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OPINION REVIEW

Comparison between recent sphincter-sparing procedures for complex anal fistulas-ligation of intersphincteric tract *vs* transanal opening of intersphincteric space

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Abstract

Complex anal fistulas are difficult to treat. The main reasons for this are a higher recurrence rate and the risk of disrupting the continence mechanism because of sphincter involvement. Due to this, several sphincter-sparing procedures have been developed in the last two decades. Though moderately successful in simple fistulas (50%-75% healing rate), the healing rates in complex fistulas for most of these procedures has been dismal. Only two procedures, ligation of intersphincteric fistula tract and transanal opening of intersphincteric space have been shown to have good success rates in complex fistulas (60%-95%). Both of these procedures preserve continence while achieving high success rates. In this opinion review, I shall outline the history, compare the pros and cons, indications and contraindications and future application of both these procedures for the management of complex anal fistulas.

Key Words: Anal fistula; Fistulotomy; Incontinence; Ligation of intersphincteric fistula tract; Transanal opening of intersphincteric space; Recurrence

Core Tip: Ligation of intersphincteric fistula tract (LIFT) and transanal opening of intersphincteric space (TROPIS) are two of the more recent innovative procedures introduced in the last decade. Both of these procedures have been shown to be quite effective in complex anal fistulas. As both procedures are primarily sphincter-sparing, they do not lead to deterioration in continence. The advantages and disadvantages, indications and contraindications of LIFT and TROPIS have been discussed in this opinion viewpoint as well as the role both these procedures are likely to play in the future.

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INTRODUCTION

The management of complex anal fistulas is challenging[1]. This is because complex fistulas involve a significant part of the sphincter complex [internal anal sphincter (IAS), external anal sphincter (EAS) or both] and if adequate care is not taken, then the sphincters may be damaged leading to permanent incontinence[1,2]. Fistulotomy is the most common procedure performed for anal fistulas but fistulotomy is contraindicated in complex fistulas as the risk of sphincter injury is high[2]. Therefore, several new sphincter-sparing procedures have been developed over the last two decades like video-assisted anal fistula treatment (VAAFT)[3-7], anal fistula plug (AFP)[8,9], over the scope clip (OTSC)[10-12], fistula laser treatment (FiLac)[2], stem cells[13,14], fixcision[15], fibrin glue[16-18], ligation of intersphincteric fistula tract (LIFT)[19-25], Bio-LIFT[26] and transanal opening of intersphincteric space (TROPIS)[27-31].

The main feature of all of these newer procedures is that they are largely sphincter-preserving especially for the EAS. Though most of these procedures demonstrated a moderate success rate in simple fistulas (40%-75%), their success rate in complex fistulas was either not satisfactory or not studied. Only two of these procedures, LIFT[19,21,22,24,25] and TROPIS demonstrated encouraging results (60%-95%) in highly complex fistulas[27-30,32]. Though these two procedures (LIFT and TROPIS) are not very old, we now have enough evidence (published studies), including a few studies with long-term results on the basis of which preliminary comparison can be done between these two procedures.

DEFINITIONS-PROCEDURE STEPS

LIFT

A curvilinear incision is made in the intersphincteric groove on the perianal skin in the quadrant where the internal opening of the fistula is located. The plane between the two sphincters (IAS and EAS) is dissected and the fistula tract traversing through the intersphincteric space is identified and a loop is passed around it. The tract in the intersphincteric space is divided. The proximal end of the intersphincteric fistula tract (towards the IAS) is suture ligated with an absorbable suture. The distal end of the intersphincteric fistula tract (towards the EAS) is suture ligated or excised along with the tract in the ischioanal fossa. The dissected out intersphincteric plane may be left open to drain or loosely sutured.

TROPIS

In this procedure, through the transanal route, an artery forceps is inserted into the fistula tract which is present in the intersphincteric plane through the internal opening. The mucosa and the internal sphincter over the artery forceps are incised and its edges are trimmed with electrocautery. Thus, the intersphincteric space is opened into the anal canal. This wound is left open to heal by secondary intention. The fistula tract lateral (external) to the EAS can be managed by any method convenient to the surgeon (excision or curettage with insertion of a drainage tube or laser ablation).

HISTORY

Until 1958, anal fistulas were classified only as per their relationship to the anorectal ring without any

importance being attached to the intersphincteric space. Eisenhammer highlighted the importance of the intersphincteric space in pathogenesis and management of anal fistula for the first time in 1958[33]. After that, it was understood that intersphincteric abscesses could be drained into the anorectum through the transanal route thereby saving the EAS from iatrogenic injury. However, for several decades (till 2017), this concept of transanal drainage of intersphincteric sepsis was limited to high intersphincteric abscesses only[29].

In 1993, Matos *et al*[34], for the first time, dissected into the intersphincteric space through the intersphincteric groove. They excised the fistula tract in the intersphincteric space and then the defect in the IAS was oversewn with 2-0 polyglactin suture[34]. In a small cohort of 13 patients, they reported a success rate of 53.8% (7/13)[34]. However, the main credit of developing and popularizing this technique goes to Rojanasakul *et al*[25,35]. Instead of excising the fistula tract in the intersphincteric space, he ligated this tract[25,35]. This made the closure more secure, the procedure simpler and the success rate higher[35]. In the last decade, LIFT has made significant inroads into the armamentarium of fistula surgeons all across the globe. Success rates ranging from 42%[8] to more than 90%[23,24] have been reported (76% in recent reviews[22,36]), implying that proper execution of the procedure is one of the key determinants to achieving a high success rate[22].

In 2017, a new dimension was added to the importance of the intersphincteric space by Garg *et al*[29]. It was postulated that the fistula tract in the intersphincteric space, whenever present in any fistula, is sepsis between two sphincter muscles and is thus similar to an abscess in a closed space[2]. As any abscess is best treated by deroofing and healing by secondary intention, therefore, this intersphincteric 'abscess' (fistula tract in the intersphincteric space) should be treated by deroofing it into the anorectum through the transanal route. This is done by the TROPIS procedure. TROPIS is quite different from just drainage of high intersphincteric abscesses into the rectum. First, whereas the latter was only for pure high intersphincteric abscesses (which accounts for less than 10% of anorectal suppuration[37]), the TROPIS procedure is applicable in all fistulas including transsphincteric, suprasphincteric and supralevator fistulas as all fistulas have at least some intersphincteric component. Second, the intent in drainage of high intersphincteric abscesses was resolution of acute sepsis and the fistula was managed later in many cases. On the other hand, in TROPIS, the intent is curative in all fistula cases including even those presenting with acute abscess[29,37]. This happens because the fistula tract in the intersphincteric space is thoroughly cauterized and opened into the anal canal, the infected crypt glands are destroyed and the resulting wound is allowed to heal by secondary intention[37]. Though this takes 6-10 wk to heal completely but the chances of recurrences are reduced substantially[37]. It is known that in presence of infection, healing by secondary intention is better and more assured than healing by primary intention[29,37]. Therefore, TROPIS is the first procedure in complex fistulas in which the internal opening is allowed to heal by secondary intention. In simple fistulas, fistulotomy also follows the same principle and therefore results in high healing rates[37].

Thus, both these procedures, LIFT and TROPIS, are different because rather than primarily focusing on closure of the internal opening (as was done by other newer procedures), these two procedures lay equal, rather more, emphasis on the fistula tract in the intersphincteric space. This could be the reason for the much higher success rate of these procedures.

Malakorn *et al*[24] published their long-term experience with LIFT in 251 anal fistula patients and reported a primary healing rate of 87.65% at a median follow-up of 71 mo. Garg *et al*[37] published their long-term experience with TROPIS in 408 patients suffering from high complex fistulas and reported healing rates of 86% at a median follow-up of 30 mo. Both these procedures have also been shown to be effective in managing fistulas associated with acute abscess definitively in the first surgery (rather than draining the abscess first and then operating to treat fistula later)[23,29,37].

PROS AND CONS

The main advantage of LIFT is that both sphincters, IAS and EAS, are completely preserved and therefore, the risk of incontinence is negligible[23,24]. Another main advantage is that the resultant wound is allowed to heal by primary intention due to which recovery is much faster (Table 1).

The disadvantages of LIFT are that it is technically demanding and it takes time and patience to master this procedure. Another disadvantage is that the tackling of infected crypt glands is less thorough in LIFT as compared to TROPIS. The healing in LIFT is by primary intention and as discussed above and in presence of infection, healing by secondary intention gives better long-term healing rates. Due to these reasons, the success rate of LIFT is perhaps less as compared to TROPIS. Recent meta-analysis has highlighted the healing rate of LIFT in 26 studies (1378 patients) to be 76.5%[22] while in the single largest study on LIFT, Malakorn *et al*[24] published healing rates of 87.65%. However, in both these, the sample consisted of simple as well as complex fistulas. There are only a few studies in which LIFT has been studied in exclusive high complex anal fistulas. A randomized controlled trial by Jayne *et al*[38] in 2020 reported a dismal success rate of 42% with LIFT in an exclusive cohort of complex fistulas.

On the other hand, the advantages of TROPIS are that it is technically simpler than LIFT. While performing the LIFT procedure, it is not uncommon to enter the submucosal space while dissecting the

Table 1 Comparison between ligation of intersphincteric fistula tract and transanal opening of intersphincteric space procedures

	LIFT	TROPIS
Fistula tract in intersphincteric space	Ligated	Deroofed into anal canal
Healing of wound	Primary intention	Secondary intention
Tackling of infected crypt glands	Done	Much better
Technically	Difficult	Simpler
Indications	Not possible/ very difficult to perform in: Pure intersphincteric fistulas; Fistulas with more intersphincteric component like horseshoe fistulas; Fistulas in which intersphincteric component is high up like supralevator fistulas, suprasphincteric fistulas	Effective in all complex fistulas
Preferred over the other (LIFT or TROPIS)	Complex high fistula with minimal fistula component in the intersphincteric space (Figure 1); Patients having simple low fistula but they are not keen for fistulotomy	Horseshoe fistulas with extensive intersphincteric component (Figure 2); Recurrent fistulas especially fistulas recurring after undergoing LIFT; High transsphincteric (involving upper one-third of EAS); Suprasphincteric fistula (Figure 3)
Healing in postoperative period	Faster	Slower
Internal sphincter	Preserved	Partially incised; Study in a large number of patients with long-term follow-up have demonstrated that if patients did regular Kegel exercises in the postoperative period, then there was no significant deterioration in continence.

LIFT: Ligation of intersphincteric fistula tract; TROPIS: Transanal opening of intersphincteric space.

intersphincteric space. In this scenario, continuation of the LIFT procedure becomes difficult. Occurrence of this digression does not make any difference to the TROPIS procedure as both the submucosal and intersphincteric spaces have to be laid open into the anal canal. Therefore, TROPIS is easy to learn and reproduce. In the LIFT procedure, a useful trick to avoid entering the submucosal space is to dissect the fistula in the intersphincteric space along the medial edge of the external sphincter.

In TROPIS procedure, the infected crypt glands are thoroughly destroyed as the fistula tract in the intersphincteric space is laid open and the resultant opened intersphincteric space is completely cauterized with electrocautery. The complete removal of infected crypt glands also happens in the LIFT procedure but the difference is that healing in LIFT occurs by primary intention whereas in TROPIS, the healing of the wound occurs by secondary intention. In the presence of infection, the healing by secondary intention is preferred and this could be the reason for high healing rates (80%-93%) by TROPIS in complex fistulas[27-29,37]. In the single largest study of TROPIS, 408 patients suffering from high complex fistulas (all fistulas involving > 1/3 of EAS), the reported healing rate was 86% at a median follow-up of 30 mo[37]. The data of 408 patients in this study[37] included 325 patients reported in an earlier study[29]. The study had several strong points. Apart from a large cohort with a fairly long follow-up, pre-operative MRI was done in all the patients and all 408 patients were documented to be high (involving > 1/3 of EAS) on clinical as well as on MRI assessment[37]. Additionally, the clinical fistula healing in the postoperative period was also documented on postoperative MRI assessment in the majority of cases[37]. So, from the evidence available so far, the healing rate of TROPIS seems better than LIFT in high complex fistulas. But, an important point to consider is that LIFT has been performed, studied and published from far more centers across the globe than the TROPIS procedure. Therefore, TROPIS would be considered highly successful in high complex fistulas only when its high success rate is replicated in many more centers in different regions of the world. For translation into practical guidelines, comparative prospective studies of LIFT and TROPIS in complex fistulas still need to be done.

The main disadvantage of TROPIS is that the intra-anal wound heals by secondary intention and the time taken for complete wound healing is relatively longer. Another disadvantage of TROPIS is that IAS is partially incised while laying open the fistula tract in the intersphincteric space. Though it is known that EAS is more important for continence mechanism than IAS[34], yet division of IAS can also lead to continence disturbances especially urgency and flatus incontinence[39]. But, studies of TROPIS in a large cohort of exclusive complex fistulas highlighted no significant deterioration in continence on long-term follow-up[29,37]. The reason for this could be that the patients were advised to do pelvic floor exercises (Kegel exercises) meticulously in the postoperative period[29,37]. These exercises perhaps compensated for the decrease in resting anal pressure (as IAS is primarily responsible for maintaining resting anal pressure)[34].

In a recent study (not published, under submission), the efficacy of Kegel exercises (KE) in improving incontinence was evaluated in 102 complex anal fistula patients in whom TROPIS procedure was performed. There were 65 recurrent fistulas, 92 had multiple tracts, 42 had associated abscess, 46 had horseshoe fistula and 34 were supralevator fistulas. All were MRI-documented high fistulas (> 1/3 EAS involved). The incontinence was evaluated objectively by Vaizey's incontinence scores [a score of 0 (minimum score) implies no continence problem while score of 24 (maximum score) implies total incontinence][40]. The scoring was done initially in the immediate postoperative period before commencement of KE (pre-KE group) and then on long-term follow-up at 18 mo after surgery (post-KE group). The incontinence scores in both groups were compared to evaluate the efficacy of KE. Overall continence disturbance occurred in 31% patients (pre-KE group) [urge and gas incontinence accounting for the majority of cases (28.3%)] but after doing regular KE, continence disturbance disappeared completely in 18 % and improved in 13 % (of 31% patients with continence disturbance in pre-KE group). The mean incontinence scores in the pre-KE group were 1.19 ± 1.96 (in 31 patients, solid = 0, liquid = 7, gas = 8, urge = 24) and in the post-KE group were 0.26 ± 0.77 (in 13 patients, solid = 0, liquid = 2, gas = 3, urge = 10) (P = 0.00001, t-test). Division of the IAS led to mainly urge incontinence and all continence disturbance due to partial division of IAS by TROPIS improved significantly with regular Kegel exercises. Thus, the negative effect of partial division of IAS by TROPIS can be countered by regular KE in postoperative period for one year.

The IAS is primarily responsible for maintaining resting anal pressures. Division of the IAS leads to a decrease in resting anal pressure. Normally, the anal canal is free of fecal matter and only when the IAS relaxes during the act of defecation, the feces enter the anal canal. The human mind is tuned to associate the presence of fecal matter in the anal canal with impending passage of feces. Therefore, in patients with a divided IAS and decreased resting anal pressure, feces when present in the lower rectum passes unrestricted into the anal canal giving the feeling that 'feces are about to pass out of the anus' (urge incontinence). That's why the urge incontinence was seen in significant numbers of patients after the TROPIS procedure but it improved substantially with Kegel exercises[37].

INDICATIONS AND CONTRAINDICATIONS

The LIFT procedure can be performed in all simple as well as most complex fistulas (Figure 1). LIFT would be difficult to perform in fistulas with a greater intersphincteric component like horseshoe fistulas (Figure 2), fistulas in which the intersphincteric component is high up (like suprasphincteric fistulas (Figure 3), supralevator fistulas, high transsphincteric fistulas involving the upper-third of the EAS) as the procedure would be technically difficult to perform in these fistulas and pure intersphincteric fistulas (Table 1)[22]. The results of LIFT are lower in recurrent fistulas as the postoperative fibrosis and scarring obscure the anatomic planes making the surgery more challenging [22]. In horseshoe fistulas, the curved anatomic location of the tract renders complete eradication of fistula pathology more challenging[22].

TROPIS can be performed in all complex fistulas including high transsphincteric fistulas. Additionally, TROPIS can also be conveniently performed in fistulas in which LIFT is difficult to perform (fistulas with a high intersphincteric component-supralevator fistulas, suprasphincteric fistulas, high transsphincteric fistulas, fistulas with a greater intersphincteric component-horseshoe fistulas, recurrent fistulas and pure intersphincteric fistulas)[29,37] (Table 1).

PRESENT AND FUTURE SCENARIO

Both LIFT and TROPIS have added immense value to the management of complex anal fistulas. Both procedures have shown moderate to high success rates in complex fistulas without negatively impacting continence. This makes these procedures stand out from all other newer procedures developed in last two decades. LIFT is a 14 year old procedure and more evidence is available whereas TROPIS is only 5 years and the evidence is just emerging. In my opinion, both these procedures are conceptually sound and are coupled with good available evidence. It is likely that these two procedures are going to stay and become useful for the treatment of complex anal fistulas. These procedures complement each other and together they could become an important tool in the armamentarium of fistula surgeons. In complex high fistula in which the fistula component in the intersphincteric space is minimal, LIFT would be a better choice than TROPIS (Figure 1). Similarly, in a simple fistula, if the patient is not keen to undergo fistulotomy, then LIFT would be a better choice. In horseshoe fistulas with an extensive intersphincteric component (Figure 2), recurrent fistulas especially fistulas recurring after undergoing LIFT procedure, high transsphincteric (involving upper one-third of EAS) and suprasphincteric fistulas (Figure 3), TROPIS would be a better choice. Comparative studies comparing LIFT and TROPIS, preferably randomized, would provide vital insight into the efficacy of these procedures and the future role each procedure would likely have in the surgical practice of complex fistulas.

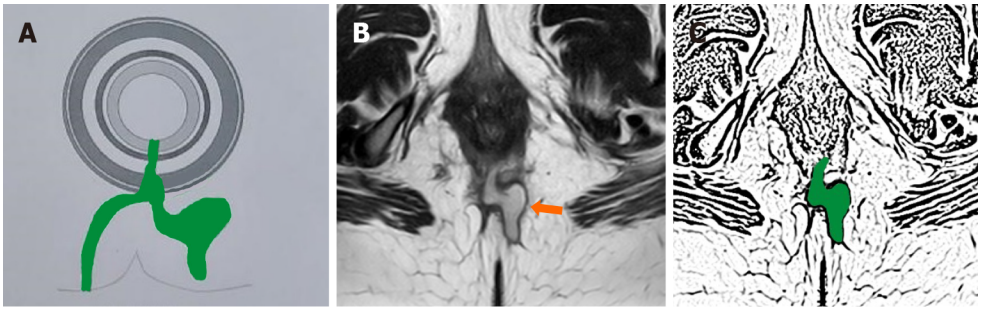

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Figure 1 A 43-year-old female patient with recurrent high transsphincteric posterior anal fistula with multiple branches. The intersphincteric component of fistula is a single linear tract at 6 o'clock (posterior) and the rest of all the fistula tracts are outside the external sphincter. This fistula is better managed by ligation of intersphincteric fistula tract procedure. A: Axial section-schematic diagram; B: T2-weighted magnetic resonance imaging axial section (orange arrow pointing the fistula tract); C: Sketch of B (fistula tract being shown in green color).

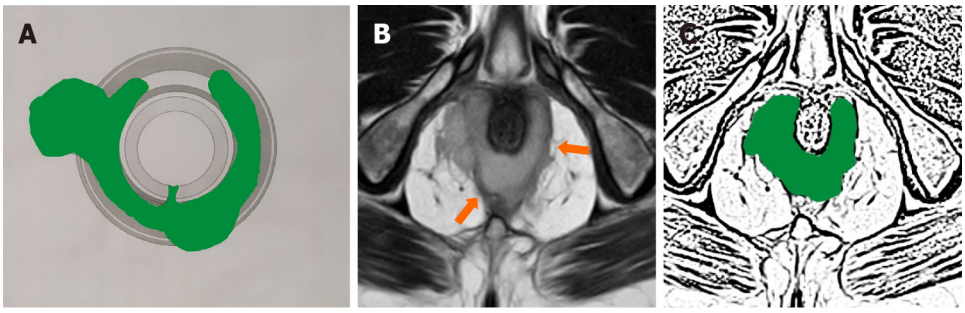

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Figure 2 A 47-year-old male patient with high posterior intersphincteric anal fistula with abscess. This fistula is difficult to manage by ligation of intersphincteric fistula tract and is better managed by transanal opening of intersphincteric space procedure. A: Axial section-schematic diagram; B: T2-weighted magnetic resonance imaging axial section (orange arrows pointing the fistula tract); C: Sketch of B (fistula tract being shown in green color).

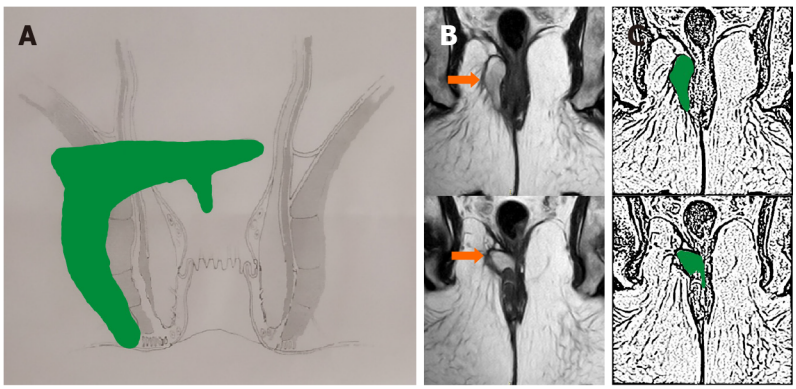

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Figure 3 A 39-year-old male patient with right sided suprasphincteric anal fistula with abscess. This fistula is difficult to manage by ligation of intersphincteric fistula tract and is better managed by transanal opening of intersphincteric space procedure. A: Coronal section-schematic diagram; B: T2-weighted magnetic resonance imaging coronal section (orange arrows pointing the fistula tract); C: Sketch of B (fistula tract being shown in green color).

It would be incorrect to conclude without discussing the third procedure which has been shown to be effective in complex anal fistulas, fistulectomy or fistulotomy with primary sphincter repair (FPR)[11,41-44]. In this procedure, the fistula tract is excised/ cored out (fistulectomy) or laid open (fistulotomy) and then the sphincter complex (IAS and EAS) is repaired primarily (sutured together) with the healing occurring by primary intention[11,41-44]. Long-term studies have shown that a high success rate (85%-95%) can be achieved with FPR in complex fistulas without having any negative effect on continence. However, the main disadvantage of this procedure is that it is technically quite demanding, the prospect of cutting a major part of anal sphincters is frightening to many patients and it is not recommended for fistulas involving the upper one-third of the EAS (especially suprasphincteric fistulas which involve

almost 100% of the EAS)[11,41-44].

CONCLUSION

To conclude, both LIFT and TROPIS are new useful continence-preserving procedures to treat complex anal fistulas with high success rates. In complex anal fistulas, newer sphincter-saving procedures (VAAFT, AFP, OTSC, FiLac, stem cells and fixcision) can also be carried out if the surgeon is more well-versed with these as they are safe procedures. However, if recurrence or repeated failures occur, then one of these three procedures-LIFT, TROPIS or FPR-should be performed depending on the fistula and the expertise of the surgeon in these procedures.

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FOOTNOTES

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REVIEW

Recent advances in diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms

Meng Dai, Christina S Mullins, Lili Lu, Guido Alsfasser, Michael Linnebacher

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Abstract

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are a rare group of tumors originating from neuroendocrine cells of the digestive system. Their incidence has increased over the last decades. The specific pathogenetic mechanisms underlying GEP-NEN development have not been completely revealed. Unfunctional GEP-NENs are usually asymptomatic; some grow slowly and thus impede early diagnosis, which ultimately results in a high rate of misdiagnosis. Therefore, many GEP-NEN patients present with later staged tumors. Motivated hereby, research attention for diagnosis and treatment for GEP-NENs increased in recent years. The result of which is great progress in clinical diagnosis and treatment. According to the most recent clinical guidelines, improved grading standards can accurately define poorly differentiated grade 3 neuroendocrine tumors and neuroendocrine carcinomas (NECs), which are subclassified into large and small cell NECs. Combining different functional imaging methods facilitates precise diagnosis. The expression of somatostatin receptors helps to predict prognosis. Genetic analyses of mutations affecting death domain associated protein (*DAXX*), multiple endocrine neoplasia type 1 (*MEN 1*), alpha thalassemia/intellectual disability syndrome X-linked (*ATRX*), retinoblastoma transcriptional corepressor 1 (*RB 1*), and mothers against decapentaplegic homolog 4 (*SMAD 4*) help distinguishing grade 3 NENs from poorly differentiated NECs. The aim of this review is to summarize the latest research progress on diagnosis and treatment of GEP-NENs.

Key Words: GEP-NENs; Functional imaging; Peptide receptor radionuclide therapy; Targeting agents; Immune checkpoint inhibitors; Genetic mutations

Core Tip: Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are a group of heterogeneous tumors arising from neuroendocrine cells of the digestive system. Researchers have achieved great improvements in diagnosis and treatment. This includes improved grading, identification of specific genetic mutations, functional imaging, and broad application of peptide receptor radionuclide therapy. Here, we systematically summarized the latest progress in diagnosis and treatment of GEP-NENs, thereby providing guidance for clinicians active in this field.

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INTRODUCTION

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) originate from neuroendocrine cells of the pancreas or the gastrointestinal tract. They represent the second most common cancer of the digestive system (Figure 1)[1]. The Surveillance, Epidemiology, and End Results (commonly known as SEER) 18 registry (2000-2012) revealed an increased incidence of GEP-NENs in the United States to 3.56/100000 inhabitants in the year 2012[2]. In European countries, the incidence also increased and was reported to be in the range of 1.33 to 2.33/100000 inhabitants[3,4]. Improvements in the detection methods have been identified as the most probable explanation for the increased incidence of GEP-NENs over the last decades[5]. These neoplasms are classified into well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). Moreover, depending on the hormone and amine secretion activity, GEP-NENs can be classified into functional and nonfunctional neoplasms[1,6]. Functional GEP-NENs produce hormones and amines, which cause specific clinical manifestations, such as hypoglycemia, refractory gastric ulcer, flushing, diarrhea, *etc*. However, immunohistochemical hormone staining is not sufficient for diagnosis[7].

Due to the clinical manifestations, functional GEP-NENs can frequently be diagnosed in early stages, what translates into a relatively good prognosis. In contrast, non-functional GEP-NENs are asymptomatic until distant metastases or mass effect cause late symptoms, such as intestinal obstruction [8]. The 2019 World Health Organization (WHO) classification of GEP-NENs consisted of the following categories: Grade 1, Grade 2, Grade 3, and NEC. This grading is based on the mitotic rate and/or the Ki-67 proliferation index, as listed in Table 1 below. The mitotic rate is determined by an immunohistochemistry method, in which 50 fields of 0.2 mm^2 are counted. The Ki-67 proliferation index value is determined by counting more than 500 cells in the regions of highest labelling using scanning magnification. The NEN grade is assigned by the proliferation index of the two, which places the neoplasm in the higher-grade according to the classification. Mixed NENs consist of both neuroendocrine and non-neuroendocrine components and are poorly differentiated, and the neuroendocrine component has proliferation indexes in the same range as other NECs. This conceptual category however allows for respect of the fact that one or both components can also be well differentiated; if feasible, every component should be graded separately[9,10]. Surgery is still the mainstay of curative treatment for localized GEP-NENs[11]. Methods of clinical diagnosis and treatment have been continuously updated because of ongoing research and study activities. This review aims at systemically summarizing the latest research advances on diagnosis and treatment of GEP-NENs.

CLINICAL PRESENTATION

GEP-NENs present as very heterogeneous, both because of different organs of origin and because of different biological behavior; consequently, clinical symptoms are various. Especially functional GEP-NENs, which secrete specific hormones, cause characteristic clinical syndromes[12]. Insulinomas produce excessive amounts of insulin, thereby causing hypoglycemia. Excessive secretion of gastrin from functional gastrinomas often results in refectory and recurrent peptic ulcerations. Glucagonoma patients regularly present with recent diabetic mellitus as well as migratory necrolytic erythema caused by extremely high glucagon levels, whereas somatostatinoma patients will present with hyperglycemia and steatorrhea. Contrary to that, non-functional GEP-NENs do not cause specific clinical symptoms, and they are often only diagnosed during routine physical examinations[13].

Table 1 The 5th classification system of World Health Organization for gastroenteropancreatic neuroendocrine neoplasms (2019)[10]

Classification	Differentiation status	Ki-67 index	Mitotic rate
Grade 1, NET	Well differentiated	< 3%	< 2
Grade 2, NET	Well differentiated	3% to 20%	2 to 20
Grade 3, NET	Well differentiated	> 20%	> 20
Small cell type, NEC	Poorly differentiated	> 20%	> 20
Large cell type, NEC	Poorly differentiated	> 20%	> 20
Mixed NEN	Well or poorlydifferentiated	Variable	Variable

NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma; NEN: Neuroendocrine neoplasm.

