gastrointestinal surgery.

Research perspectives

More clinical multicenter, large-sample, high-quality studies are needed to further evaluate the effect of early EN support on patient's nutritional status.

FOOTNOTES

Author contributions: He LB and Liu MY contributed equally to this study; He LB designed this study; He LB and He Y analyzed the data; Guo AL wrote manuscript; and all authors read and approved the final manuscript.

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CASE REPORT

Precise mapping of hilar cholangiocarcinoma with a skip lesion by SpyGlass cholangioscopy: A case report

Cheng-Han Chiang, Kuan-Chih Chen, Benedict Devereaux, Chen-Shuan Chung, Kuei-Chang Kuo, Chien Chu Lin, Cheng-Kuan Lin, Hsiu-Po Wang, Kuo-Hsin Chen

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Abstract

BACKGROUND

Cholangiocarcinoma (CC) is a very aggressive cancer with a poor prognosis. As surgery is the only curative therapy, preoperative evaluation of the tumor extent is essential for surgical planning. Although high-quality image modalities such as computed tomography and magnetic resonance imaging have been used extensively in preoperative evaluation, the accuracy is low. To obtain precise localization of tumor spread arising from the hilar region preoperatively, the development of an acceptable imaging modality is still an unmet need.

CASE SUMMARY

A 52-year-old female presented to our emergency department with jaundice, abdominal pain, and fever. Initially, she was treated for cholangitis. Endoscopic retrograde cholangiopancreatography with the cholangiogram showed long segment filling defect in the common hepatic duct with dilatation of bilateral intrahepatic ducts. Transpapillary biopsy was performed, and the pathology suggested intraductal papillary neoplasm with high-grade dysplasia. After treatment of cholangitis, contrasted-enhanced computed tomography revealed a hilar lesion with undetermined Bismuth-Corlette classification. SpyGlass cholan-

gioscopy showed that the lesion involved the confluence of the common hepatic duct with one skip lesion in the posterior branch of the right intrahepatic duct, which was not detected by previous image modalities. The surgical plan was modified from extended left hepatectomy to extended right hepatectomy. The final diagnosis was hilar CC, pT2aN0M0. The patient has remained disease-free for more than 3 years.

CONCLUSION
SpyGlass cholangioscopy may have a role in precision localization of hilar CC to provide surgeons with more information before the operation.

Key Words: Hilar cholangiocarcinoma; Jaundice; SpyGlass cholangioscopy; Bismuth-Corlette classification; Hepatectomy; Case report

Core Tip: The precise localization of hilar cholangiocarcinoma (CC) is important for surgical planning. This case highlights the important role that SpyGlass cholangioscopy can have in precise localization. However, SpyGlass cholangioscopy may be difficult to perform during the first encounter because of obstruction. A two-step approach for obstructive jaundice caused by hilar CC was proposed: (1) Insertion of biliary plastic stents to relieve jaundice and dilate the stricture site; and (2) Removal of biliary plastic stents after relieving jaundice and subsequent examination of hilar CC involvement by SpyGlass cholangioscopy.

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INTRODUCTION

Since the first clinical use of SpyGlass cholangioscopy (Microvasive Endoscopy; Boston Scientific Corp, Natick, MA, United States) in 2007, numerous clinical studies of the SpyGlass system have been published[1]. However, no definite guidelines were created for the application of SpyGlass cholangioscopy in cholangiocarcinoma (CC) mapping. One study showed that the overall procedure success rate was 89%, and the yielding rate of device-assisted biopsy for histological examination was 88%[2]. Another study showed that the accuracy of SpyGlass visual impression for differentiating malignant from benign ductal lesions was 89%, and the targeted biopsy accuracy rate was 82%[3].

Many patients diagnosed with early stage hilar CC who accepted radical left or right extended hepatectomy have a high recurrence rate (up to 52% 3 years after R0 resection)[4]. Intraepithelial neoplasia skip lesions and intraductal papillary neoplasm in the bile duct or indeterminate classification of CC could lead to the high recurrence rate[5,6]. The advent of SpyGlass cholangioscopy with high resolution images of the bile duct may provide a role in the precise localization of hilar CC. This will lead to more accurate and precise surgical planning.

Herein, we reported a case of hilar CC that was precisely mapped by SpyGlass cholangioscopy, which detected an intrahepatic duct (IHD) skip lesion. In addition, we demonstrated the potential benefit of preoperative SpyGlass cholangioscopy in the field of precise localization of hilar CC to guide the surgical plan.

CASE PRESENTATION

Chief complaints

A 52-year-old female presented with acute onset right upper quadrant abdominal pain for 1 d.

History of present illness

Three days prior to presentation, the patient experienced progressive tea-colored urine and generalized yellowish skin with an itching sensation. She had a fever of 38 °C.

History of past illness
The patient denied any past illness.

Personal and family history
The patient denied any personal and family history.

Physical examination
Physical examination showed right upper quadrant tenderness without rebound pain.

Laboratory examinations
The biochemistry test revealed hyperbilirubinemia (12.5 mg/dL; normal range: 0.2-1.5 mg/dL).

Imaging examinations
Subsequent abdominal sonography revealed acute calculous cholecystitis, suspected common bile duct (CBD) stone with dilated CBD, and bilateral IHDs (Figure 1A). Ultrasound-guided percutaneous gallbladder drainage and endoscopic retrograde cholangiopancreatography (ERCP) were performed to relieve the patient's symptoms. The cholangiogram revealed a long filling defect from the proximal CBD to the common hepatic duct (CHD) confluence (Figure 1B). Moreover, some tissue fragments were extracted *via* balloon lithotripsy during the ERCP exam and sent for pathological examination. In addition, brushing cytology was performed. Endoscopic retrograde biliary drainage was placed into the right IHD to relieve the patient's jaundice symptoms. Furthermore, subsequent contrast-enhanced computed tomography revealed similar findings as ERCP (Figure 1C). Later, left percutaneous transhepatic cholangiography drainage was performed to relieve unresolved jaundice after the endoscopic retrograde biliary drainage (Figure 1D). The patient's hyperbilirubinemia was resolved gradually. The final pathology of the CHD lesion showed intraductal papillary neoplasm, with high-grade dysplasia.

FINAL DIAGNOSIS
CC, pT2aN0.

TREATMENT
After serial work-up and management, a general surgeon was consulted for the curative surgery. Initially, extended left hepatectomy was planned for the patient because the patient's right lobe was larger than the left lobe. This strategy would preserve more liver without preoperative portal vein embolization.

However, the surgical plan was modified after the SpyGlass cholangioscopy, which revealed an intraductal lesion from the CHD to the margin of bifurcation of the IHDs (Figure 2A). A skip lesion in the right posterior branch of the bile duct (2 cm proximally away from bifurcation of the CHD) (Figure 2B and C). The cholangioscopy showed normal appearance of the mucosa in the left proximal IHD (Figure 2D). Based on these findings, the surgeon changed the initial surgical plan of extended left hepatectomy (LH) to extended right hepatectomy (RH).

Before the operation, embolization of the right portal vein was performed because the volume of the left lobe of the liver would not be adequate after extended RH. Atrophy of the right lobe of the liver and enlargement of the left lobe of the liver was confirmed 4 wk later by imaging with indocyanine green (retention ratio: 6%; normal range: < 10 %). Laparoscopic extended RH was performed uneventfully 8 wk after portal vein embolization. The surgical specimen showed one skip lesion in the right posterior branch hepatic duct, which was compatible with the SpyGlass cholangioscopy findings (Figure 3A, arrow). The histology showed well differentiated CC that invaded beyond the wall of the bile duct to the surrounding adipose tissue (Figure 3B).

OUTCOME AND FOLLOW-UP
During the follow-up period of more than 3 years, the patient's symptoms resolved and have not recurred. Liver triphasic computed tomography confirmed that the patient has remained disease free.

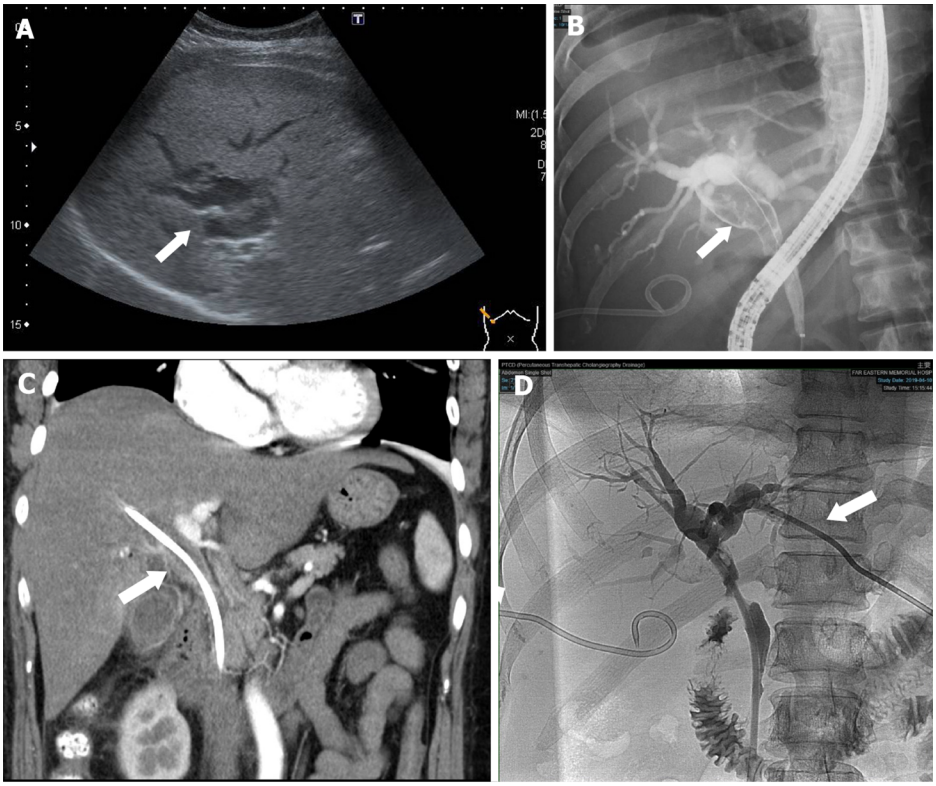

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Figure 1 Imaging results. A: Abdominal sonography showed dilated intrahepatic ducts (arrow); B: The cholangiogram revealed a long filling defect (arrow) from the proximal common bile duct (CBD) to the common hepatic duct; C: Contrast-enhanced computed tomography also showed soft tissue density (arrow) from the proximal CBD to the common hepatic duct; D: Percutaneous transhepatic cholangiography drainage (arrow) was performed on the left intrahepatic duct to alleviate jaundice.

DISCUSSION

CC is the second most common hepatic malignancy, following hepatocellular carcinoma. Hilar CC is the most common type, accounting for 50%-60% of CC cases[6]. The only curative treatment is extended semihepatectomy with hilar resection. Therefore, choosing left or right extended hepatectomy is the most crucial issue for surgeons. The choice depends on the precise localization of the hilar lesion preoperatively. Before 2007, ERCP plus triphasic dynamic computed tomography or magnetic resonance cholangiopancreatography were the only methods to identify the location of the lesion and perform preoperative mapping[7,8].

Since the SpyGlass cholangioscopy system first appeared in 2007, many studies have shown its diagnostic and therapeutic value over indeterminate biliary strictures[9-11]. However, no studies have focused on the preoperative mapping of hilar CC. According to the previous studies and case series, the high recurrence rate of hilar CC may result from skip lesions or residual intraductal papillary neoplasm of the bile duct on the contralateral IHD[4]. For this case, a residual intraductal papillary neoplasm skip lesion in the right posterior branch of the bile duct was detected by SpyGlass cholangioscopy, which was valuable information for surgical planning. Typically for Bismuth type I or type II hilar CC, extended LH is preferred because extended LH and extended RH with en bloc resection have shown similar long-term survival. Extended LH hilar en bloc resections are more feasible and safer perioperatively and postoperatively[12,13]. However, because more precise information of the tumor extent was detected by SpyGlass cholangioscopy, the surgical plan was changed for our patient.

Based on the experience from this case, a two-step approach for obstructive jaundice caused by hilar CC was proposed: (1) Insertion of biliary plastic stents to relieve jaundice and to dilate the stricture site; and (2) Removal of biliary plastic stents after jaundice is resolved and examination of the hilar CC extent by SpyGlass cholangioscopy. Notably, cross-sectional images were still required for evaluation of nodal involvement and distal metastases. In addition, for patients with periductal-infiltrating type CC, SpyGlass cholangioscopy may have a limited role. Thus, combination of SpyGlass cholangioscopy, cross-sectional imaging, and cholangiogram may provide more precise information of hilar CC localization and staging, which will provide the most suitable treatment for patients.

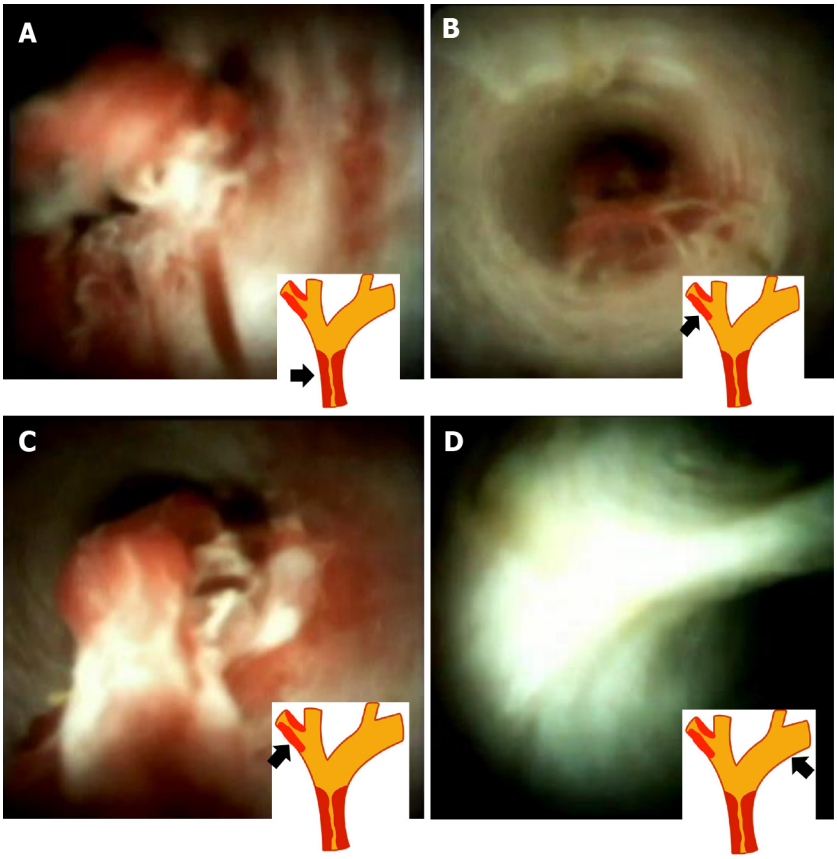

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Figure 2 SpyGlass cholangioscopy. A: SpyGlass cholangioscopy showed one intraductal mass that involved bifurcation of the intrahepatic ducts; B: The far view of the skip lesion in the right posterior branch of the bile duct; C: The near view of the skip lesion, which was 2 cm proximally away from bifurcation of the common hepatic duct; D: Normal appearance of the mucosa in the proximal left intrahepatic duct.