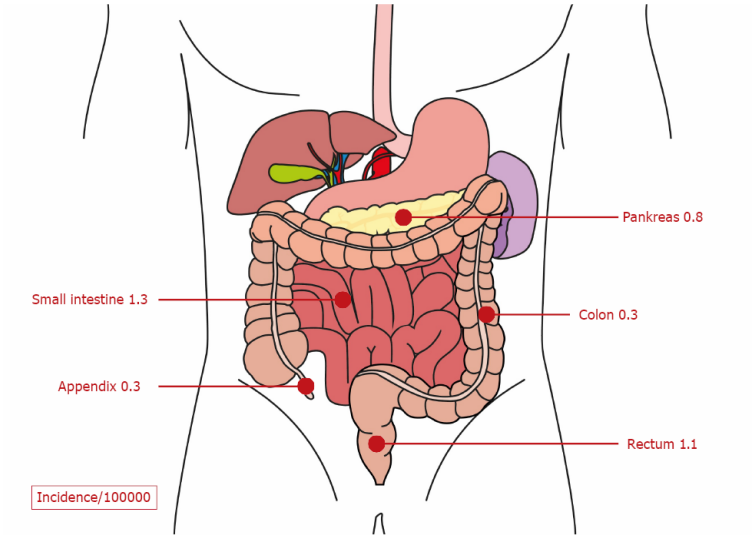

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Figure 1 Incidence in gastroenteropancreatic organs.

DIAGNOSIS OF GEP-NENS

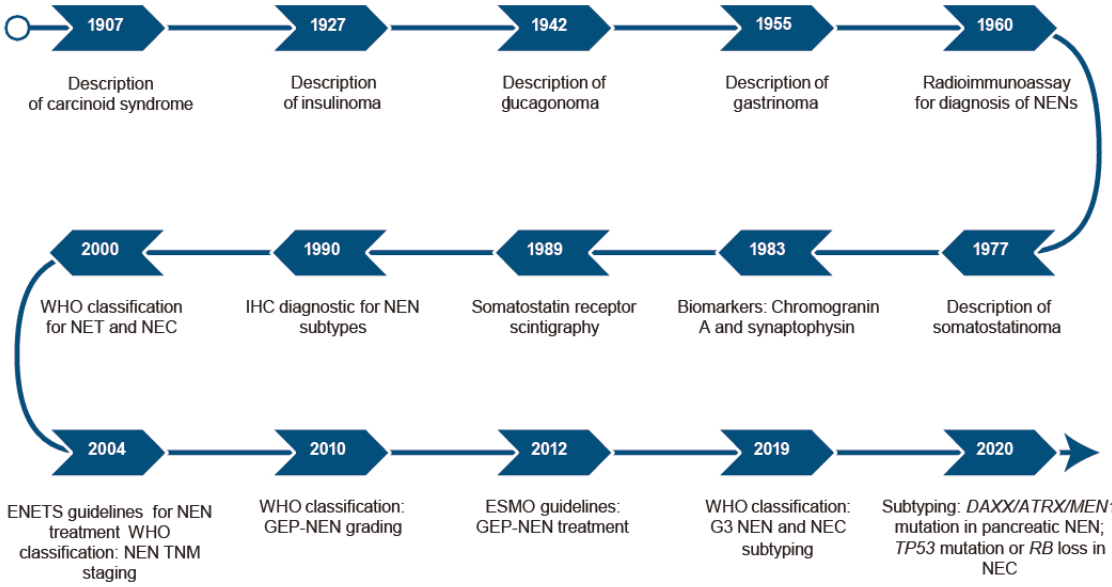
Diagnostic improvements over time are shown in Figure 2.

Biomarkers for diagnosis of NENs

Chromogranin-A: Chromogranin-A (CgA) is a member of the chromogranin glycoprotein family and is physiologically secreted by neurons and neuroendocrine cells[14]. In clinical diagnosis, CgA is established as a universal routine diagnostic biomarker of neuroendocrine neoplasms. Sensitivity of CgA assays varies between 32% and 92%, depending on the NET type, secretory status, and tumor burden. The specificity can approach 100% if other diseases affecting serum CgA levels, such as kidney insufficiency and chronic atrophic gastritis, can be excluded[15].

Serotonin: Serotonin is assessed by measuring its degradation product, 5hydroxyindoleacetic acid (5-HIAA), in 24-h urine of patients with carcinoid symptoms[16]. A meta-analysis demonstrated that 5-HIAA can be a predictive biomarker for 1-year mortality rate of NEN patients[17]. However, since specific nutritious substances (such as eggplants, bananas, tomatoes, *etc*) and medications (such as nicotine, ephedrine, diazepam, *etc*) can affect 5-HIAA measurement, patients need to be guided to omit these substances.

Gastrin: Gastrinomas can result in elevation of serum gastrin levels. With excessive secretion of gastrin, patients will suffer from refractory peptic ulcers. Therefore, serum levels of gastrin are routinely measured in patients suspected to have gastrinomas. Criteria for diagnosis of Zollinger-Ellison syndrome as a result of gastrinomas are: At least 10-fold elevated serum gastrin levels and a gastric pH below 2.1. However, proton pump inhibitors (PPIs) can elevate serum gastrin levels. Patients receiving PPIs need to wean this medication for at least 1 wk before gastrin measurement[18].



Year	Events
1907	Carcinoid syndrome described by Oberndorfer[94]
1927	Insulinoma described by Wilder[95]
1942	Glucagonoma reported by Becker[96]
1955	Gastrinoma reported by Robert Zollinger and Edvin Ellison[97]
1960	Radioimmunoassays for diagnosis of NENs by Rosalyn and Solomon[98]
1977	Somatostatinoma described by Ganda[99]
1983	Biomarkers: chromogranin A and synaptophysin[100]
1989	Somatostatin receptor scintigraphy introduced by Eric Krenning[101]
1990	IHC for diagnosing subtype of NENs[102]
2000	WHO classification for NET and NEC[103]
2004	ENETS guidelines for NETs; WHO classification TNM stage for NETs[104]
2010	WHO classification grading for GEP-NENs[105]
2012	ESMO guidelines for GEP-NENs[106]
2019	WHO classification for (re) definition of G3 NEN and G3 NEC[9]
2020	ESMO recommendation: DAXX/ATRX/MEN1 mutation in pancreatic NEN; p53 mutation or RB loss in NEC[66]

Figure 2 Milestones in the diagnosis of neuroendocrine neoplasms[94-106]. ENETS: European Neuroendocrine Tumor Society; ESMO: European Society for Medical Oncology; GEP-NEN: Gastroenteropancreatic neuroendocrine neoplasm; IHC: Immunohistochemistry; NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma; NEN: Neuroendocrine neoplasm; TNM: Tumor, Node, Metastasis; WHO: World Health Organization.

Insulin: Insulin is measured for diagnosis of insulinomas after a 72-h gastric fasting. If, during fasting-induced hypoglycemia, serum insulin levels reach more than 3 mcIU/mL, serum pro-insulin levels rise above 5 pmol/L, and Cpeptide concentrations are at least 0.6 ng/mL, an insulinoma is a probable diagnosis; especially in patients with concurrent pancreatic mass[19].

Glucagon: Glucagon is measured in the blood of patients suspected to suffer from glucagonomas and meeting the following criteria: Recently diagnosed with diabetes mellitus, migratory necrolytic erythema, and a positive imaging confirmation of a gastroenteropancreatic mass[20].

In summary, although these serum molecular tests are in standard use for GEP-NEN differential diagnosis, a consensus conference of multinational experts repeated that a single biomarker to diagnose efficaciously and predict prognosis for patients with GEP-NENs would be beneficial[7].

Imaging for diagnosis of GEP-NENs

Computed tomography and magnetic resonance imaging: Computed tomography and magnetic resonance imaging are conventional techniques used to determine localization and to evaluate neoplasm burden of GEP-NENs. Multiphase computed tomography (CT) or magnetic resonance imaging (MRI) scans are recommended to diagnose distant metastatic lesions[21,22], because GEP-NENs are highly vascularized and thus show the same resolution as the liver in conventional CT scanning. They can, however, be detected by either of these advanced imaging techniques. Similarly, contrast CT chest scanning is recommended for the evaluation of lung metastases. Small peritoneal, liver, and lymphatic metastases < 1 cm cannot be detected by CT analyses[23].

Functional imaging: Nowadays, functional somatostatin receptor (SSR) imaging is widely used in clinical diagnosis of NENs. Beside localizing tumors and selecting SSR-positive patients for specific

therapies, it can be used to evaluate therapeutic responses[24]. Five subtypes of SSRs (SSR1 to SSR5) have been identified, and their molecular mechanisms of regulation and signaling have been elucidated [25]. The most prominent SSR subtype in GEP-NENs is SSR2, followed by SSR1 and SSR5; SSR3 and SSR4 are less frequently expressed[26]. Moreover, SSR2 and SSR5 are usually expressed in insulinomas [27].

The ^{68}Ga-DOTA somatostatin analogues (SSA) imaging system consists of ^{68}Ga-DOTA-Tyr3-octreotide (^{68}Ga-DOTA-TOC), ^{68}Ga-DOTA-Nal3-octreotide (^{68}Ga-DOTA-NOC), and ^{68}Ga-DOTA-Tyr3-octreotate (^{68}Ga-DOTA-TATE). These different imaging agents display distinct affinities to variable SSRs. Compared to ^{111}In-pentetreotide functional imaging, ^{68}Ga-DOTA-SSA imaging has been shown to improve diagnosis and staging for NENs[28] and has become the imaging method of choice. ^{68}Ga-DOTA-TOC shows a higher affinity to SSR-2, ^{68}Ga-DOTA-NOC towards SSR-2, SSR-3, and SSR-5, whereas ^{68}Ga-DOTA-TATE towards SSR-2 and SSR-5[29]. Clinicians are supposed to select appropriate imaging agents for specific NENs. ^{18}Fluorodeoxyglucose (^{18}FDG), a tracer for glucose metabolism, can indirectly assess metabolic activity of GEP-NENs. The ability of tumor cells to take up glucose is positively correlated with the tumor growth rate[30], which is in turn related to aggressiveness. Combining ^{18}FDG-PET/CT with ^{18}Ga-DOTA-TATE imaging is another functional imaging method for NENs[31]. Even for GEP-NENs with low or negative SSR expression, positive ^{18}FDG PET/CT imaging denotes worse prognosis[32]. For the detection of tumor site and activity, the combination of SSR imaging and ^{18}FDG imaging has proven to be complementary[33,34].

Endoscopy, ultrasonography, and endoscopic ultrasonography

Endoscopy, ultrasonography, and endoscopic ultrasonography are also recommended for the diagnosis and treatment of GEP-NENs. For early-stage and smaller GEP-NENs, endoscopic resection should be taken into consideration when lymphatic metastases have been excluded by endoscopic ultrasonography (US) or imaging[35]. Endoscopic resection should be reserved for GEP-NENs with a diameter < 1 cm, superficial position, and low grading[35]. US can serve as the initial diagnostic approach for liver metastases. Moreover, it can guide the biopsy needle to collect tissues for histopathological assessment. Endoscopic US is currently the most sensitive diagnostic approach for pancreatic NENs and allows biopsy collection at the same time[36], whereas intraoperative US can detect tumors in liver and pancreas, otherwise not detected by imaging methods[37].

Histopathological examination

Histopathological examination is the gold standard for GEP-NEN diagnosis; both from biopsies and resected tissues. Hematoxylin and eosin staining is used to determine cytological and histomorphological indices, and immunohistochemical staining of CgA and synaptophysin are mandatory for differential diagnosis in pathological reports[38]. Immunohistochemical Ki-67 index determination and mitotic counts per mm^2 are the basis of grade classification for GEP-NENs (see Table 1). According to the latest National Comprehensive Cancer Network (NCCN) guidelines, histological classification, the resection margin status, Tumor, Node, Metastasis (commonly known as TNM) stage, and the presence of vascular invasion are also mandatory in pathological reports, because these factors are significantly associated with patient prognosis[39].

Somatic mutations

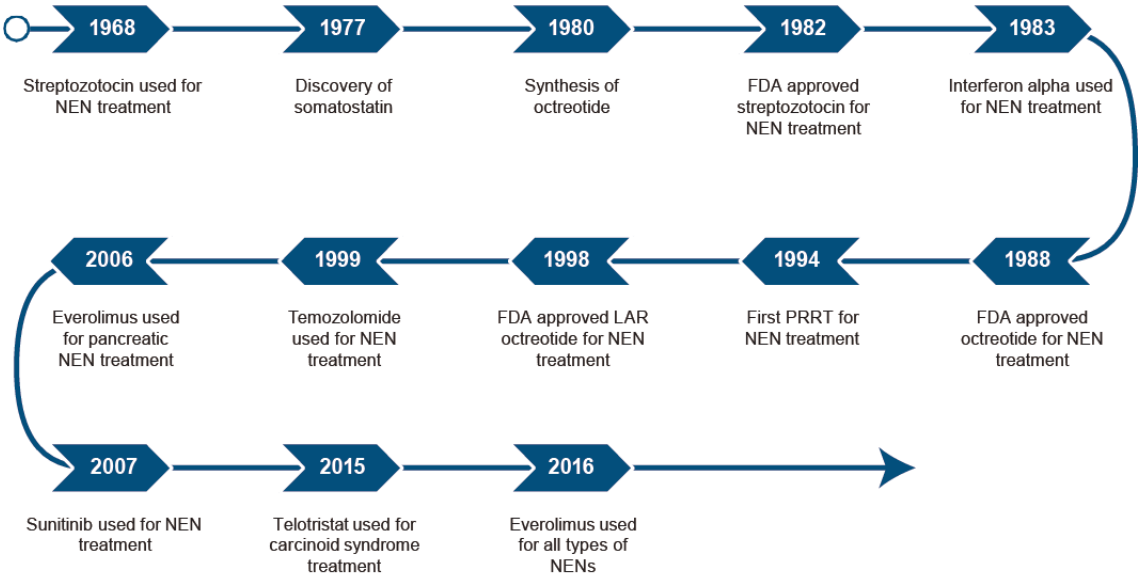
For WHO grade 3 NENs, somatic mutations in the genes death domain associated protein (*DAXX*), multiple endocrine neoplasia type 1 (*MEN1*), and alpha thalassemia/intellectual disability syndrome X-linked (*ATRX*) are most frequent. Whereas, in NECs, mutations affect the genes retinoblastoma transcriptional corepressor 1 (*RB1*), mothers against decapentaplegic homolog 4 (*SMAD4*), and tumor protein p53 (*TP53*)[40,41]. This difference in the occurrence of somatic mutations can be exploited to discriminate GEP-NECs from WHO grade 3 GEP-NENs in challenging cases[42]. In addition, NECs of the small intestine often show mutations in the cyclin-dependent kinase inhibitor 1B (*CDKN1B*)[43], and lack of *CDKN1B* gene expression has been described as a negative prognostic factor in GEP-NENs[6,44]. Insulinoma-associated protein 1 (*INSM1*) has proven to be a specific and sensitive biomarker for diagnosing NECs[45,46].

TREATMENT APPROACHES FOR GEP-NENS

An overview of treatment developments is shown in Figure 3.

Surgery

Surgical resection remains the sole curative form of therapy for patients with GEP-NENs[47]. Patients with local or locoregional GEP-NENs should be recommended for curative resection of the primary and the locoregional lymph nodes[48]. For patients with asymptomatic pancreatic NENs < 2 cm, a cautious surveillance with yearly imaging is recommended[49]. Patients with pancreatic NENs > 2 cm should



Year	Events
1968	Streptozotocin for NETs by Murray-Lyon[107]
1977	Discovery of somatostatin by Roger Guillemin and Andrew Schally[108]
1980	Synthesis of octreotide by Bauer[109]
1982	US FDA approved streptozotocin for NENs
1983	Interferon alpha[110]
1988	FDA approved octreotide
1994	First PRRT treatment[111]
1998	FDA approved long-acting release (LAR) octreotide
1999	Temozolomide for NENs[112]
2006	Everolimus for pancreatic NENs[113]
2007	Sunitinib for NENs[114]
2015	Telotristat for carcinoid syndrome[93]
2016	Everolimus for all types of NENs

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Figure 3 Milestones in the treatment of neuroendocrine neoplasms[107-114]. US FDA: United States Food and Drug Administration; NEN: Neuroendocrine neoplasm; LAR: Long-acting repeatable; PRRT: Peptide receptor radionuclide therapy.

receive pancreatectomy with regional lymphadenectomy[50]. Localized small intestinal NENs are resected radically, including removal of mesenteric lymph nodes[51]. This can also reduce the risk of associated comorbidities, such as intestinal obstruction. A clinical study including 581 patients operated on with metastatic NENs demonstrated that the median overall survival (OS) was 110.4 mo for curative resection. In comparison, resections resulting merely in debulking (OS: 89.2 mo) or performed in a palliative situation (OS: 50.0 mo) had significantly shorter OS rates ($P < 0.001$). Patients receiving cytoreductive surgery survived, in median, 89.2 mo, whereas when all metastatic lesions could be removed, the longest median survival of 112.5 mo could be reached ($P < 0.001$)[52]. Another clinical retrospective analysis of grade 3 GEP-NENs reported a 2-year OS rate after radical surgery of 64.5%, a 2-year progression-free survival (PFS) rate of 44.9%, and a median PFS of 14 mo[53]. Therefore, the 2021 NCCN guidelines[6] recommended that, for small (< 2 cm) and low-grade NENs, surgery or close monitoring should be individualized. For large (> 2 cm) and higher-graded NENs, resection with negative margins and removal of regional lymph nodes should be conducted. Cytoreductive or debulking resection for distant metastases is recommended when more than 90% of the lesions can be removed safely, especially if patients present with serious hormonal symptoms[54,55].

Systemic therapies

Somatostatin: Somatostatin is a general endocrine "off-switch" due to its not only endocrine but also, exocrine, autocrine, and paracrine inhibitory effects. In the digestive system, somatostatin can inhibit bowel movements, decrease the blood flow of mesenteric vessels, inhibit gastrointestinal absorption as well as gallbladder contraction, and suppress hormone secretion[56]. The half-life of somatostatin is only 3 min, thus preventing its pharmacological use. Hence, SSAs with longer half-lives were developed to treat patients with GEP-NENs[57]. SSAs can control hormonal symptoms induced by GEP-NENs[58] by binding to SSRs, thereby preventing the activation. Currently, the most commonly used SSAs for GEP-NENs are octreotide and lanreotide. In the placebo-controlled, double-blind, prospective, and randomized study on the "effect of octreotide long-acting repeatable (LAR) in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors (PROMID)" clinical trial, it was

demonstrated that octreotide significantly delayed tumor progression time (LAR 14.3 mo *vs* placebo 6 mo)[59]. The controlled study of lanreotide anti-proliferative response in NEN (CLARINET) trial confirmed that lanreotide was associated with significantly higher 2-year PFS rates in patients with metastatic enteropancreatic NEN (65.1% in the lanreotide group *vs* 33.0% in the placebo group)[60]. In a phase III trial, pasireotide, a second generation SSA[61], was compared to octreotide. It prolonged the median PFS from 6.8 mo in the octreotide LAR control group to 11.8 mo in the pasireotide LAR group [62]. The guidelines of the European Neuroendocrine Tumor Society (ENETS) and the NCCN guidelines recommended SSAs as first-line therapeutic agents for GEP-NENs. For patients receiving LAR SSAs, cholecystectomy is recommended in case of cholecystitis and gallstones[63].

Interferon-α: Interferon-α (IFNα) has been used to inhibit hormone secretion and proliferation in NENs in the past decades[64]. The phase III clinical study of the Southwest Oncology Group compared octreotide LAR plus IFNα with octreotide LAR plus bevacizumab. Antitumor effectiveness was similar with median PFS of 15.4 mo and 16.6 mo, respectively[65]. When other available therapeutic options failed, IFNα could thus be taken into cautious consideration as a rescue antiproliferative therapy[66].

Molecular targeted agents

Mammalian target of rapamycin inhibitors: When the phosphatase and tension homolog protein is phosphorylated, a negative feedback regulation *via* phosphatidylinositide 3-kinase (PI3K) is normally activated, which inhibits cell proliferation and promotes cell apoptosis. However, the reduction of phosphatase and tension homolog messenger RNA expression stimulates activation of the PI3K-AKT-mammalian target of rapamycin (mTOR) pathway and can trigger tumor formation[67]. The key role of this signaling pathway in GEP-NEN development inspired mechanistic research with the aim to develop drugs targeting PI3K-Akt-mTOR[68,69]. Phase III clinical studies of RAD001 application for patients with advanced NEN (RADIANT)-3 and -4, lead to the approval of everolimus. This targeted inhibitor of mTOR with the capacity to delay NEN progression attained approval for treatment of GEP-NENs[70,71]. Both ENETS and NCCN guidelines recommend everolimus as a second or third-line drug for advanced GEP-NENs. In patients with insulinomas, everolimus showed the positive side-effect of stabilizing glycemic levels[72]. However, low expression of SSR2 in patients with insulinomas results in poor response to SSAs[73]. Even worse, SSA treatment of patients with insulinomas can exacerbate hypoglycemia due to an inhibition of glucagon[56,74]. Therefore, everolimus should be prioritized for patients with insulinomas.

Vascular endothelial growth factor receptors inhibitors: Sunitinib, a broadly acting tyrosine kinase inhibitor targeting vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptors, has been affirmed to defer progression of pancreatic NENs in a phase III clinical trial[75]. Sunitinib was thus included for treatment of advanced pancreatic NENs in the ENETS and NCCN guidelines. However, there is a lack of clinical data for the effects of sunitinib on gastroenteric NENs. The Grupo Espanol de Tumores Neuroendocrinos (GETNE 1509) phase II trial has proven that lenvatinib, another VEGFR inhibitor, achieved an overall response rate of 29.9% (44.2% in pancreatic and 16.4% in gastrointestinal NENs), a median response duration of 21.5 mo (19.9 mo in pancreatic and 33.9 mo in gastrointestinal NENs), a median PFS of 15.7 mo (15.6 mo and 15.7 mo respectively), and a median OS of 32 mo in the pancreatic NEN group. The median OS was not reached in the gastrointestinal NEN group. The phase III trial of surufatinib, a novel VEGFR inhibitor, in advanced extrapancreatic and pancreatic neuroendocrine tumors (SANET-ep and SANET-p) showed a meaningful improvement of PFS to 9.2 mo and 10.8 mo in the surufatinib groups *vs* 3.8 mo and 3.7 mo in the placebo groups for patients with advanced, progressive, well differentiated, extrapancreatic NENs, and advanced pancreatic NENs[76], respectively.

Immune checkpoint inhibitors

Immune checkpoint inhibitors, which target for example programmed death protein-1 (PD-1), its receptor programmed death-ligand 1 (PD-L1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), showed promising antitumor efficacy in various tumor types[77]. In a phase IB study of the anti-PD-1 antibody pembrolizumab in advanced solid tumors (KEYNOTE-028), pembrolizumab monotherapy proved antitumor efficacy in patients with PD-L1-positive carcinoid and pancreatic NENs with high stable disease rates of 60% and 88%, respectively; however, only a disappointing objective response rate (ORR) of 12% and 6.3%, respectively[78]. In a subsequent phase II (KEYNOTE-158) study, pembrolizumab monotherapy had an ORR of only 3.7%, a median PFS of 4.1 mo and a median OS of 24.2 mo in patients with previously treated advanced well-differentiated NENs[79]. Pembrolizumab is also proposed for patients with tumor progression after previous treatment, tumors with high tumor mutational burden and no adequate alternative treatment regimens[80,81]. A phase II clinical trial of dual anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) inhibition in patients with nonpancreatic NENs reported an auspicious ORR of 44% (18 of 32 patients) with high-grade NENs. This trial demonstrated that dual immunotherapy preferentially plays a role in grade 3 NENs[82]. A similar phase II study (CA209-538) also verified the significant efficacy of combination immunotherapy with ipilimumab and nivolumab in high-grade NEN patients (the median PFS of 4.8 mo and the OS of 14.8

mo in all the patients with NENs)[83].

Peptide receptor radionuclide therapy

Peptide receptor radionuclide therapy is actually a kind of systemic and targeted radiotherapy in one [84]. SSAs are structured with a radioisotope [such as Yttrium-90 (^{90}Y) and Lutetium-177 (^{177}Lu)] *via* a chelating agent. The emitted radiation kills the cancer cells that express SSRs on the tumor cells' surface [85]. ^{177}Lu-DOTA-TATE was approved by the European Medicines Agency for the treatment of patients with GEP-NENs in 2017 and a year later by the American Food and Drug Administration[86,87]. In a comprehensive meta-analysis of 1920 patients with unresectable metastatic NENs receiving ^{177}Lu-DOTATATE therapy from 18 studies, the ORR was between 29.1% and 30.6%, and the disease control rate was 74.1% to 81.1%[88].

Chemotherapies

For G1 and G2 pancreatic NENs, SSAs are recommended as first-line therapeutic regimen. When ineffective, however, both NCCN and ENETS guidelines recommend temozolomide combined with capecitabine or streptozotocin-based therapies. To date, there is no recommendation for systematic chemotherapy for G1 and G2 gastroenteric NENs from NCCN and ENETS. Similarly, no standard chemotherapeutic regimens are currently recommended for G3 NETs. The NORDIC NEC study demonstrated that NEC patients with Ki-67 < 55% were less sensitive to platinum-based chemotherapy than those with Ki-67 ≥ 55% (response rate: 15% *vs* 42%, respectively), yet survival times were better for patients with Ki-67 < 55% (14 mo *vs* 10 mo, respectively)[89]. Thus, ENETS and NCCN guidelines do not suggest platinum- but temozolomide-based chemotherapies for patients with Ki-67 < 65%. For grade 3 NEN patients with Ki-67 < 55%, temozolomide-based chemotherapies are recommended; whereas, patients with Ki-67 ≥ 55% should receive platinum-based regimens, such as cisplatin or carboplatin, both in combination with etoposide[90]. These regimens are also recommended for GEP-NEC patients in the 2021 NCCN guideline as first-line chemotherapy.

Related agents for controlling clinical manifestations

PPIs can control hypersecretion of gastric acid in patients with gastrinomas. However, related studies have proven that PPIs can lead to hypomagnesemia and vitamin B12 deficiency in patients with long-term use[91], suggesting a cautious use paired with regular control of magnesium and vitamin B12 levels.

Tryptophan hydroxylase is the rate-limiting enzyme for the conversion of tryptophan to serotonin. The tryptophan hydroxylase inhibitor telotristat can reduce the serotonin production. It is thus used in clinical practice to treat patients with refractory diarrhea resulting from a carcinoid syndrome[92] and it has been validated to normalize bowel movements and urinary levels of 5-HIAA[93].

CONCLUSION

In summary, the pathogenesis of GEP-NENs is still largely unclear. Multiple classification systems and treatment schedules have been accurately (re)defined thanks to the efforts of GEP-NEN experts. Because of the great improvement of detection technologies, an increasing number of suspicious patients can be diagnosed with GEP-NENs already at an early stage. Novel treatment approaches, including small molecule inhibitors, SSAs, and peptide receptor radionuclide therapy targeting GEP-NENs, have evolved remarkably. However, prospective research still needs to be conducted to confirm their efficacy. Also, many controversies concerning the therapy regimens for specific GEP-NENs of different types remain. Beside identifying and developing novel molecular targeted drugs, the rational combination of targeted, chemo-, and immunotherapy seems to be the future research direction in the field of GEP-NEN therapy.

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MINIREVIEWS

Role of surgical treatments in high-grade or advanced gastroenteropancreatic neuroendocrine neoplasms

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Abstract

Over the last 40 years, the incidence and prevalence of gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) have continued to increase. Compared to other epithelial neoplasms in the same organ, GEP-NENs exhibit indolent biological behavior, resulting in more chances to undergo surgery. However, the role of surgery in high-grade or advanced GEP-NENs is still controversial. Surgery is associated with survival improvement of well-differentiated high-grade GEP-NENs, whereas poorly differentiated GEP-NENs that may benefit from resection require careful selection based on Ki67 and other tissue biomarkers. Additionally, surgery also plays an important role in locally advanced and metastatic disease. For locally advanced GEP-NENs, isolated major vascular involvement is no longer an absolute contraindication. In the setting of metastatic GEP-NENs, radical intended surgery is recommended for patients with low-grade and resectable metastases. For unresectable metastatic disease, a variety of surgical approaches, including cytoreduction of liver metastasis, liver transplantation, and surgery after neoadjuvant treatment, show survival benefits. Primary tumor resection in GEP-NENs with unresectable metastatic disease is associated with symptom control, prolonged survival, and improved sensitivity

toward systemic therapies. Although there is no established neoadjuvant or adjuvant strategy, increasing attention has been given to this emerging research area. Some studies have reported that neoadjuvant therapy effectively reduces tumor burden, improves the effectiveness of subsequent surgery, and decreases surgical complications.

Key Words: Gastroenteropancreatic neuroendocrine neoplasms; Neuroendocrine carcinomas; Surgery; Hepatic debulking; Liver transplant; Transplant oncology

Core Tip: Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) encompass a heterogeneous group of tumors with unique indolent biological behavior. The role of surgery in high-grade or advanced GEP-NENs is still controversial. There are several highlights of this review. First, we address the surgical benefits of selected high-grade GEP-NENs and summarize the tumor biological markers correlated with a prognosis. Second, we review various surgical strategies, including curative resection, debulking, resection after neoadjuvant therapy for metastatic GEP-NENs, and the latest clinical evidence. Finally, liver transplantation presents a curative therapeutic option for GEP-NEN patients with liver metastasis. We summarize the new findings and propose directions for future development.

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INTRODUCTION

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are rare lesions arising from neuroendocrine cells scattered throughout the body. Although GEP-NENs are still regarded as uncommon neoplasms, both their incidence and prevalence have continued to increase over the last 40 years[1,2]. As GEP-NENs are morphologically and biologically heterogeneous[3,4], the World Health Organization has classified them into three grades based on the proliferation index (Ki67) and differentiation level[5]. G3 NENs, showing a Ki67 value (> 20%) and/or mitotic index (> 20 mitoses/10 high-power field), are further subdivided into two subgroups as follows: Well-differentiated neuroendocrine tumors (G3 NET) and poorly differentiated neuroendocrine carcinomas (G3 NEC) (Table 1)[6]. The incidence of liver metastasis (LM) in GEP-NENs is high, and the median overall survival (OS) for patients with metastatic GEP-NENs is 2-4 years[7].

Given the associated high risk of developing distant metastases, the role of surgery in the treatment regimen for high-grade GEP-NEN (hgGEP-NEN) remains controversial. Since treatment strategies for hgGEP-NEN have generally been extrapolated from the findings for small-cell lung cancer[8,9], surgery is not included in the primary therapeutic regimen[10,11]. Given the differences in prognoses and therapeutic responses between pulmonary and digestive neuroendocrine carcinomas, it is necessary to evaluate the role of surgery in GEP-NENs. Moreover, surgery is generally considered nonbeneficial for patients with metastatic diseases. However, as a large proportion of GEP-NEN patients exhibit relatively indolent biology, some studies also report the survival benefits of surgery[12,13]. Therefore, the purpose of this review is to summarize and discuss surgical management strategies for high-grade or advanced GEP-NENs.

SURGERY FOR LOCALIZED HGGEP-NEN

Platinum-based chemotherapy is considered the standard treatment for hgGEP-NEN, whereas the role of surgery has not been fully assessed. In this setting, Merola *et al*[14] investigated survival outcomes in 60 patients with localized hgGEP-NEN who underwent radical surgical procedures. The 2-year OS rate was 64.5%, and the 2-year recurrence-free survival (RFS) rate was 44.9%[14]. Moreover, in a Nordic multicenter retrospective cohort study, the median OS in 201-G3 GEP-NEN patients upon surgical resection was 32 mo[15]. In a large retrospective study consisting of 1517 G3 GEP-NEC patients, surgery was significantly associated with improved OS [hazard ratio (HR): 0.41][16]. Despite the lack of high-quality long-term prospective trials, there is sufficient evidence to suggest that careful patient selection for surgical resection can increase clinical benefits in G3 GEP-NENs. Many factors can predict the

Table 1 Classification for gastroenteropancreatic neuroendocrine neoplasms by World Health Organization

Terminology	Differentiation	Grade	Ki67 index, %	Mitotic count, 2 mm^2
NET, G1	Well differentiated	Low	< 3	< 2
NET, G2	Well differentiated	Intermediate	3–20	2–20
NET, G3	Well differentiated	High	> 20	> 20
NEC, G3	Poorly differentiated	High	> 20	> 20

NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma.

prognosis of GEP-NENs and may aid in the selection of suitable patients for surgery; among them, differentiation and the Ki67 value are the two most important prognostic factors[17-19].

Since hgGEP-NENs are highly heterogeneous, comprising both G3 NETs and G3 NECs, G3 NENs cannot be considered a single entity[20]. In contrast to well-differentiated NENs, G3 NEC is highly aggressive and metastasizes early, resulting in a poor prognosis[4]. Tumor differentiation is associated with surgical prognosis. In a retrospective study consisting of 67 patients, including 21 with pancreatic G3 NETs and 46 with pancreatic G3 NECs, those with G3 NETs were found to benefit from surgical resection, unlike those with G3 NENs who did not show any significant improvements[21]. Consistently, Merola *et al*[14] drew a similar conclusion from their study involving 60 hgGEP-NEN patients [14]. The OS of patients with G3 NET was significantly better than that in G3 NEC patients; G3 NEC was a marker of a poor prognosis (NEC G3 *vs* NET G3: HR 4.24, $P = 0.05$). However, in another study, no significant difference was observed in postsurgical survival between G3 NETs and G3 NECs in patients with pancreatic hgGEP-NENs[22]. In a large-scale retrospective study consisting of 2245 patients with GEP NECs, the median survival after surgery was 31 mo ($n = 1549$) *vs* 9 mo after nonoperative therapy ($n = 696$, $P < 0.001$)[23]. The 5-year OS rates were 39% and 10%, respectively. Abdel-Rahman *et al*[16] performed propensity score matching between 233 G3 GEP NEC patients who did not undergo surgery and 233 G3 GEP NEC surgical patients. They reported that radical surgery was significantly associated with improved survival ($P < 0.001$)[16]. GEP G3 NECs were further distinguished based on poorly differentiated histology and undifferentiated histology; poorly differentiated histology was significantly associated with improved OS compared with undifferentiated histology (HR: 0.83), which could explain the discrepancy in the results of the abovementioned studies. Additionally, heterogeneity within hgGEP-NENs could lead to differences in surgical outcomes, which may be observed in a small sample size. Moreover, the heterogeneity is not only derived from hgGEP-NENs themselves but also the difficulty associated with the morphological diagnoses by pathologists[9,24]. A high percentage of inconclusive diagnoses have been reported (61%), which may be attributed to limited pathological resources, a lack of well-defined histological criteria, and the complexity underlying GEP-NEN origins [25].

The Ki67 value is easier to examine and provides a more objective basis for evaluation. Ki67 can reflect the heterogeneity of hgGEP-NENs and predict responsiveness to treatment[4,26]. Sorbye *et al*[27] evaluated 305 hgGEP-NEN cases and obtained a cutoff value (55% Ki67) by ROC analysis[27]. Patients with Ki67 < 55% showed a better OS than those with Ki67 ≥ 55% but a lower response rate to platinum-based chemotherapy. Differences in treatment responses were also observed for surgical resection. Merola *et al*[14] reported that the median OS for Ki67 ≤ 55% was not achieved *vs* 26 mo in patients with Ki67 > 55% after surgery[14]. Similarly, in a study from Tokyo, 63 hgGEP-NEN patients who underwent surgical resections between 2005 and 2018 were reviewed[28]. Patients were divided into low-Ki67 (Ki67 < 52%) and high-Ki67 (Ki67 ≥ 52%) groups according to the median Ki67 value (52%). In the low Ki67 group, the median survival times were 82.7, 16.3, and 27.7 mo for patients in the R0/1, R2, and chemotherapy groups, respectively. Surgery ($P = 0.013$, HR = 0.46) and low Ki67 ($P = 0.007$, HR = 0.43) were independent prognostic factors related to improved OS.

Recently, the National Comprehensive Cancer Network guidelines have recommended hgGEP-NENs with Ki67 < 55%, slow growth, and positivity for somatostatin receptor as the criteria for surgery, although caution for heterogeneity remains[29]. In addition to the Ki67 value, other tissue biomarkers are also correlated with differentiation, including the neuroendocrine markers synaptophysin, chromogranin-A (CgA), death domain-associated protein (DAXX), p53, and Rb1. At present, a conclusive decision for the prognostic value remains lacking for all these biomarkers. Therefore, there is a need for large, long-term studies using GEP-NEN cohorts and assessing the effects of tissue and blood biomarkers.

SURGERY FOR LOCALLY ADVANCED GEP-NEN

Recently, experts from the European Neuroendocrine Tumor Society acknowledged that the surgical strategy for locally advanced pancreatic NENs (pNENs) is an important unanswered query[30]. Birnbaum *et al*[13] evaluated 43 cases of advanced pNENs and 91 cases of isolated pNENs[13]. In the advanced pNEN group, the median survival time for 16 patients who underwent resections of adjacent organs was 90 mo, and the 5-year OS (84%) was not significantly different from that in the isolated pNEN group (P = 0.175), which indicated that nonmetastatic locally advanced pNENs showed a favorable prognosis after surgery. A case series study reviewed 99 locally advanced pNEN patients who underwent surgical resection between 2003 and 2018, including 84 G1/G2, 1 G3, and 14 'tumor grade not available' patients[31]. The 5-year disease-free survival (DFS) was 61%, and the 5-year OS was 91%. Although there was no control group in this study, the excellent prognosis suggested that surgery could be beneficial in patients with locally advanced pNEN. In another study, 25% of patients showed major vascular involvement on preoperative imaging; however, only 17% required resection and reconstruction. Similar to previous studies, major vascular invasion implicated by preoperative imaging might not be fully consistent with intraoperative situations, as the tumors were only abutting or distorting the vein rather than invading in most cases[32,33]. Even though 17% of patients underwent venous resection/reconstruction, none of them died postoperatively. Based on these impressive results, the latest guidelines from the North American Neuroendocrine Tumor Society (NANETS) also recommend that isolated major vascular involvement should not be an absolute contraindication to surgery for patients with advanced pNEN[34]. However, it should be noted that these conclusions were drawn for advanced pNEN only. The outcomes for patients with different primary tumor sites may vary correspondingly. Future studies should examine the role of surgery in GEP-NENs for different primary tumor sites.

Retrospective studies suggest that neoadjuvant peptide receptor radionuclide therapy (PRRT) can effectively reduce the tumor burden and improve surgical safety[35,36]. Parghane *et al*[36] evaluated 57 patients with locally advanced GEP-NENs who had received PRRT[36]. They found that 48 (84%) patients exhibited symptomatic responses, and 15 patients were eligible for resection according to the National Comprehensive Cancer Network criteria for pancreatic ductal adenocarcinoma. Although long-term survival following surgery has not been reported, regression of primary tumors following PRRT was observed, and no hematological or renal side effects were encountered. Therefore, neoadjuvant PRRT may be a potential therapeutic option for locally advanced GEP-NETs.

SURGERY FOR METASTATIC GEP-NEN

Metastasis is the main feature of GEP-NENs, and its most common location is the liver. The incidence of LM is 40%-95%[37-39], which varies based on the origin of primary NEN, with extremely low rates in gastric, appendiceal, and rectal NENs, an incidence rate of 28%-78% in pNENs, and 67%-91% in small intestinal NENs. LM represents a major risk factor for cancer-related death in GEP-NENs, and the only potentially curative option is surgery. However, strategies for surgery and selection of the appropriate patients remain controversial.

Surgery for primary GEP-NEN

According to NANETS guidelines, primary tumor resection (PTR) is recommended for small bowel NEN in unresectable disease, but for pNEN in unresectable disease, there is no consensus[34,40]. Possible benefits for PTR include the reduction of tumor burden, which controls functional symptoms or prevents obstructive complications, and improvement in survival by decreasing the likelihood of distant metastasis and increasing sensitivity toward systemic therapies. A substantial number of studies based on the Surveillance, Epidemiology, and End Results database have demonstrated that PTR is significantly associated with prolonged survival in metastatic GEP-NEN patients[41-43]. Zheng *et al*[42] evaluated a large cohort of 1547 GEP-NEN cases with unresectable LM, including 897 cases with PTR and 650 nonresection patients, using the Surveillance, Epidemiology, and End Results database[42]. They found that the 5-year OS rate for PTR patients was 57% *vs* 15.4% in those who did not undergo PTR; a significant difference in median OS between the groups was observed (not reached *vs* 14 mo, P < 0.001). When the two groups were further stratified into four groups according to their primary tumor locations (gastric, small intestinal, colorectal, and pancreatic NENs), the 5-year OS rates were significantly prolonged in all groups compared with non-PTR patients. However, some differences were observed among the groups, as PTR groups patients were younger, had many small tumors, and presented well-differentiated and a few poorly differentiated neoplasms. All these factors were significantly associated with survival in both the univariate and multivariate analyses.

Another large study evaluating PTR in a total of 854 IV stage GEP-NEN cases with unresectable or resectable LM from the California Cancer Registry showed similar results[44]. To reduce selection bias, Hüttner *et al*[43] used propensity matching to 442 stage IV pNEN patients who did not receive surgery for metastasis[43]. After propensity score adjustment, significant differences in 5-year OS rates were

found between the two groups (52.5% of the PTR group *vs* 20.6% of the non-PTR group). Daskalakis *et al* [45] performed a similar study with 363 asymptomatic stage IV SBNEN cases, including 161 patients undergoing PTR[45]. After propensity matching, no substantial differences were found in the median OS and cancer-specific survival between the surgical and nonsurgical groups. This study suggested that surgery for asymptomatic patients is a topic of further discussion. The survival benefits in the overall GEP-NEN cases may arise from the survival improvement in functional GEP-NENs. Some studies have shown that systemic agents can effectively improve the prognosis of GEP-NENs[46,47]. The use of systemic agents as an adjuvant treatment cannot be controlled in retrospective studies, which leads to an inevitable bias. A lower tumor burden further increases the responsiveness of GEP-NENs to PRRT[7, 48]. A retrospective study reviewed 889 GEP-NEN cases; among them, 483 patients who underwent PTR before PRRT and 403 patients who did not undergo PTR before PRRT[49]. In this study, 56 of the 617 patients showed G3 tumors (based on the available grading data). In the prior PTR group, the median OS was 134 mo, and the 5-year OS rate was 70.8%, while in the nonresected group, the median OS was 67 mo, and the 5-year OS rate was 41.7% ($P < 0.001$). Additionally, in patients with pNENs or SBNENs, accounting for 70% of the total patients, these remarkable differences were detected.

Taken together, although several retrospective studies have reported a potential benefit of PTR in metastatic GEP-NENs, the selection bias may be inadvertent. Some factors may aid in the identification and distinction of GEP-NENs from PTR, including functional metastatic GEP-NENs, young age, a small tumor size, and well-differentiated tumor characteristics. The excellent clinical benefits of postoperative PRRT have been previously reported. Based on these encouraging results, a large-scale multicenter prospective study is warranted to confirm and obtain further novel definitive prognostic factors.

Surgery for liver metastasis

Current guidelines propose that G1/G2 NEN LM patients without extrahepatic disease should undergo surgical interventions, while for those with G3 NET LM, resection is not recommended[34,50], as the prognoses and survival outcomes in G3 NEN LM are suboptimal (median OS range: 4.6-29 mo)[51-54]. However, several studies in G3 GEP-NEN patients with resectable LMs have yielded encouraging results in recent years. Galleberg *et al*[55] reviewed the central Nordic GEP-NEC database and reported an OS and RFS in 32 G3 NEN LM cases (8 NETs and 24 NECs) after resection/radiofrequency ablation of 35.9 mo and 8.4 mo, respectively[55]. Ki67 < 55% along with adjuvant chemotherapy were independent significant prognostic factors for favorable outcomes. Consistently, in a retrospective study of a stage IV G3 GEP-NEN cohort, Merola *et al*[56] analyzed 15 patients who underwent radical resection (R0/R1); among them, 7 had G3 NETs, 6 had G3 NECs, and 2 had MiNENs[56]. The median OS was 59 mo, and the median RFS was 8 mo. Unfortunately, there were no comparison groups in these two trials. A direct comparison of different results from the literature is unreliable, especially due to the heterogeneity in G3 GEP-NENs as discussed above, varying range of metastases, and selection biases. However, these findings suggest that highly advanced G3 GEP-NEN cases might benefit from radical resection procedures. Thus far, the lack of studies and small sample sizes limit the identification of subgroups suitable for surgical interventions.

As NEN LMs are seldom isolated or few and most cannot be removed completely, debulking, also referred to as "cytoreductive resection" or "R2 resection", is used to treat unresectable NEN LMs. Several retrospective studies have suggested that cytoreduction of NEN LMs improves both symptoms and survival[57,58]. Forty years ago, Foster *et al*[59,60] reported good symptom control in 44 cases with at least 95% surgical cytoreduction[59,60]. Likewise, three subsequent studies from the Mayo Clinic reported that at least 90% hepatic cytoreduction provides effective symptomatic palliation and prolongs survival[61,62] However, 90% as the debulking threshold was not carefully calculated using an algorithm but was chosen with the intent to select a suitable threshold, which may result in a loss of potential operative and curative opportunities for numerous patients.

Additionally, the development of new adjuvant therapies (such as the availability of somatostatin analog) may further enhance the efficacy of cytoreduction and expand the beneficiary population. Recently, studies have attempted to propose a lower threshold, and some have demonstrated that cytoreduction > 70% provides survival benefits. Maxwell *et al*[63] estimated the threshold level by dividing 28 pNEN LM cases and 80 SB NEN LM cases into < 50%, ≥ 50%, ≥ 70%, and ≥ 90% categories [63]. The 5-year PFS of all patients was 30.2%, and the 5-year OS was 76.1%. Patients with cytoreduction ≥ 70% showed better OS and PFS than those with cytoreduction < 50%. In this study, only 38.9% of patients showed debulking ≥ 90%, while 63.9% of patients exhibited cytoreduction with a lower threshold of > 70%.

Scott *et al*[64] reviewed 188 NEN LM patients who underwent cytoreductive procedures and stratified them into three groups according to the number of treated metastases (1-5, 6-10, and > 10)[64]. The median OS was 89 mo, and the PFS was 23 mo; there were no significant differences in OS or PFS among the three groups. In both univariate and multivariate analyses, age, grade, Ki67 index, percent liver replacement, and debulking > 70% were significantly associated with OS. When the study population was grouped by percent cytoreduction, the debulking > 70% group showed an improved OS compared with the debulking < 70% group (median 134.3 mo *vs* 37.6 mo, $P < 0.01$); debulking > 90% was not significantly associated with a better outcome compared to the 70%-90% or < 90% groups. This study provided further evidence for adopting a debulking threshold > 70% and indicated that NEN LM

patients who underwent cytoreduction for > 10 lesions had acceptable OS. Moreover, the grade was associated with a poor OS and PFS, with HRs of 2.12 for the G2 (97 cases) and 11.69 for the G3 (15 cases) groups. The 23-mo median OS and absence of 5-year OS of G3 did not improve after debulking, unlike previously reported results[65]. However, whether G3 GEP-NEN LM patients may benefit from cytoreduction remains difficult to address based on the current data, and evidence of heterogeneity between primary tumors and LMs is scarce. NANETS recommends that G2 primary or LM is not a contraindication for hepatic cytoreduction[34].

Neoadjuvant therapy may convert unresectable GEP-NEN LMs to resectable forms, reduce the difficulty of surgery, and decrease postoperative complications. To date, various systemic treatments demonstrated their efficacy in controlling tumor progression and reducing tumor burden[66,67]. However, whether neoadjuvant treatments can improve the surgical prognoses in GEP-NEN LM remains unclear. Murase *et al*[68] analyzed 106 pNEN cases with LM or locally advanced tumors[68]. All patients received sunitinib, among which 31 underwent surgery after sunitinib treatment. The median OS was not achieved in the surgical group *vs* 36.7 mo in the nonsurgical group. Poor predictive factors included the absence of surgical resection (HR: 13.1, $P = 0.001$), poor differentiation, and bilateral liver metastases. Thus, surgery after sunitinib treatment could improve OS for distant metastases or in locally advanced pNEN.

Liver transplantation for hepatic metastases

Compared with debulking, liver transplantation (LT) offers a long-term curative solution to expand the conventional margin in surgical oncology and LT for LMs, an important component of transplant oncology. The world-renowned LT expert Makowka *et al*[69] and Mazzaferro *et al*[70] proposed the Milan NEN criteria in 1995 (Table 2)[69,70]. In their recent report, Mazzaferro *et al*[71] prospectively analyzed 280 GEP-NEN LM cases during a 15-year follow-up[71]. Ultimately, 88 unresectable GEP-NEN LM patients who met the predetermined criteria were included, 42 of whom underwent LT. The 5- and 10-year OS rates for LT patients were 97.2% and 88.8%, respectively, *vs* 50.9% and 22.4% in the non-LT group, with eligibility according to Milan-NEN criteria ($n = 46$). Moreover, the researchers estimated that the 5- and 10-year survival benefits associated with LT were 12.79 mo and 48.62 mo, respectively, which suggested that the survival benefits increased over time. However, there was an inherent selection bias between the LT and non-LT groups, including a more advanced T-stage and older patients with less locoregional treatments included in the non-LT group. Considering the shortage of donated organs, it is necessary to weight carefully the benefits against the risks.

Kim *et al*[72] performed a systematic review of GEP-NEN LM patients who underwent LT and reported that the 5-year DFS rate ranged from 20% to 32%, which was worse than that of hepatocellular carcinoma (HCC) patients who underwent LT[72]. Due to these high rates of recurrence, Sposito *et al*[73] focused on the postrecurrence survival of GEP-NEN LT patients and observed excellent long-term survival (5-year survival rate of 76.5%, 10-year survival rate of 45.5%)[73]. In conclusion, despite the high recurrence rate, GEP-NEN LT patients still have promising long-term outcomes, which may be attributable to the indolent biological behaviors of GEP-NENs.

For resectable GEP-NEN LM patients who are consistent with the Milan criteria, surgical resection may still be the first option. Ruzzenente *et al*[74] investigated the long-term survival of a multi-institutional cohort of GEP-NEN LM patients undergoing surgical resection and found that 28 of 238 patients met Milan criteria with a 5-year OS of 83%, which was comparable to that reported in GEP-NEN LM patients undergoing LT within Milan criteria[74].

Similar to findings for LT in HCC, patients conforming to the Milan criteria show excellent prognoses from LT; however, this does not imply that the Milan criteria cover all patients who may potentially benefit from LT[75,76]. In a retrospective study, 15 NEN LMs who were up to 64 years of age with 12 of the 15 exceeding 50% hepatic involvement were included; the 5-year OS rate was 90%[77]. Downstaging in HCC has been extensively discussed[75], while in GEP-NEN LMs, high-quality studies are lacking.

Taken together, the survival benefits for resectable GEP-NEN LMs are limited, but for unresectable GEP-NEN LM patients who meet the Milan-NEN criteria, LT is recommended. Several outstanding questions remain to be addressed, including the following: (1) Can the Milan-NEN criteria be safely expanded, and what is the exact threshold? (2) What are the appropriate prognostic factors of GEP-NEN LMs? and (3) How can neoadjuvant be used as downstaging/bridging therapy before LT?

NEOADJUVANT PRRT FOR GEP-NEN

Recently, neoadjuvant therapy has become a critical treatment for various tumors, which may potentially reduce the tumor load, increase the likelihood that patients undergo surgical resection, enhance the safety of surgery, monitor the tumor response, and guide subsequent treatment based on the response to neoadjuvant therapy. Neoadjuvant therapy for NENs primarily includes chemotherapy small molecule drugs and PRRT. At present, the effectiveness of chemotherapy for NENs is not clear [78]. However, neoadjuvant PRRT, particularly ^{90}Y-DOTATATE and ^{177}Lu-DOTATATE, has been used in NENs with good prospects. In a randomized phase III trial (NETTER-1 Clinical Trial), PRRT for well-

Table 2 Milan neuroendocrine neoplasms criteria

	Milan selection criteria of GEP-NEN LM
1	Low grade NEN
2	Portal drainage of the primary tumor with complete resection of extrahepatic disease
3	Liver involvement < 50%
4	Duration of stable disease over 6 mo
5	Age < 60 yr (relative criteria)

GEP-NEN: Gastroenteropancreatic neuroendocrine neoplasms; LM: Liver metastasis.

differentiated, metastatic GEP-NEN effectively reduced the tumor burden, suppressed tumor progression, and prolonged survival[79]. In a study reported by van Vliet *et al*[35], PRRT was used as neoadjuvant therapy in 29 borderline or unresectable nonfuctional pNEN[35]. Thirty-one percent of these patients underwent successful surgery and achieved a better median PFS than those who were not resected (69 mo *vs* 49 mo). In addition to PTR, neoadjuvant PRRT has been evaluated in unresectable NEN LMs and successfully aids downstaging[80]. Several clinical studies are currently underway, including a phase II trial aimed at assessing the safety and efficacy of neoadjuvant PRRT for resectable pNENs with a high recurrence risk (NCT04385992), indicating that neoadjuvant PRRT for GEP-NEN is a promising field.

CONCLUSION

In conclusion, surgery plays a crucial role in the management of GEP-NENs and comprises curative resection, debulking, resection after neoadjuvant therapy, and LT for LMs. Compared with epithelial neoplasms of the same organs, GEP-NENs exhibit indolent biology and better outcomes, which increases the possibility of surgery for patients with hgGEP-NENs or advanced GEP-NENs. HgGEP-NEN is correlated with a poor prognosis. However, its heterogeneity is the major feature, and after careful selection for tumor biology, hgGEP-NENs with low Ki67 show greater benefits from resection. In metastatic GEP-NENs, radical surgery represents a favorable outcome but is limited to only a few patients. For unresectable LMs, cytoreduction improves the prognoses of patients, and the threshold for cytoreduction is reduced from 90% to 70%. LT for hgGEP-NEN LMs shows therapeutic advantages, but several problems need to be addressed. Additionally, neoadjuvant and adjuvant therapies have been investigated in the setting of advanced GEP-NENs, which may further control tumor recurrence. However, in cases of low prevalence and incidence, most of the evidence comes from retrospective studies that include less than 100 cases, and the administration of systemic therapy is not well controlled. The heterogeneity in GEP-NENs further influences the accuracy of the conclusions. Therefore, further multicenter collaborative prospective studies are needed to assess the effects of surgery and determine the prognostic factors.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Laparoscopic *vs* open liver re-resection for cirrhotic patients with post-hepatectomy hepatocellular carcinoma recurrence: A comparative study

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Abstract

BACKGROUND

Repeated liver resection is an effective treatment for recurrent hepatocellular carcinoma (HCC). However, few studies have compared the outcome of laparoscopic repeat hepatectomy (LRH) and open repeat hepatectomy (ORH) for recurrent HCC, and few of those have included cirrhotic patients.

AIM

To compare short-term and long-term outcomes of cirrhotic patients with LRH and ORH for recurrent HCC.

METHODS

We retrospectively analysed the clinical records retrieved from a prospectively collected database of all patients who underwent hepatectomy for post-hepatectomy recurrent HCC at our institute between May 2006 and June 2021. Cases of recurrent HCCs larger than 7 cm were excluded. Patient demographics, operative details, perioperative outcomes, pathologic details, disease-free survival (DFS), and overall survival (OS) data of LRH and ORH were compared.

RESULTS

Data from 29 patients with LRH and 22 with ORH were compared. The LRH group showed significantly better outcomes for blood loss (median 300 mL *vs* 750 mL, $P = 0.013$) and length of hospital stay (median 5 d *vs* 7 d, $P = 0.003$). The 1-, 3- and 5-year OS rates in the LRH group were 100.0%, 60.0% and 30.0%, respectively; the corresponding rates in the ORH group were 81.8%, 36.4% and 18.2% ($P = 0.336$). The 1-, 3- and 5-year DFS rates in the LRH group were 68.2%, 27.3% and 4.5%, respectively; the corresponding rates in the ORH group were 31.3%, 6.3% and 6.3% ($P = 0.055$). There were no significant differences in overall and DFS between the two groups.

CONCLUSION
Laparoscopic re-resection should be considered for patients presenting with recurrent HCC less than or equal to 7 cm after previous hepatectomy.

Key Words: Hepatocellular carcinoma; Recurrence; Repeat hepatectomy; Laparoscopic hepatectomy; Outcome; Overall survival; Disease-free survival

Core Tip: Laparoscopic liver re-resection for recurrent hepatocellular carcinoma had similar oncological outcomes compared with open surgery, even in patients with cirrhosis. Laparoscopic re-resection should be considered for all patients suitable for liver re-resection for recurrent hepatocellular carcinoma.

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INTRODUCTION

Hepatocellular carcinoma (HCC) can be cured by liver resection[1]. Although, the oncological outcome of liver resection is frequently jeopardized by tumour recurrence, with a reported 5-year recurrence rate of 50%-70%[2-4], and intrahepatic recurrence accounts for approximately 80% of postoperative recurrences[2]. Repeated liver resection has been demonstrated to be an effective treatment for recurrent HCC, and has low morbidity and mortality[5-7]. However, owing to multiple liver metastases, reduced liver function, and poor general health, less than 30% of patients with recurrences can undergo recurrent resection[8].

Laparoscopic liver resection (LLR) has emerged as a valuable treatment option for HCC during the last decade. LLR has a shorter operative time, less blood loss, shorter hospital stay, and lower overall morbidity than open liver resection, along with comparable disease-free and overall survival (OS)[9-15]. However, because of the development of adhesions, altered anatomy, the establishment of collateral circulation, reduced liver function, and loss of liver parenchyma following the prior surgery, laparoscopic repeat hepatectomy (LRH) is technically more complex than primary resection. Patients with HCC are likely to suffer from liver cirrhosis and portal hypertension resulting from underlying hepatitis B or C infection, and intraoperative haemorrhage and haemostasis associated with abnormal primary haemostasis are a challenge even for surgeons experienced in LLR[16,17]. Furthermore, these patients are more likely to develop postoperative complications like pleural effusion, chest infection, ascites, portal vein thrombosis, kidney failure and liver failure after hepatectomy[18,19].

Few retrospective studies have compared the outcome of LRH and open repeat hepatectomy (ORH) for recurrent HCC, and few of those have included cirrhotic patients[20-29]. This study aimed to compare the short-term and long-term outcomes of cirrhotic patients with post-hepatectomy HCC recurrence and undergoing LRH or ORH.