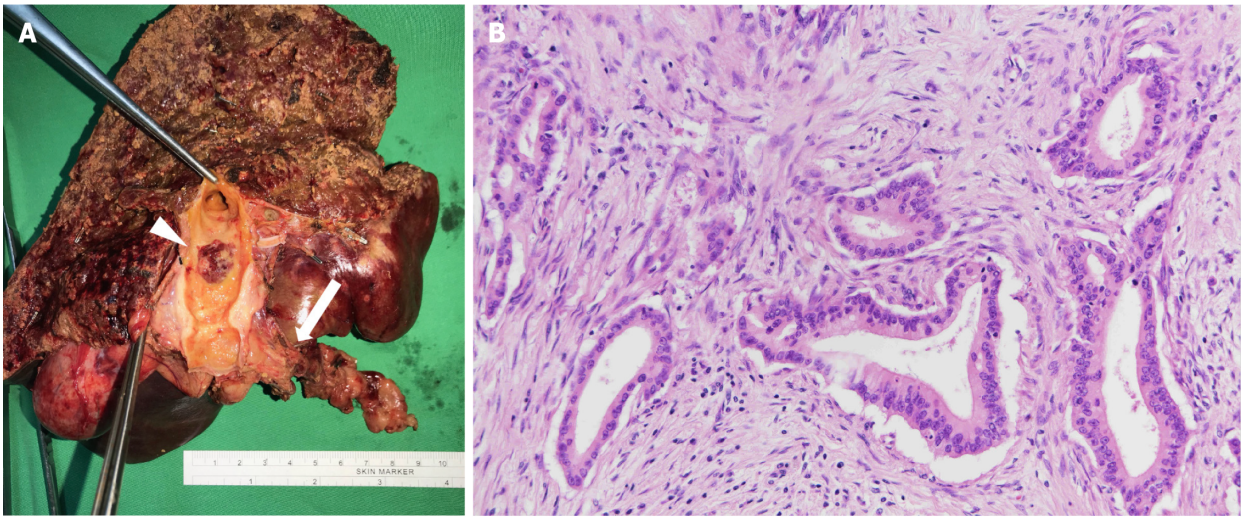

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Figure 3 The macroscopic and microscopic images of the lesions. A: The main cholangiocarcinoma lesion (arrow) and skip lesion (arrowhead); B: Pathology of cholangiocarcinoma (hematoxylin and eosin, × 200 magnification).

CONCLUSION

SpyGlass cholangioscopy may have an important role in the precise localization of hilar CC for surgical planning. However, a larger scale study is warranted.

FOOTNOTES

Author contributions: Chiang CH and Chen KC contributed equally to this work; Chiang CH and Chen KC wrote the manuscript; Chen KH performed the surgery and revised the manuscript; Chiang CH, Chen KC, Devereaux B, Lin CC, and Chung CS performed the SpyGlass cholangioscopy; Kuo KC and Lin CK contributed to the literature review; Wang HP provided instruction of the procedure; All authors have read and approved the final manuscript.

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CASE REPORT

Mallory-Weiss syndrome from giant gastric trichobezoar: A case report

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Abstract

BACKGROUND

Mallory-Weiss syndrome (MWS), representing a linear mucosal laceration at the gastroesophageal junction, is a quite frequent cause of upper gastrointestinal bleeding, usually induced by habitual vomiting. The subsequent cardiac ulceration in this condition is likely due to the concomitance of increased intragastric pressure and inappropriate closure of the gastroesophageal sphincter, collectively inducing ischemic mucosal damage. Usually, MWS is associated with all vomiting conditions, but it has also been described as a complication of prolonged endoscopic procedures or ingested foreign bodies.

CASE SUMMARY

We described herein a case of upper gastrointestinal bleeding in a 16-year-old girl with MWS and chronic psychiatric distress, the latter of which deteriorated following her parents' divorce. The patient, who was residing on a small island during the coronavirus disease 2019 pandemic lockdown period, presented with a 2-mo history of habitual vomiting, hematemesis, and a slight depressive mood. Ultimately, a huge intragastric obstructive trichobezoar was detected and discovered to be due to a hidden habit of continuously eating her own hair; this habit had persisted for the past 5 years until a drastic reduction in food intake and corresponding weight loss occurred. The relative isolation in her living status without school attendance had worsened her compulsory habit. The hair agglomeration had reached such enormous dimensions and its firmness was so hard that its potential for endoscopic treatment was judged to be impossible. The patient underwent surgical intervention instead, which culminated in complete removal of the mass.

CONCLUSION
According to our knowledge, this is the first-ever described case of MWS due to an excessively large trichobezoar.

Key Words: Mallory-Weiss syndrome; Upper gastrointestinal bleeding; Trichobezoar; Ringworm; Psychiatric distress; Case report

Core Tip: We presented the case of an adolescent female with Mallory-Weiss syndrome due to a giant intragastric trichobezoar formed after several years of a misunderstood condition of hair-eating, worsened by the forced isolation during the coronavirus disease 2019 pandemic. Accurate anamnesis, the strong involvement of family that has always denied any responsibility, and upper gastrointestinal endoscopy were used to reach the diagnosis. Since the excessive dimension of the trichobezoar inhibited endoscopic treatment, the entire foreign body was removed *via* surgery. After an uneventful postoperative period, the patient was referred to a Psychiatric Unit for further treatment.

Citation: Lieto E, Auricchio A, Belfiore MP, Del Sorbo G, De Sena G, Napolitano V, Ruggiero A, Galizia G, Cardella F. Mallory-Weiss syndrome from giant gastric trichobezoar: A case report. *World J Gastrointest Surg* 2023; 15(5): 972-977
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INTRODUCTION

Mallory-Weiss syndrome (MWS) represents a linear mucosal laceration at the gastroesophageal junction, which usually forms due to habitual vomiting conditions[1]. The etiology, however, is unknown. The mechanism underlying the mucosal lesion development likely involves an incoordination between raised intragastric pressure and the lower esophageal sphincter remaining closed during vomiting episodes. As a consequence, the mucosal layer is subject to ischemia and ultimately tears apart.

Alcohol intake is the most common predisposing condition for MWS[2], being present in more than 60% of diagnosed cases. Hiatal hernia, bulimia nervosa, and gastroesophageal reflux disease may also contribute to MWS onset, each accompanying smaller percentages of cases than alcohol intake. However, in about 25% of cases, no risk factor is identified. In 0.07%-0.49% of cases, MWS is reportedly iatrogenic, especially as a complication of prolonged endoscopic procedures[3].

Reports of upper gastrointestinal tract bleeding cases encountered in the clinic point to MWS as the culprit for 7%-14% and explain the hemorrhage as occurring when the erosion advances to a submucosal vessel[4,5]. Even in overall asymptomatic MWS cases, however, about 85% experience an episode of bleeding[6], with other nonspecific symptoms being strictly linked to the amount of blood loss. Therefore, MWS should be suspected when a hematemesis occurs during a vomiting episode in a patient without cirrhosis. Diagnosis is made by upper gastrointestinal endoscopy, which also presents the opportunity for convenient management of any active bleeding[7].

We described herein a unique case of MWS due to a giant trichobezoar occupying the entire gastric cavity in a young woman caused by a hair-eating psychiatric condition exacerbated by psychological factors, including social isolation during the coronavirus disease 2019 (COVID-19) pandemic lockdown and emotional distress following her parents' divorce.

CASE PRESENTATION

Chief complaints

A 16-year-old female presented to our surgical unit with recurrent episodes of food vomiting that had persisted over the prior 2 mo and was complicated by recent hematemesis.

History of present illness

The patient had stopped eating solid food and switched to an almost-exclusive fluid diet due to the ongoing symptoms; this led to significant unintentional weight loss.

History of past illness

At the age of 11 years, during the transition from elementary to middle school, the patient began to rip out her hair and swallow it. This compulsory habit remained consistent for the next 5 years, and the patient often hid it from her family. During the lockdown due to the COVID-19 pandemic, the patient's psychiatric condition worsened. The patient's parents divorced, and she experienced a severe state of social isolation due to remote schooling, lack of interaction with family and friends, and the fact that she lived on an island with few possibilities of getting away from home. The manipulation of her hair and the particular act of tearing it off reduced her anxiety, while swallowing and eating the hair was a consequence of feeling the need to hide the torn pieces. These behaviors also worsened the aesthetical aspect of the girl, as she became hairless and over time anorexic as the mass of hair grew to become a blockage in her gut.

Personal and family history

No remarkable event was referred in her personal and family history.

Physical examination

The patient was visibly underweight and presented with an irregular and hard abdominal mass that filled the left abdominal quadrants and the hypogastrium. It clearly caused a conspicuous deformation of her silhouette shape. The patient did not complain of any symptoms besides the vomiting and hematemesis after water/food intake.

Laboratory examinations

Blood analysis revealed a severe nutritional impairment, with iron deficiency anemia and reduced body mass index (Table 1).

Imaging examinations

An abdominal ultrasound detected a dense ovoidal formation with an average diameter of about 14 cm occupying the left lateral abdomen. Computed tomography showed a considerable gastric over-distension due to a voluminous conglomerate with inhomogeneous densitometry and cranio-caudal length of more than 30 cm. The mass occupied the gastric lumen entirely, partially preserving the fundic and prepyloric portion (Figure 1A). Upper gastrointestinal endoscopy revealed a dense mass of ingested hair, which occupied the antrum and the body of the stomach completely causing complete pyloric obstruction. At the gastroesophageal junction, a 7-mm linear mucosal erosion was observed, which bled easily during the endoscope transit (Figure 1B).

MULTIDISCIPLINARY EXPERT CONSULTATION

Napolitano V, MD, PhD, Assistant Professor, Surgical Endoscopy Unit, Vanvitelli University

Due to the concurrent esophageal bleeding and the impossibility to perform endoscopic treatment, the patient should undergo primary surgery.

Lieto E, MD, PhD, Assistant Professor, Surgical Oncology of Gastro-intestinal Tract, Vanvitelli University

Given the huge dimension of the trichobezoar, a median laparotomy should be performed.

Galizia G, MD, PhD, Full Professor, Surgical Oncology of Gastro-intestinal Tract, Vanvitelli University

Surgical planning and instrumental choice.

FINAL DIAGNOSIS

MWS and gastric obstruction from giant trichobezoar.

TREATMENT

At the median laparotomy, a greatly expanded stomach was observed with remarkably thickened and hyperemic walls, extending down to the pelvis. The entire organ was occupied by a fixed compact mass, which was absolutely unmovable in any direction. A 10-cm incision of the gastric anterior wall was made at the mesogastric level, as necessary to allow for extraction of the mass. Thereafter, two-layer suturing was performed manually. In this case, the extreme thickness of the wall served to advise

Table 1 Laboratory examination results

Factor	Result	Normal range
Ferritin	7 ng/dL	13-50 ng/dL
Total protein	5.5 g/dL	6.6-8.7 g/dL
Serum albumin	3.3 mg/dL	3.5-5.5 mg/dL
Iron	34 ng/dL	37-145 ng/dL
Red blood cell count	4.04×10^6 µ/L	$(4.0\text{-}5.0) \times 10^6$ µ/L
Hemoglobin	10.5 g/dL	12-16 g/dL
Body mass index	14.52 kg/m^2	18.50-24.99 kg/m^2

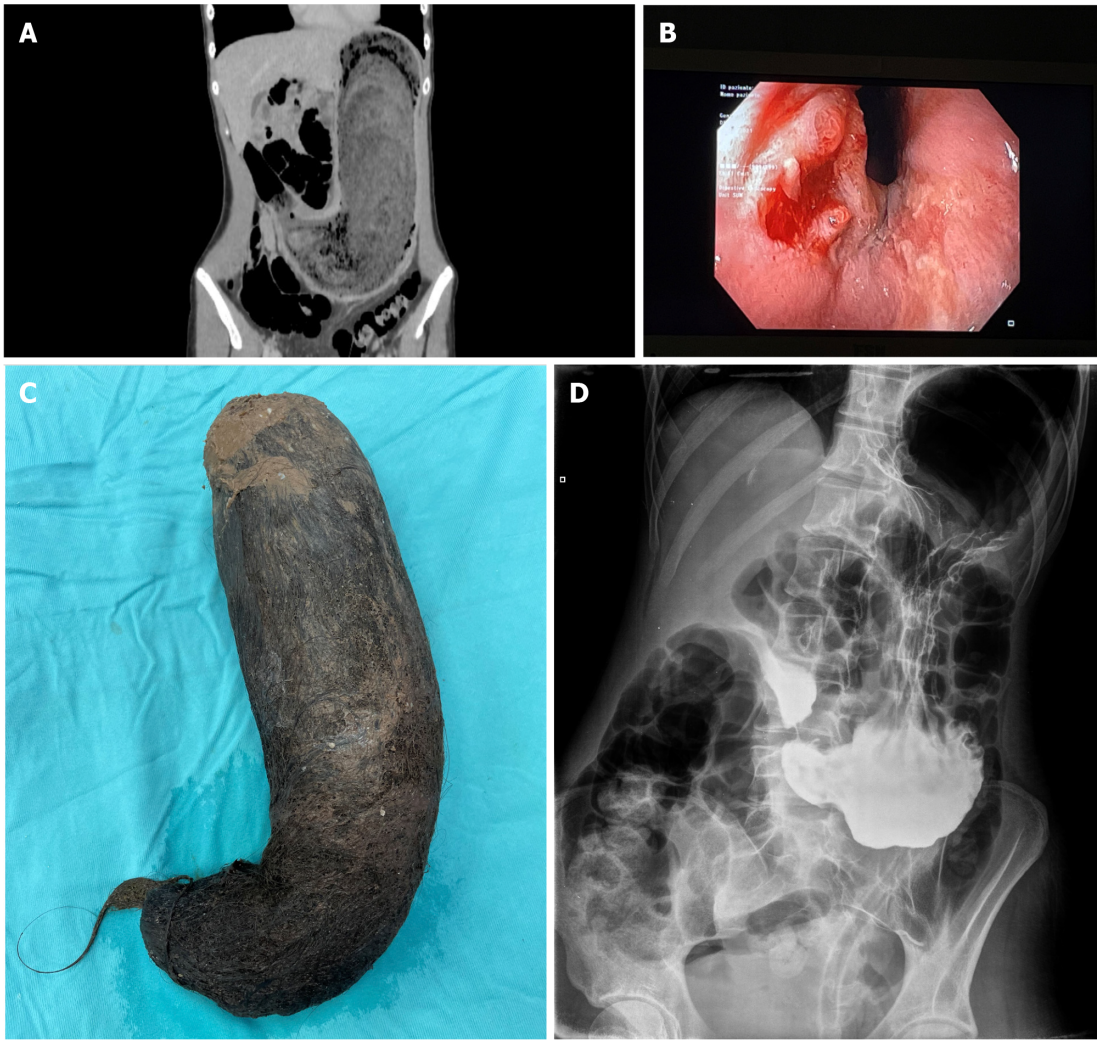

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Figure 1 Images of this case report. A: Computed tomography image of the enormous elongation in the stomach due to the trichobezoar; B: Endoscopic image of the mucosal tear located in the subcardial region; C: Postoperative image of the removed trichobezoar; D: Postoperative radiological image of the stomach emptying regularly.

against the use of mechanical staplers. A drainage tube was placed near the gastrotomy. The removed mass consisted of a solid accumulation of hair, measuring 52 cm × 7 cm and weighing 2.5 kg (Figure 1C). The operating time was 95 min.

OUTCOME AND FOLLOW-UP

No postoperative complications were recorded. A nasogastric tube was placed to protect the suture and removed on the fourth postoperative day. A postoperative radiological control with soluble contrast demonstrated the tightness of the gastric suture and effective emptying of the stomach in the absence of any intragastric foreign body (Figure 1D). The patient progressively returned to normal food intake and was discharged on the 9th postoperative day. Two months after the operation, the patient had gained 7 kg and returned to eating a regular, solid-food diet. Endoscopic examination showed no esophageal lesion. The patient's hair had regrown and was no longer being pulled out; she was successfully followed up by a psychiatrist for the management of her mental stress.

DISCUSSION

MWS represents tearing of the esophageal mucosal layer at the level of the gastroesophageal junction, generally together with repeated episodes of vomiting[1]. In the majority of cases, the disease arises as an upper gastrointestinal bleeding episode that generally stops spontaneously within 48 h[3,8,9]. In occasional cases, the hemorrhage requires endoscopic or surgical hemostasis[7]. Hiatal hernia, chronic nonsteroidal anti-inflammatory drug abuse, hyperemesis gravidarum, or repeated abdominal efforts are usually the more frequent predisposing factors, even if this condition may also appear in absence of any other pathology[5].

Based on our knowledge, the concomitance of MWS with a gastric trichobezoar[10], which is a solid cluster of hair voluntarily or accidentally ingested, has never been described in the scientific literature until now. In this case report, the young patient, who suffered from anxious neurosis since the age of 11, tried to hide the compulsory hair-eating behavior from her family for many years. Due to the significant weight loss and continuous vomiting episodes, an eating disorder, rather than obstruction, was suspected. During the COVID-19 pandemic, the patient experienced forced isolation due to living on a small island, with compromised social relationships; in this particular condition, her compulsive attitude worsened. Only the appearance of the bleeding prompted the patient to seek medical treatment, and the condition was diagnosed and treated surgically. Surgical intervention was required because the patient's eating capability was definitely compromised, and the huge dimension of the intragastric foreign body was not suitable for an endoscopic removal.

In our opinion, the interesting aspect of this clinical case is the unusual contradiction between the presentation modality of a chronic condition, such a gastric trichobezoar, with an acute condition, such as bleeding MWS. A pathological amount of indigestible material, such as vegetable fibers or plastic or paper objects, in the gastric cavity is possible in different categories of patients, both for obstructive conditions, such as inflammatory stenoses, or for specific eating habits. Among teenagers, psychiatric disorders are the most frequent cause of chronic foreign body ingestion[11]. Eating something other than food may be a variation of anorexia or indicative of a feeling of discomfort caused by stressful events[12]. Repeated hematemesis episodes in an adolescent could be caused by a progressive onset of a nonspecific dyspeptic syndrome due to a gastric obstruction from a bezoar and should be considered by clinicians treating this type of patient.

CONCLUSION

MWS can be induced by a giant intragastric foreign body such as the trichobezoar presented in this case report. In patients who suffer from eating disorders, endoscopic examination can help verify the cause of MWS. If a bezoar is present, then early endoscopic intervention to remove it would be ideal, before its large dimension requires surgical intervention. Very often the clinical history of teenagers is completely misinterpreted by the social context in which they live, and only an overwhelming occurrence can help improve their quality of life.

FOOTNOTES

Author contributions: Lieto E and Auricchio A conceptualized and designed the study, and contributed equally; Cardella F drafted and reviewed the manuscript for important intellectual content; Del Sorbo G and Ruggiero A reviewed the literature and drafted the manuscript; Belfiore MP contributed radiologic findings; Napolitano V and De Sena G contributed endoscopic findings; Galizia G and Lieto E critically reviewed the final manuscript and provided final approval of its content; and all authors issued final approval for the version to be submitted.

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CASE REPORT

Giant teratoma with isolated intestinal duplication in adult: A case report and review of literature

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Abstract

BACKGROUND

A combination of diseases is a rare phenomenon. Their clinical manifestations can vary, and the diagnosis can be challenging. Intestinal duplication is a rare congenital malformation, whereas retroperitoneal teratoma is a tumor in the retroperitoneal space, derived from the remaining embryonic tissue. There are relatively few clinical findings on adult retroperitoneal benign tumors. It is hard to believe that these two rare diseases can happen to the same person.

CASE SUMMARY

A 19-year-old woman complaining of abdominal pain with nausea and vomiting was admitted. Abdominal computed tomography angiography was suggested for invasive teratoma. Intraoperative exploration revealed that the giant teratoma was connected to an isolated intestinal tract in the retroperitoneum. The postoperative pathological examination revealed that mature giant teratoma was present with intestinal duplication. This was a rare intraoperative finding that was successfully treated surgically.

CONCLUSION

The clinical manifestations of intestinal duplication malformation are various, and difficult to diagnose before the operation. The possibility of intestinal replication should be considered when intraperitoneal cystic lesions are present.

Key Words: Teratoma; Intestinal duplication; Chimera; Case report

Core Tip: Giant teratoma with intestinal duplication has not been reported yet. Here, we report a case of a 19-year-old woman with giant teratoma and isolated intestinal duplication who complained of abdominal pain with nausea and vomiting; a rare intraoperative finding successfully by surgery.

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INTRODUCTION

Intestinal duplication is a congenital malformation usually observed in pediatric patients[1]. However, its diagnosis in adults is rare, and preoperative diagnosis is difficult, particularly when combined with other diseases[2]. Teratomas are benign neoplasms, that arise from more than one embryonic germ layer. Morphologically, it can be divided into cystic and solid parts. Retroperitoneal teratomas are rare, and, patients often present compression symptoms due to large tumors[3]. A giant teratoma with intestinal duplication has not been reported yet.

CASE PRESENTATION

Chief complaints

A case of a 19-year-old woman admitted to the hospital suffering from abdominal pain for 5 d with nausea and vomiting for 2 d was investigated.

History of present illness

The patient had no obvious inducement of abdominal pain 5 d ago, nausea and vomiting for 2 d, chills, fever, and discomforts such as anus-stopping exhaust and defecation.

History of past illness

The patient had good health history.

Personal and family history

The patient and her mother have mental retardation.

Physical examination

Hard round mass with a diameter of about 30 cm in the right abdomen.

Laboratory examinations

Blood analysis revealed potassium level was 2.9 mmol/L (normal range: 3.5-5.5), carcinoembryonic antigen level was 7.16 μg/L (normal range: 0-5), and other tumor markers of the digestive tract and gynecology were normal. Blood routine count, liver function indexes, and renal function markers were also normal.

Imaging examinations

Computed tomography angiography (CTA) showed the presence of a huge (29.6 cm × 17.4 cm × 10.2 cm) mass with mixed density in the right retroperitoneum and irregular tortuous bowel canal (Figures 1A-E). The inferior vena cava was significantly compressed and became thinner and the lumen density was uneven. The right kidney was pushed outward, and the liver was pushed upward. Moreover, the gallbladder was compressed, the right renal vein and inferior vena cava were pushed forward, and the left renal vein, pancreas, gastric antrum, intestine, portal vein and mesenteric vessels were pushed to the left (Figures 1B-G).

FINAL DIAGNOSIS

The final diagnosis of the presented case was a benign tumor.

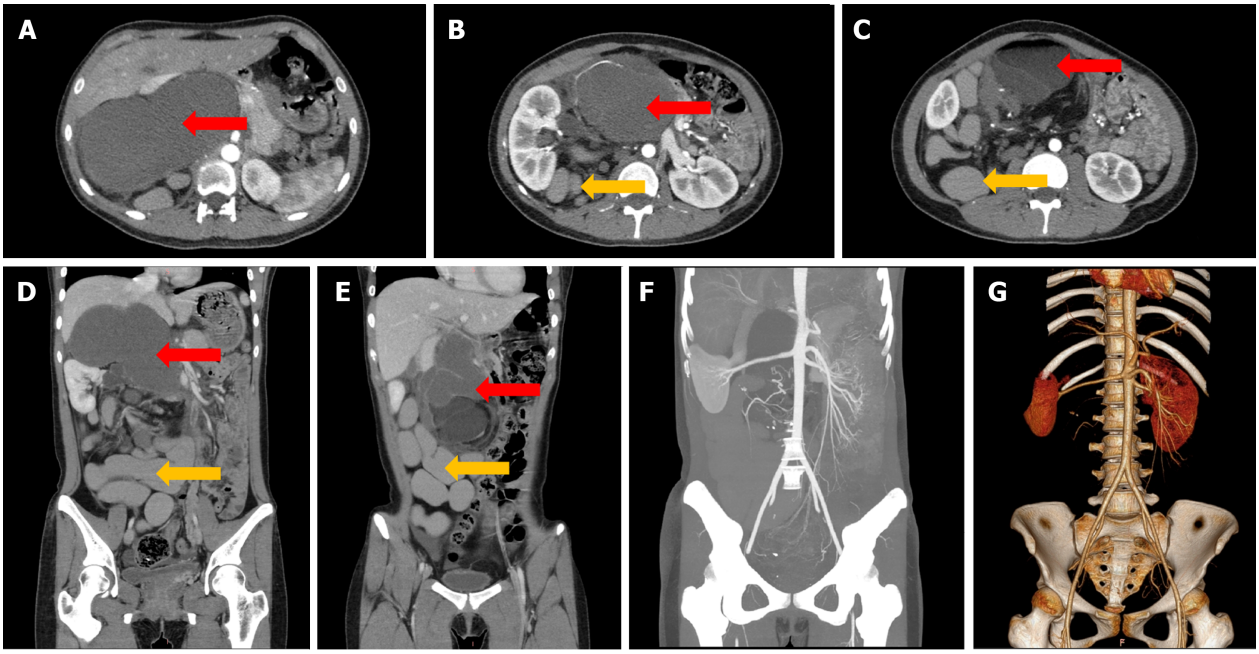

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Figure 1 Abdominal computed tomography angiography showed a huge mass in the right retroperitoneum (red arrows) and the intestinal duplication (yellow arrows). A-C: Transverse view; D and E: Coronal view; F and G: Abdominal angiography.

TREATMENT

During the exploratory, a huge lobulated retroperitoneal tumor was observed. A jelly-like substance was found inside the tumor. The left renal vein was densely adhered and the tumor was connected to an isolated retroperitoneal intestinal tract (Figures 2A-D). The intestinal tube extended from the back of the inferior vena cava up to the middle peritoneum, and then down to the right retroperitoneum to form another 110 cm long blind end. It had multiple branches, with severe expansion and multiple localized stenosis (Figures 2E and F). It was not connected to the normal digestive tract, and was thus considered a repeat bowel tube. Further, we studied again in the order of stomach, duodenum, jejunum, ileum, cecum, colon and rectum, and found a complete digestive system, confirming isolated intestinal duplication. Intraoperative exploration did not reveal the presence of additional tumors or enlarged lymph nodes. Therefore, we performed retroperitoneal tumor resection, intestinal duplication resection, and left renal vein reconstruction. After resection, a large amount of turbid and viscous intestinal fluid was found through diagnostic puncture of intestinal duplication.

OUTCOME AND FOLLOW-UP

Post-operation the patient was given symptomatic treatment such as anti-infection and nutritional support. After three days, the patient was gradually shifted to a regular diet. One week later, the patient recovered and was discharged from the hospital. The patient was then followed up after a month, showing no discomfort. Specimen showed a lobulated tumor about 9.0 cm × 8.5 cm × 4.5 cm in the distal mucosa of the duplication malformation intestine (Figure 2F). Pathological examination of the excised tissue showed mature teratoma (Figures 3A-C) with intestinal duplication (Figures 3D-I).

DISCUSSION

Intestinal duplication is a rare congenital disease, more commonly found in children than adults[4]. Although intestinal duplication can affect any part of the digestive tract, 60% occurs in the ileum or cecum. At present, the mechanism of intestinal duplication is unclear. Theories suggest abnormal separation of notochord and gastrula, a vascular insult, persistence of embryonic diverticula, and partial twining[5-7]. Clinically, patients are often treated for abdominal mass, intestinal obstruction, perforation, enteritis, gastrointestinal bleeding, and peritonitis[1,2,8,9]. According to the pathological anatomy, Intestinal duplication can be divided into the intestinal septum, wall cyst, extraintestinal tube, extraintestinal cyst and isolated type. An independent structure without direct connection with the

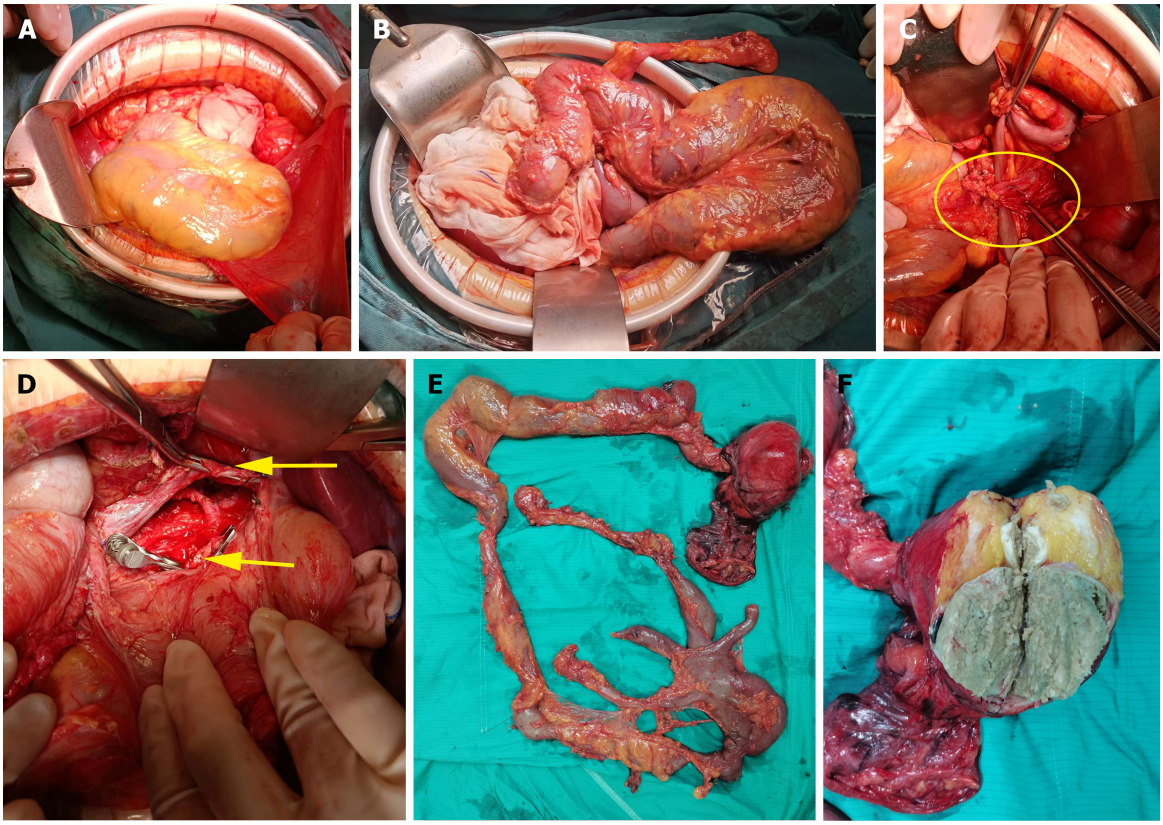

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Figure 2 Intraoperative findings. A and B: Intraoperative procedure found solitary dilated intestinal duplication; C: Intestinal duplication after the inferior vena cava (circle); D: The abdominal cavity and the affected left renal vein after dissection (yellow arrow), E: Excised intestinal duplication and teratoma; F: Open teratoma showing sebum and bone in some sections.

primary intestine characterizes the isolated type.