MATERIALS AND METHODS

This study was approved by the Hong Kong Hospital Authority Research Ethics Committee (Kowloon Central/Kowloon East; Ref. KC/KE-21-0278/ER-4). The clinical records of all patients undergoing hepatectomy for post-hepatectomy recurrent HCC at our institute from May 2006 to June 2021 were retrieved and retrospectively analyzed from a prospectively collected database. Patients with radiological features typical of recurrent HCC of less than or equal to 7 cm in size on contrast-enhanced computed tomography or magnetic resonance imaging were included. All patients received the same perioperative care and evaluation protocols. Functional liver reserve for major hepatectomy was assessed by indocyanine green retention at 15 min and computed tomography liver volumetry. The criteria for LLR and open hepatectomy were previously described[30]. The same team of hepatobiliary surgeons performed all the operations. Liver resection was described using the Brisbane 2000 terminology[31].

Patient demographics and preoperative characteristics included in the analysis were the date and extent of the previous operation, date of recurrence, liver function tests, and serum alpha-fetoprotein

(AFP) levels. Operative details, including the operative time, extent of liver resection, operative approach, volume of blood loss, and blood transfusion requirements, were collected. Short-term outcomes included operative factors (operative time, use of Pringle manoeuvre, blood loss, blood transfusion, and conversion) and postoperative factors (length of hospital stay, resection margin, and complications). Long-term outcomes included OS and disease-free survival (DFS). Major hepatectomy was defined as resection of three or more Couinaud liver segments. Cirrhosis was diagnosed by histology findings. Perioperative outcomes included 30-d mortality and Clavien-Dindo complications [32]. International Study Group of Liver Surgery criteria were used to define post-hepatectomy liver failure and bile leakage[33,34]. The number of tumors, the size of the largest tumor nodule, and the resection margin were all derived from the specimens' histological information. The presence of tumor cells within 1 mm of the transection line was classified as a positive resection margin.

Blood tests for liver function, AFP, chest X-ray, and abdominal computed tomography scan with contrast, or ultrasonography of the liver if contrast injection was contraindicated, were all part of the patient's follow-up routine. Patients were checked every three months for the first two years after surgery and then every six months after that. If a patient missed an appointment, they were actively contacted for follow-up. Recurrence was reported as the date of radiological recurrence. A multidisciplinary team of surgeons, radiologists, and oncologists chose subsequent treatments, such as re-resection, microwave or radiofrequency ablation (RFA), transarterial chemo-embolisation, or systemic therapy.

Surgical procedures

All hepatectomies, except for lesions near important vascular structures, aimed to achieve a gross resection margin of 1 cm, and intraoperative ultrasonography was performed. A right subcostal incision with an upper midline extension was used for open liver re-resections. Hepatic parenchymal transection was performed with a Cavitron Ultrasonic Surgical Aspirator (Olympus, Tokyo, Japan). Haemostasis was achieved by electrocautery or suture. For laparoscopic procedures, patients were placed in a Lloyd-Davies position (right side up for posterosuperior lesions). The chief surgeon stood between the patient's legs and two assistants stood at the patient's left side. The open Hasson technique was used to introduce the first trocar and pneumoperitoneum was established at a pressure of 12 mmHg. Depending on the tumor site, four working ports were inserted with direct vision after introducing the flexible laparoscope. Harmonic Scalpel (Ethicon, Somerville, NJ, United States) was used to accomplish adhesiolysis. The procedure was then followed by intraoperative ultrasonography. For major or segmental liver resections, the extrahepatic Glissonian method was used to control hepatic inflow, liver parenchymal transection was accomplished with Harmonic Scalpel, and haemostasis was achieved by bipolar diathermy, clips, or sutures. Resected specimens were placed in plastic bags and removed using a Pfannenstiel incision or the extension of one of the ports. In both laparoscopic and open surgery, the Pringle manoeuvre was used selectively in cases with excessive bleeding, and drains were placed only when indicated. Intraoperative RFA was occasionally used for small lesions deep within the liver parenchyma and was carried out using a Cooltip RFA system (Medtronic, Minneapolis, MN, United States) by either the surgeon or interventional radiologist.

Statistical analysis

Statistical analysis was performed with SPSS version 26 (IBM Corp., Armonk, NY, United States). Mann-Whitney *U* test was used to compare differences between the values of quantitative variables and Pearson chi-squared or Fisher's exact test was used to compare categorical variables. Survival analysis was analysed by the Kaplan-Meier method and differences were compared using the log-rank test. Statistical significance was set at $P \leq 0.05$.

RESULTS

During the study period, 52 patients had liver resection for recurrent HCC following an initial curative liver resection at our center. There were no missing data. One patient with a 7.5-cm diameter tumour and ORH was excluded, and the remaining 29 patients with LRH and 22 patients with ORH were included. Of the 29 LRH patients, 18 had one previous liver resection and 11 had two or more (Table 1). The demographic and clinicopathological characteristics are shown in Table 2. Between-group differences in baseline characteristics, including age, sex, cirrhosis, hepatitis B carrier status, liver function, AFP level, tumour size, number, and location, type of resection, and concurrent ablation, were not significant. Preoperative bilirubin was higher in the LRH (median 17 mmol/L) than in the ORH (13 mmol/L) group ($P = 0.007$). The median tumour size was 1.75 cm in the LRH group and 2.75 cm in the ORH group. There was one hepatitis C patient in the ORH group and none in the LRH group.

Operative outcomes are shown in Table 3. Blood loss (median 300 mL *vs* 750 mL, $P = 0.013$) and length of hospital stay (median 5 d *vs* 7 d, $P = 0.003$) were significantly better in the LRH group. One patient in the ORH group who underwent right anterior sectionectomy died within 30 d after the operation because of chest infection, sepsis, and multiorgan failure. All other complications were successfully treated by conservative measures or interventional radiological drainage. There were six

Table 1 Details of hepatectomy in previous liver resection

Previous liver resection	LRH, *n* = 29	ORH, *n* = 22	*P* value
Approach			0.395
Laparoscopic	14 (48.3)	8 (36.4)	
Open	15 (51.7)	14 (63.6)	
Type of resection			0.224
Major	24 (82.8)	15 (68.2)	
Minor	5 (17.2)	7 (31.8)	
Tumour location, segment			0.780
II, III, IV, V, VI	16 (55.2)	13 (59.1)	
VII, VIII	13 (44.8)	9 (40.9)	
Number of previous hepatectomy			0.478
1	17 (58.6)	16 (72.7)	
2	9 (31.0)	5 (22.7)	
3	2 (6.9)	0 (0.0)	
4	0 (0.0)	1 (4.5)	
5	1 (3.4)	0 (0.0)	
Microscopic lymphovascular invasion			1.000
No	20 (69.0)	15 (68.2)	
Yes	4 (13.8)	4 (18.2)	
Not assessed	5 (17.2)	3 (13.6)	

Values are *n* (%). LRH: Laparoscopic repeat hepatectomy; ORH: Open repeat hepatectomy.

conversions from laparoscopic to open surgery. Three were owed to insecure margins, two due to dense adhesions from previous open surgery, and one due to profuse bleeding from the hepatic vein.

Median follow-up was 54 mo (interquartile range 28-85 mo). No patients were lost to follow-up. OS and DFS are shown in Figure 1. The 1-, 3- and 5-year OS rates were 100.0%, 60.0% and 30.0% in the LRH group and 81.8%, 36.4% and 18.2% in the ORH group, respectively. Except for the single case of 30-d postoperative mortality mentioned above, all patients died of malignant cachexia. The 1-, 3- and 5-year DFS were 68.2%, 27.3% and 4.5% in the LRH group and 31.3%, 6.3% and 6.3% in the ORH group, respectively. Differences in overall (P = 0.336) and DFS (P = 0.055) between the two groups were not significant.

DISCUSSION

Although the benefits of LLR over open liver resection in terms of improved short-term postoperative outcomes and equivalent oncological outcomes are well established[9-15], the importance of LLR in recurrent HCC has yet to be determined. The short-term benefits of LRH were established in this trial, including decreased blood loss, a shorter hospital stay, and oncological results were comparable to ORH.

The presence of abdominal adhesions makes re-resection more challenging. Menzies and Ellis[35] observed that 93% of patients with past laparotomy had intra-abdominal adhesions in a prospective analysis, and their findings were corroborated in an autopsy investigation by Weibel *et al*[36], who detected adhesions in 67% of cases with prior abdominal surgery. For surgeons doing laparoscopic liver resection, dense or highly vascularized adhesions, particularly those around the hepatic hilum or major vessels, remain a significant challenge. However, optical magnification during laparoscopic re-resection increases the precision of dissection, and the pneumoperitoneum tightens the adhesion bands, making the dissection and adhesiolysis easier. LLR may also decrease the formation of adhesions and injury to the liver parenchyma, collateral arteries, and surrounding structures, allowing for further resections[37, 38]. In this retrospective study, although adhesion scoring was not documented, the conversion rate was higher than reported in our previously reported series of primary LLR patients (20% *vs* 10%)[15,30].

Table 2 Patient and tumour characteristics

Characteristic	LRH, *n* = 29	ORH, *n* = 22	*P* value
Age	64 (57.5-67.5)	65.5 (59.75-69.25)	0.607
Sex			0.688
Male	25 (86.2)	20 (90.9)	
Female	4 (13.8)	2 (9.1)	
Cirrhosis on histology	19 (65.5)	13 (59.1)	0.638
HBsAg-positive	27 (93.1)	20 (90.9)	1.000
Albumin in g/L	39 (36-41)	36 (34-40)	0.109
Total bilirubin in μmol/L	17 (13-20)	13 (10-16)	0.007
International normalized ratio	1.1 (1.05-1.20)	1.085 (1.055-1.148)	0.587
Platelet count as × 10^9/L	123 (99-173)	161.5 (115.25-201.00)	0.092
Alpha-fetoprotein in IU/mL	11 (4.25-288.00)	17 (4.0-174.5)	0.814
Type of resection			0.055
Sub-segmentectomy	19 (65.5)	8 (36.4)	
Segmentectomy	5 (17.2)	2 (9.1)	
Left lateral sectionectomy	2 (6.9)	1 (4.5)	
Right bisegmentectomy	1 (3.4)	4 (18.2)	
Left hepatectomy +/− extended	1 (3.4)	1 (4.5)	
Right hepatectomy +/− extended	1 (3.4)	5 (22.7)	
Central bisectionectomy	0 (0.0)	1 (4.5)	
Intraoperative ablation	1 (3.4)	2 (9.1)	0.571
Tumour size in cm			0.054
< 1	2 (6.9)	1 (4.5)	
≥ 1-2	15 (51.7)	7 (31.8)	
≥ 2-3	5 (17.2)	3 (13.6)	
≥ 3-4	5 (17.2)	2 (9.1)	
≥ 4-5	1 (3.4)	8 (36.4)	
≥ 5	1 (3.4)	1 (4.5)	
Number of tumours			0.295
Single	25 (86.2)	16 (72.7)	
Multiple	4 (13.8)	6 (27.3)	
Tumour location, segment			0.491
I	2 (6.9)	0 (0.0)	
II, III, IV, V, VI	14 (48.3)	9 (40.9)	
VII, VIII	13 (44.8)	13 (59.1)	

Values are *n* (%) or median (interquartile range). HBsAg: Hepatitis B surface antigen; LRH: Laparoscopic repeat hepatectomy; ORH: Open repeat hepatectomy. Right bisegmentectomy: Right anterior sectionectomy or right posterior sectionectomy; Left hepatectomy +/− extended: Left hepatectomy or extended left hepatectomy; Right hepatectomy +/− extended: Right hepatectomy or extended right hepatectomy.

Two of the conversions to open surgery were because of adhesions related to previous open surgery. The conversions illustrate the impact of adhesions on liver resection.

In this series, 62.7% of the patients had a histological diagnosis of cirrhosis, and more than 90% were hepatitis B carriers. Even for cirrhotic patients with recurrent HCC, LRH was safe and feasible, and it had a superior short-term outcome than ORH. Over a decade ago, Belli *et al*[39] suggested that laparo-

Table 3 Operative outcomes

Outcome	LRH, *n* = 29	ORH, *n* = 22	*P* value
Operative time in min	250 (177.5-320.5)	300.5 (223.00-378.75)	0.224
Pringle manoeuvre used	2 (6.9)	3 (13.6)	0.641
Blood loss in mL	300 (200-700)	750 (300-1450)	0.013
Blood transfusion	6 (20.7)	8 (36.4)	0.214
Conversion	6 (20.7)		
Hospital stay in d	5 (4-7)	7 (5.75-11.50)	0.003
Resection margin in mm	7.25 (5.00-13.25)	4.25 (1.00-8.25)	0.073
Positive margin	2 (7.1)	2 (9.1)	0.801
Complications	3 (10.3)	6 (27.3)	0.150
Chest infection	0	1	
Pleural effusion	1	3	
Arrhythmia	2	0	
Bile leak	0	2	
Liver failure	0	0	
UTI	0	1	
Intra-abdominal infection	1	1	
Clavien-Dindo severity of complications			
IIIa	1 (1.1)	5 (22.7)	0.073
IIIb	0	0	
IV	0	0	
V	0 (0.0)	1 (4.5)	0.431

Values are *n* (%) or median (interquartile range). LRH: Laparoscopic repeat hepatectomy; ORH: Open repeat hepatectomy; UTI: Urinary tract infection.

scopic liver re-resection was only indicated for HCC in patients with well-compensated Child-Pugh class A chronic liver disease without signs of severe portal hypertension, a single exophytic or subcapsular HCC located in the left (segments II, III, or IVb) or right (segments V or VI) liver and a maximum size of 4 cm to 5 cm. Increased experience and advances in technology have extended the indications for laparoscopic hepatectomy. After a previous hepatectomy, intrahepatic recurrence in the liver remnant might benefit from LRH with less blood loss and a shorter hospital stay.

RFA has been recommended as an alternative to repeat liver resection for recurrent HCC. A recent meta-analysis by Liu *et al*[40] found that 1-, 3- and 5-year OS and 1-year DFS rates following repeated liver resection for recurrent HCC were similar to those achieved by RFA in patients who satisfied the Milan criteria (*i.e.* maximal diameter of a single tumour ≤ 5 cm, or ≤ 3 tumours ≤ 3 cm each). Repeated liver resection was superior to RFA in 3- and 5-year DFS, but if the tumour size for RFA was not limited, 3- and 5-year OS and 1-, 3- and 5-year DFS were better with repeated liver resection than with RFA. RFA should therefore be reserved for patients with small deep-seated tumors that meet the Milan criteria, and liver re-resection should be the first-line treatment for subcapsular or massive tumors.

There were a few study limitations. First, it was a retrospective analysis, and there were missing data on the adhesion scores after the first hepatectomy. Second, only 51 patients had repeated hepatectomy during the study period. The small sample size was prone to type 2 errors. Third, we conducted only univariate analysis, which is subject to confounding factors. For confounder control, Cox regression or propensity score matching should be considered. However, our sample size was too small for such an analysis. Fourth, we included patients with hepatectomies between 2006 and 2021. Surgical instruments and techniques have improved throughout time, despite the fact that all of the operations were performed by the same group of devoted hepatobiliary surgeons.

Larger studies, or even randomized controlled trials, are needed to further understand the role of LRH in the treatment of recurrent HCC. Documentation of the adhesion score upon repeated hepatectomy would allow an analysis of the benefits of laparoscopic surgery on the formation of adhesions.

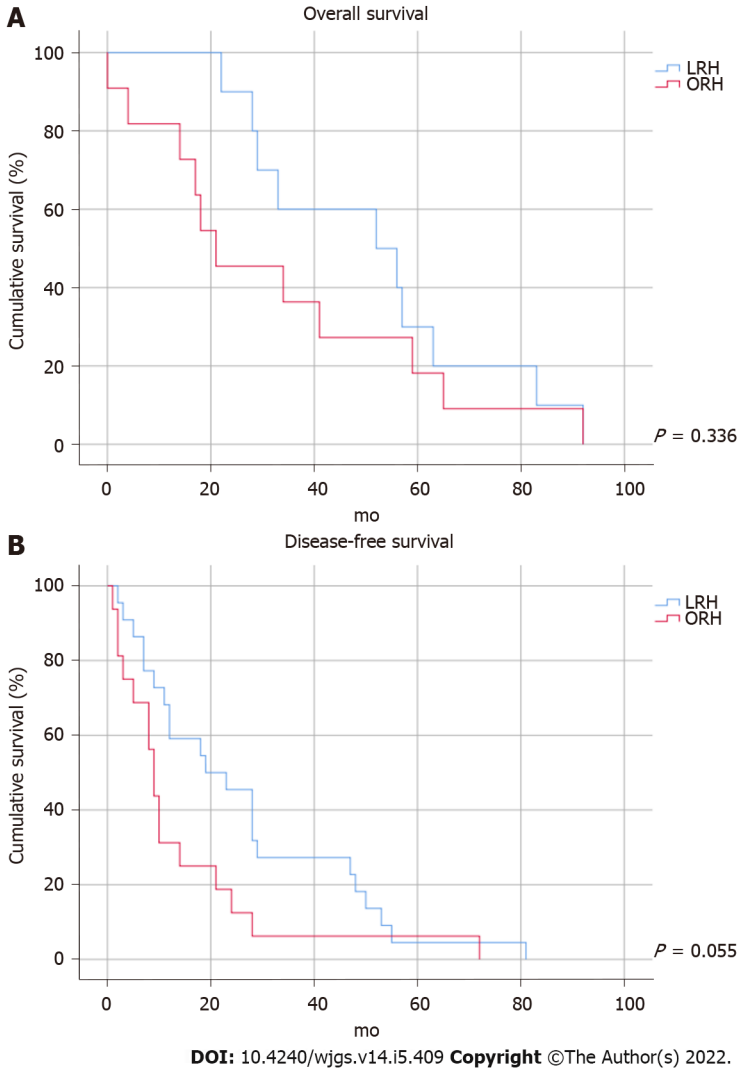

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Figure 1 Kaplan-Meier curve. A: Kaplan-Meier curve comparing overall survival of laparoscopic repeat hepatectomy and open repeat hepatectomy; B: Kaplan-Meier curve comparing disease-free survival of laparoscopic repeat hepatectomy and open repeat hepatectomy. LRH: Laparoscopic repeat hepatectomy; ORH: Open repeat hepatectomy.

CONCLUSION

Laparoscopic liver re-resection for recurrent HCC was associated with less blood loss and shorter hospital stays than open surgery, even in patients with cirrhosis. According to the long-term assessment, overall and DFS was similar between the two groups. Laparoscopic re-resection should be considered for patients who have undergone previous hepatectomy and present with recurrent HCC of less than or equal to 7 cm in size. Regardless, more extensive prospective trials are required to guide the optimal treatment choice for patients with recurrent HCC.

ARTICLE HIGHLIGHTS

Research background

Recurrent hepatocellular carcinoma can be effectively treated with repeated liver resection (HCC). For recurrent HCC, few studies have compared the outcomes of laparoscopic repeat hepatectomy (LRH) with open repeat hepatectomy (ORH), and even fewer have included cirrhotic patients.

Research motivation

Currently, there is a lack of evidence of the effectiveness of LRH for the treatment of recurrent HCC in cirrhotic patients.

Research objectives

This study aimed to compare the short-term and long-term outcomes for cirrhotic patients with LRH and ORH for recurrent HCC. The study was intended to provide insights on performing LRH for cirrhotic patients with recurrent HCC.

Research methods

A prospectively collected database identified all patients undergoing repeat hepatectomy for recurrent HCC between May 2006 and June 2021. Recurrent HCC with tumours > 7 cm were excluded. Patient demographics, operative details, perioperative outcomes, pathologic details, disease-free survival (DFS) and overall survival (OS) associated with LRH and ORH were compared.

Research results

Cirrhosis was histologically diagnosed in 62.7% of our patients and more than 90% were hepatitis B carriers. Blood loss (median 300 mL *vs* 200 mL, $P = 0.013$) and length of hospital stay (median 5 d *vs* 7 d, $P = 0.003$) were significantly better in the LRH group. There were no significant differences in the 1-, 3- and 5-year OS and DFS rates between the LRH and ORH groups.

Research conclusions

Even in patients with cirrhosis, laparoscopic liver resection for recurrent HCC was associated with decreased blood loss, a shorter hospital stay, and equivalent overall and DFS to open surgery.

Research perspectives

Laparoscopic re-resection should be considered for patients with recurrent HCC of less than or equal to 7 cm in size that develop subsequent to a previous hepatectomy. However, larger studies or randomised controlled trials should be conducted to confirm the advantages of LRH for the management of recurrent HCC.

FOOTNOTES

Author contributions: Cheng KC designed the research study, performed the research, analyzed the data and drafted the manuscript; Ho KM wrote and revised the manuscript; All authors have read and approve the final manuscript.

Institutional review board statement: The protocol was approved by The Hong Kong Hospital Authority Research Ethics Committee (Kowloon Central/Kowloon East) (Ref: KC/KC-21-0278/ER-4) following the applicable laws and regulations (including Hong Kong laws), hospital authority policy, professional code of conduct, International Council for Harmonisation, Good Clinical Practice, and the Declaration of Helsinki.

Informed consent statement: Written consent was not required as this was a retrospective study, and no data were collected prospectively.

Conflict-of-interest statement: The authors declare that they have no conflicting interests.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Effect of overtime pancreaticoduodenectomy on the short-term prognosis of patients

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Abstract

BACKGROUND

Due to the large number of operations, surgeons sometimes need to work overtime or even stay up late to perform pancreaticoduodenectomy. Fatigue and sleep deprivation can result in an increased error rate at work. There have been numerous studies about the effect of overtime surgery on the prognosis of patients. However, the effect of overtime work for pancreaticoduodenectomy on the prognosis of patients is unclear. This study explores the impact of overtime work for pancreaticoduodenectomy on the prognosis of patients.

AIM

To explore the impact of overtime work for pancreaticoduodenectomy on the short-term prognosis of patients.

METHODS

This was a single-center, retrospective cohort study. The patients who underwent pancreaticoduodenectomy between January 2017 and December 2019 were included. Patients were stratified by operative start time into the control group (surgery that started between 8:00 and 16:49) and the overtime group (surgery that started between 17:00 and 22:00) and compared intraoperative and postoperative parameters. The following parameters were compared between the overtime group and the control group: Operative time, blood loss, number of lymph nodes removed, duration of treatment in the Intensive Care Unit (ICU), and incidence of complications.

RESULTS

From January 2017 to December 2019, a total of 239 patients underwent pancreaticoduodenectomy in the Department of Hepatobiliary Surgery of our institution. Four patients were excluded from this study due to lack of clinical data. A total of 235 patients were included, with 177 in the control group and 58 in the overtime group. There was no difference between the two groups in operative time, blood

loss, number of lymph nodes removed, ICU length of stay, hospital length of stay, mortality during hospitalization. Compared with the control group, the overtime group had a higher incidence of pancreatic fistula (32.8% *vs* 15.8%, $P < 0.05$). Multivariate analysis showed that overtime work, higher Body Mass Index were independent risk factors for pancreatic fistula ($P < 0.05$).

CONCLUSION
Overtime work for pancreaticoduodenectomy increases the incidence of pancreatic fistula. The effect of overtime surgery on the long-term prognosis of patients' needs to be further studied.

Key Words: Pancreaticoduodenectomy; Fatigue; Surgery; Pancreatic fistula; General surgery; Overtime surgery

Core Tip: The effect of overtime work for pancreaticoduodenectomy on the prognosis of patients is unclear. We explore the impact of overtime work for pancreaticoduodenectomy on the prognosis of patients. A total of 235 patients were included, with 177 in the control group and 58 in the overtime group. Overtime work for pancreaticoduodenectomy increases the incidence of pancreatic fistula. The effect of overtime surgery on the long-term prognosis of patients' needs to be further studied.

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INTRODUCTION

Due to the large number of operations, surgeons sometimes need to work overtime to perform elective surgery. When this occurs, surgeons performing the operation are faced with fatigue or even sleep deprivation. Fatigue and sleep deprivation affect cognitive function, leading to an increased error rate at work[1-3]. There have been numerous studies about the effect of overtime surgery on the prognosis of patients. However, the impact of surgery on patients due to surgeon fatigue and sleep deprivation is still controversial. Halvachizadeh *et al*[4] observed higher complication and mortality rates for after-hour orthopedic trauma surgery. Boscà *et al*[5] suggest that the prognosis of patients undergoing liver transplantation by fatigued surgeons is not poor. Brunschot *et al*[6] reported that nighttime kidney transplantation is associated with less pure technical graft failure.

Pancreaticoduodenectomy is widely used to treat pancreatic cancer, bile duct carcinoma, duodenal carcinoma, and ampullary carcinoma[7]. The operation is complicated[8], and usually lasts more than 5 h. Postoperative complications such as pancreatic fistula, delayed gastric emptying, abdominal infection, and postoperative hemorrhage are prone to occur[9]. Extensive literature has clarified the risk factors related to complications after pancreaticoduodenectomy[10,11]. At present, there is no report on the effect of pancreaticoduodenectomy over time on the prognosis of patients. Therefore, the study explores the impact of overtime work for pancreaticoduodenectomy on the prognosis of patients.

MATERIALS AND METHODS

Study design and population

Approval of the Ethics Committee of the Peking University People's Hospital was obtained. Patients who underwent pancreaticoduodenectomy at the Department of Hepatobiliary Surgery, Peking University People's Hospital from January 2017 to December 2019 were reviewed. Patients with missing clinical data were excluded. All patients were scheduled to undergo elective surgery. The center stipulates that the working hours of surgeons are 8:00-17:00 from Monday to Friday. The definition of overtime surgery in this study is that the surgeon starts the operation after 17:00. So Patients were stratified by operative start time into the control group (surgery that started between 8:00 and 16:49) and the overtime group (surgery that started between 17:00 and 22:00). Since the off-hours in our institution begin at 17:00, five o'clock was set as the cutoff point. The operating room did not accept new elective surgery after 22:00.

Table 1 Preoperative clinical characteristic of all patients

Characteristic	Total (*n* = 235)
Age (median, range), yr	64 (range 14-89)
Sex, *n* (%)	
Male	153 (65.1)
Female	82 (34.9)
Preoperative comorbidities, *n* (%)	
Diabetes	46 (19.6)
Hypertension	98 (37.4)
Coronary heart disease	19 (8.1)
Hepatobiliary and pancreatic diseases	46 (19.6)
Location of the lesions, *n* (%)	
Pancrea	95 (40.4)
Bile duct	81 (34.6)
Duodenum	59 (25.1)

The following parameters were included as possible confounders: patient age, sex, body mass index (BMI), American Society of Anesthesiologists grade, preoperative comorbidities, preoperative total bilirubin, site of lesion, surgeon, technique of reconstruction, and techinique of pancreaticojejunostomy. The following parameters were compared between the overtime group and the control group: operative time, blood loss, number of lymph nodes removed, duration of treatment in the Intensive Care Unit (ICU), incidence of complications and number of hospital death.

Surgery and surgeons

A total of 6 surgeons performed pancreaticoduodenectomy at the institution. All surgeons had more than 10 years of experience in performing pancreaticoduodenectomy. Each surgeon performed operations two days a week. Karolinska Sleepiness Scale (KSS)[12] was used to assess surgeon sleepiness. The surgeons involved in this study self-assessed their level of sleepiness for each surgery, and expressed with KSS.

Pancreaticoduodenectomy was used to treat pancreatic cancer, cholangiocarcinoma, duodenal cancer, ampullary cancer, and a small number of benign diseases. All pancreaticoduodenectomy were performed by laparotomy. Roux-en-y or child surgery was used to reconstruct the digestive tract, and pancreaticojejunostomy was performed by duct-mucosa or invagination.

Definition of postoperative pancreatic fistula and delayed gastric emptying

A clinically relevant postoperative pancreatic fistula is defined as a drain output of any measurable volume of fluid with an amylase level > 3 times the upper limit of institutional normal serum amylase activity[13]. Delayed gastric emptying was defined as the patient not removing the gastric tube or needing to have the tube reinserted for more than 3 d after the operation[14]. Delayed gastric emptying can be classified as grade A (3-7 d), B (8-14 d), and C (more than 14 d) according to the duration of retention of the gastric tube. In this study, only grades B and C of delayed gastric emptying were included in the postoperative complication analysis.

Statistical analysis

Continuous variables were tested with the Shapiro-Wilk test to determine whether they were normally distributed. Continuous variables that were proven to have a normal distribution are reported as the mean and standard deviation. Otherwise, continuous variables are reported by medians. Categorical variables are reported as frequencies or percentages. Continuous, normally distributed variables were compared with the t-test and non-normally distributed variables were compared with the Mann-Whitney test. The chi-square test was used to compare categorical variables. Reverse stepwise multivariable logistic regression was performed to assess the effects of the potential covariates on outcome. Variables with p-values less than 0.2 in univariate logistic regression models will be included in the multivariable logistic regression analysis. *P* values less than 0.05 were considered significant. Data were analyzed in Statistical Package for the Social Sciences version 21.0 (SPSS 21.0). The study was reviewed by our expert Biostatistic Da-Fang Zhang.