Teratoma is a germ cell tumor, that occurs in young women and infants. Mature cystic teratomas are the most common, accounting for 98% of teratomas[10]. Teratoma mainly occurs in the gonad, whereas those that occur in other parts are called extragonadal teratomas. They can occur on both sides of the midline of the body, such as the mediastinum, sacrococcygeal, retroperitoneal, and pineal[11]. Extragonadal teratomas can also occur in other parts, including the liver, hepatoduodenal ligament, hepatorenal space, diaphragm and abdominal wall[12].

Intestinal duplication with giant teratoma is rare. In the present study, the patient was prepared for surgical excision for a large retroperitoneal tumor. We found intestinal anatomical structure variation during the operation, and our exploration confirmed that it was an isolated intestinal duplication. Thus, the retroperitoneal tumor and the intestinal duplication were excised entirely. Post-operation, the abdominal CTA was re-read, and combined with the findings during the operation; it was found that the irregular tortuous bowel canal was an isolated intestinal duplication (Figures 1B-E).

Both the patient and her mother had mental retardation; thus, there could be a possibility of familial genetic history. Chromosome and gene testing can further confirm the correlation. However, the case was not been tested for chromosomes and genes in the present study. The possibility of a reabsorbed twin or chimera should also be considered.

Diagnosing a disease before the operation is quite challenging. Barium meal examination can diagnose intestinal duplication only when connected to the intestinal cavity. CT scan shows the focus. However, it is difficult to differentiate the disease from the mesenteric cyst, appendix abscess, and other abdominal cavity cystic lesions. The clinical diagnosis is generally complex, and most of them are diagnosed after laparotomy, similar to our case report. Three-dimensional reconstruction can show the location and scope, complications, related abnormalities, and anatomical relationship with surrounding structures of the repeated malformations. They mostly manifest as well-bounded, thick-walled cystic masses in flat, spherical, or tubular lesions without invading neighboring organs. Thus, it can advance the preoperative diagnostic rate. Therefore, the possibility of intestinal replication should be considered when intraperitoneal cystic lesions are present. Virtual colonoscopy can fully display the intestinal anatomy and lesion site, the anatomy and lesion of the intestinal cavity from both ends of the stenosis and obstruction. The combination of three-dimensional images can also help understand the conditions in the intestinal wall and outside the intestinal cavity, which has unique advantages for the combination of other diseases. Therefore, a virtual colonoscopy can help in the diagnosis of intestinal duplication. In

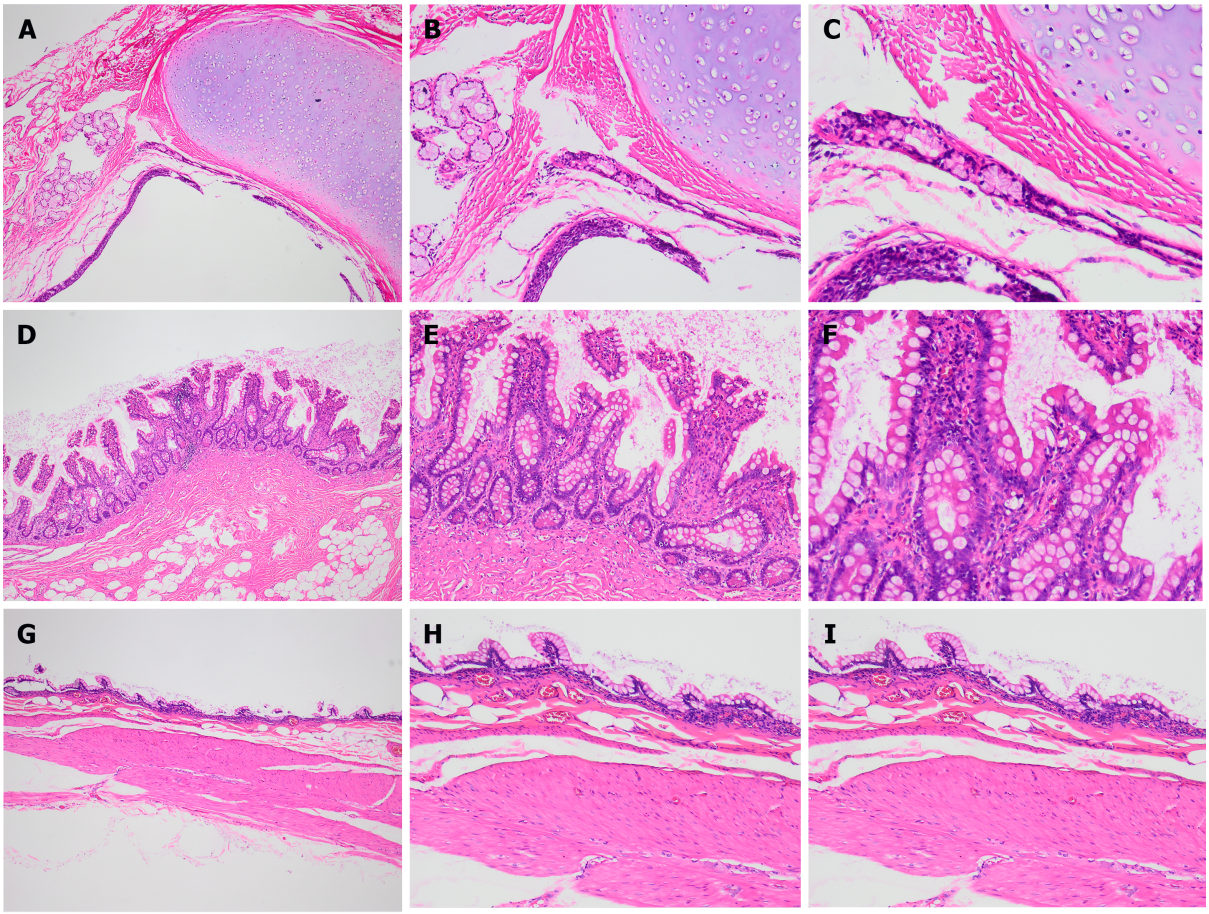

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Figure 3 Postoperative pathological examination. A-C: Hematoxylin-eosin stain of excised tissue showed mature cartilage tissue, small salivary glands and squamous epithelium; D-F: The intestinal mucosa and glands of the narrow intestinal cavity; G-I: The intestinal mucosa at the expansion site becomes thinner and the glands disappear. A, D and G: 40 × microscope; B, E and H: 100 × microscope; C, F and I: 200 × microscope.

conclusion, the clinical manifestations of intestinal duplication are varied, and preoperative diagnosis is difficult, which requires a combination of various imaging data. For asymptomatic recurrent intestinal malformations, especially for patients with intestinal abnormalities shown on imaging, careful exploration of intestinal conditions during the operation can avoid missed diagnosis.

The only treatment for giant teratoma with isolated intestinal duplication is surgery. For symptomatic intestinal duplication, it is recommended to remove the diseased bowel. For the asymptomatic intestinal duplication, the study believes that timely surgery after diagnosis can avoid complications such as perforation, bleeding, obstruction and malignant changes, and the incidence of complications of early resection is low, and the hospital stay is short. The most common surgical method for intestinal duplication is to remove the diseased intestine. In case of cyst type duplication, simple cyst resection and cyst mucosa stripping can be used. However, if there is communication with normal intestine, adjacent intestine should be removed to ensure complete cyst removal. If other diseases such as tumor and ectopic organ are combined, they should be treated together. However, the specific operation method should be determined according to the specific form of the diseased bowel.

CONCLUSION

Intestinal duplication with giant teratoma is rare, and preoperative diagnosis is very challenging. Combined with multiple imaging techniques, the diagnosis and its accuracy may can be improved. The anatomic variation is often found during surgery, and surgical resection is the only cure for this disease.

FOOTNOTES

Author contributions: Ye MX and Li J proposed the idea and supervised, revised the writing; Xiong PF collected the data, analyzed the literature, and wrote the manuscript; Yang L assisted with data collection and imaging guidance;

Ye MX, Jiang Y, Mou ZQ were the patient's surgeons and participated in the entire operation; and all authors read and approved the manuscript.

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CASE REPORT

Computer-assisted rescue of the inferior mesenteric artery in a child with a giant ganglioneuroblastoma: A case report

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Abstract

BACKGROUND

Ganglioneuroblastoma (GNB) is a peripheral neuroblastoma (NB) with malignant degree between highly malignant NB and benign ganglioma (GN). Pathology is the gold standard of diagnosis. Although GNB is not uncommon in children, biopsy alone may lead to an inaccurate diagnosis, especially for giant tumors. However, surgical resection may be associated with significant complications. Here, we report a case of computer-assisted surgical resection of a giant GNB in a child and successful rescue of the inferior mesenteric artery.

CASE SUMMARY

A 4-year-old girl was admitted to our department for a giant retroperitoneal lesion, which was considered to be an NB by her local hospital. The symptoms of the girl disappeared spontaneously without treatment. On physical examination, a mass of about 10 cm × 7 cm could be palpated in her abdomen. Ultrasonography and contrast-enhanced computed tomography performed in our hospital also showed an NB, and there was a very thick blood vessel inside the tumor. However, aspiration biopsy revealed GN. Surgical resection is the best treatment option for this giant benign tumor. For precise preoperative evaluation, three-dimensional reconstruction was performed. It was clear that the tumor was close to the abdominal aorta. The superior mesenteric vein was pushed forward, and the inferior mesenteric artery passed through the tumor. Because GN generally does not invade blood vessels, we split the tumor with a CUSA knife during the operation and found that there was indeed a straight and intact vascular sheath.

Arterial pulsation was observed in the completely exposed inferior mesenteric artery. The pathologists interpreting the tissue finally diagnosed it as a mixed GNB (GNBi), which is more malignant than GN. However, both GN and GNBi usually have a good prognosis.

CONCLUSION
This was a case of successful surgical resection of a giant GNB, and aspiration biopsy underestimated the pathological staging of the tumor. Preoperative three-dimensional reconstruction assisted with the radical resection of the tumor and rescue of the inferior mesenteric artery.

Key Words: Surgery; Children; Ganglioneuroblastoma; Computer-assisted; Tumor; Case report

Core Tip: The diagnosis and treatment of ganglioneuroblastoma is complex. Sampling errors associated with aspiration biopsy may lead to inaccurate diagnosis, while difficult surgical resection leads to many postoperative complications. Three-dimensional reconstruction and other technologies may contribute to the safety of surgery. Here, we introduce a child who underwent computer-assisted accurately guided surgical excision of a giant ganglioneuroblastoma, and her inferior mesenteric artery was rescued.

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INTRODUCTION

Ganglioneuroblastoma (GNB) derives from primitive neural crest cells of the neuroectoderm[1,2], and its biological behavior and degree of differentiation are between highly malignant neuroblastoma (NB) and benign ganglioneuroma (GN). These three types are difficult to distinguish and can be transformed into each other, which often leads to difficulties in clinical diagnosis and disease progression. GNB can be divided into nodular (GNBn) and mixed (GNBi) based on histological features[3,4]. GN/GNBi commonly has a good prognosis due to good differentiation[5]. However, it is seldom found because it is nonfunctional and without significant clinical symptoms in the early stages. When a tumor is found, it often compresses and even encases blood vessels due to its large volume. In addition, it is insensitive to chemotherapy and easily recurs. The above characteristics increase the difficulty of radical surgical resection and treatment[6,7]. Computer-assisted system (CAS) three-dimensional (3D) image reconstruction can be used to accurately evaluate and preoperatively plan the treatment to optimize surgical modalities by clearly displaying the spatial anatomical relationship between the tumor and surrounding vessels and organs in different colors. This may be beneficial to improve the prognosis of these children[8,9]. Here, we report a child who underwent computer-assisted accurately guided surgical excision of a giant GNB, and her inferior mesenteric artery was rescued.

CASE PRESENTATION

Chief complaints

A 4-year-old girl visited her local hospital due to abdominal pain and vomiting for one day. Then, she was admitted to our department for a giant retroperitoneal lesion, which was considered an NB.

History of present illness

The girl's abdominal computed tomography (CT) scan showed a giant retroperitoneal lesion, which was considered an NB. For further diagnosis and treatment, she visited our department. Her symptoms such as abdominal pain and vomiting had disappeared spontaneously without treatment after admission.

History of past illness

Previously, she did not have a specific past medical history.

Personal and family history

The girl did not have any significant family history. Both her father and mother were healthy.

Physical examination

On physical examination, a mass was found on palpation of abdomen, mainly in the left upper and left lower quadrants, extending to the right lower quadrant, of about 10 cm × 7 cm in size. It was firm mass without tenderness, and had an unclear boundary and limited mobility.

Laboratory examinations

Tumor markers revealed a neuron-specific enolase level of 42.45 ng/mL. All other blood test findings, including other tumor markers, coagulation, liver and renal function tests, were within normal values.

Imaging examinations

Ultrasonography showed a giant hypoechoic mass in the left retroperitoneal space, and the mass had a patchy strong echogenicity and no obvious cystic area. The lesion size was 12.4 cm × 10.5 cm × 6.3 cm with irregular morphology, and the mass crossed the midline. A tumor blood supply vessel with a diameter of 0.3 cm branched from the abdominal aorta (Figure 1). Contrast-enhanced CT showed that the huge lesion appeared well defined and was 123 mm × 85 mm in maximum cross-section, while the inferior mesenteric artery was fully encased 360°. Mixed density and patchy calcification were seen within the mass, the solid component was significantly enhanced, and adjacent structures were pushed out. The radiologists considered it to be a tumor (NB?) (Figure 2).

Further diagnostic work-up

To clarify the diagnosis and decide the next treatment, ultrasound-guided abdominal mass aspiration biopsy was performed. Pathology revealed a retroperitoneal neoplastic lesion, and some cells were spindle-shaped and considered Schwann stroma. As a whole, the tumor was differentiated, while some of the cells were suspected to have undergone ganglion cell differentiation. Some areas appeared to be immature, but no definite NB nesting mass was observed. Immunohistochemical results showed calretinin (+-), Syn (+-), NF (+-), and SOX10 (+-). Therefore, the pathologists first considered it to be a GN (Figure 3).

FINAL DIAGNOSIS

Macroscopically, the two postoperative masses were grayish-white and nodule-like, they were approximately 15 cm × 8 cm and 10 cm × 2 cm in size; and they had soft cut surfaces and fibrous capsules. Microscopically, the tumor was mainly composed of nerve fibers and ganglion cells. However, there were a few scattered small round cells with deeply stained nuclei, and these were considered neuroblasts (less than 10% of the tumor). Immunohistochemistry showed NSE (+), S100 (+), Ki-67 (+, 2%), calretinin (nodal cells +), and NeuN (-). Therefore, the pathologists finally diagnosed it as a GNBi. In addition, metastasis was not observed in the abdominal aortic lymph nodes (Figure 4).

TREATMENT

Surgical resection is the best option for this type of benign tumor. Then, for precise preoperative evaluation, 3D reconstruction was performed using CAS. The reconstructed image clearly showed that the tumor was located in the retroperitoneum, and the mass had a volume of 676.7 mL. The mass was extremely close to the abdominal aorta. The superior mesenteric vein was pushed forward, and the inferior mesenteric artery passed through the tumor (Figure 5). In fact, GN mostly grows along the space around the organs and encases blood vessels but does not invade. Also, it generally does not cause occlusion or stenosis of blood vessels. Therefore, we evaluate that surgical treatment would be feasible in this case.

After sufficient preoperative preparation, radical surgical resection was performed (Figure 6). The intraoperative situation was completely consistent with the preoperative CAS evaluation. The giant tumor was located in the retroperitoneum and was completely surrounded by a fibrous capsule. We carefully separated tissues and protected the intestinal canal and mesentery around the tumor, especially the superior mesenteric vein on the surface of the tumor. The vessels supplying the tumor were ligated. Then, the tumor was exposed clearly and was seen to be close to the abdominal aorta, and the inferior mesenteric artery was penetrating the tumor. During the operation, we tried to block the distal inferior mesenteric artery but found that the color of the distal sigmoid colon and rectum became darker. Therefore, we split the tumor with a CUSA knife from the junction of the posterior of the tumor and the abdominal aorta and carefully peeled out the complete inferior mesenteric artery. The tumor section was yellowish-white with a straight vascular sheath. Arterial pulsation was observed in the

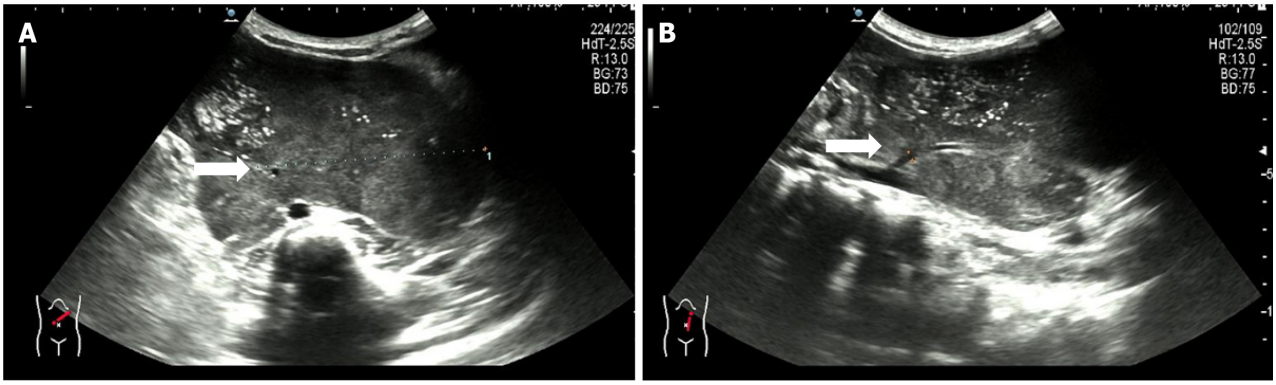

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Figure 1 Ultrasound showing a retroperitoneal left-sided hypoechoic mass of 12.4 cm × 10.5 cm × 6.3 cm with irregular morphology. A: A supply blood vessel with an internal diameter of 0.3 cm was present in the tumor; B: This supply blood is from the abdominal aorta.

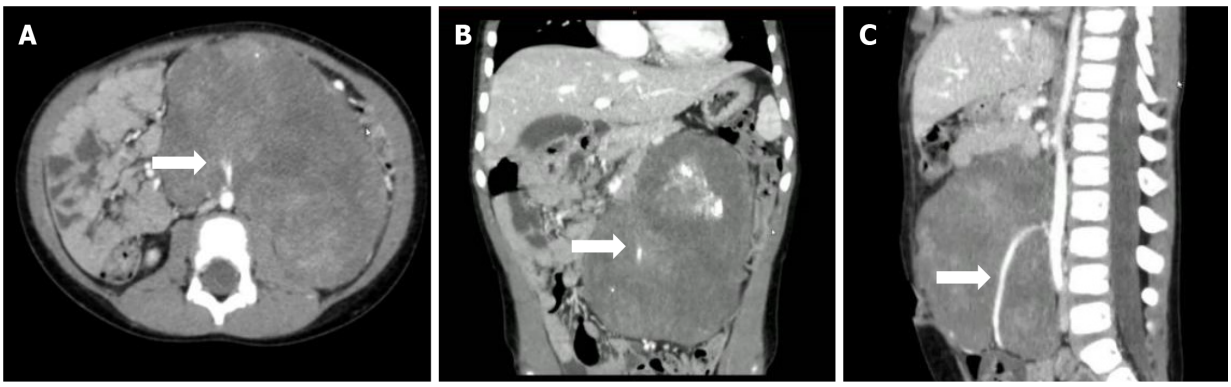

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Figure 2 Enhanced computed tomography of the abdomen showing a huge mass-like mixed density lesion in the abdominal cavity with a maximum cross-section of about 123 mm × 85 mm and well-defined margins, encasing the inferior mesenteric artery. A: Computed tomography (CT) transverse section view; B: CT coronal section view; C: CT sagittal section view. The arrow points to the inferior mesenteric artery.

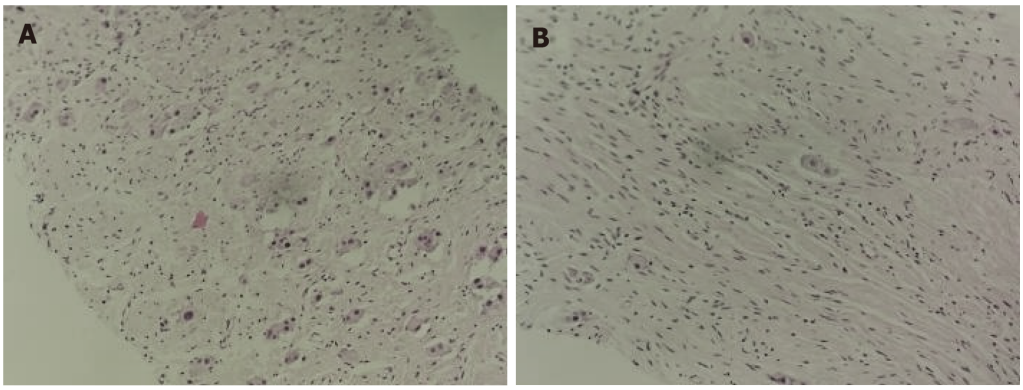

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Figure 3 Ultrasound-guided abdominal mass puncture biopsy pathology of the tumor. No definite neuroblastoma nesting mass was observed. A: Some of the cells were cytoplasm rich, nucleoli were visible, ganglion cell differentiation was suspected, and some areas appeared immature [hematoxylin & eosin (H&E), × 100]; B: Some cells were spindle-shaped, Schwann stroma was considered (H&E, × 100).

completely exposed inferior mesenteric artery, and the intestinal canal was ruddy. This operation took 3.5 h, and the bleeding volume was approximately 20 mL.

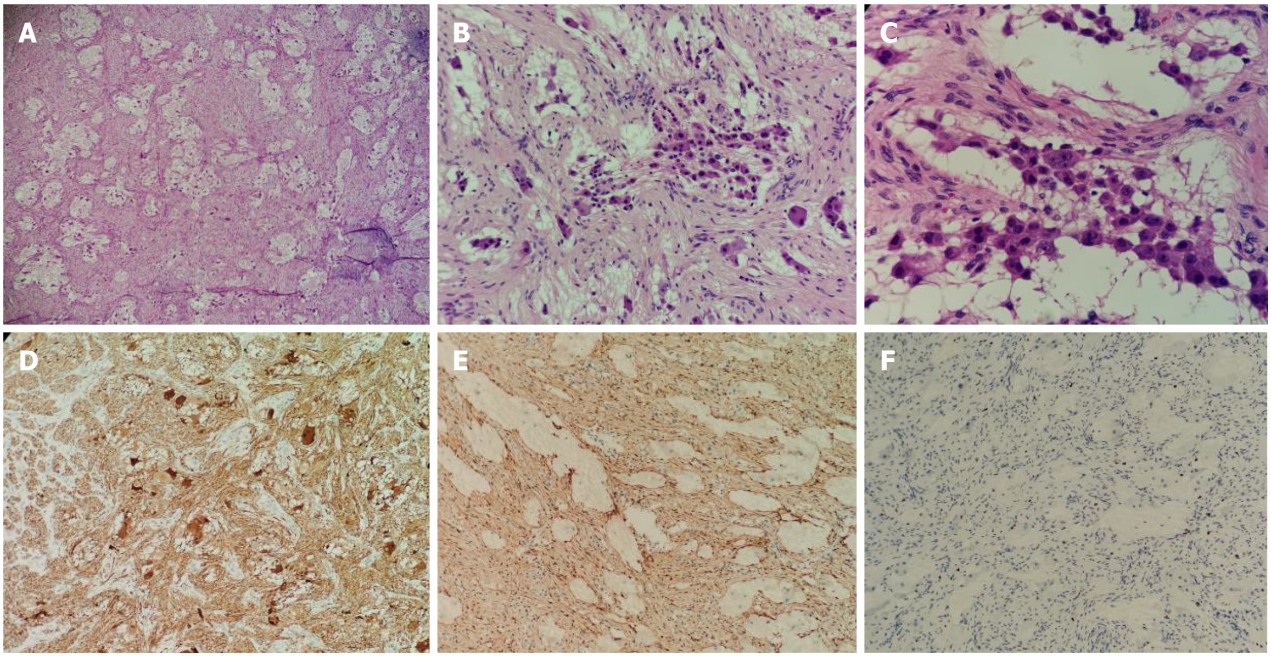

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Figure 4 Pathology of the postoperative tumor specimen. A: The tumor was mainly composed of nerve fibers and ganglion cells [hematoxylin & eosin (H&E), × 40]; B: Some ganglion cells did not mature in differentiation (H&E, × 100); C: Only a few scattered small round cells with deep-stained nuclei were seen locally, which were considered to be neuroblastoma cells, and these cells made up less than 10% of the tumor (H&E, × 200); D: Neuron specific enolase positive (H&E, × 40); E: S100 positive (H&E, × 40); F: Ki-67 positive (H&E, × 40).

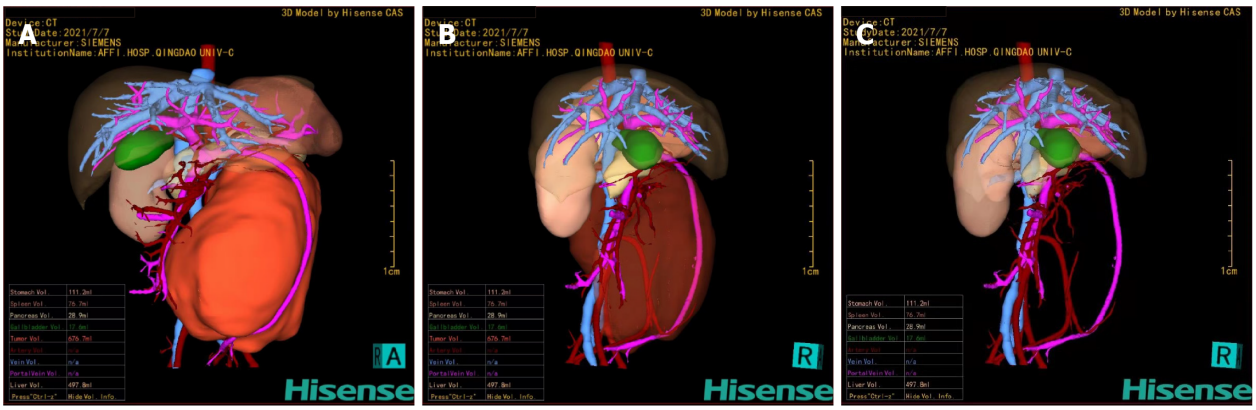

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Figure 5 Hisense computer-assisted system three-dimensional reconstruction. A: The tumor could be clearly located in the retroperitoneum and had a giant volume of 676.7 mL; B and C: Through the translucency and transparency function, the tumor was close to the abdominal aorta, and the superior mesenteric vein was pushed anteriorly. The inferior mesenteric artery passed through the tumor and was completely encased in the tumor.

OUTCOME AND FOLLOW-UP

The child recovered well after surgery without complications such as bleeding and intestinal obstruction. Postoperative positron emission tomography-CT did not show any abnormal increase in metabolism. No tumor cells were found on bone marrow biopsy pathology. We comprehensively considered that she was very low risk, and she did not receive any radiotherapy or chemotherapy. After more than one year of follow-up, no tumor recurrence or metastasis was found in the imaging examinations.

DISCUSSION

GN/GNBi accounts for approximately 25% of focal NTs. Compared with immature NTs (NB/GNBn), GN/GNBi often has better clinical and biological behavior[6,10]. However, GN/GNBi is generally

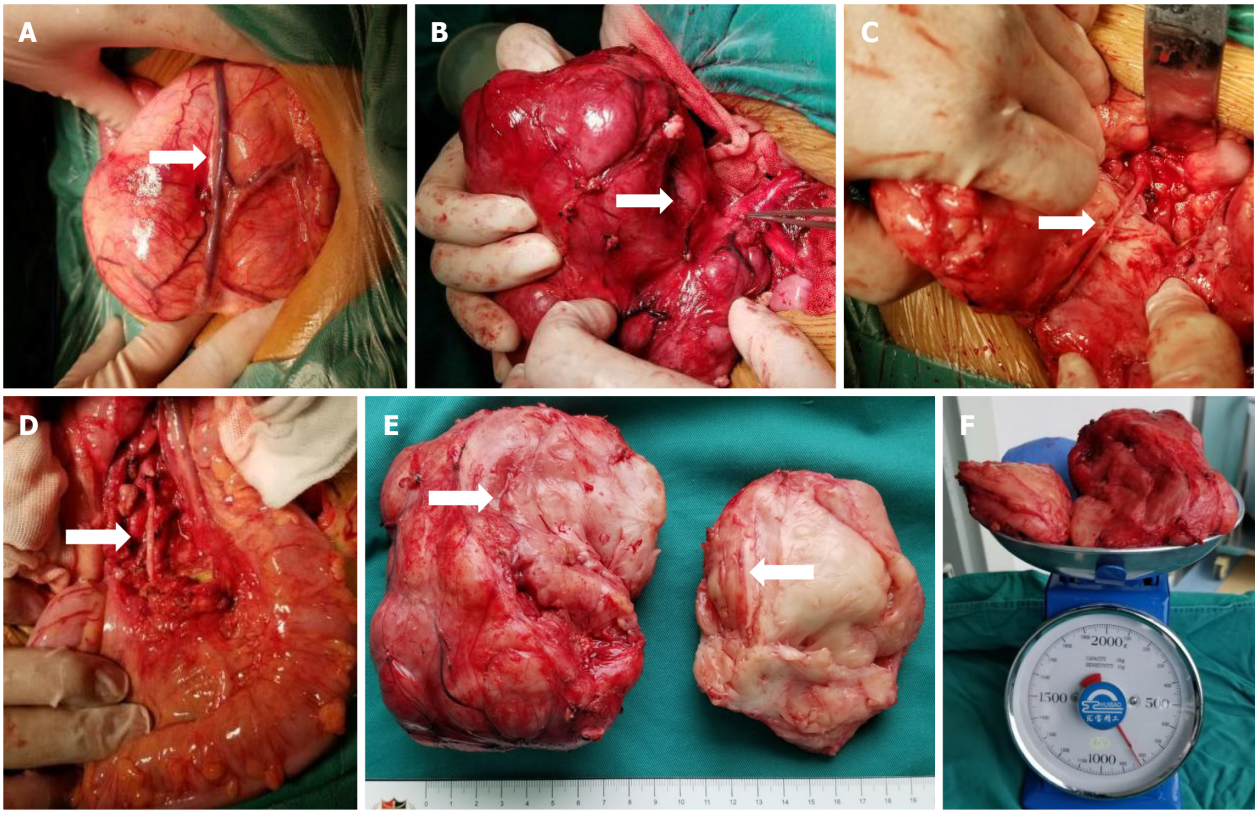

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Figure 6 The intraoperative exploration was completely consistent with the preoperative three-dimensional evaluation, and the tumor had a relatively complete fibrous capsule. A: The superior mesenteric vein was pushed to the front of the tumor; B: The tumor was close to the abdominal aorta, and the inferior mesenteric artery was penetrating the tumor; C: After splitting the tumor with a CUSA knife, the inferior mesenteric artery that was encased by the tumor could be seen; D: Arterial pulsation was seen in the exposed inferior mesenteric artery, and the distal sigmoid colon and rectum was ruddy; E: The tumor section was yellowish-white with a straight and intact vascular sheath; F: The preoperative tumor volume was 676.7 mL, and the postoperative tumor weight was 820 g.

insensitive to chemotherapy, and surgical resection of suspected GN or GNB can be performed to avoid sampling errors associated with aspiration biopsy. Existing tumor compression symptoms can be relieved by surgery, and surgery can also reduce the possibility of malignant transformation[11,12]. Due to the large volume of the tumor and its impact on important blood vessels, the operation is difficult and highly risky, can lead to numerous surgical complications and affect the short-term and long-term quality of life of children. Therefore, in recent years, some scholars have advocated cytoreductive surgery or follow-up observation for GN/GNBi[13,14]. However, on the premise of minimizing surgical complications, complete radical surgical resection is still the best choice for a definite diagnosis and cure of the disease[6,7,10,14,15]. In this case, the surgery was precisely guided by CAS, resulting in complete resection of the tumor and skeletonization of the vessels without postoperative complications, which may indicate a better clinical prognosis.