Table 2 Patient characteristics and operative parameters

	Control group (*n* = 177)	Overtime group (*n* = 58)	*P* value
Age (yr)	63 (14-89)	64 (29-84)	0.987
Sex			0.694
Male	114 (64.4%)	39 (67.2%)	
Female	63 (35.6%)	19 (32.8%)	
BMI (kg/m^2)	22.7 (14.8-36.8)	22.9 ± 2.79	0.922
ASA classification			0.227
I	14 (7.9%)	3 (5.2%)	
II	130 (73.4%)	49 (84.5%)	
III	33 (18.6%)	6 (10.3%)	
History of hepatobiliary and pancreatic disease	32 (18.1%)	14 (24.1%)	0.313
Diabetes	33 (18.6%)	13 (22.4%)	0.53
Hypertension	67 (37.9%)	21 (36.2%)	0.822
Coronary artery disease	14 (7.9%)	5 (8.6%)	0.863
Cerebrovascular disease	16 (9.0%)	2 (3.4%)	0.165
Preoperative total bilirubin	85.8 (5.4-793.5)	93.8 (5.3-610.2)	0.566
Primary site			0.644
Pancreas	74 (41.8%)	21 (36.2%)	
Bile duct	61 (34.5%)	20 (34.5%)	
Duodenum	42 (23.7%)	17 (29.3%)	
Surgeon			0.085
A	21 (11.9%)	5 (8.6%)	
B	30 (16.9%)	17 (29.3%)	
C	32 (18.1%)	13 (22.4%)	
D	17 (9.6%)	6 (10.3%)	
E	34 (19.2%)	3 (5.2%)	
F	43 (24.3%)	14 (24.1%)	
Technique of reconstruction			0.233
Roux-en-Y	94 (53.1%)	36 (62.1%)	
Child surgery	83 (46.9%)	22 (37.9%)	
Pancreaticojejunostomy technique			0.686
Duct-to-mucosa	53 (29.9%)	19 (32.8%)	
Invagination	124 (70.1%)	39 (67.2%)	
Operative time (min)	413 (260-796)	421.1 ± 83.4	0.757
Blood loss (mL)	600 (100-4700)	700 (150-2800)	0.185
Number of lymph nodes removed	9 (0-62)	10 (1-45)	0.994

BMI: Body mass index.

RESULTS

Preoperative clinical characteristic

From January 2017 to December 2019, a total of 239 patients underwent pancreaticoduodenectomy in the Department of Hepatobiliary Surgery of our institution. Four patients were excluded from this

Table 3 Intraoperative and postoperative clinical characteristic of all patients

Characteristic	Total (*n* = 235)
Operating time (median, range), min	416 (260-796)
Blood loss volume (median, range), mL	600 (100-4700)
Number of lymph nodes removed (median, range)	10 (0-62)
ICU length of stay (median, range), h	16 (0-518)
Hospital length of stay (median, range), d	19 (7-160)
Postoperative complications, *n* (%)	
Pancreatic fistula	47 (20.0)
Delayed gastric emptying (B/C)	39 (16.6)
Gastrointestinal bleeding	25 (10.6)
Abdominal infection	14 (3.0)
Pneumonia	6 (2.6)
Arrhythmia	6 (2.6)
Thromboembolism	2 (0.9)
Respiratory failure	1 (0.4)
Gastrointestinal bleeding	1 (0.4)
Death during hospitalization, *n* (%)	
Gastrointestinal bleeding	2 (0.9)
Pancreatic fistula	4 (1.7)
Abdominal infection	1 (0.4)
Pneumonia	3 (1.3)

ICU: Intensive Care Unit.

Table 4 Postoperative factors and complications

	Control group (*n* = 177)	Overtime group (*n* = 58)	*P* value
Operative time (min)	413 (260-796)	421.1 ± 83.4	0.757
Blood loss (mL)	600 (100-4700)	700 (150-2800)	0.185
Number of lymph nodes removed	9 (0-62)	10 (1-45)	0.994
Duration of treatment in ICU after surgery	17 (0-325)	14 (0-518)	0.511
Duration of postoperative hospitalization	20 (7-160)	18 (7-61)	0.181
Postoperative pancreatic fistula	28 (15.8%)	19 (32.8%)	0.005
Delayed gastric emptying (B/C)	30 (16.9%)	9 (15.5%)	0.799
Gastrointestinal bleeding	17 (9.6%)	8 (13.8%)	0.369
Abdominal infection	12 (6.8%)	2 (3.4%)	0.352
Pneumonia	3 (1.7%)	3 (5.2%)	0.162
Arrhythmia	6 (3.4%)	0	0.341
Thromboembolism	2 (1.1%)	0	1.000
Respiratory failure	1 (0.6%)	0	1.000
Hemothorax	1 (0.6%)	0	1.000
Hospital death	7 (4.0%)	3 (5.2%)	0.690

ICU: Intensive Care Unit.

study due to lack of clinical data. A total of 235 patients were included in this study. A total of 177 (75.3%) patients underwent surgery before 16:59. In addition, 58 (24.7%) patients underwent surgery after 17:00. The median age of the patients was 64 (range 14-89) years. There were 153 (65.1%) males and 82 (34.9%) females. The preoperative clinical characteristic of all patients were shown in Table 1. There was no significant difference in any baseline characteristic between the two groups of patients (Table 2).

Outcome

The intraoperative and postoperative clinical characteristic of all patients were shown in Table 3. Ten patients (4.3%) died during postoperative hospitalization. Of the ten patients who died, 2 died of gastrointestinal bleeding, 4 died of pancreatic fistula, 3 died of pneumonia, and 1 died of abdominal infection. Compared with the control group, the overtime group had a higher incidence of pancreatic fistula (32.8% *vs* 15.8%, $P = 0.005$). There was no difference between the two groups in operative time, blood loss, number of lymph nodes removed, ICU length of stay, hospital length of stay, mortality during hospitalization or complications except pancreatic fistula (Table 4).

Univariate and multivariate logistic regression analysis of the risk factors for pancreatic fistula

To identify the prognostic factors of pancreatic fistula, we performed univariate and multivariate logistic regression analyses. In the multivariate logistic regression, parameters that significantly increased the risk of pancreatic fistula were high BMI and overtime surgery (Tables 5 and 6).

KSS of surgeons during overtime and non-overtime operations

The average values of KSS in the control group and overtime group were 1.95 ± 0.6 and 6.4 ± 1.0, respectively. The statistical analysis demonstrates differences between groups regarding KSS ($P < 0.001$), with increased mean KSS in overtime group (Table 7).

DISCUSSION

Due to the large demand for surgery, surgeons often need to work overtime or even stay up late to complete a surgery. In a state of fatigue and sleep deprivation, surgeons may make more mistakes during the operation, which may result in a worse prognosis for the patient after surgery. McCormick *et al*[15] reported that residents' fatigue levels were predicted to increase the risk of medical error by 22% compared with well-rested historical control subjects. Taffinder *et al*[16] found that surgeons who were sleep deprived made 20% more mistakes in laparoscopic procedures and had an increase in operating time of 14%. Because of pancreaticoduodenectomy is complicated operation with long operation time, its requirements for the surgeon's physical and mental stamina are higher. Although a large number of studies on pancreaticoduodenectomy have been reported. To the best of our knowledge, our study is the first to explore the relationship between the overtime surgery and the short-term prognosis of pancreaticoduodenectomy. All surgeons at our center perceive a decrease in alertness during overtime surgery. Therefore, the KSS of the overtime group were higher than control group. This means that surgeons tend to be fatigued when they work overtime.

There was no significant difference in the preoperative and intraoperative results of patients between the overtime group and the control group. However, the postoperative results showed that the overtime group had a higher incidence of pancreatic fistula. In the multivariate regression analysis, operation time was still the influencing factor on pancreatic fistula. The incidence of pancreatic fistula in the night shift group was approximately twice that in the day shift group (32.8% *vs* 15.8%). In addition, elevated BMI was risk factors for pancreatic fistula. Relevant studies have confirmed that high BMI is a risk factor for pancreatic fistula[17,18]. High BMI causes abdominal fat to increase, which in turn leads to increased difficulty in surgery, thereby increasing the incidence of pancreatic fistula.

Pancreatico-enteric anastomosis in pancreaticoduodenectomy places stricter requirements on the operation of the surgeon. Due to more than 8 h of work during the day, the surgeon is physically and mentally exhausted, which may lead to a decline in surgical proficiency. Therefore, overtime surgery may cause a significant increase in the incidence of pancreatic fistula. This study confirmed that overtime pancreaticoduodenectomy increased the incidence of postoperative pancreatic fistula in patients. According to previous literature[19-21], about 16.3%-23.9% of patients who underwent pancreaticoduodenectomy developed pancreatic fistula after surgery. The result was consistent with the report in our center. Postoperative pancreatic fistula can prolong the patients' hospital stay, increase the patient's medical expenses, and even lead to the patient's death. So avoiding pancreatic fistula as much as possible is crucial for surgeons.

Table 5 *P* values, odds ratios, and selected 95%CI for pancreatic fistula from univariate logistic regression models

Parameter	*P* value	Odds ratio	95%CI
Age (yr)	0.474	1.011	0.981-1.042
Male	0.068	1.986	0.951-4.149
BMI (kg/m^2)	0.036	1.113	1.007-1.229
ASA classification			
I	0.723	0.733	0.132-4.066
II	0.373	1.532	0.599-3.920
III		Reference	
History of hepatobiliary and pancreatic disease	0.368	0.669	0.278-1.607
Diabetes	0.368	0.669	0.278-1.607
Hypertension	0.071	1.813	0.950-3.460
Coronary artery disease	0.905	1.073	0.339-3.396
Cerebrovascular disease	0.714	0.786	0.218-2.837
Preoperative total bilirubin	0.324	1.001	0.999-1.003
Primary site			
Pancreas	0.581	0.777	0.317-1.905
Bile duct	0.087	2.063	0.899-4.735
Duodenum	Reference		
Surgeon			
A	0.44	1.482	0.545-4.030
B	0.55	0.757	0.303-1.888
C	0.308	0.605	0.231-1.589
D	0.053	0.127	0.016-1.028
E	0.076	0.339	0.103-1.119
F		Reference	
Overtime case	0.006	2.592	1.312-5.122
Reconstruction technique			
Roux-en-Y		Reference	
Child surgery	0.743	1.113	0.586-2.114
Pancreaticojejunostomy technique			
Duct-to-mucosa	0.572	1.217	0.617-2.4
Invagination		Reference	

BMI: Body mass index.

The institution stipulates that surgeons cannot start new elective operations after ten o'clock in the evening. However, clinicians need to complete a large number of surgical tasks on their own surgery days. To extend working hours, surgeons will schedule short-term operations such as cholecystectomy to be completed during the day and long-term operations such as pancreaticoduodenectomy to be performed near ten o'clock in the evening. Therefore, a large number of pancreaticoduodenectomies are performed after hours in our institution. Working overtime to perform pancreaticoduodenectomy reduces the safety of the operation and increases the incidence of postoperative pancreatic fistula. In addition, overtime work has an adverse effect on doctors' health. Studies have confirmed that overtime work will lead to an increase in the incidence of cardiovascular diseases[22,23].

The government and hospital administrators may need to take measures to change the situation where surgeons frequently work overtime or even stay up late for surgery. At the government level, investment in medical care should be increased to alleviate the shortage of medical resources. In

Table 6 *P* values, odds ratios, and selected 95%CI for pancreatic fistula from multivariate logistic regression models

Parameter	*P* value	Odds ratio	95%CI
BMI (kg/m^2)	0.034	1.12	1.008-1.243
Primary site			
Pancreas	0.773	0.873	0.346-2.201
Bile duct	0.062	2.273	0.960-5.380
Duodenum		Reference	
Overtime case	0.004	2.803	1.382-5.685

BMI: Body mass index.

Table 7 Karolinska Sleepiness Scale of surgeons during overtime and non-overtime operations

	Control group	Overtime group	*P* value
KSS	1.95 ± 0.6	6.4 ± 1.0	0

KSS: Karolinska Sleepiness Scale.

addition, the government can legislate to limit the working hours of medical staff. At the hospital level, the clinical workload of surgeons should be appropriately reduced to ensure medical safety. Surgeons should try to avoid working overtime to perform pancreaticoduodenectomy. For patients undergoing overtime pancreaticoduodenectomy, surgeons should pay close attention to the amylase content of the patient's drainage fluid to find potential postoperative pancreatic fistulas in a timely manner.

There are still some limitations in this study. The subgroup analysis considering different diagnosis (not only location of lesions), and also different types of surgeries, and the different surgical teams, might render the final analysis difficult to interpret (due to small numbers considering the subgroups). Therefore, the results of this study should be interpreted with caution. Also, this study was a single-center retrospective cohort study, and only six surgeons performed pancreaticoduodenectomy. The conclusions of this study may not be convincing enough to extend to all institutions. Finally, this study did not analyze the long-term prognosis of patients, such as progression-free survival, and overall survival. More research is needed in the future.

CONCLUSION

Overtime pancreaticoduodenectomy may increase the incidence of postoperative pancreatic fistula. The government and hospital administrators may need to take measures to change the situation where surgeons frequently work overtime or even stay up late for surgery.

ARTICLE HIGHLIGHTS

Research background

Fatigue and sleep deprivation can result in an increased error rate at work. The effect of overtime work for pancreaticoduodenectomy on the prognosis of patients is unclear.

Research motivation

Overtime surgery may result in an increased incidence of intraoperative errors. This study is intended to be further clarified.

Research objectives

To explore the impact of overtime work for pancreaticoduodenectomy on the short-term prognosis of patients.

Research methods

Patients were stratified by operative start time into the control group (surgery that started between 8:00 and 16:49) and the overtime group (surgery that started between 17:00 and 22:00) and compared intraoperative and postoperative parameters.

Research results

The overtime group had a higher incidence of pancreatic fistula than control group (32.8% *vs* 15.8%, $P < 0.05$).

Research conclusions

The overtime group had a higher incidence of pancreatic fistula.

Research perspectives

This study did not analyze the long-term prognosis of patients, such as progression-free survival, and overall survival. More research is needed in the future.

FOOTNOTES

Author contributions: Zhang JZ designed the study, acquired and analyzed the data, and wrote the paper; Li S acquired and analyzed the data, and revised the paper; Zhu WH acquired and analyzed the data, and revised the paper; Leng XS revised the paper; Zhang DF designed the study, revised the paper, and supervised the study.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Para-aortic lymph node involvement should not be a contraindication to resection of pancreatic ductal adenocarcinoma

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Abstract

BACKGROUND

Para-aortic lymph nodes (PALN) are found in the aortocaval groove and they are staged as metastatic disease if involved by pancreatic ductal adenocarcinoma (PDAC). The data in the literature is conflicting with some studies having associated PALN involvement with poor prognosis, while others not sharing the same results. PALN resection is not included in the standard lymphadenectomy during pancreatic resections as per the International Study Group for Pancreatic Surgery and there is no consensus on the management of these cases.

AIM

To investigate the prognostic significance of PALN metastases on the oncological outcomes after resection for PDAC.

METHODS

This is a retrospective cohort study of data retrieved from a prospectively maintained database on consecutive patients undergoing pancreatectomies for PDAC where PALN was sampled between 2011 and 2020. Statistical comparison of the data between PALN+ and PALN- subgroups, survival analysis with the Kaplan-Meier method and risk analysis with univariable and multivariable time to event Cox regression analysis were performed, specifically assessing oncological outcomes such as median overall survival (OS) and disease-free survival

(DFS).

RESULTS

81 cases had PALN sampling and 17 (21%) were positive. Pathological N stage was significantly different between PALN+ and PALN- patients (P = 0.005), while no difference was observed in any of the other characteristics. Preoperative imaging diagnosed PALN positivity in one case. OS and DFS were comparable between PALN+ and PALN- patients with lymph node positive disease (OS: 13.2 mo *vs* 18.8 mo, P = 0.161; DFS: 13 mo *vs* 16.4 mo, P = 0.179). No difference in OS or DFS was identified between PALN positive and negative patients when they received chemotherapy either in the neoadjuvant or in the adjuvant setting (OS: 23.4 mo *vs* 20.6 mo, P = 0.192; DFS: 23.9 mo *vs* 20.5 mo, P = 0.718). On the contrary, when patients did not receive chemotherapy, PALN disease had substantially shorter OS (5.5 mo *vs* 14.2 mo; P = 0.015) and DFS (4.4 mo *vs* 9.8 mo; P < 0.001). PALN involvement was not identified as an independent predictor for OS after multivariable analysis, while it was for DFS doubling the risk of recurrence.

CONCLUSION

PALN involvement does not affect OS when patients complete the indicated treatment pathway for PDAC, surgery and chemotherapy, and should not be considered as a contraindication to resection.

Key Words: Para-aortic lymph node; Pancreatectomy; Survival; Pancreatic adenocarcinoma; Chemotherapy; Lymph node sampling

Core Tip: Currently there is no consensus on the prognostic significance of para-aortic lymph node (PALN) involvement in pancreatic ductal adenocarcinoma (PDAC), which is staged as metastatic disease (M1). Our study has demonstrated that patients with PALN involvement have comparable oncological outcomes, overall survival (OS) and disease free survival, to ones without PALN disease, when the appropriate treatment pathway is competed (surgery and chemotherapy). Multivariable risk analysis did not identify PALN involvement as an independent predictor for OS, while it doubled the risk of disease recurrence. Our data support that PALN involvement should not be considered a contraindication to resection for PDAC.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) presents as localised disease for only a small subset of patients for whom only 20% are eligible for resection[1] with 5-year survival of 6.8%[2]. Nodal status is amongst the most important prognostic indicators. Early lymph node involvement can be as common as 90% and may lead to tumour recurrence even after complete resection[3]. Survival difference has been demonstrated between N0 and lymph node positive disease within variances of lymph node ratio[4] and nodal stations[5] However, para-aortic lymph nodes found in the aortocaval groove (PALN, station Ln16b1) are distinct from regional lymph node stations and are staged as distant metastatic (M1) disease [6]. PALN metastases are found in 14%-18% of pancreatic head/uncinate PDAC at resection[7]. The exact significance and management of PALN is yet to be fully determined. Within the literature, various studies have alluded to PALN metastases being associated with poor prognosis, whereas others have failed to replicate this effect[8,9] and a meta-analysis[10] has only concluded the need for intra-operative assessment of PALN. A consensus statement from the International Study Group for Pancreatic Surgery (ISGPS) supported standard lymphadenectomy for pancreatic resections, as evidence do not support any benefit with an extended approach[11]. There was no recommendation to include PALN in standard lymphadenectomy, however it was acknowledged that PALN may be included in the resection plane based on individual practice. Currently, whether intra-operative assessment should be undertaken or whether there is sufficient evidence that resection should be abandoned depends on

surgeon or unit policy.

The aim of this study was to determine the prognostic significance of PALN metastases on the oncological outcomes after pancreatic resections for PDAC.

MATERIALS AND METHODS

The study was conducted in line with STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines[12]. It was conducted at the University Hospitals of Birmingham, a tertiary specialist centre for the treatment of pancreatic cancer, after departmental approval. Staging of the tumours was based on the NCCN staging criteria[13]. The unit adopts a policy of fast-track[14] upfront surgery approach for resectable and borderline resectable PDAC with venous only involvement as supported by the United Kingdom National Institute for Care and Health Excellence[15], patients with borderline tumours with arterial involvement and locally advanced PDAC undergo neoadjuvant chemotherapy before resection is contemplated. All patients are referred for adjuvant chemotherapy after resection. In the early part of the study gemcitabine-based regimens were used both in the neoadjuvant and adjuvant setting. In the more recent years, modified FOLFIRINOX has been the preferred regimen, with gemcitabine-based regimens as back-up option depending on patients' status and tolerance. PALN were sampled from the infra-renal, aortacaval lymph nodes and more specifically from the level of the third part of the duodenum to the angle of the left renal vein (station 16). PALN sampling was performed at the discretion of the operating surgeon. Over the last 3 years of the study 3 surgeons sampled PALN routinely, accounting for 36% of the cases in the study. Pre-operative staging included a computer tomography (CT) with IV contrast of the thorax, abdomen and pelvis and endoscopic ultrasound (EUS) with fine needle aspiration when preoperative cytological diagnosis was required. Magnetic resonance imaging (MRI) liver and positron emission tomography/CT (PET/CT) were used selectively if there were concerns for metastatic disease based on the CT scan. The management of all cases was discussed and agreed in the hepatopancreaticobiliary multidisciplinary meeting. Follow-up of patients was determined from time of diagnosis until disease recurrence or death. The study cohort included all patients that had PALN sampling during pancreatic resection for PDAC between 2011 and 2020. Clinical, radiological and pathological data were obtained from the hospital's electronic records and the departmental prospectively maintained database. The American Joint Committee on Cancer 8th edition was used for tumor-node-metastasis (TNM) staging statistical analysis. Overall survival (OS) was defined as the time from diagnosis to death or last follow-up and disease free survival as the time from resection to diagnosis of disease recurrence.

The cohort characteristics are presented with standard descriptive statistical analysis. One way Anova, Chi-Square and Mann-Whitney *U* tests were used as appropriate to compare variables and outcomes between PALN positive and negative subgroups, with statistical significance set at $P < 0.05$. Exact statistics were used for all tests to account for small sample size. Survival analysis was performed with the Kaplan-Meier method and log rank test was used to compare survival curves. Univariable and multivariable time to event analyses were performed using the Cox proportional hazard model to determine risk factors for median OS and disease-free survival (DFS). Variables were subjected to a univariable analysis first and those with $P < 0.2$ were introduced into a multivariable model. Hazard ratios and associated 95% confidence intervals (CI) were calculated. A two-tailed P value < 0.05 was considered statistically significant. All statistical analyses were performed using the software package SPSS Statistics for Windows (version 25.0; SPSS Inc., Chicago, IL, United States).

RESULTS

During the study period there were 81 patients who underwent pancreatectomies for PDAC where PALN were sampled. PALN metastasis was identified in 17 (21%) cases. The median sampled LNs were 2 (range 1-7) and median positivity ratio 0.5 (range 0.14-1). Patient, tumour and post-operative parameters for the whole cohort, as well as for the PALN positive and negative subgroups, are displayed in Table 1. Pathology N stage (pN) was significantly different between patients with PALN positive and negative disease ($P = 0.005$). All patients with PALN metastases also had regional lymph node disease, with 82% having pN2 disease (in contrast to 45% of PALN negative patients). There was no difference observed in any of the other characteristics. PALN sampling did not cause any significant morbidity in terms of chyle leak or post-pancreatectomy haemorrhage.

Radiological detection of PALN

Amongst patients with metastatic PALN on pathology, there was no modality of investigation which detected this during preoperative staging (CT 1/81, EUS 0/5 or PET 0/3).

Table 1 Patient demographics, operative and pathological characteristics and outcomes

Factors	Total (*n* = 81)	PALN+ (*n* = 17)	PALN- (*n* = 64)	*P* value
Demographics				
Age (median and range in years)	69 (43-84)	68.8 (61-72.3)	69 (61-75)	0.404
Gender, male (%)	38 (47)	12 (71)	33 (52)	0.171
BMI (kg/m^2)	25.1 (22.0-27.8)	26.2 (22.2-27.8)	24.9 (21.9-27.7)	0.413
Non-smoker (%)	13 (73)	14 (82)	46 (72)	0.462
Preoperative CA19-9 levels (KU/L)	286 (2-36000)	410 (14-2784)	252 (2-36000)	0.594
Charlson comorbidity index	4 (3-5)	4 (3-5)	4.5 (3-5)	0.079
Preoperative radiological stage *n* (%)				
Resectable	41 (51)	8 (47)	33 (52)	0.601
Borderline resectable	31 (38)	8(47)	23 (36)	
Locally advanced	9 (11)	1 (6)	8 (12)	
Operation, *n* (%)				
Distal pancreatectomy	1 (1)	0	1 (1)	0.681
Total pancreatectomy	14 (17)	2 (12)	12 (19)	
Pancreaticoduodenectomy	66 (82)	15 (88)	51 (80)	
Vein resection	33 (41)	7 (41)	26 (41)	0.310
Arterial resection	3 (4)	1 (6)	2 (3)	0.842
Pathological staging, *n* (%)				1.000
pT1	13 (16)	3 (18)	10 (16)	0.951
pT2	46 (57)	9 (53)	37 (58)	
pT3	21 (26)	5 (29)	16 (25)	
pT4	1 (1)	0	1 (1)	
pN0	14 (79)	0	14 (22)	0.005
pN1	24 (30)	3 (18)	21 (33)	
pN2	43 (53)	14 (82)	29 (45)	
Resection margin, *n* (%)				
Negative	39 (48)	6 (35)	33 (52)	0.282
Positive	42 (52)	11 (65)	31 (48)	
Perineural invasion	66 (83)	15 (88)	51 (80)	0.722
Perivascular invasion	59 (73)	13 (77)	46 (72)	1.000
Chemotherapy, *n* (%)	55 (74)	12 (71)	43 (67)	0.746
Neoadjuvant therapy	13 (16)	2 (12)	11 (17)	0.726
Adjuvant chemotherapy	49 (66)	12 (71)	37 (58)	0.553
Post-operative complications, *n* (%)				
Clavien Dindo category ≥ 3	10 (12)	2 (11.8)	8 (12.5)	0.549
Chyle leak	1 (1)	0	1 (1.56)	0.835
Perioperative haemorrhage	2 (2)	0	2 (3.13)	0.712
Comprehensive complication index	0 (0-20.9)	0 (0-20.9)	0 (0-20.9)	0.083
Hospital length of stay (median and range in days)	9 (1-76)	8 (5-30)	10 (1-76)	0.138

BMI: Body mass index; PALN: Para-aortic lymph nodes.

OS

OS was better in PALN negative patients with a median of 20.6 mo compared to 13.2 mo in PALN positive patients (P = 0.037) (Figure 1A). However, OS among patients with lymph node disease (pN1 and pN2) was comparable between PALN positive and negative cases (13.2 mo *vs* 18.8 mo, P = 0.161) (Figure 1B).

Similarly, when patients were stratified based on receipt of chemotherapy, either in the neoadjuvant or the adjuvant setting, no difference in OS was observed between PALN positive and negative patients who had chemo-therapy (23.4 mo *vs* 20.6 mo, P = 0.192). Interestingly OS of PALN positive patients was slightly longer by about 3 mo (Figure 1C). On the contrary, when patients did not receive chemotherapy, PALN metastatic disease had substantially shorter OS (5.5 mo *vs* 14.2 mo; P = 0.015) (Figure 1D).

Univariable Cox regression analysis showed that pT, pN, presence of PALN metastases, resection margin status and receipt of chemotherapy were associated with OS (Table 2). Multivariable analysis identified pT, pN, margin status and receipt of chemotherapy as independent predictors of survival (Table 2). Of note PALN positivity was not identified as an independent prognostic factor for OS.

Disease-free survival

Median DFS in the PALN positive group was 13 mo compared to 20.5 mo in the PALN negative one (Figure 2A). This approached but did not achieve statistical significance (P = 0.093). However, among patients with lymph node disease (pN1 and pN2), DFS was comparable between PALN positive and negative cases (13 mo *vs* 16.4 mo, P = 0.179) (Figure 2B).

When the patients were stratified based on receipt of chemotherapy, either in the neoadjuvant or the adjuvant setting, no difference in DFS was observed between PALN positive and negative patients that had chemotherapy (23.9 mo *vs* 20.5 mo, P = 0.718). Interestingly DFS of PALN positive patients was slightly longer by about 3 mo (Figure 2C). When patients did not receive chemotherapy, PALN metastatic disease had substantially shorter DFS (4.4 mo *vs* 9.8 mo; P < 0.001) (Figure 2D).

Univariable Cox regression analysis showed that pT, resection margin status and receipt of chemotherapy were associated with DFS. Age, pN, PALN metastases, perineural and perivascular invasion approached but did not achieve significance (Table 3). On multivariable analysis PALN positivity was identified as an independent predictor of DFS, doubling the risk of recurrence. Other predictors were age, pT, margin status, PNI and chemotherapy (Table 3).