Giant GN/GNBi tumors derived from the retroperitoneum often have mesenteric roots at the base of the tumor body. The involvement of either the abdominal aorta, inferior vena cava, or mesenteric arteries or all of them is usually the main factor that affects the complete resection of tumors. At present, traditional ultrasound and two-dimensional CT images can only be displayed along a specific interface and cannot display the anatomical relationship as a whole, especially the origin and shape of curved vessels[16]. CAS is a 3D reconstruction based on CT data that can be used for precise preoperative evaluation and surgical planning by reconstructing organs and tumors and tracking arteries. It can display the adjacent relationship between the tumor and surrounding vascular organs in a 3D, dynamic and overall way[17]. The CAS of this patient clearly showed that the giant retroperitoneal tumor completely encased the inferior mesenteric artery with a clear vessel shape and normal tube wall shape. The tumor also pushed up the superior mesenteric vein and was close to the abdominal aorta. Therefore, the key point of this surgery is to preserve the inferior mesenteric artery and protect the abdominal aorta and the superior mesenteric vein. Thus, it reduces recurrence and prevents complications such as bleeding, intestinal obstruction, and intestinal necrosis[18].

CONCLUSION

Radical surgical resection is the best choice for the diagnosis and cure of GN/GNBi. CAS can be used to accurately evaluate and plan surgery from the overall perspective, and this planning has great significance to determine the origin and shape of curved blood vessels.

FOOTNOTES

Author contributions: Xiu WL, Liu J, and Zhang JL contributed to data curation and writing of the original draft; Wang FJ and Wang FF contributed to data curation; Su N, Hao XW, and Dong Q contributed to manuscript review and editing; all authors have read and approved the final manuscript.

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CASE REPORT

Curative resection of leiomyosarcoma of the descending colon with metachronous liver metastasis: A case report

Soo-Hyeon Lee, Sang-Ho Bae, Sang-Cheol Lee, Tae-Sung Ahn, Zisun Kim, Hae-Il Jung

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Abstract

BACKGROUND

Leiomyosarcoma (LMS) has a poor prognosis and rarely originates from the colon. If resection is possible, surgery is the first treatment most commonly considered. Unfortunately, no standard treatment exists for hepatic metastasis of LMS; although, several treatments, such as chemotherapy, radiotherapy, and surgery, have been used. Subsequently, the management of liver metastases remains controversial.

CASE SUMMARY

We present a rare case of metachronous liver metastasis in a patient with LMS originating from the descending colon. A 38-year-old man initially reported abdominal pain and diarrhea over the previous two months. Colonoscopy revealed a 4-cm diameter mass in the descending colon, 40 cm from the anal verge. Computed tomography revealed intussusception of the descending colon due to the 4-cm mass. The patient underwent a left hemicolectomy. Immunohistochemical analysis of the tumor revealed that it was positive for smooth muscle actin and desmin, and negative for cluster of differentiation 34 (CD34), CD117, and discovered on gastrointestinal stromal tumor (GIST)-1, which are characteristic of gastrointestinal LMS. A single liver metastasis developed 11 mo postoperatively; the patient subsequently underwent curative resection thereof. The patient remained disease-free after six cycles of adjuvant chemotherapy (doxorubicin and ifosfamide), and 40 and 52 mo after liver resection and primary surgery, respectively. Similar cases were obtained from a search of Embase, PubMed, MEDLINE, and Google Scholar.

CONCLUSION
Early diagnosis and surgical resection may be the only potential curative options for liver metastasis of gastrointestinal LMS.

Key Words: Leiomyosarcoma; Colon; Liver metastasis; Surgical resection; Treatment; Case report

Core Tip: Leiomyosarcoma (LMS) rarely originates from the colon; hepatic metastasis of LMS lacks standard treatment. We present a case report of a 38-year-old man who was found to have intussusception in the descending colon due to a 4-cm LMS. The patient underwent a left hemicolectomy, however, a single liver metastasis developed 11 mo after the primary surgery. He underwent curative resection of the metastatic lesion and six cycles of adjuvant chemotherapy. The patient remained disease-free for 52 mo after the primary surgery. An early diagnosis and R0 resection may be the only potential curative approach to liver metastasis of gastrointestinal LMS.

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INTRODUCTION

Leiomyosarcoma (LMS) is a rare cancer that accounts for approximately 14% of soft tissue sarcomas (STSs), with an incidence of < 1/100000/year in Europe[1]. LMS is primarily observed in middle-aged patients; it is equally prevalent in men and women. Approximately 20% of LMSs are found in the gastrointestinal tract, of which the small intestine is the most common site. LMS within the colorectum is extremely rare, accounting for < 1% of all malignancies of the colon and rectum[2]; however, colonic LMSs appear to be highly aggressive tumors. In 62% of all visceral sarcomas, hepatic metastases occur frequently owing to hematogenous spread *via* the portal vein[3]. Unfortunately, there is currently no standard treatment for LMS with metachronous liver metastasis. Therefore, a database search of Embase, PubMed, MEDLINE, and Google Scholar was performed to identify similar case reports using the following terms: LMS, hepatic metastases, and treatment. Through a literature review and case presentation of metachronous liver metastasis in a patient with LMS originating from the descending colon, we discuss which potential treatment options may be used in such cases.

CASE PRESENTATION

Chief complaints

A 38-year-old man was admitted to our hospital with an initial presentation of abdominal pain and diarrhea over the preceding 2 mo.

History of present illness

The patient visited a local hospital with abdominal pain and diarrhea over the previous 2 mo. Colonoscopy performed at a local hospital revealed a 4-cm diameter mass in the descending colon, 40 cm from the anal verge.

History of past illness

The patient had no remarkable past medical history.

Personal and family history

There were no significant findings in the patient's personal and family history.

Physical examination

The patient complained of tenderness in the left lower abdomen upon palpation, but no rebound tenderness. The abdomen was otherwise soft, undistended, and revealed no palpable mass. There were

no evidence of a mass or hematochezia on digital rectal examination.

Laboratory examinations

White blood cell count was mildly increased to 13960 cells/μL; however, laboratory investigations, including markers of liver function and renal function, were normal. The patient's carcinoembryonic antigen (CEA; 3.04 ng/mL) and carbohydrate antigen 19-9 (CA 19-9; 7.44 U/mL) levels were normal.

Imaging examinations

Colonoscopy showed a 4-cm diameter mass in the descending colon, and a biopsy was performed (Figure 1). The colonoscopy biopsy specimen result showed an atypical spindle cell lesion, suggestive of a malignant mesenchymal tumor. Immunohistochemically, the tumor was positive for smooth muscle actin (SMA) and desmin, and negative for cluster of differentiation 34 (CD34), CD117, and discovered on gastrointestinal stromal tumor (GIST)-1 (DOG-1). Abdomino-pelvic computed tomography (CT) revealed intussusception in the descending colon due to a mass of approximately 4 cm with liquefaction, a small amount of ascites, and no distant metastasis in other solid organs (Figure 2). There was no abnormal finding on chest CT.

Further hospital course

Based on the results of the biopsy and CT, a diagnosis of LMS arising from descending colon was suspected. The patient underwent a left hemicolectomy; no intraoperative or postoperative complications were noted. The pathology report showed a 7.5 cm × 5.5 cm × 4.0 cm LMS without necrosis in the descending colon with a clear resection margin and no metastasis in all 27 lymph nodes (Figure 3). Mitotic counts were as high as 32/10 high-power field, and immunohistochemical analysis revealed SMA and focal desmin positivity, and CD34, CD117, DOG-1, and S-100 protein negativity. Without adjuvant treatment, the patient underwent a checkup every 3 mo using a routine blood test and CT. The patient was found to have a possibly newly developed liver metastasis in segment 8 on an abdomino-pelvic CT performed 11 mo after the primary surgery; however, there were no evidence of local recurrence at the anastomosis site (Figure 4A). In addition, magnetic resonance imaging of the liver identified a suspected 2.3-cm-sized liver metastasis in the same region (Figure 4B). The patient's CEA level had also increased to 10.23 ng/mL. The patient's Child-Pugh score was 5 points.

FINAL DIAGNOSIS

Metachronous liver metastasis in segment 8 originating from the LMS in the descending colon.

TREATMENT

Intraoperative ultrasonography revealed a single metastatic lesion of the liver. A segmentectomy of segment 8 was performed to resect the tumor.

OUTCOME AND FOLLOW-UP

The pathology report showed a metastatic LMS measuring 2.4 cm × 2.2 cm × 2.0 cm with no hepatic capsular invasion; the safety margin was 1.1 cm (Figure 5). After the second operation, the patient was administered six cycles of doxorubicin and ifosfamide combination chemotherapy (doxorubicin 60 mg/m^2 iv on Day 1 and ifosfamide 2500 mg/m^2 iv on Days 1-3). On the last day of each cycle, tripegfilgrastim 6 mg iv was administered 24 h after the end of administration of the last treatment. Allergic dermatitis and myalgia appeared as side effects of chemotherapy; however, chemotherapy dose reduction was not performed. After the end of adjuvant chemotherapy, we performed a blood test, CT, and bone scans for the patient's follow-up. Abdomino-pelvic CT, chest CT, and bone scans were performed every 3 mo; there was no tumor recurrence or distant metastasis. In addition, the levels of CEA and CA 19-9 were maintained within the normal range without significant changes. There was no evidence of recurrence or metastasis after 52 and 40 mo after the first and second surgeries, respectively.

DISCUSSION

GISTs have a good prognosis for targeted therapy with tyrosine kinase inhibitors and their treatment guidelines have been established. However, other STSs, including LMSs, lack effective standardized treatment and thus have a poor prognosis. Factors affecting the prognosis of STS include malignancy

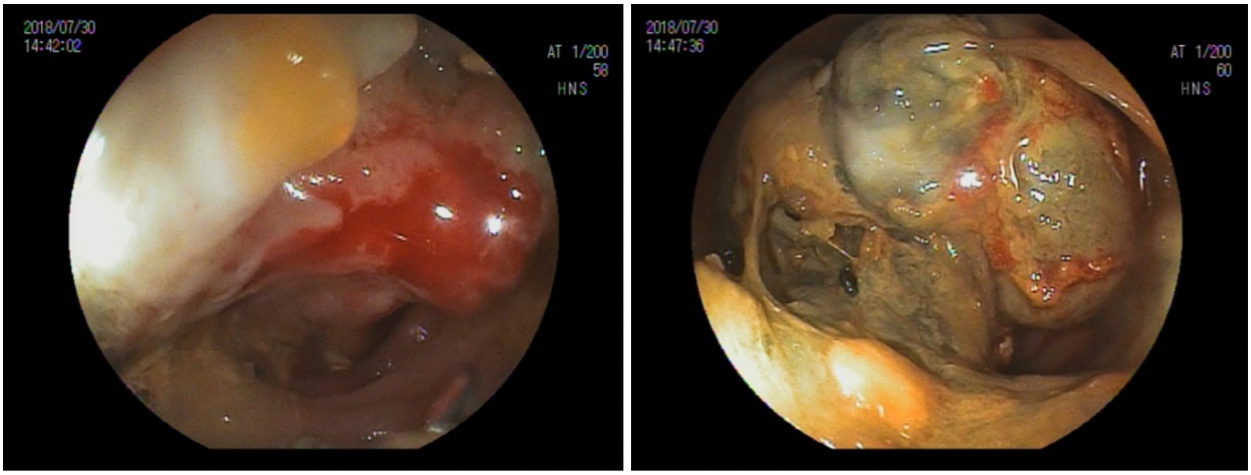

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Figure 1 Endoscopic findings of large polypoidal mass in the descending colon.

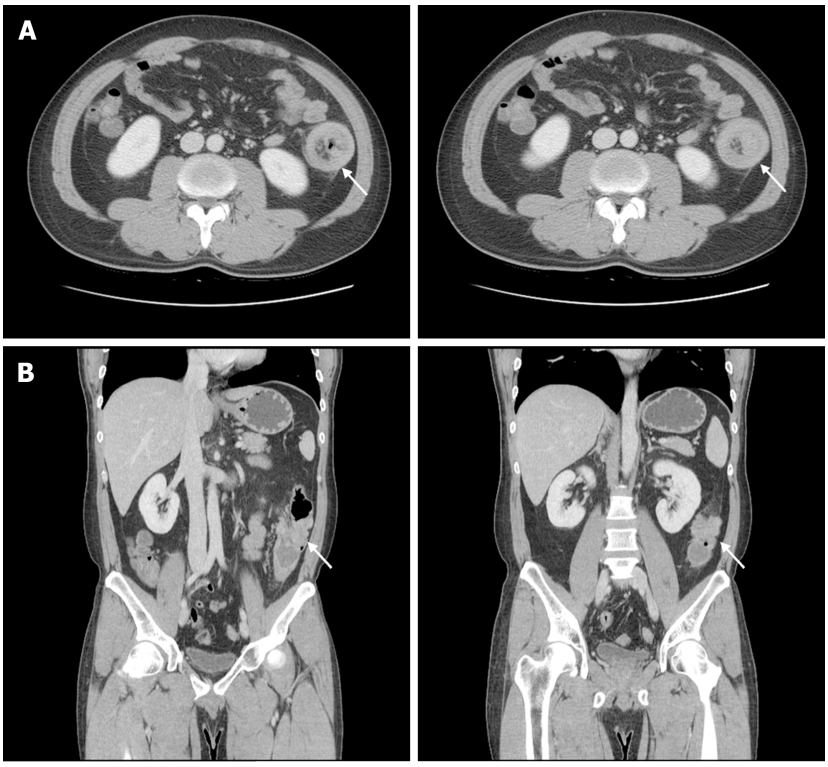

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Figure 2 Contrast-enhanced abdominal computed tomography. Computed tomography shows the lead point (white arrow) of the intussusception in the descending colon due to an approximately 3-cm cystic mass. A: Axial view; B: Coronal view.

grade, tumor size, primary tumor location, tumor resectability, surgical margin quality, and preoperative/intraoperative tumor rupture[4]. However, the most important prognosticator is the presence of metastases. For this reason, studies on the standard treatment for STSs (excluding GISTs), especially metastatic STSs, have been conducted. However, there are limitations, particularly the remarkably small number of patients that were included. Based on a search of the main online databases (Embase, PubMed, MEDLINE, and Google Scholar), 37 cases of colonic LMS have been published. Among them, liver metastases were found in eight patients, and two patients were referred for resection for liver metastases, all of which were synchronous metastases[5,6]. One patient was a 74-year-old woman who was diagnosed with a descending colon cancer with liver metastasis in segment 5/6 of the liver. Unfortunately, she died 10 mo after surgery due to multiple lung metastases[6]. In another case, a 66-year-old woman underwent surgery and received adjuvant chemotherapy for gastric cancer with liver metastases. She was subsequently diagnosed with LMS of the sigmoid colon with multiple liver metastases and underwent resection of four liver tumors. However, she died 7 mo later because of

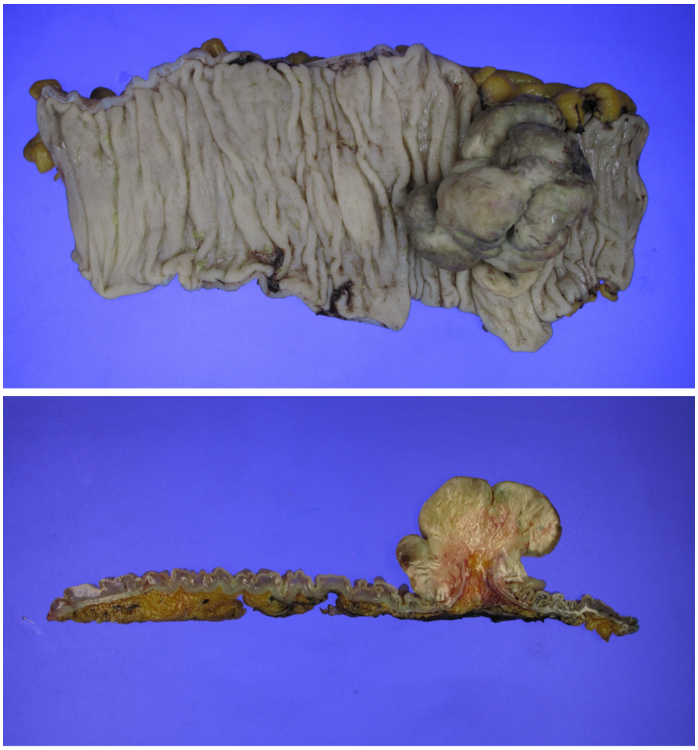

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Figure 3 Gross pathological specimen after the left hemicolectomy. A 7.5 cm-sized leiomyosarcoma originating from the descending colon was identified.

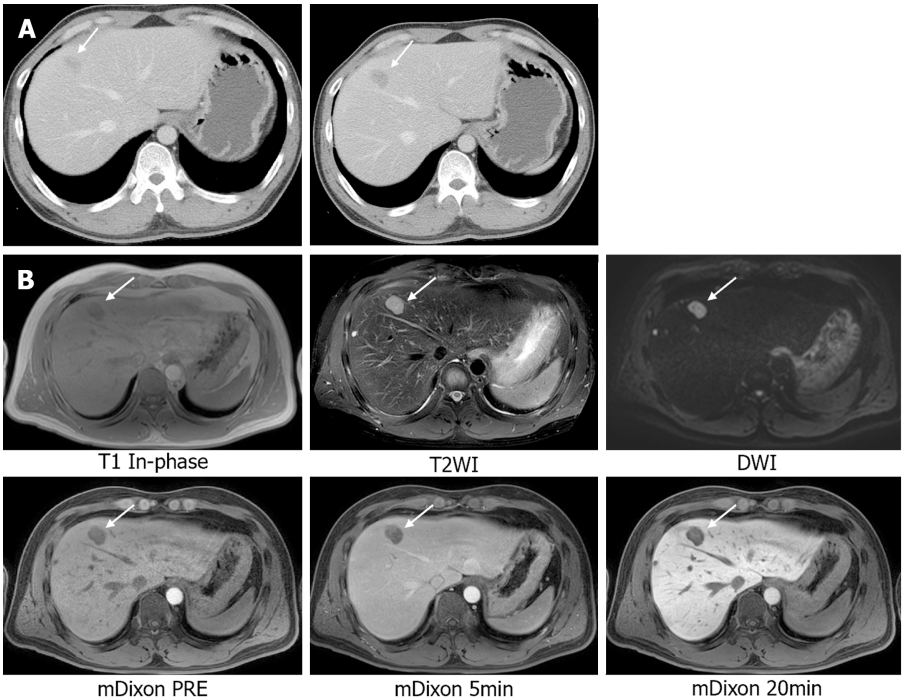

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Figure 4 Abdominopelvic computed tomography and liver dynamic magnetic resonance imaging. A: Abdominopelvic computed tomography performed 11 mo after left hemicolectomy reveals a new low-density mass, with possible liver metastasis in segments 4 and 8. There is no evidence of local tumor recurrence at the anastomotic site; B: Liver dynamic magnetic resonance imaging reveals a 2.3-cm solid mass with peripheral enhancement and diffusion restriction in segments 4 and 8 of the liver.

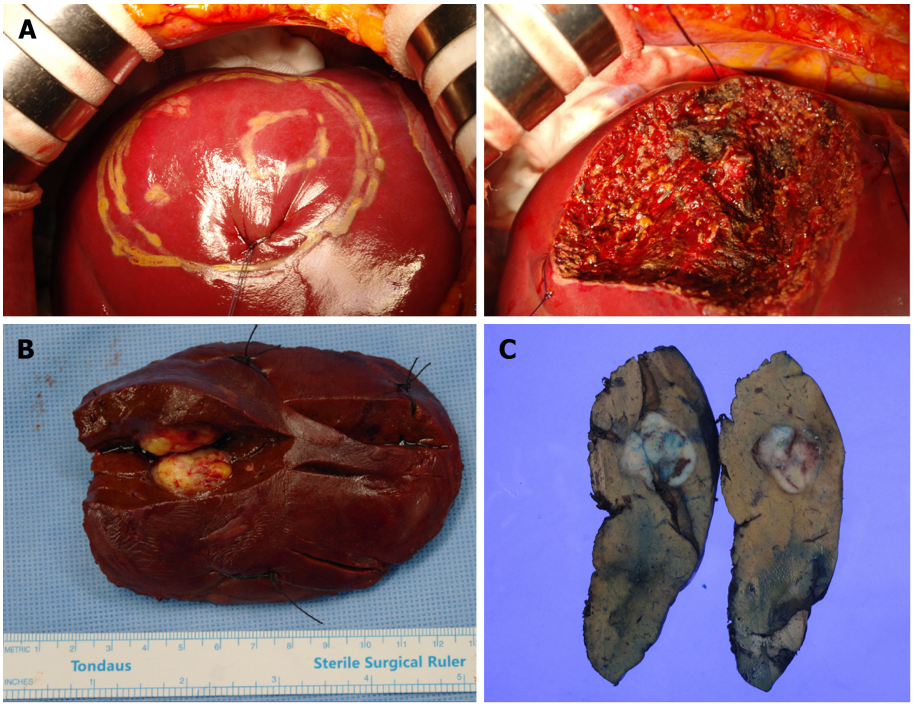

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Figure 5 Intraoperative finding, gross finding, and pathological specimen. A: Intraoperative finding. After demarcating the tumor location and resection margin using intraoperative ultrasonography, liver segmentectomy of segment 8 was performed; B and C: Gross finding of the resected liver (B) and pathological specimen (C). The resected specimen exhibits a 2.4 cm × 2.2 cm × 2.0 cm white-yellowish solitary mass that is firm and relatively well-demarcated.

multiple liver and lung metastases[7]. Thus, reports of colon LMS with liver metastasis are significantly rare, making it difficult to establish treatment guidelines.

According to the clinical practice guidelines recently published by the European Society for Medical Oncology, surgery is considered the standard treatment for locoregional soft tissue and visceral sarcomas, and en bloc excision with R0 resection is required. Except for patients with a high risk of death from surgery, adjuvant and neoadjuvant chemotherapies are not standard treatments. Radiotherapy can be added to surgery as part of the standard treatment for high-grade (Grade 2–3) lesions; however, local control and overall survival (OS) are not influenced by the timing of radiotherapy. The standard treatment for advanced STS is surgery for metachronous and resectable lung metastases without extrapulmonary disease, and chemotherapy for synchronous lung metastases without extrapulmonary disease. Anthracycline-based chemotherapy is recommended for the treatment of unresectable STS[1]. However, even in these guidelines, the treatment of the liver metastases is insufficient, and most of the patients documented in the guideline had STSs arising from the extremities and trunk walls.

Several reports have confirmed that LMS is relatively resistant to chemotherapy and radiotherapy; therefore, it is difficult to expect favorable effects through these treatment strategies[6,8]. Thus, a greater emphasis has been placed on the importance of surgical resection. The 5-year survival rate of patients with LMS who did not undergo surgical resection is only 4%, which is lower compared to that of patients undergoing resection (20%–30%)[9]. Liver resection for metastatic STS has a median OS of 46 mo and a median progression-free survival (PFS) after liver resection of 16 mo. Even after R2 resection, the median survival period is 20 mo, which is longer than that of patients treated with chemotherapy (10 mo), as mentioned in the European Organisation for Research and Treatment of Cancer trial[3]. In addition, when liver resection is performed for metachronous metastases, the median PFS is better than that for synchronous metastases[3,10]. However, in some studies, synchronous disease showed a lower median OS than metachronous disease, although the difference was not statistically significant. Therefore, it is difficult to consider it a prognostic factor of OS[11]. The most important point to improve OS mentioned in most reports is R0 resection; the number and size of liver metastases or the extent of liver resection does not affect survival[10]. Lymph node metastases are remarkably rare and lymph node dissection is unnecessary[12]. In our case, all 27 lymph nodes were nonmetastatic, although the primary LMS in the descending colon was > 7 cm in diameter and had a high mitotic rate.

LMS may remain asymptomatic for a long time; therefore, there may be no operability at the time of discovery. In the case of liver-dominant metastatic LMS which cannot be surgically resected, chemotherapy is provided; unfortunately, the patients' response is poor. The median OS period is up to 21.9 mo, and the PFS period is 6.9 mo. In such cases, liver-directed treatment can be provided instead of chemotherapy. When comparing transarterial chemoembolization with doxorubicin-eluting beads,

yttrium-90 radioembolization, and percutaneous microwave ablation, the median OS period was 27 mo from the development of liver metastases and the median liver PFS period increased by 9 mo, similar to patients who underwent surgical resection[13]. However, there is a disadvantage in that Grade 1 or 2 clinical toxicities due to liver-directed treatment appear in 96% of patients during the first 3 mo. In addition, the effect of extrahepatic metastases on liver resection in patients who have undergone liver metastasectomy is controversial. Extrahepatic metastases in patients undergoing liver resection are a negative prognostic factor[14]; however, the presence of resectable extrahepatic disease does not interfere with liver resection[11,15]. For this reason, there remains controversy about performing liver resection for liver metastases accompanied by extrahepatic metastases; therefore, additional studies are required.

CONCLUSION

Existing studies recommend surgery for resectable metastases in advanced STS arising from the extremities. Furthermore, in gastrointestinal LMS with liver metastases, if there is no other organ metastasis and resection is possible, regardless of the number of metastases, synchronous or metachronous, surgical resection is helpful for OS and PFS. Therefore, aggressive surgical interventions, rather than chemotherapy or radiotherapy, should be considered, including R0 resection.

FOOTNOTES

Author contributions: Jung HI contributed to the design of the case report; Lee SH wrote the draft of the manuscript; Ahn TS and Bae SH performed the operations that led to the pathological diagnosis; Lee SC and Kim Z managed the patient's condition; Jung HI supervised this study; all authors have read and approved the final manuscript and agree to be held accountable for all aspects of this report.

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CASE REPORT

Modified endoscopic submucosal tunnel dissection for large esophageal submucosal gland duct adenoma: A case report

Su-Yu Chen, Zhao-Fei Xie, Yan Jiang, Juan Lin, Hong Shi

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Abstract

BACKGROUND

With the recent improvement of endoscopic techniques, endoscopic ultrasound-guided fine needle aspiration and endoscopic submucosal tunnel dissection (ESTD) have been widely used for accurate diagnosis and dissection acceleration of esophageal tumors.

CASE SUMMARY

We used a modified submucosal tunnel technique during endoscopic *en bloc* resection in a 58-year-old man with large esophageal submucosal gland duct adenoma (ESGDA). During modified ESTD, the oral end of the involved mucosa was cut transversely, followed by a submucosal tunnel created from the proximal to the distal end, and the anal end of the involved mucosa blocked by the tumor was incised. As a result of retaining submucosal injection solutions using the submucosal tunnel technique, it was possible to reduce the amount of injection required and increase the efficiency and safety of dissection.

CONCLUSION

Modified ESTD is an effective treatment strategy for large ESGDAs. Single-tunnel ESTD appears to be a time-saving procedure compared with conventional endoscopic submucosal dissection.

Key Words: Esophageal submucosal gland duct adenoma; Endoscopic ultrasound-guided fine needle aspiration; Endoscopic submucosal tunnel dissection; Case report

Core Tip: With the recent improvement of endoscopic techniques, endoscopic ultrasound-guided fine needle aspiration and endoscopic submucosal tunnel dissection (ESTD) have been widely used for accurate diagnosis and dissection acceleration. Here we used a modified submucosal tunnel technique during endoscopic *en bloc* resection in a 58-year-old man with large esophageal submucosal gland duct adenoma (ESGDA) 3.5 cm × 2.2 cm in size with negative margins. Modified ESTD is an effective treatment strategy for large ESGDAs. Single-tunnel ESTD appears to be a time-saving procedure compared with conventional ESD.

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INTRODUCTION

The esophageal glands reside in the submucosal layer of the upper and lower segments of the esophagus, opening at the esophageal lumen by tortuous tubules. The glands play a role in protecting the esophagus from damage caused by acid exposure through the secretion of bicarbonate and prostaglandin. Esophageal submucosal gland duct adenoma (ESGDA) is quite rare and usually presents as a submucosal lesion with or without a central depression[1-2]. This is the first report of the successful resection of a large esophageal submucosal tumor (SMT) using endoscopic-related techniques.

METHODS

As described in the published literature, single-tunnel ESTD[3] has shown greater efficiency for large superficial esophageal squamous cell neoplasms. In contrast to conventional ESTD, modified ESTD does not begin with cutting the distal end of the involved mucosa, which is occluded by a large esophageal SMT. First, the oral end of the involved mucosa was cut transversely. Subsequently, a submucosal tunnel was created from the proximal to the distal end. After completion of the tunnel, the lateral mucosa was incised, followed by the anal end of the involved mucosa, until complete removal of the tumor was achieved. Modified ESTD can be faster than conventional ESD for large esophageal tumors.

CASE PRESENTATION

Chief complaints

A 58-year-old man was referred to our hospital with a complaint of gastro-esophageal reflux symptoms for one month.

History of present illness

Symptoms started 1 mo before presentation with recurrent retro-sternal heartburn.

History of past illness

He was made a definite diagnosis of hypertension, and his blood pressure control is steady by oral anti-hypertensive drugs.

Personal and family history

The patient denied any family history of malignant tumors.

Physical examination

On physical examination, the vital signs were as follows: Body temperature, 36.5°C; blood pressure, 140/85 mmHg; heart rate, 85 beats per min; respiratory rate, 18 breaths per min. Furthermore, no enlargement was found in superficial lymph nodes. There was no obvious redness and swelling. Digital anal examination was not performed.