DISCUSSION

The prognostic significance of PALN positivity has long been an area of debate. The anatomic location of PALN in the aortocaval groove and away from the peri-pancreatic area has resulted in staging these as extra-regional lymph nodes and therefore metastatic disease on TNM if involved[16]. On the other hand, PALN (LN16b1) drain lymph nodes around groups 13 and 14[7,17,18] which are commonly involved in PDAC and therefore PALN could be considered the next lymph node station involved in cases of node positive disease. Furthermore, one theory that has been proposed to explain PALN acting similarly to nodal disease rather than metastatic is that LN16 involvement is due to local invasion through the fascia of Treitz[19] and this is why it is also associated with a high incidence of positive resection margins[9,19]. In this case, PALN excision may allow extensive mesopancreas dissection[20]. The published evidence on the significance of PALN positive disease and its impact in oncological outcomes is conflicting. A consensus statement from the ISGPS suggested that extended lymphadenectomy is not indicated in pancreatic resections[11]. The same group defined standard lymphadenectomy for pancreaticoduodenectomy to include lymph nodes in the hepatoduodenal ligament (stations 5, 6, 8a, 12b, 12c), pancreaticoduodenal groove (stations 13 and 17), right side of the superior mesenteric artery (stations 14a and 14b) and for distal pancreatectomy those along the splenic artery (station 11), along the inferior border of the pancreas (station 18) and in the splenic hilum (station 10), with station 9 to be included only in pancreatic body tumours. Resection of PALN (station 16) was not recommended based on the reported poor outcomes of patients with PALN positive disease. Nonetheless, it was acknowledged that PALN may be included in the resection plane based on individual practice. Some studies have stated no impact of PALN involvement on survival[7,19,21] with others suggested the opposite and even abandoning resection if this is identified intra-operatively upon sampling[8,22,23]. A confounding flaw in many studies is the comparison of survival between PALN+ and PALN-, where the latter group includes a subgroup of N0 patients with invariably better survival rates. A meta-analysis by Agalianos *et al*[9] made a pertinent comparison of PALN+ with pN1 PALN- patients, showing that survival rates at 1 and 2 years were significantly worse in PALN+ group. This was contested by Hempel *et al*[6] who showed that the OS of PALN+ and pN1 PALN- patients were not significantly different. In our study all PALN positive patients also had regional lymph node disease, whereas 22% of PALN negative patients were staged as pN0. No significant difference in OS and DFS was identified in regional lymph node positive (pN1 and pN2) PALN positive patients compared to PALN negative ones. Given that resection in the presence of nodal disease has been shown to prolong survival[24-28] there is

Table 2 Risk analysis for overall survival

	Univariable		Multivariable	
	***P* value**	**HR (CI)**	***P* value**	**HR (CI)**
Age	0.668	0.994 (0.966-1.022)		
Sex	0.359	0.756 (0.416-1.374)		
Preoperative CA19-9	0.626	1.000 (1.000-1.000)		
Pre-operative stage	0.949	0.986 (0.641-1.517)		
Resection type	0.517	1.141 (0.765-1.702)		
Venous resection	0.659	1.146 (0.625-2.104)		
Arterial resection	0.327	2.045 (0.489-8.559)		
pT	0.001	2.148 (1.368-3.371)	0.008	
pT1			0.842	1.114 (0.385-3.226)
pT2			0.115	2.459 (0.803-7.536)
pT3			0.008	31.275 (2.491-392.605)
pN	0.002	2.195 (1.337-3.604)	0.004	
pN1			0.329	2.332 (0.427-12.740)
pN2			0.016	7.564 (1.459-39.224)
PALN positivity	0.041	1.970 (1.028-3.776)		
Margin status	0.007	2.331 (1.261-4.308)	0.049	1.986 (1.003-3.932)
Perineural invasion	0.212	1.691 (0.741-3.861)		
Perivascular invasion	0.464	1.278 (0.663-2.461)		
Chemotherapy	0.033	0.487 (0.251-0.944)	0.002	0.283 (0.129-0.622)

All parameters with $P < 0.200$ on univariable entered into multivariable model. HR: Hazard ratios; CI: Confidence intervals; PALN: Para-aortic lymph nodes.

no indication on this basis to abandon resection.

The appropriateness of PALN+ being termed M1 disease has also been challenged where long term survival after PALN+ resection has been achieved by various studies[6,29,30] including a multicentre study of 102 (12.4%) PALN+ which has shown survival of 2 years of PALN+ patients[20]. Our study covers a 10 year period during which the chemotherapy practice has changed from single agent gemcitabine to gemcitabine combined with capecitabine and more recently FOLFIRINOX. This along with the fact that approximately 30% of patients did not receive any systemic treatment can explain the OS of 20.6 mo in PALN negative and 13.2 mo in PALN positive patients. However, in patients who received chemotherapy, whether NAT or adjuvant chemotherapy, this disparity disappeared. Furthermore, on multivariable analysis PALN positivity was not an independent predictor for OS. Interestingly, OS was slightly longer in the PLAN positive patients after chemotherapy (23.4 mo *vs* 20.6 mo). This may reflect a treatment selection bias by the oncology teams as patients with more aggressive disease received more commonly chemotherapy in the adjuvant period (71% for PALN positive disease compared to 58% for PALN negative), even though this difference did not reach statistical significance. During the same time period, patients diagnosed with metastatic disease intra-operatively had a medial OS of 14.1 mo after palliative treatment (6.1 mo if they did not receive any palliative treatment), which is substantially less than the 23.4 mo OS recorded for PALN+ patients with chemotherapy.

Similarly, DFS was only worse in PALN positive patients if they did not receive any systemic treatment. However, in patients that had systemic treatment DFS was slightly longer in PALN positive patients (23.9 mo *vs* 20.5 mo). Similar to OS, this is most likely a reflection of oncological treatment selection bias. Furthermore, the fact that PALN positivity was identified on multivariable analysis as an independent predictor of DFS, doubling the risk for recurrence, is not an unexpected finding, as nodal disease is a well established prognostic factor for recurrence of PDAC.

The survival benefit of completion of the treatment pathway (surgery and chemotherapy) in patients with PDAC is well established and the sequence of chemotherapy is based on preoperative staging (neoadjuvant or adjuvant setting)[31,32]. With regards to PALN involvement, this is further supported by the results of this study as well as others on PALN disease[20,33,34]. Therefore, the comparable OS

Table 3 Risk analysis for disease-free survival

	Univariable		Multivariable	
	P value	HR (CI)	*P* value	HR (CI)
Age	0.129	0.979 (0.952-1.006)	0.023	0.964 (0.933-0.995)
Sex	0.881	0.955 (0.526-1.736)		
Preoperative CA19-9	0.773	1.000 (1.000-1.000)		
Preoperative stage	0.943	1.016 (0.656-1.573)		
Resection type	0.215	1.272 (0.869-1.862)		
Venous resection	0.739	0.899 (0.481-1.681)		
Arterial resection	0.567	0.048 (0.000-1578.950)		
pT	0.002	2.102 (1.308-3.378)	0.004	
pT1			0.265	1.726 (0.661-4.509)
pT2			0.015	3.689 (1.287-10.576)
pT3			0.002	49.543 (4.018-610.815)
pN	0.121	1.387 (0.917-2.097)		
PALN positivity	0.101	1.748 (0.896-3.410)	0.045	2.287 (1.018-5.136)
Margin status	0.032	1.927 (1.057-3.514)	0.007	2.48 (1.275-4.822)
Perineural invasion	0.103	2.084 (0.862-5.036)	0.041	2.938 (1.045-8.255)
Perivascular invasion	0.152	1.657 (0.830-3.308)		
Chemotherapy	0.047	0.509 (0.261-0.992)	0.001	0.242 (0.105-0.559)

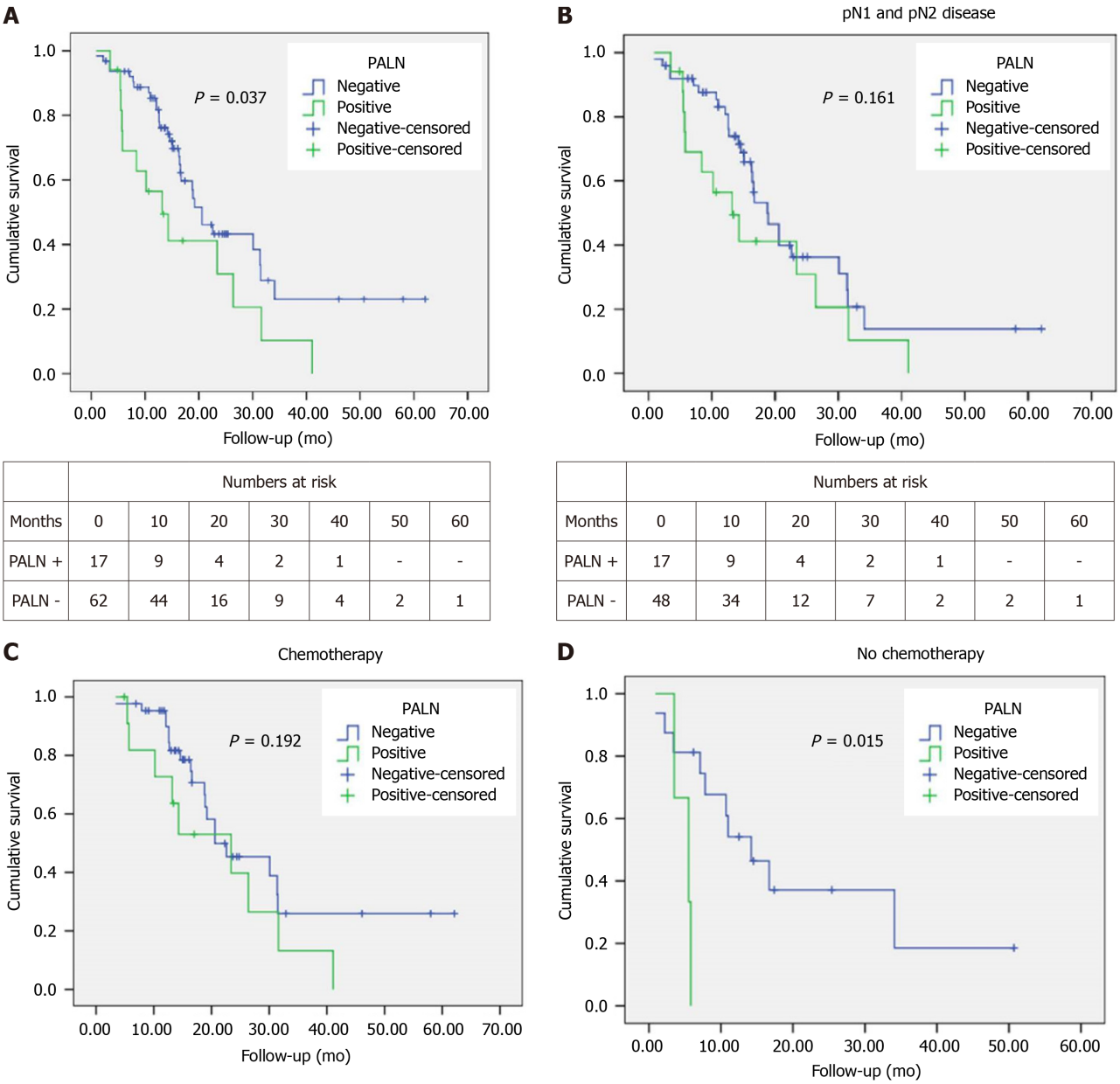
All parameters with $P < 0.200$ on univariable entered into multivariable model. HR: Hazard ratios; CI: Confidence intervals; PALN: Para-aortic lymph nodes.

and DFS after completion of the whole treatment, surgery and chemotherapy, suggest that PALN should not be considered as a contraindication for resection if identified intra-operatively. The substantially worse OS in patients who did not receive any chemotherapy, stresses the importance of considering PALN positive disease in preoperative staging as an indication for NAT. Pre-operative CA19-9 Levels have been associated with PALN+[20,23,35]. Nonetheless, preoperative staging investigations have a very low sensitivity for this in the current as well as other studies to provide the required confirmation. The sensitivity of CT and MRI has been suggested to be close to zero for PALN+[36] while ^{18}F-flurodeoxyglucose positron emission tomography (FDG-PET) was shown to have sensitivity 37%-50%[37-39]. EUS is used for staging of nodal involvement with accuracy reaching around 65%[40,41] though one small study of 21 patients with PALN+ was shown to have 95% sensitivity[42]. In our study only one case of PALN metastasis was identified on preoperative staging scans, while operative excisional sampling upstaged the diagnosis in 21% of the cases without increasing the risk of perioperative complications.

The limitations of this study include its retrospective and single centre nature, as well as the selection bias associated with intra-operative PALN sampling. Additionally, as the study covers a 10 year period with changes in the preferred systemic treatment regimens for PDAC, systemic treatment selection time bias is inevitable. The small number of PALN positive patients precluded a subgroup analysis of types and duration of NAT or adjuvant chemotherapy. Despite these limitations, the study accurately reflects the practice around PALN over the previous decade and the results clearly add to the body of evidence advocating against considering PALN involvement in the absence of evidence of distant metastases as unresectable disease and against treating these patients with palliative intent.

CONCLUSION

This study suggests that PALN sampling is safe and should be routinely performed during resection of PDAC for accurate staging, even in the absence of involvement in the pre-operative imaging. PALN involvement does not affect OS when patients complete the indicated treatment pathway (surgery and chemotherapy) and occult involvement identified intra-operatively should not be considered as a contraindication to resection. Future studies should focus on improving pre-operative diagnosis and on



	Numbers at risk						
Months	0	10	20	30	40	50	60
PALN +	17	9	4	2	1	-	-
PALN -	62	44	16	9	4	2	1

	Numbers at risk						
Months	0	10	20	30	40	50	60
PALN +	17	9	4	2	1	-	-
PALN -	48	34	12	7	2	2	1

	Numbers at risk						
Months	0	10	20	30	40	50	60
PALN +	12	8	4	2	1	-	-
PALN -	42	32	12	7	3	2	1

	Numbers at risk						
Months	0	10	20	30	40	50	
PALN +	-	-	-	-	-	-	
PALN -	16	9	3	2	1	1	

	Subgroups	Overall survival PALN+	Overall survival PALN-	*P* value
A	Total cohort	13.2 (6.531-19.869)	20.6 (16.457-24.743)	0.037
B	Nodal disease	13.2 (6.531-19.869)	18.8 (14.869-22.731)	0.161
C	Chemotherapy	23.400 (9.718-37.082)	20.6 (9.918-31.282)	0.192
D	No chemotherapy	5.50 (2.299-8.701)	14.20 (7.714-20.686)	0.015

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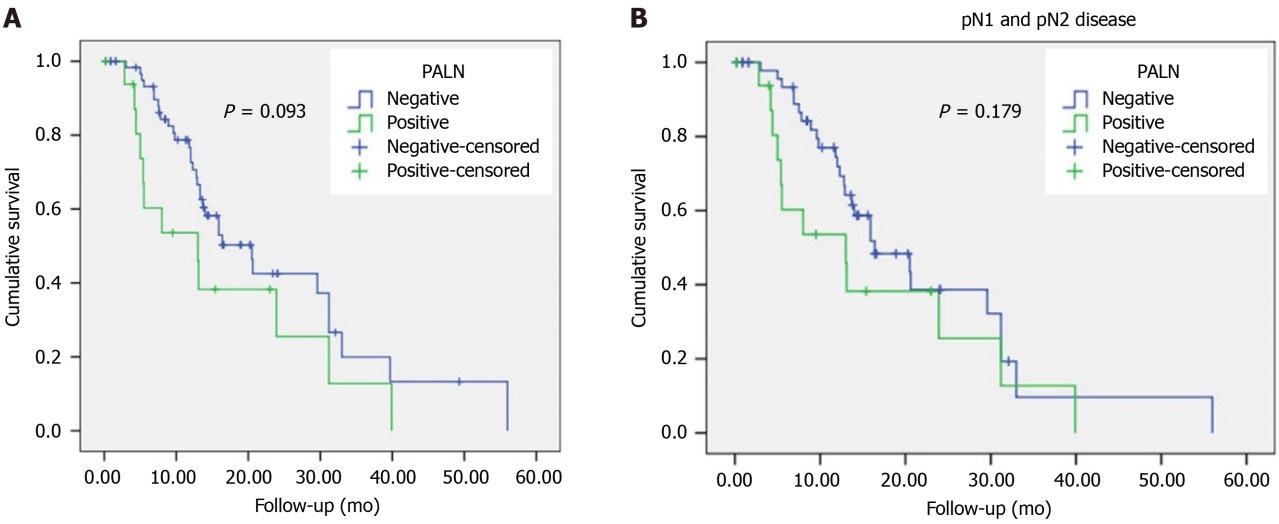
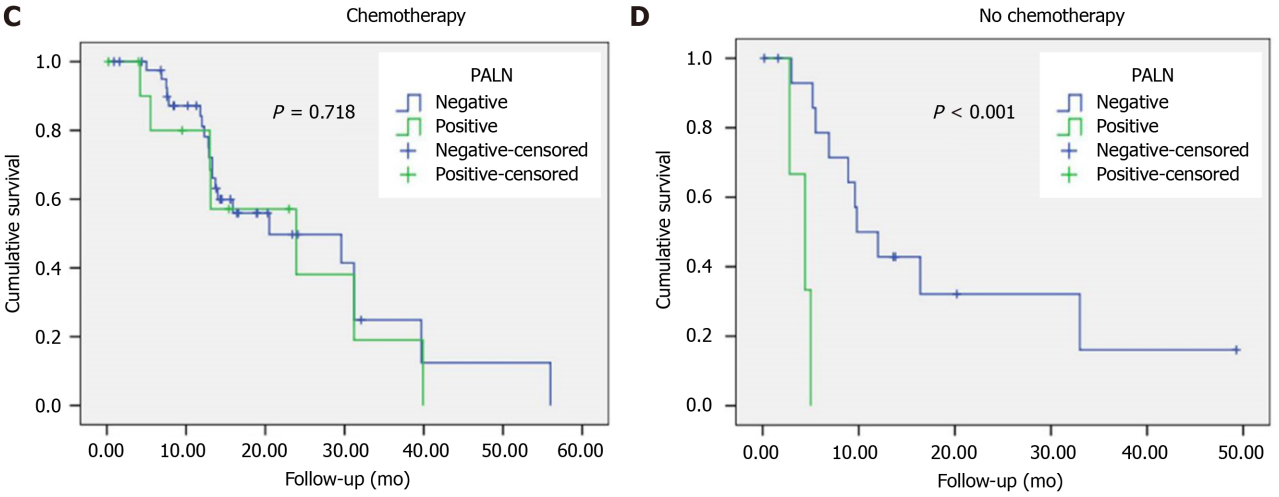
Figure 1 Kaplan Meier curves comparing overall survival in patients with para-aortic lymph nodes(+) *vs* para-aortic lymph nodes(-). A: Total cohort; B: Patients with positive nodal disease; C: Patients who received chemotherapy; D: Patients who did not receive chemo-therapy. PALN: Para-aortic lymph nodes.



	Numbers at risk					
Months	0	10	20	30	40	50
PALN +	16	7	4	2	-	-
PALN -	59	35	13	7	2	1

	Numbers at risk					
Months	0	10	20	30	40	50
PALN +	16	7	4	2	-	-
PALN -	46	27	10	5	1	1



	Numbers at risk					
Months	0	10	20	30	40	50
PALN +	11	7	4	2	-	-
PALN -	40	26	9	5	1	1

	Numbers at risk					
Months	0	10	20	30	40	50
PALN +	-	-	-	-	-	-
PALN -	15	6	3	2	1	-

	Subgroup	Disease-free survival PALN+	Disease free survival PALN-	*P* value
A	Total cohort	13.0 (4.123-21.877)	20.5 (14.135-26.865)	0.093
B	Nodal disease	13.0 (4.123-21.877)	16.4 (9.361-23.439)	0.179
C	Chemotherapy	23.9 (2.782-45.018)	20.5 (2.505-38.495)	0.718
D	No chemotherapy	4.40 (1.839-6.961)	9.80 (5.400-14.200)	< 0.001

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Figure 2 Kaplan Meier curves comparing disease-free survival in patients with para-aortic lymph nodes(+) *vs* para-aortic lymph nodes(-). A: Total cohort b; B: Patients with positive nodal disease; C: Patients who received chemotherapy; D: Patients who did not receive chemotherapy. PALN: Para-aortic lymph nodes.

the value of NAT for these cases.

ARTICLE HIGHLIGHTS

Research background

Pancreatic ductal adenocarcinoma (PDAC) presents as localised disease for only a small subset of patients for whom only 20% are eligible for resection with 5-year survival of 6.8%. Nodal status is amongst the most important prognostic indicators. Para-aortic lymph nodes found in the aortocaval groove (PALN) are staged as distant metastatic (M1) disease and are found in 14%-18% of pancreatic head/uncinate PDAC at resection. Various studies have alluded to PALN metastases being associated with poor prognosis, whereas others have failed to replicate this effect and a meta-analysis has only concluded the need for intra-operative assessment of PALN. A consensus statement from the International Study Group for Pancreatic Surgery supported standard lymphadenectomy for pancreatic resections, which does not include PALN.

Research motivation

Currently, whether intra-operative assessment of PALN should be undertaken or whether there is sufficient evidence that resection should be abandoned depends on surgeon or unit policy.

Research objectives

The aim of this study was to determine the prognostic significance of PALN metastases on the oncological outcomes after pancreatic resections for PDAC.

Research methods

This is a retrospective cohort study of data from a prospectively maintained database on consecutive patients undergoing pancreatectomies for PDAC where PALN was sampled between 2011 and 2020 in a tertiary specialist centre. The study was conducted in line with STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines. Staging of the tumours was based on the NCCN staging criteria. PALN were sampled from the infra-renal, aortacaval lymph nodes and more specifically from the level of the third part of the duodenum to the angle of the left renal vein (station 16). PALN sampling was performed at the discretion of the operating surgeon. Over the last 3 years of the study 3 surgeons sampled PALN routinely, accounting for 36% of the cases in the study. Follow-up of patients was determined from time of diagnosis until disease recurrence or death. OS was defined as the time from diagnosis to death or last follow-up and disease free survival as the time from resection to diagnosis of disease recurrence.

The cohort characteristics are presented with standard descriptive statistical analysis. One way Anova, Chi-Square and Mann-Whitney *U* tests were used as appropriate for statistical comparisons with statistical significance set at $P < 0.05$. Exact statistics were used for all tests to account for small sample size. Survival analysis was performed with the Kaplan-Meier method and log rank test was used to compare survival curves. Univariable and multivariable time to event analyses were performed using the Cox proportional hazard model to determine risk factors for median OS and disease-free survival (DFS). Variables were subjected to a univariable analysis first and those with $P < 0.2$ were introduced into a multivariable model. Hazard ratios and associated 95% confidence intervals were calculated. A two-tailed *P* value < 0.05 was considered statistically significant. All statistical analyses were performed using the software package SPSS Statistics for Windows (version 25.0; SPSS Inc., Chicago, IL, United States).

Research results

81 cases had PALN sampling and 17 (21%) were positive. Pathological N stage was significantly different between PALN+ and PALN- patients ($P = 0.005$), while no difference was observed in any of the other characteristics. Preoperative imaging diagnosed PALN positivity in one case. OS and DFS were comparable between PALN+ and PALN- patients with lymph node positive disease (OS: 13.2 mo *vs* 18.8 mo, $P = 0.161$; DFS: 13 mo *vs* 16.4 mo, $P = 0.179$). No difference in OS or DFS was identified between PALN positive and negative patients when they received chemotherapy either in the neoadjuvant or in the adjuvant setting (OS: 23.4 mo *vs* 20.6 mo, $P = 0.192$; DFS: 23.9 mo *vs* 20.5 mo, $P = 0.718$). On the contrary, when patients did not receive chemotherapy, PALN disease had substantially shorter OS (5.5 mo *vs* 14.2 mo; $P = 0.015$) and DFS (4.4 mo *vs* 9.8 mo; $P < 0.001$). PALN involvement was not identified as an independent predictor for OS after multivariable analysis, while it was for DFS doubling the risk of recurrence.

Research conclusions

This study suggests that PALN sampling is safe and should be routinely performed during resection of PDAC for accurate staging, even in the absence of involvement in the pre-operative imaging. PALN

involvement does not affect OS when patients complete the indicated treatment pathway (surgery and chemotherapy) and occult involvement identified intra-operatively should not be considered as a contraindication to resection.

Research perspectives

Future studies should focus on improving pre-operative diagnosis and on the value of NAT for these cases.

FOOTNOTES

Author contributions: Pande R, Chughtai S, Ahuja M, Brown R, Chatzizacharias NA developed this protocol/project, collected data and performed the research; Pande R, Chughtai S, Ahuja M, and Chatzizacharias NA contributed analytical tools; Pande R, Chughtai S, Ahuja M, Brown R, Chatzizacharias NA, Bartlett DC, Marudanayagam R, Mirza D, Isaac J, Sutcliffe RP, and Roberts KJ analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Prognostic factors for patients with mass-forming intrahepatic cholangiocarcinoma: A case series of 68 patients

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Abstract

BACKGROUND

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer in humans after hepatocellular carcinoma and a rare epithelial malignancy that results in a poor prognosis. According to the Liver Cancer Study Group of Japan classification, ICC can be divided into three types: Mass-forming (MF) type, periductal-infiltrating (PI) type, and intraductal-growth type. The MF type is the most common, accounting for 57.1-83.6% of ICCs. Nevertheless, little is known about the epidemiology and treatment of MF ICC.

AIM

To examine the prognostic factors for patients with MF ICC.

METHODS

We carried out a retrospective analysis of consecutive patients with MF ICC treated at the Faculty of Hepato-Pancreato-Biliary Surgery of Chinese PLA General Hospital between January 2008 and December 2018. According to the treatment received, the patients were divided into either a resection group or an exploration group.

RESULTS

The pooled 1-, 3-, and 5-year survival rates in the 68 patients with MF ICC were 66.5%, 36.3%, and 9.3%, respectively. Univariate analysis revealed that surgical resection ($P < 0.001$), nodal metastasis ($P < 0.001$), tumor location ($P = 0.039$), vascular invasion ($P < 0.001$), ascites ($P < 0.001$), and differentiation ($P = 0.009$) were significantly associated with the prognosis and survival of MF ICC.

Multivariate analysis revealed that ascites (hazard ratio [HR] = 5.6, 95% confidence interval [CI]: 1.6-18.9, P = 0.006) and vascular invasion (HR = 2.5, 95%CI: 1.0-6.1, P = 0.045) were independent risk factors for MF ICC. The pooled 1-, 3-, and 5-year survival rates in the 19 patients of the exploration group were 5.3%, 5.3%, and 0, respectively. Among the 49 patients who underwent surgical resection, the pooled 1-, 3-, and 5-year survival rates were 93.5%, 49.7%, and 14.4%, respectively. Univariate and multivariate analyses revealed that vascular invasion (HR = 3.1, 95%CI: 1.2-8.5, P = 0.024) and nodal metastasis (HR = 3.2, 95%CI: 1.4-7.6, P = 0.008) were independent prognostic risk factors for surgical resection patients.

CONCLUSION

The prognosis of MF ICC patients is dismal, especially those with ascites or vascular invasion. Surgical resection is a key factor in improving overall survival in patients with MF ICC, and vascular invasion and lymph node metastasis affect the efficacy of surgical resection.

Key Words: Intrahepatic cholangiocarcinoma; Mass-forming; Treatment; Prognosis

Core Tip: This is a single-center, large-scale retrospective study on mass-forming intrahepatic cholangiocarcinoma (MF ICC) to examine the prognostic factors for MF ICC and improve the outcomes. The study found the patients with MF ICC with ascites and vascular invasion have a poor prognosis. Surgical resection is a key factor in improving overall survival in patients with MF ICC, and patients with vascular invasion and lymph node metastasis have poor surgical results.

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INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) refers to a malignant tumor originating from the branching epithelial cells of the intrahepatic secondary bile duct and above, with a poor prognosis[1-2]. It has been reported that both the morbidity and mortality have gradually increased in recent years[1-4]. Surgical resection is currently the only potentially curative treatment for ICC[3-5], but the cure rates and survival of patients with ICC remain very low because of the high aggressiveness of the disease[6-7]. It has been reported that many factors influence the prognosis of surgical resection[8-11].

According to the Liver Cancer Study Group of Japan classification, ICC can be divided into three types: Mass-forming (MF) type, periductal-infiltrating (PI) type, and intraductal-growth (IG) type[11]. Among them, the MF type is the most common, accounting for 57.1-83.6% of ICCs[12-14].

Nevertheless, little is known about the epidemiology and treatment of MF ICC. Therefore, the aim of the present retrospective study was to analyze prognostic factors for patients with MF ICC.

MATERIALS AND METHODS

Study design

This was a retrospective analysis of consecutive patients with MF ICC treated at the Faculty of Hepato-Pancreato-Biliary Surgery of Chinese PLA General Hospital between January 2008 and December 2018. The study was approved by the Medical Ethics Committee of the Chinese PLA General Hospital.

Patients

The inclusion criteria were: (1) ≥ 18 years of age; (2) Hospitalized patients; (3) Confirmed as MF ICC by histopathological examination; and (4) No prior history of any malignancy. The exclusion criteria were: (1) Incomplete data; (2) Metastasis; (3) Hilar cholangiocarcinoma; (4) Cystadenocarcinoma; (5) PI ICC; or (6) IG ICC. The patients were divided into either a resection group or an exploration group according to the received treatment.

Treatments

All cases were discussed in tumor boards before any treatment. The indications for radical hepatectomy were: (1) No distant metastases preoperatively; (2) Preoperative imaging suggesting that the tumors could be completely resected, including eventual satellite lesions; (3) Child-Pugh grade A or B; and (4) Good cardiopulmonary function and no surgical or anesthetic contraindications.

The surgical principle was to achieve R0 resection. The pattern of hepatectomy was based on residual liver function, tumour size, and tumour-vessel relationship. Anatomic resection (AR) was the priority if feasible, while non-AR (NAR) was more frequently applied if the tumour was adjacent to major vascular structure. Surgical exploration was only performed in patients with extensive metastases in the liver, abdominal wall, and omentum. Lymph node dissection of the hepatoduodenal ligament was performed for patients with lymphadenectasis found by imaging or intraoperatively. Tumor and lymph node biopsies were performed in patients undergoing surgical exploration.

Data collection

General data and results of auxiliary examinations were recorded, including carbohydrate antigen 19-9 (CA19-9), hepatitis B virus (HBV), glutamic pyruvic transaminase (ALT), glutamic oxaloacetic transaminase, alkaline phosphatase, gamma-glutamyltransferase, and total bilirubin tests.

Follow-up

All patients were followed after surgery. Follow-up visits were performed once every 3 mo during the first year, once every 6 mo during the second and third years, and once a year later. Items checked during the follow-up visits included routine laboratory tests, tumor markers, chest roentgenogram, abdominal ultrasound, CT, and/or MRI examinations. The follow-up deadline was December 31, 2019, and the follow-up duration ranged from 1 to 82 mo, with a median duration of 13 mo.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics ver. 21.0 (IBM Co, Armonk, NY, United States). Continuous data meeting a normal distribution are presented as the mean ± SD. Differences between the two groups were determined using independent sample *t* test. Continuous data not meeting a non-normal distribution are presented as the median (range). The non-parametric Mann-Whitney *U* test was used to determine the differences between the two groups. The chi-square test or the Fisher's exact test was used for categorical data. Univariate Cox proportional hazard regression model analysis was used for survival data. Variables with $P < 0.05$ in univariate analysis were included in the multivariate Cox proportional hazard regression model. Kaplan-Meier analysis was used to calculate the survival rate. Log-rank method was used for group-wise comparison. Two-sided *P* values < 0.05 were considered statistically significant.

RESULTS

Characteristics of the patients

Among the 68 patients, 50 were male and 18 female, ranging from 24 to 74 years with a median age of 54. There were 40 patients with tumors in the right lobe of the liver and 28 with tumors in the left lobe of the liver. The median tumor diameter was 7.0 cm (range, 2.2-14.0). Twenty-eight (41.2%) patients had elevated CA 19-9 levels, five of whom had CA 19-9 > 1000 U/mL. Sixteen and four had concomitant hepatitis B and C viral infections, respectively. Fourteen cases were accompanied with ascites. The characteristics were similar between the two groups, except that the exploration group had higher levels of ALT ($P = 0.031$), higher frequencies of ascites ($P < 0.001$), nodal metastasis ($P < 0.001$), and vascular invasion ($P < 0.001$), and the tumors were mostly located in the left lobe ($P < 0.001$) (Table 1).

Survival

All patients were discharged successfully from the hospital. During follow-up, 48 patients died and 20 survived. Survival time ranged from 1 to 82 mo (median, 24 mo). The pooled 1-, 3-, and 5-year survival rates in the 68 patients with MF ICC were 66.5%, 36.3%, and 9.3%, respectively (Table 2). Univariate analysis revealed that surgical resection ($P < 0.001$), nodal metastasis ($P < 0.001$), tumor location ($P = 0.039$), vascular invasion ($P < 0.001$), ascites ($P < 0.001$), and differentiation ($P = 0.009$) were significantly associated with the prognosis and survival of MF ICC (Table 3). Multivariate analysis revealed that ascites (hazard ratio [HR] = 5.6, 95% confidence interval [CI]: 1.6-18.9, $P = 0.006$) and vascular invasion (HR = 2.5, 95%CI: 1.0-6.1, $P = 0.045$) were independent risk factors for MF ICC (Table 3).

Subgroup analysis

The pooled 1-, 3-, and 5-year survival rates in the 19 patients of the exploration group were 5.3%, 5.3%, and 0, respectively. Correspondingly, the pooled 1-, 3-, and 5-year survival rates in the 49 patients of the surgical resection group were 93.5%, 49.7%, and 14.4%, respectively. The survival rates of the resection

Table 1 Baseline characteristics of the patients

Variable	All (*n* = 68)	Surgery (*n* = 49)	Exploration (*n* = 19)	*P* value
Age (yr)	54.3 ± 1.4	52.6 ± 1.7	58.6 ± 2.2	0.435
Gender, Male	50 (73.5%)	34 (69.4%)	16 (84.2%)	0.924
HBV infection	16 (23.5%)	13(26.5%)	3 (15.8%)	0.997
HCV infection	4 (5.9%)	2 (4.1%)	2 (10.5%)	0.314
Ascites	14 (20.6%)	1 (2.0%)	13(68.4%)	< 0.001
Tumor size(cm)	6.9 ± 0.3	6.8 ± 0.4	7.63 ± 0.5	0.495
ALT (IU/L)(median)	1.8-92.1 (26)	1.8-92.1 (24.9)	23-76.3 (32.1)	0.031
AST (IU/L) (median)	9.6-74.2 (29)	9.6-74.2 (27.3)	18.2-61.9 (31)	0.142
ALP (U/L) (median)	13.4-280.5 (82.8)	13.4-280.5 (81.4)	45.3-109.9 (85.4)	0.149
GGT (U/L) (median)	11-325.6 (42.4)	11-325.6 (41.1)	28.9-104.7 (45.8)	0.512
TBIL (mg/dL) (median)	4.2-140.0 (18)	4.2-140 (18.1)	4.2-42.6 (17.8)	0.707
CA19-9 (U/mL) (median)	21-2000 (34.5)	21-1891 (36)	22-2000 (30)	0.104
Differentiation				0.536
Poor	30 (44.1%)	20 (40.8%)	10 (40.052.6	
Poor-moderate	24 (35.3%)	19 (38.8%)	5 (26.3%)	
Moderate	14 (20.6%)	10 (20.4%)	4 (21.1%)	
Nodal metastasis	33 (48.5%)	14 (28.6%)	19 (100.0%)	< 0.001
Tumor location				< 0.001
Left lobe	28 (41.2%)	11 (22.4%)	17 (89.5%)	
Right lobe	40 (58.8%)	38 (77.6%)	2 (10.5%)	
Vascular invasion	31 (45.6%)	13 (26.5%)	19 (100.0%)	< 0.001

HBV: Hepatitis B virus; HCV: Hepatitis C virus; ALT: Glutamic pyruvic transaminase; AST: Glutamic oxaloacetic transaminase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyltransferase; TBIL: Total bilirubin; CA19-9: Carbohydrate antigen 19-9.

Table 2 Overall survival of the patients with mass-forming intrahepatic cholangiocarcinoma

	All (*n* = 68)	Surgery (*n* = 49)	Exploration (*n* = 19)	*P* value
Follow-up (mo)	1-82	3-82	1-57	
Survival				< 0.001
1 yr	66.5%	93.5%	5.3%	
3 yr	36.3%	49.7%	5.3%	
5 yr	9.3%	14.4%	0.00%	

group were significantly better than those of the exploration group ($P < 0.001$) (Figure 1). Table 4 presents the univariate and multivariate analyses of the factors associated with survival in the surgery group. Unlike the whole group of patients, univariate and multivariate analyses revealed that vascular invasion (HR = 3.1, 95%CI: 1.2-8.5, $P = 0.024$) and nodal metastasis (HR = 3.2, 95%CI: 1.4-7.6, $P = 0.008$) were independent prognostic risk factors for surgical resection patients.

DISCUSSION

Little is known about the epidemiology and treatment of MF ICC. Therefore, this study aimed to examine the prognostic factors for patients with MF ICC. The results showed that the prognosis of MF ICC patients is dismal, especially those with ascites or vascular invasion. Resectable patients have a

Table 3 Univariate and multivariate analyses of clinical and pathological factors for overall survival of 68 patients with mass-forming intrahepatic cholangiocarcinoma

Variable	Patients (*n*)	1 yr (%)	3 yr (%)	5 yr (%)	*P* value	HR	95%CI	*P* value
Age (yr)					0.278			
≤ 54	35	71.8	39.8	13.5				
>54	33	61.4	32.7	6.1				
Gender					0.292			
Male	50	62.2	34.2	9.7				
Female	18	79.6	43.0	10.8				
HBV infection					0.327			
Yes	16	74.0	24.7	0				
No	52	64.0	40.0	13.3				
Ascites					< 0.001	5.553	1.628-18.941	0.006
Present	14	0	0	0				
Absent	54	84.0	45.8	11.8				
Tumor size (cm)					0.230			
≤ 7	41	64,3	49.0	10.1				
> 7	27	70.2	12.5	6.3				
CA 19-9 (IU/mL)					0.881			
≤ 27	40	62.7	36.6	7.8				
> 27	28	72.3	34.8	15.5				
Differentiation					0.009	0.769	0.466-1.270	0.305
Poor	30	56.4	21.7	0				
Poor-moderate	24	78.5	62.4	12.8				
Moderate	14	66.1	23.6	23.6				
Nodal metastasis					< 0.001	2.294	0.983-5.353	0.055
Yes	35	97.0	64.0	21.7				
No	33	37.8	9.1	0				
Tumor location					0.032	2.186	0.801-5.965	0.127
Left lobe	28	40.9	28.6	0				
Right lobe	40	86.8	43.9	12.4				
Vascular invasion					< 0.001	2.501	1.020-6.131	0.045
Yes	31	35.5	9.7	0				
No	37	97.1	66.3	22.2				
Group					< 0.001	1.619	0.351-7.469	0.537
Resection	49	93.5	49.7	14.4				
Exploration	19	5.3	5.3	0				

HBV: Hepatitis B virus; CA19-9: Carbohydrate antigen 19-9.

better prognosis, and vascular invasion and lymph node metastasis affected the efficacy of surgical resection. It is reported that the morbidity of ICC in males is 40-63.5%[14,16-18], and the age at diagnosis is mainly in the 6th decade of life, but ranges from 21 to 86 years[17-20]. Among the 68 cases in the current study, 50 were males, accounting for 73.5% of the patients, which was higher than that reported in the literature. The age of onset was 24-74 years with a median age of 54 years, which was consistent with literature reports but could still be a little younger than that in the literature. This discrepancy

Table 4 Univariate and multivariate analyses of clinical and pathological factors for overall survival of patients in the surgery group

Variable	Patients (*n*)	1 yr (%)	3 yr (%)	5 yr (%)	*P* value	HR	95%CI	*P* value
Age (yr)					0.633			
≤ 54	27	92.3	48.6	21.2				
> 54	22	95.0	50.7	9.5				
Gender					0.441			
Male	34	90.9	48.2	18.1				
Female	15	100.0	54.0	13.5				
HBV infection					0.063			
Yes	13	92.3	30.8	0				
No	36	94.0	57.1	22.5				
Ascites					0.836			
Present	1	0	0	0				
Absent	48	93.4	49.6	14.4				
Tumor size (cm)					0.044	1.273	0.485-3.339	0.624
≤ 7	28	92.9	69.6	16.9				
> 7	21	94.1	33.6	8.4				
CA 19-9 (IU/mL)					0.571			
≤ 27	26	96.0	53.9	12.9				
> 27	23	90.6	43.7	19.4				
Differentiation					0.061			
Poor	20	89.7	34.5	0				
Poor-moderate	19	94.7	73.9	23.9				
Moderate	10	100.0	35.7	35.7				
Nodal metastasis					0.001	3.221	1.364-7.610	0.008
Yes	35	97.0	64.0	21.7				
No	14	85.7	11.9	0				
Tumor location					0.545			
Left lobe	11	100.0	66.7	33.3				
Right lobe	38	91.4	46.3	13.0				
Vascular invasion					< 0.001	3.148	1.160-8.544	0.024
Yes	12	83.3	16.7	0				
No	37	97.1	66.3	22.2				
Pattern of liver resection					0.773			
AR resection	23	96.0	50.6	11.4				
NAR resection	25	95.5	51.7	9.7				
Resection margin(cm)					0.361			
≤ 1	21	95.2	40.3	16.1				
> 1	27	96.0	57.3	14.6				

CA19-9: Carbohydrate antigen 19-9.

could be due to a number of reasons including genetics, environment, and methods of detection.

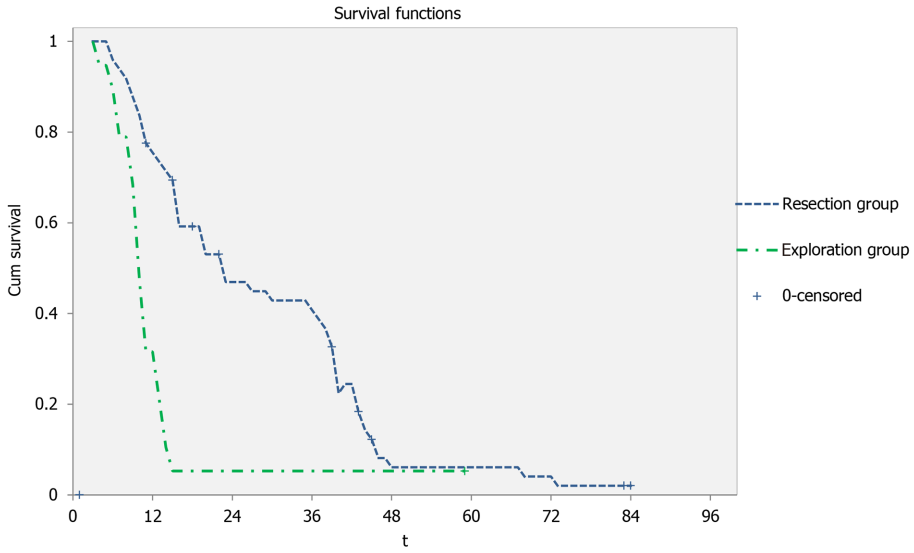

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Figure 1 The resection group (blue line) *vs* the exploration group (green dashed line) (*P* < 0.001).

Many previous studies showed that HBV and hepatitis C virus (HCV) infections were associated with the occurrence of ICC. It has been reported that the rate of HBV infection ranges from 3.9% to 28.8% in ICC patients, and the rate of HCV infection ranges from 0.6% to 16.5%[20-22]. In the present study, the infection rates of HBV and HCV were 23.5% and 5.9%, respectively, which were similar to those reported in the literature. Currently, the relationship between HBV and ICC prognosis is still controversial. Pan *et al*[23] reported that the 1- and 3-year overall survival rates of patients with HBV infection was higher than that of patients without (67.6% and 47.2% *vs* 43.8% and 18.4%, respectively). Ahn *et al*[24] reported that HBV infection itself was not regarded as an independent prognostic factor. Tao *et al*[25] described that 1-, 3-, and 5-year cumulative survival rates of HBsAg-positive ICC patients are significantly lower than those of HBV-negative ICC patients. The present study found that there was no significant difference in survival between patients with HBV infection and those without. Nevertheless, among the 68 patients, the 5-year survival was 0 in patients with HBV infection, while it was 13.3% in those without HBV infection. In the surgery group, the 5-year survival was 0 in patients with HBV infection, while it was 22.5% in patients without HBV infection. These rates raise the question of the impact of HBV infection on the survival of ICC patients and further study is needed to investigate this point.

Surgical resection is the most important factor for long-term survival of ICC patients. In this study, the 5-year survival rate was 14.4% for patients in the resection group, while it was 0% for patients in the exploration group. The surgical approach required tumor-free surgical margins, *i.e.*, R0 resection. The literature has reported that the R0 resection rate of ICC ranges from 24.1% to 92.8%[10,26], but the relationship between margins and survival is still controversial in patients with ICC. Bagante *et al*[13] deemed that patients with positive margins had a poor prognosis. Tang *et al*[16] reported that the prognosis in patients with margins > 1 cm was better than that of patients with margins ≤ 1 cm, while Bartsch *et al*[10] showed that the margin width was not related to prognosis. Other studies reported that no significant difference in survival was observed between patients with R0 resection and patients with R1 resection[7,27,28]. In the present study, the resection rate was 72.1% (49/68), and all resections were R0. Whether the margins were > 1 cm or not was not related to survival. Furthermore, there was no significant difference in 1-, 3-, and 5-year survival rates between AR and NAR resection (96.0%, 50.6%, and 11.4% *vs* 95.5%, 51.7%, and 9.7%, respectively). These results suggest that the objective is to achieve R0 no mater using AR or NAR resection. A number of studies have indicated that patients with positive lymph nodes have a poor prognosis[11,13,17,18]. Bagante *et al*[13] showed that the 5-year survival rate in patients with positive lymph nodes was 9.4%, while in patients with negative lymph nodes, it was 45.5%. In the present study, the 5-year survival rate in patients of the resection group and with positive lymph nodes was 0%, compared with 21.7%, in patients with negative lymph nodes. Lymph node metastasis could be an important prognostic factor for ICC. Nevertheless, there is still no definite conclusion as to whether resection of positive lymph nodes can extend survival or not[17,18,29,30].

Previous studies showed that vascular invasion was an important factor affecting the prognosis of ICC[27,31,32] . Our results revealed that the 3- and 5-year survival rates in the resection group with vascular invasion were 16.7% and 0%, respectively, compared with 66.3% and 22.2%, respectively, in patients without. The survival rate in patients without vascular invasion was higher than that of patients with vascular invasion. The multivariate analysis revealed that vascular invasion was an independent prognostic factor in patients with ICC.

In the present study, there was no significant difference in survival for left and right lobe tumors in the resection group. However, in the whole group of 68 patients, the resection rate of tumor in the right lobe was 95.0% (38/40), and that in the left lobe was 39.3% (11/28), indicating that the resection rate of tumors in the left lobe was low. Survival analysis also suggested that the survival rate was low for patients with tumors in the left lobe, which may be because tumors in the left lobe are more prone to metastasis through the ligament of the liver and stomach. In addition, we also noted that tumors in the left lobe could metastasize from the round ligament of the liver and sickle ligament of the liver to the abdominal wall. Nevertheless, further study is necessary for confirmation.

Data revealed that 25%-40% of the tumors with metastasis could not be dissected by surgical exploration for ICC patients whose tumors are considered to be removable before surgery. Therefore, laparoscopic examination should be performed before operation for patients with multicentric lesions, high CA19-9, suspected vascular infiltration, or peritoneal carcinomatosis[4]. In the present study, 19 patients (27.9%) underwent surgical exploration. Among the 40 cases with tumors in the right lobe of the liver, 5% (n = 2) underwent surgical exploration, while 60.7% (n = 17) underwent surgical exploration among the 28 patients with tumors in the left lobe of the liver, suggesting that the exploration rate was high for tumors in the left lobe of the liver. Among the 14 cases with preoperative ascites, there were 13 cases with abdominal metastasis and peritoneal metastasis. Therefore, we believe that routine laparoscopic exploration should be performed before operation for patients with tumors in the left lobe of the liver or with ascites in order to avoid meaningless laparotomy.

The present study is not without limitations. This was a retrospective, single-center study with a small sample size. In addition, it was limited to Chinese patients. Thus, the results should be validated using multicenter studies.

CONCLUSION

The prognosis of MF ICC patients is dismal, especially those with ascites or vascular invasion. Surgical resection is a key factor in improving overall survival in patients with MF ICC, and vascular invasion and lymph node metastasis affect the efficacy of surgical resection.

ARTICLE HIGHLIGHTS

Research background

The mass-forming (MF) type is the most common intrahepatic cholangiocarcinoma (ICC), accounting for 57.1%-83.6% of ICCs. Nevertheless, little is known about the epidemiology and treatment of MF ICC.

Research motivation

To improve the outcomes of ICC.

Research objectives

To examine the prognostic factors for patients with MF ICC.

Research methods

We carried out a retrospective analysis of consecutive patients with MF ICC. The patients were divided into either a resection group or an exploration group according to the treatment received.

Research results

The pooled 1-, 3-, and 5-year survival rates in the 68 patients with MF ICC were 66.5%, 36.3%, and 9.3%, respectively. Univariate analysis revealed that surgical resection (P < 0.001), nodal metastasis (P < 0.001), tumor location (P = 0.039), vascular invasion (P < 0.001), ascites (P < 0.001), and differentiation (P = 0.009) were significantly associated with the prognosis and survival of MF ICC. Multivariate analysis revealed that ascites (hazard ratio [HR] = 5.6, 95% confidence interval [CI]: 1.6-18.9, P = 0.006) and vascular invasion (HR = 2.5, 95%CI: 1.0-6.1, P = 0.045) were independent risk factors for MF ICC. The pooled 1-, 3-, and 5-year survival rates in the 19 patients of the exploration group were 5.3%, 5.3%, and 0, respectively. Among the 49 patients who underwent surgical resection, the pooled 1-, 3-, and 5-year survival rates were 93.5%, 49.7%, and 14.4%, respectively. Univariate and multivariate analyses revealed that vascular invasion (HR = 3.1, 95%CI: 1.2-8.5, P = 0.024) and nodal metastasis (HR = 3.2, 95%CI: 1.4-7.6, P = 0.008) were independent prognostic risk factors for surgical resection patients.

Research conclusions

The prognosis of MF ICC patients is dismal, especially those with ascites or vascular invasion. Surgical resection is a key factor in improving overall survival in patients with MF ICC, and vascular invasion

and lymph node metastasis affect the efficacy of surgical resection.

Research perspectives

Surgical resection is a key factor in improving overall survival in patients with MF ICC, and vascular invasion and lymph node metastasis affect the efficacy of surgical resection.

FOOTNOTES

Author contributions: Zhao XQ is the guarantor of integrity of the entire study, carried out the study design, defined the intellectual content, participated in the literature search, and reviewed the manuscript; Feng J and Liang B performed the research, wrote the first draft, and analyzed the data; Feng J and Liang B should be regarded as co-first authors; Zhang HY carried out the clinical studies and acquired the data; Liu Z and Jiang K carried out the clinical studies; all authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Short and long-term outcomes between laparoscopic and open total gastrectomy for advanced gastric cancer after neoadjuvant chemotherapy

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Abstract

BACKGROUND

Neoadjuvant chemotherapy (NACT) combined with surgery is regarded as an effective treatment for advanced gastric cancer (AGC). Laparoscopic surgery represents the mainstream of minimally invasive surgery. Currently, surgeons focus more on surgical safety and oncological outcomes of laparoscopic gastrectomy after NACT. Thus, we sought to evaluate short- and long-term outcomes between laparoscopic total gastrectomy (LTG) and open total gastrectomy (OTG) after NACT.

AIM

To compare the short and long-term outcomes between LTG and OTG for AGC after NACT.

METHODS

We retrospectively collected the clinicopathological data of 136 patients who accepted gastrectomy after NACT from June 2012 to June 2019, including 61 patients who underwent LTG and 75 who underwent OTG. Clinicopathological characteristics between the LTG and OTG groups showed no significant difference. SPSS 26.0, R software, and GraphPad PRISM 8.0 were used to perform

statistical analyses.

RESULTS

Of the 136 patients included, eight acquired pathological complete response, and the objective response rate was 47.8% (65/136). The LTG group had longer operation time (P = 0.015), less blood loss (P = 0.003), shorter days to first flatus (P < 0.001), and shorter postoperative hospitalization days (P < 0.001). LTG spent more surgical cost than OTG (P < 0.001), while total hospitalized cost of LTG was less than OTG (P < 0.001). 21 (28.0%) patients in the OTG group and 14 (23.0%) in the LTG group had 30-d postoperative complications, but there was no significant difference between the two groups (P = 0.503). The 3-year overall survival (OS) rate was 60.6% and 64.6% in the LTG and OTG groups, respectively [hazard ratio (HR) = 0.859, 95% confidence interval (CI): 0.522-1.412, P = 0.546], while the 3-year disease-free survival (DFS) rate was 54.5% and 51.8% in the LTG and OTG group, respectively (HR = 0.947, 95%CI: 0.582-1.539, P = 0.823). Multivariate cox analysis showed that body mass index and pTNM stage were independent risk factors for OS while vascular invasion and pTNM stage were independent risk factors for DFS (P < 0.05).

CONCLUSION

After NACT, LTG shows comparable 30-d postoperative morbidity as well as 3-year OS and DFS rate to OTG. We recommend that experienced surgeons select LTG other than OTG for proper AGC patients after NACT.

Key Words: Neoadjuvant chemotherapy; Gastric cancer; Laparoscope; Total gastrectomy; Morbidity; Survival

Core Tip: Neoadjuvant chemotherapy (NACT), defined as chemotherapy before surgery, is currently a hot research topic of perioperative therapy for advanced gastric cancer. In this study, we focused on the short- and long-term outcomes between laparoscopic total gastrectomy (LTG) and open total gastrectomy (OTG) after NACT. We found that the LTG group had longer operation time, less blood loss, shorter time to first flatus, and shorter postoperative hospitalization days. LTG showed comparable 30-d postoperative morbidity as well as 3-year overall survival and disease-free survival rate to OTG. Based on our results, we recommend that experienced surgeons select LTG for proper patients after NACT.

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INTRODUCTION

Gastric cancer (GC) is the fifth most prevalent malignant tumor and its tumor-related death ranks fourth according to the updated database of GLOBOCAN in 2020[1]. In China, it is the second most lethal tumor[2]. Perioperative integrated therapy is gradually taken into account in the treatment of GC. Neoadjuvant chemotherapy (NACT), as a crucial part of integrated therapy, is currently a hot research topic. Unlike postoperative chemotherapy, NACT puts chemotherapy prior to surgery, which brings advantages as follows: (1) More possibility of reducing tumor stages and increasing R0 resection rate[3]; (2) Better tolerance to chemotherapy before surgery; (3) Identical surgical safety compared with surgery-first therapy[4,5]; (4) High complete rate of total chemotherapy; and (5) Potential survival benefit relative to other interventional treatments. After MAGIC study[6] first proved the surgical safety and long-term survival benefit of perioperative chemotherapy, more prospective randomized clinical trials like FLOT4[7], RESOLVE[8], and RESONANCE[9] sprung up and acquired the initial conclusion that NACT showed superiority in terms of pathological complete response (pCR) rate and long-term survival. This contributed to its further clinical utilization.

Laparoscopy is a representative of minimally invasive surgery techniques in the 21st century. Since Kitano *et al*[10] reported the first laparoscopic gastrectomy in 1994, laparoscopy has emerged as a standard surgical approach especially for distal gastrectomy proved by several high-quality trials[11,12].

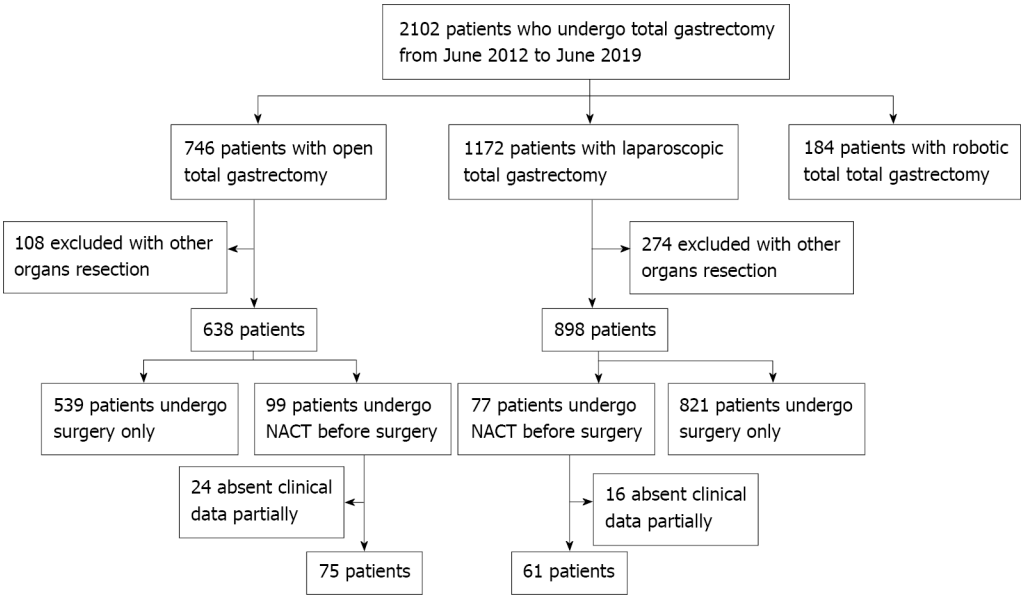

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Figure 1 Flow diagram of patient enrollment. NACT: Neoadjuvant chemotherapy.

Laparoscopic total gastrectomy (LTG) was carried out relatively late due to its complex surgical procedure and anastomotic technical difficulty. Although LTG has been proved safer than open total gastrectomy (OTG) for clinical stage I GC by CLASS-02 study[13], the option of LTG is still conservative in the treatment of advanced GC (AGC). At present, a multitude of retrospective articles conducted in experienced medical centers demonstrated comparable short- and long-term outcomes between LTG and OTG[14,15], but prospective studies have not acquired final results.

Currently, surgical safety and oncological outcomes after NACT have gradually attracted surgeons' attention. Based on standardization of NACT for AGC in Western countries, which was advised by European guidelines, van der Wielen *et al*[16] conducted STOMACH trial as the first multi-institutional RCT study which demonstrated the comparable complication rate and non-inferiority of 1-year overall survival (OS) and disease-free survival (DFS) between LTG and OTG after NACT in Western countries [16]. However, it is still unclear whether LTG has superior short and long-term outcomes compared with OTG or not for AGC patients who accepted NACT in China. As minimally invasive surgery is gaining popularization and great importance is attached to NACT in China, more studies should be conducted for the proper application of LTG after NACT.

MATERIALS AND METHODS

Patients

This is a retrospective study conducted at the General Surgery Department of the Chinese PLA General Hospital. Clinical and pathological data of patients with AGC who accepted NACT before LTG or OTG plus D2 lymphadenectomy from June 2012 to June 2019 were collected. The eligible criteria were: (1) Clinical tumor stage II-III (including Bulky N or large type 3-4) proved by endoscopic ultrasonography, abdominal computed tomography (CT), and positron emission tomography-CT (PET-CT); (2) Histologically proved gastric adenocarcinoma by preoperative gastroscopy and biopsy; (3) Ages ranging from 18 to 75 years; (4) ASA score ≤ III; (5) Integrated clinical and pathological data; and (6) No conversion to OTG in the LTG group. All patients accepted LTG or OTG followed by NACT (chemotherapeutic regimen: SOX, XELOX, SF, or DCF) according to the consultation of a multi-disciplinary team.