Laboratory examinations

Levels of serum tumor markers were normal (carcinoembryonic antigen, 2.8 ng/mL; carbohydrate antigen 12-5, 12 U/mL; carbohydrate antigen 724, 0.33 U/mL), except elevated carbohydrate antigen 19-

9 at the level of 45.25 U/mL. No abnormality was found in routine blood, stool and urine analyses.

Imaging examinations

White-light endoscopy showed one 35-mm SMT located in the lower thoracic esophagus, with a central depression with a reddish appearance, just above the squamous-columnar epithelium junction (Figure 1). Endoscopic ultrasound (EUS) showed that the SMT was a well-defined heterogeneous, hypoechoic lesion with scattered small anechoic areas in the third layer (Figure 2A). No vascular flow was noted on color Doppler within the lesion (Figure 2B). Elastography revealed a hard mass (Figure 2C). Both cytological and histological analysis of fine-needle aspiration (FNA) specimens reported atypical glandular epithelial cells, ruling out squamous carcinoma (Figure 3). Thorax computed tomography (CT) revealed an eccentric soft tissue density mass in the esophagus.

FINAL DIAGNOSIS

Combined with the patient's medical history, the final diagnosis was esophageal benign submucosal mesenchymal tumor.

TREATMENT

Given that the mass did not involve the muscularis propria, modified ESTD was performed using a single-accessory channel endoscope with a transparent cap attached to the front. First, the oral end of the involved mucosa was cut transversely. Subsequently, a submucosal tunnel was created from the proximal end to the distal end. After completion of the tunnel, the lateral mucosa was incised, followed by the anal end of the involved mucosa, until complete removal of the tumor was achieved (Figure 4). The post-ESTD defect was closed using repositionable clips in the distal–proximal sequence.

Subsequently, cefazolin sodium 1 g was administered intravenously twice a day for three days from the day of the resection.

OUTCOME AND FOLLOW-UP

The procedure was completed without any adverse events, and the patient was discharged on postoperative day 7. Post-ESTD pathology confirmed an ESGDA 3.5 cm × 2.2 cm in size with negative margins. A cystic pattern with distinct 2-cell layers was observed, and the inner luminal cells were eosinophilic (Figure 5). Immunohistochemical staining showed the positive expression of P63, CK7, CK8/18, and Ki-67.

At 12 mo postoperatively, the patient received gastroscopy showing the esophageal wound healed well.

DISCUSSION

To the best of our knowledge, this present study represents the largest ESGDA treated by modified ESTD to be reported in the literature. Published literature reports suggest a potential biological pathway for ESGDA to progress to malignancy; thus, resection of these tumors is recommended if possible.

As an esophageal subepithelial tumor, ESGDA is extremely easily mistaken for esophageal carcinoma. EUS evaluation is essential for evaluating subepithelial lesions. The typical EUS feature of ESGDA is a heterogeneous hypoechoic submucosal tumor located in the third sonographic layer, with a few cystic lesions, considered dilated adenomatous gland ducts[4]. Differentiation through EUS-guided FNA is helpful to judge the origin of pathology and make the decision for conservative management *vs* endoscopic or thoracoscopic intervention[5]. In our case, both cytological and histological analyses showed atypical glandular epithelial cells, so modified ESTD was selected for resection.

As reported previously[3], the major advantage of ESTD over ESD for large superficial esophageal squamous cell neoplasms is that most submucosal injection solutions can be retained in the submucosal layer, resulting in increased efficiency and safety of dissection. Also tunnel endoscopy can be used to expose the intact submucosal lesion between the mucosa and muscular layer of the esophagus. In view of the aforementioned advantages, we performed ESTD for *en bloc* resection of the large ESGDA, rather than conventional ESD that was be adopted in the literature on ESGDA[1,2,4,6-8]. During routine ESTD, the distal end of the involved mucosa was first cut transversely. In this case, the obstruction caused by a large esophageal tumor made it difficult to cut the distal end of the involved mucosa at the beginning of the operation. An adjustment of the operative sequence was made in the modified ESTD. The oral end

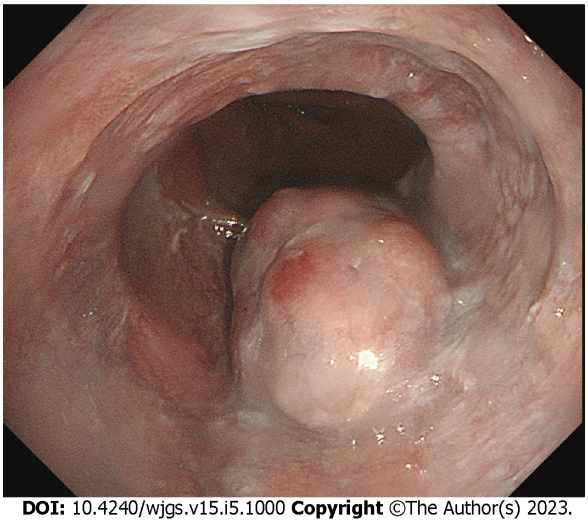

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Figure 1 Endoscopic findings. One 35-mm submucosal tumor was located in the lower thoracic esophagus, with a central depression with a reddish appearance.

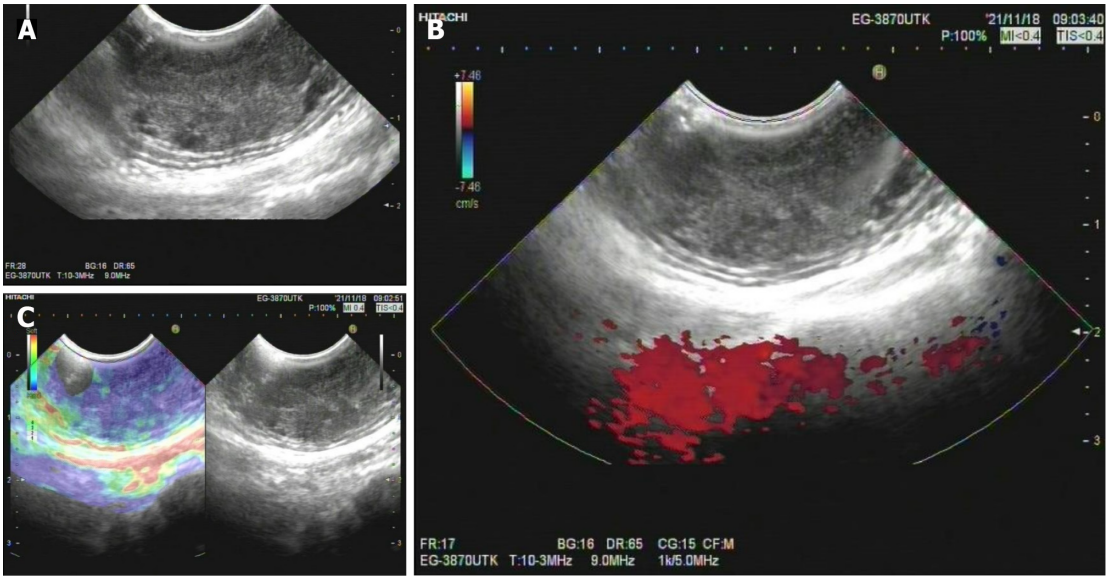

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Figure 2 Endoscopic ultrasound findings. A: A well-defined heterogeneous, hypoechoic lesion with scattered small anechoic areas in the third layer; B: No vascular flow within the lesion; C: A hard mass revealed by elastography.

of the involved mucosa was first cut transversely, then the lateral mucosa was incised, followed by the anal end of the involved mucosa, after completion of the tunnel.

With regard to the disadvantages of ESTD, they include visual field loss when arterial bleeding requiring immediate endoscopic hemostasis occurs, due to the limited tunnel space. Furthermore, arterial bleeding in ESTD for lower esophageal tumors is relatively more common, differing from that involving the upper and middle esophagus.

CONCLUSION

Modified ESTD is an effective treatment strategy for large ESGDAs. Single-tunnel modified ESTD appears to be a time-saving procedure compared with conventional ESD[9-10].

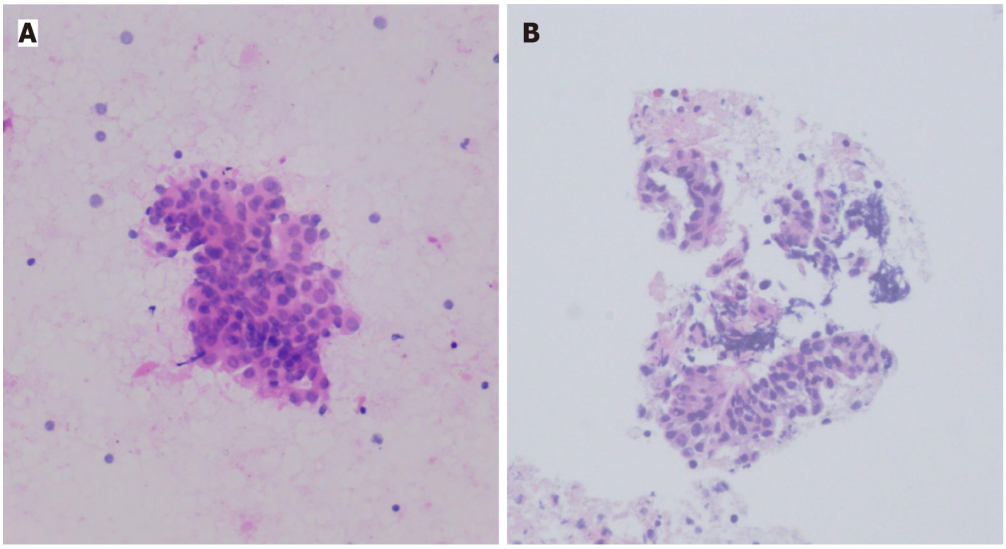

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Figure 3 Endoscopic ultrasound - fine-needle aspiration findings. A: Cytological analysis; B: Histological analysis.

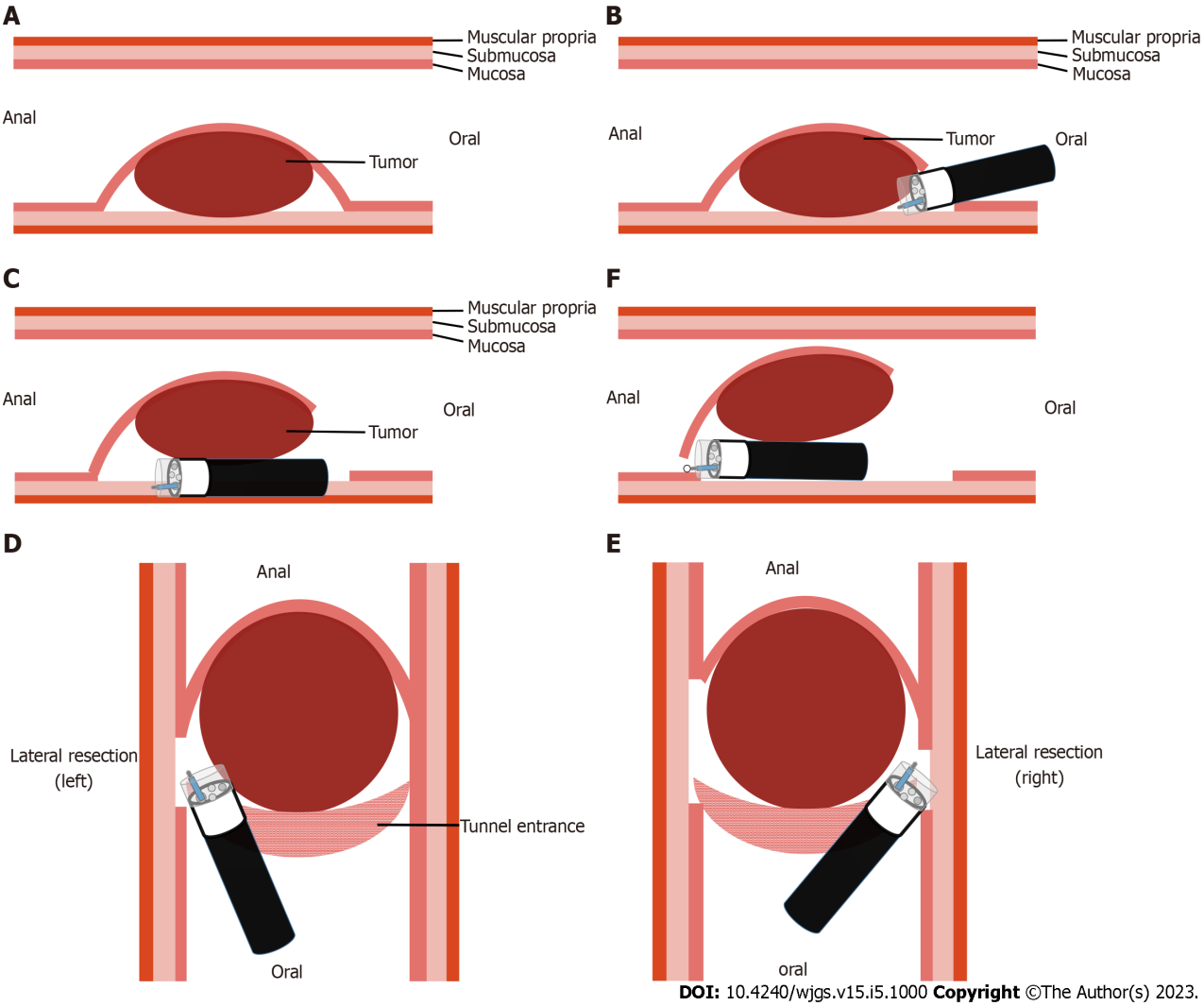

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Figure 4 Schema of modified endoscopic submucosal tunnel dissection. A: Endoscopic submucosal tunnel dissection located in the submucosal layer; B: Oral end of the involved mucosa cut transversely; C: Submucosal tunnel created from the proximal end to the distal end; D: One lateral mucosa resected; E: The other lateral mucosa resected; F: Anal end of the involved mucosa resected.

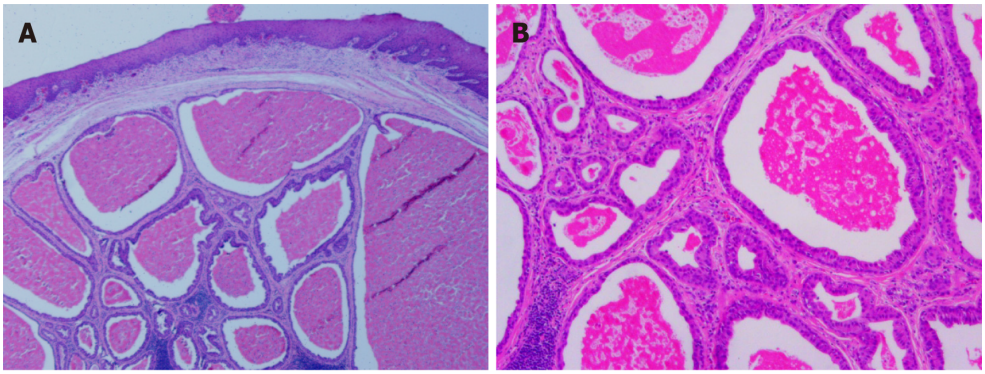

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Figure 5 Post-Endoscopic submucosal tunnel dissection pathology. A: A cystic pattern with distinct 2-cell layers; B: Eosinophilic inner luminal cells.

FOOTNOTES

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