Surgical approach

Surgical procedures were conducted according to Japanese Gastric Cancer Treatment Guidelines[17]. D2 lymphadenectomy was performed, including resection of No. 1, 2, 3a, 4sa, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, 11d, and 12a. Dissection of No. 10 lymph nodes was performed when a tumor was located in the upper stomach invading the greater curvature. Roux-en-Y reconstruction was achieved after tumor dissection. One month after surgery, residual adjuvant chemotherapy was carried out under the guidance of surgeons with rich experience.

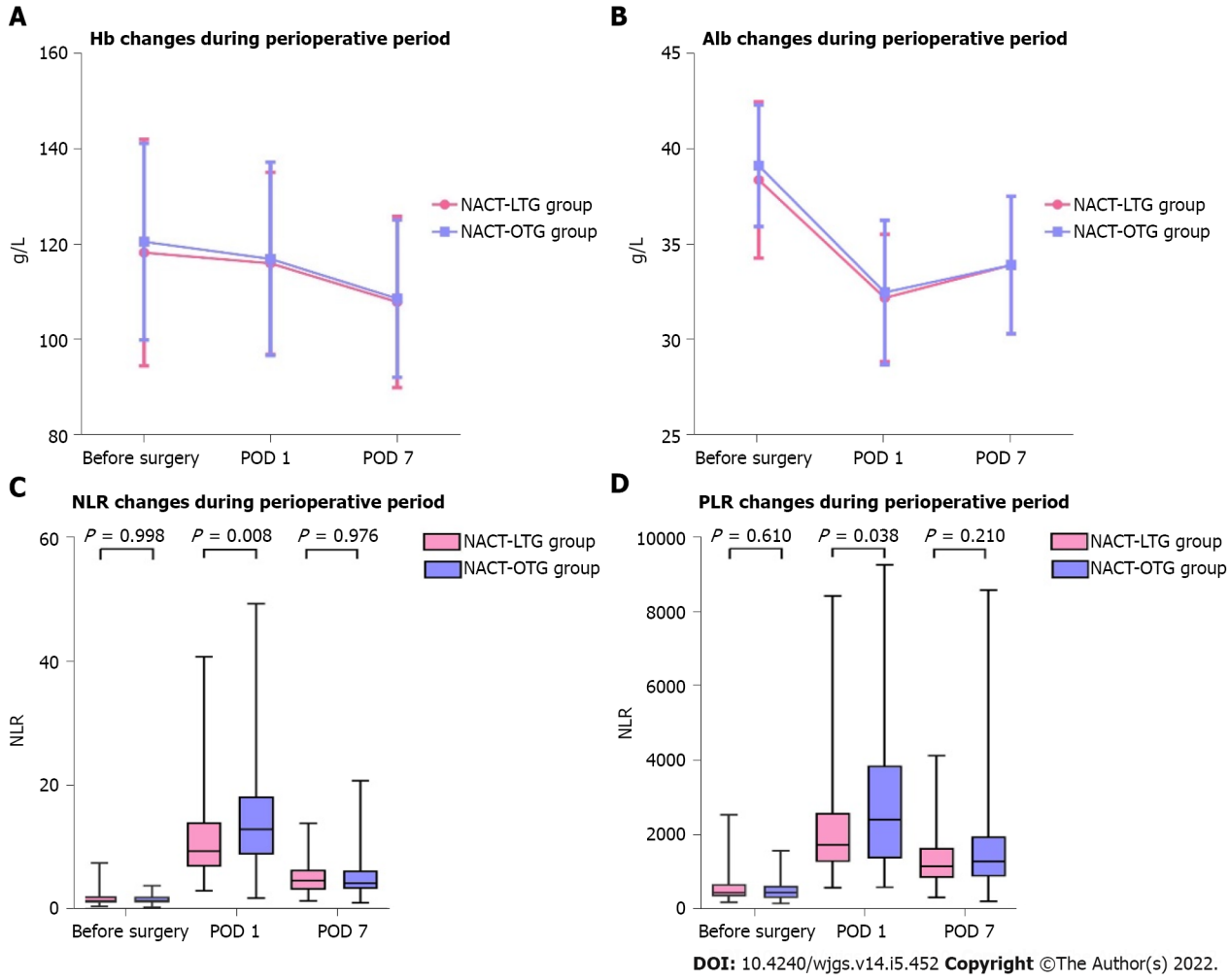

Figure 2 Comparisons of laboratorial indexes during the perioperative period. A: Hemoglobin changes between laparoscopic total gastrectomy (LTG) and open total gastrectomy (OTG) groups; B: Albumin changes between LTG and OTG groups; C: Neutrophil-to-lymphocyte ratio changes between LTG and OTG groups; D: Platelet-to-lymphocyte ratio changes between LTG and OTG groups. NACT: Neoadjuvant chemotherapy; LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio.

Perioperative indexes

We retrospectively collected clinicopathologic indicators including blood loss, operation time, time to first flatus (days), postoperative hospitalization days, surgical and hospitalized cost, retrieved lymph nodes, tumor length, *etc*. The 30-d morbidity and mortality were recorded from case report form and its severe degree was assessed in accordance with the Clavien-Dindo classification[18]. We defined Clavien-Dindo classification ≥ IIIa as severe complication.

Follow-up started 3 mo after operation by outpatient visit or telephone until patients' death. Frequency of adjuvant chemotherapy, survival status, and recurrence or not were mentioned during inquiries. If patients dropped out, the time of last accessible follow-up or last discharge was defined as cutoff value.

Statistical analysis

We used SPSS statistical package, version 26 (IBM software), R software, and GraphPad PRISM 8.0 software to perform statistical analyses. Continuous variables are described as mean ± SD for normal distributions, while medians and interquartile ranges are used to represent skew distributions. Comparison tests were performed by the Student's *t* test and Mann–Whitney U test as appropriate. Categorical variables are described as frequencies with percent, and Chi square test was performed to demonstrate difference of categorical variables between two groups. Moreover, the difference of perioperative laboratorial index between two groups is vividly presented by line chart and box diagram.

To show long-term oncological outcomes, overall survival and disease-free survival were analyzed using Kaplan-Meier method and log-rank test was used to determine significance. We used univariate cox analyses to explore the related indexes and put indicators with $P < 0.10$ into multivariate analysis. Multivariate analyses, with backward variable selection, were conducted using the Cox proportional hazards regression model. All tests were two-sided and statistical significance was set at $P < 0.05$.

Table 1 Baseline characteristics of 136 gastric cancer patients after neoadjuvant chemotherapy (mean ± SD)

Clinical characteristic	LTG group (*n* = 61)	OTG group (*n* = 75)	*P* value
Gender			0.821
Male	47	59	
Female	14	16	
Age (yr)	57.56 ± 10.35	56.84 ± 11.95	0.712
BMI (kg/m^2)	22.81 ± 2.67	23.67 ± 3.31	0.099
CCI score, *n* (%)			0.982
0-2	43	53	
> 2	18	22	
History of abdominal surgery			0.179
No	54	60	
Yes	7	15	
Clinical tumor stage			
cT			0.695
T2	1	6	
T3	22	23	
T4	38	46	
cN			0.191
N0	7	4	
N+	54	71	
cTNM			0.468
II	5	9	
III	56	66	
Historical factor			0.088
2012-2015	22	38	
2016-2019	39	37	

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; CCI: Comprehensive complication index; BMI: Body mass index; NACT: Neoadjuvant chemotherapy.

RESULTS

Clinicopathologic characteristics

We collected the clinical data of 2102 patients who underwent total gastrectomy from June 2012 to June 2019 at the Chinese PLA General Hospital. After screening as described in Figure 1, 136 patients were included into this case-control study with 61 patients in NACT-LTG group and 75 patients in NACT-OTG group. Clinicopathologic characteristics of patients in the two groups are summarized in Tables 1 and 2. Groups were comparable according to sex, age, body mass index (BMI), comprehensive complication index score, proportion of previous abdominal surgery, tumor diameter, clinical and pathologic TNM stage, tumor location, nerve or vascular invasion, and histological type with no significant difference.

NACT

All the 136 patients accepted NACT before surgery. Among them, 113 patients adopted SOX regimen (48 in LTG group and 65 in OTG group), 17 used XELOX regimen (8 in LTG group and 9 in OTG group), and 6 accepted other regimens like DCF and SF; no significant difference was found in the utilization of chemotherapy regimen between the two groups (P = 0.143). Cycles of NACT was determined mainly by patients' chemotherapeutic reaction and tumor response, with no significant difference between the two groups (P = 0.467). We recorded adverse events during chemotherapy by patients' self-report and

Table 2 Pathological characteristics of 136 gastric cancer patients after neoadjuvant chemotherapy

Pathological characteristic	LTG group (*n* = 61)	OTG group (*n* = 75)	*P* value
Tumor diameter, cm (median, IQR)	4.0 (2.5-6.5)	4.0 (2.0-6.0)	0.366
Site of tumor			0.244
Upper 1/3	30	27	
Middle 1/3	21	29	
Diffused	10	19	
ypT			0.751
T0	1	7	
T1	5	5	
T2	10	14	
T3	34	30	
T4	11	19	
ypN			0.190
N0	19	35	
N1	14	11	
N2	12	11	
N3	16	18	
ypTNM			0.300
0	1	7	
I	8	17	
II	22	16	
III	29	34	
IV	1	1	
Nerve invasion			0.545
Yes	20	21	
No	41	54	
Vascular invasion			0.982
Yes	18	22	
No	43	53	
Differentiation			0.616
Well/moderate	27	30	
Poor/undifferentiated	34	45	

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; NACT: Neoadjuvant chemotherapy.

laboratorial index, and classified severe degree *via* CTCAE version 4.0. We found that patients in the two groups had comparable adverse events with no significant difference (P = 0.535). The LTG group had significantly longer chemotherapy–surgical procedure interval compared with the OTG group (5.07 ± 1.67 wk *vs* 4.55 ± 1.33 wk; P = 0.047). There was no significant difference in adjuvant therapy between the two groups (P = 0.545) (Table 3).

Clinical response was another factor defined in accordance with RECIST criteria[19]. In this study, 8 (5.9%) patients achieved a completed response while 57 (41.9%) had a partial response. However, other patients did not have obvious downstage after NACT and were defined as stable disease (62 patients) and progressive disease (9 patients).

Table 3 Neoadjuvant chemotherapy characteristics

Variable	LTG group (*n* = 61)	OTG group (*n* = 75)	*P* value
Number of cycles of NACT			0.467
1-2	13	12	
3-4	45	59	
> 4	3	4	
NACT regimen			0.143
SOX	48	65	
XELOX	8	9	
Other	5	1	
Clinical response			0.659
CR	1	7	
PR	28	29	
SD	28	34	
PD	4	5	
Adverse effects after NACT			0.535
Grade 0	13	17	
Grade I	16	21	
Grade II	17	23	
Grade III	11	12	
Grade IV	4	2	
Chemotherapy–surgical procedure interval (wk)	5.07 ± 1.67	4.55 ± 1.33	0.047
Adjuvant therapy			0.545
Yes	52	61	
No	9	14	

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; NACT: Neoadjuvant chemotherapy; CR: Complete response; PR: Partial response; PD: Progressive disease.

Surgical indicators and postoperative recovery

Of 58 (95.1%) patients in the LTG group and 74 (98.7%) patients in the OTG group acquired R0 resection (P = 0.471). Compared with the OTG group, the LTG group had longer operation time (255.66 ± 40.10 min *vs* 238.59 ± 40.30 min, P = 0.015) and less blood loss [150 (100-300) mL *vs* 200 (200-300) mL, P = 0.003]. The number of retrieved lymph nodes was similar between the two groups (33.38 ± 13.26 in LTG group *vs* 34.75 ± 16.69 in OTG group, P = 0.603).

Regarding postoperative recovery, we found that the LTG group showed advantages of enhanced recovery after surgery in comparison with the OTG group with regard to days to first flatus (4.36 ± 1.28 d *vs* 5.41 ± 1.16 d, P < 0.001) and postoperative hospitalization days (9.48 ± 3.98 d *vs* 11.89 ± 3.36 d, P < 0.001).

Perioperative expenditure was another concern to evaluate cost-effectiveness of different surgical approaches. In this study, even though LTG spent more surgical cost than OTG (P < 0.001), LTG seemed more economical compared with OTG in terms of total hospitalized cost (P < 0.001). Specific indicators mentioned above are presented in Table 4.

In subgroup analysis, we compared the difference between the LTG and OTG groups on the basis of different pathological tumor stages. After balancing the baseline characteristics, similar results were obtained like above in ypTNM 0-II patients (Table 5). Whereas, for patients with ypTNM III-IV, no significant difference was observed on surgical time (P = 0.332) or blood loss (P = 0.159) between the two groups (Table 6).

Laboratorial indexes before surgery and at postoperative days 1 and 7

We selected partial laboratorial indexes like hemoglobin (Hb) and albumin (Alb) in the perioperative

Table 4 Perioperative clinical indexes and postoperative outcomes between laparoscopic total gastrectomy and open total gastrectomy groups after neoadjuvant chemotherapy (mean ± SD)

Variable	LTG group (*n* = 61)	OTG group (*n* = 75)	*P* value
Surgical time, min	255.66 ± 40.10	238.59 ± 40.30	0.015
Blood loss, mL (median, IQR)	150 (100-300)	200 (200-300)	0.003
Blood loss (mL), *n* (%)			0.003
< 200	31	13	
200-400	20	51	
> 400	10	11	
Retrieved lymph nodes, *n*	33.38 ± 13.26	34.75 ± 16.69	0.603
No. 10 lymph nodes dissection			0.339
No	41	56	
Yes	20	19	
Extent of resection			0.471
R0	58	74	
R1/R2	3	1	
Time to first flatus, d	4.36 ± 1.28	5.41 ± 1.16	0.000
Postoperative stay, d	9.48 ± 3.98	11.89 ± 3.36	0.000
Surgery costs, $	5419.99 ± 1315.39	4162.36 ± 791.93	0.000
Hospitalization costs, $ (median, IQR)	13105.92 (11713.18-14640.53)	14873.96 (13501.66-17131.31)	0.000
Total complication rate (%)	14 (23.0)	21 (28.0)	0.503
Clavien-Dindo classification			
Grade II	12	19	
Peritoneal infection	2	2	
Lymphatic leakage	2	0	
Anastomotic leakage	1	0	
Pancreatic fistula	1	1	
Ileus	1	2	
Cardiac failure	1	0	
Hypoproteinemia	2	8	
Anemia	2	2	
Cholecystitis	0	1	
Incision infection	0	2	
Pneumonia	0	1	
Grade IIIa	1	2	
Deep venous thrombosis	1	0	
Pleural effusion	0	1	
Anastomotic leakage	0	1	
Grade V	1	0	
Septic shock	1	0	
Severe complication rate (%)	2 (3.3)	2 (2.7)	1.000

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; NACT: Neoadjuvant chemotherapy.

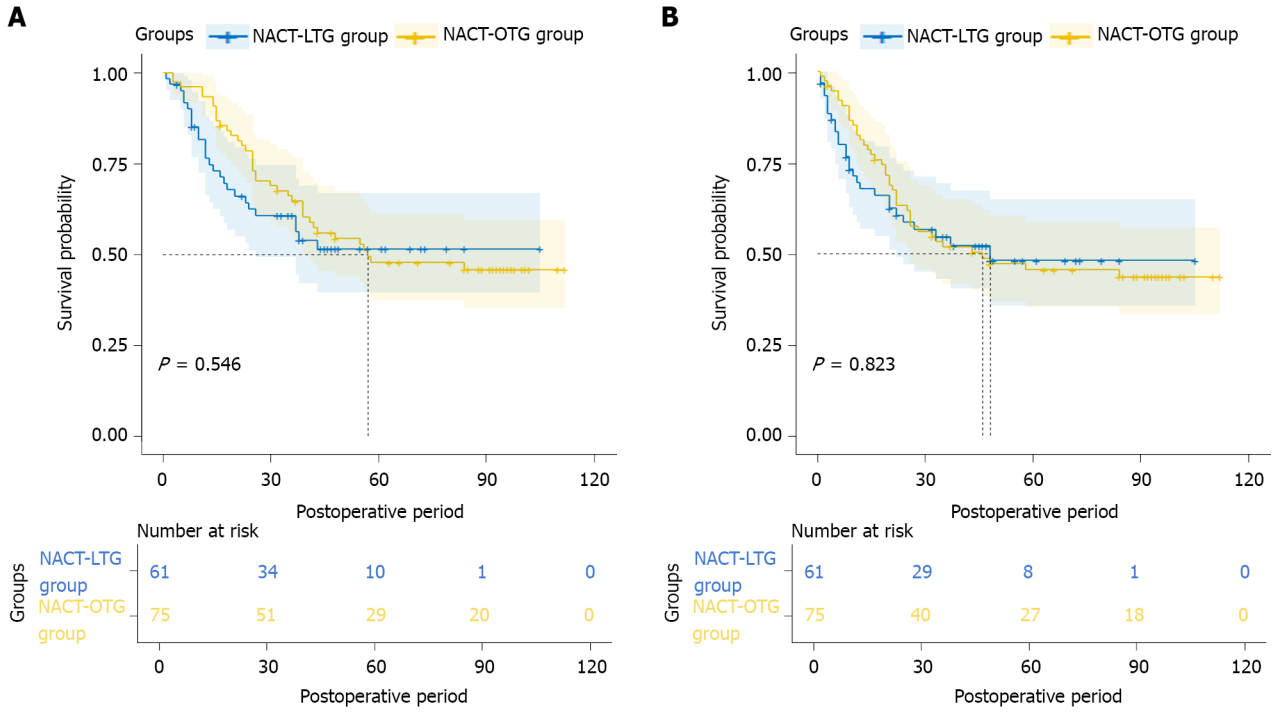

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Figure 3 Overall survival and disease-free survival in neoadjuvant chemotherapy-laparoscopic total gastrectomy and neoadjuvant chemotherapy-open total gastrectomy groups. A: Overall survival between the two groups; B: Disease-free survival between the two groups. NACT: Neoadjuvant chemotherapy; LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy.

period to figure out the changes of perioperative nutritional status between LTG and OTG. In spite of different timelines including before surgery, postoperative day 1 (POD 1), and POD 7, there were no significant difference in Hb or Alb between the two groups.

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were also calculated through laboratory tests. In this study, except for a higher NLR in the OTG group compared with the LTG group at POD 1 (P = 0.008) and PLR in the OTG compared with the LTG group at POD 1 (P = 0.038), no significant difference was observed between the two groups in other periods. Visualized comparison is depicted in Figure 2.

30-d postoperative morbidity

Of the 136 patients who underwent surgery after NACT, 21 (28.0%) in the OTG group and 14 (23.0%) in the LTG group developed Grade II or above postoperative complications evaluated by the Clavien-Dindo classification, with no significant difference between the two groups (P = 0.503). Two (3.3%) patients who underwent LTG had severe complications, wherein one patient died because of septic shock at POD 3. The rate of severe complications after OTG (2/75, 2.7%) did not differ significantly from that in the LTG group (P = 1.000). Table 4 gives the detailed items of complications.

Subgroup analysis showed that regardless of ypTNM 0-II or ypTNM III-IV patients, there was no significant difference in overall or severe complication rate between the two groups (P > 0.05) (Tables 5 and 6).

Long-term oncological outcomes

Of the 136 patients included, 127 (93.4%) completed follow-up. The last follow-up day was December 30, 2021. The median follow-up period was 69 (range, 1–112) mo. The 3-year OS rate was 60.6% and 64.6% in the LTG and OTG groups, respectively [hazard ratio (HR) = 0.859, 95% confidence interval (CI): 0.522-1.412], which demonstrated no significant difference between the two groups (log-rank χ^2 = 0.364, P = 0.546). The 3-year DFS rate was 54.5% and 51.8% in the LTG and OTG groups, respectively (HR = 0.947, 95%CI: 0.582-1.539), which presented no significant difference (log-rank χ^2 = 0.05, P = 0.823). Kaplan-Meier curves are shown in Figure 3.

Additionally, we set up two subgroups according to different ypTNM stages to explore the oncological impact of the two surgical approaches. For ypTNM 0-II patients, there was no significant difference in 3-year OS rate (P = 0.264) or DFS rate (P = 0.262) between LTG and OTG, neither were the subgroup of ypTNM III-IV patients (P > 0.05).These results illustrated the similar long-term outcomes between LTG and OTG after NACT no matter what ypTNM stage was. Kaplan-Meier curves for different subgroups are shown in Supplementary Figure 1.

Table 5 Clinical characteristics and perioperative indexes in ypTNM 0-II patients after neoadjuvant chemotherapy (mean ± SD)

Variable	LTG group (*n* = 31)	OTG group (*n* = 40)	*P* value
Gender			0.841
Male	25	33	
Female	6	7	
Age (yr)	59.10 ± 10.51	57.63 ± 11.16	0.574
BMI (kg/m^2)	22.58 ± 2.77	23.72 ± 2.93	0.102
CCI score			0.594
0-2	22	26	
> 2	9	14	
Tumor diameter, cm (median, IQR)	3.00 (2.20-4.50)	2.30 (1.42-4.00)	0.158
Surgical time, min	260.97 ± 37.20	237.93 ± 35.51	0.010
Blood loss, mL (median, IQR)	150 (100-200)	200 (200-300)	0.002
Blood loss (mL), *n* (%)			0.000
0-200	19	5	
200-400	9	31	
> 400	3	4	
Retrieved lymph nodes, *n*	34.00 ± 15.11	36.38 ± 17.64	0.552
Time to first flatus, d	4.32 ± 1.28	5.45 ± 1.24	0.000
Postoperative stay, d	8.94 ± 3.63	11.65 ± 3.03	0.001
Surgery costs, $	5641.18 ± 1351.17	4163.48 ± 627.86	0.000
Hospitalization costs, $	13389.70 ± 2254.38	15024.88 ± 23358.95	0.004
Total complication rate (%), C-D classification	5 (16.1)	9 (22.5)	0.503
II	4	8	
IIIa	0	1	
V	1	0	
Severe complication rate (%)	1(3.2)	1 (2.5)	1.000

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; NACT: Neoadjuvant chemotherapy; CCI: Comprehensive complication index; BMI: Body mass index; C-D classification: Clavien-Dindo classification

Multivariate Cox analysis of OS and DFS

Multivariate Cox analyses are shown in Tables 7 and 8. In the univariate analysis, BMI, pTNM stage, tumor diameter, estimated blood loss, and vascular and nerve invasion were significantly correlated with OS ($P < 0.10$), and pTNM stage, tumor diameter, estimated blood loss, and vascular invasion were significantly correlated with DFS ($P < 0.10$). In the multivariate analysis, BMI and pTNM stage were independent risk factors for OS while vascular invasion and pTNM stage were independent risk factors for DFS ($P < 0.05$). Historical factor was not significantly associated with OS or DFS ($P > 0.05$).

DISCUSSION

The application of NACT to AGC rapidly increased because of its potential oncological benefit[20]. At present, surgeons focus mainly on the impact of NACT on gastrectomy[16,21]. In this study, we reported mono-institutional retrospective outcomes aiming to evaluate surgical safety and oncological efficacy between LTG and OTG after NACT in China, which could provide a reference to the reasonable utilization of minimally invasive surgery for AGC patients who accepted NACT.

NACT before surgery has several advantages over surgery first for AGC, such as tumor regression, better tolerance, and improved R0 resection. Previous studies which consisted of over 100 cases of NACT showed that pCR rate ranged from 5%-17.2%[22]. In the present research, 8 (5.9%) patients

Table 6 Clinical characteristics and perioperative index in ypTNM III-IV patients after neoadjuvant chemotherapy (mean ± SD)

Variable	LTG group (*n* = 30)	OTG group (*n* = 35)	*P* value
Gender			0.931
Male	22	26	
Female	8	9	
Age (yr)	55.97 ± 10.10	55.94 ± 12.90	0.993
BMI (kg/m^2)	23.03 ± 2.60	23.63 ± 3.73	0.468
CCI score			0.514
0-2	21	27	
> 2	9	8	
Tumor diameter, cm	5.5 (3.5-8.0)	5.0 (4.0-8.0)	0.916
Surgical time, min	250.17 ± 42.99	239.34 ± 45.69	0.332
Blood loss, mL (median, IQR)	200 (100-350)	300 (200-400)	0.159
Blood loss (mL), *n* (%)			0.404
0-200	12	8	
200-400	11	20	
> 400	7	7	
Retrieved lymph nodes, *n*	32.73 ± 11.24	32.89 ± 15.58	0.965
Time to first flatus, d	4.40 ± 1.30	5.37 ± 1.09	0.002
Postoperative stay, d	10.03 ± 4.30	12.17 ± 3.73	0.036
Surgery costs, $	4793.57 (4032.20-6242.77)	3871.55 (3686.28-4416.86)	0.000
Hospitalization costs, $	13190.05 (12036.98-14591.47)	15263.28 (13162.85-17143.01)	0.000
Total complication rate (%), C-D classification	9 (30.0)	12 (34.3)	0.647
II	8	11	
IIIa	1	1	
Severe complication rate (%)	1 (3.3)	1 (2.9)	1.000

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; NACT: Neoadjuvant chemotherapy; CCI: Comprehensive complication index; BMI: Body mass index; C-D classification: Clavien-Dindo classification.

achieved a pathologic complete response while 65 (47.8%) gained an objective response that was consistent with the results mentioned above. Better chemotherapeutic response was the crucial premise of radical gastrectomy. In this study, 58 (95.1%) patients in the LTG group and 74 (98.7%) in the OTG group achieved R0 resection, and no significant difference (P = 0.471) was found between the two groups. These results indicated that LTG could ensure considerable R0 resection in comparison to OTG after NACT.

Perioperative laboratorial indexes could evaluate the extent of surgical damage and nutritional status, and even might predict prognosis[23]. In our series, no significant difference was observed in Alb and Hb between LTG and OTG at three time points, including before surgery, POD 1, and POD 7. The incidence of hypoproteinemia seemed lower in the LTG group (3.3%) compared with the OTG group (10.7%), but the difference was not significant (P = 0.190), which indicated that LTG after NACT did not obviously improve postoperative nutritional status with advantages of minimally invasive surgery. NLR and PLR were regarded as potential markers to predict further prognosis[24]. Our results found no significant difference in PLR or NLR between the LTG and OTG groups before surgery and at POD 7, which implied that LTG and OTG after NACT had analogical long-term outcomes up to a point. However, higher NLR and PLR were observed at POD 1 in the OTG group than in the LTG group. We attributed this interesting phenomenon to stronger stress response at early period after OTG[25], which might elevate inflammation and suppress inherit immunity, leading to higher NLR and PLR. Hence, most studies selected pre-operation as a factor rather than other time points[26].

Adhesion of tissues, lack of anatomical layer, and peri-gastric edema and fibrosis might occur after NACT, which increased the surgical difficulty. Laparoscopy has several advantages like delicate

Table 7 Univariate and multivariate analyses for overall survival

Factor	Univariate analysis		*P* value	Multivariate analysis		*P* value
	HR	95%CI		HR	95%CI	
Sex			0.127			
Male	1.000					
Female	1.541	0.885-2.684				
Age			0.647			
< 65	1.000					
≥ 65	1.129	0.671-1.900				
BMI (kg/m^2)			0.091			0.049
< 25	1.000			1.000		
≥ 25	0.601	0.333-1.086		0.547	0.300-0.998	
Surgical approach			0.549			
Laparoscopy	1.000					
Open	1.164	0.708-1.914				
CCI score			0.438			
0-2	1.000					
≥ 2	1.225	0.733-2.049				
pTNM stage			0.000			0.006
0-II	1.000			1.000		
III-IV	2.632	1.569-4.413		2.224	1.258-3.930	
Tumor diameter (cm)			0.039			0.153
≤ 3	1.000			1.000		
> 3	1.838	1.031-3.277		1.577	0.844-2.945	
Operation time (min)			0.483			
≤ 240	1.000					
> 240	1.192	0.730-1.948				
Estimated blood loss (mL)			0.074			0.588
≤ 200	1.000			1.000		
> 200	1.559	0.958-2.536		1.154	0.688-1.935	
Vascular invasion			0.008			0.062
No	1.000			1.000		
Yes	1.987	1.200-3.289		1.712	0.974-3.010	
Nerve invasion			0.079			0.567
No	1.000			1.000		
Yes	1.580	0.949-2.632		0.838	0.456-1.537	
Differentiation			0.261			
Well/moderate	1.000					
Poor/undifferentiated	1.335	0.806-2.212				
Complications			0.662			
No	1.000					
Yes	1.131	0.651-1.968				
Historical factor			0.861			

2012-2015	1.000	
2016-2019	0.957	0.587-1.560

HR: Hazard ratio; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; CCI: Comprehensive complication index; BMI: Body mass index.

manipulation, regional amplification, faster recovery, and damage control that might reduce the surgical risk of NACT. Li *et al*[21] found that laparoscopic distal gastrectomy had remarkably lower postoperative morbidity compared with open distal gastrectomy (20% *vs* 46%, $P = 0.007$) for patients with AGC who received NACT[21]. In this study, our perioperative clinical indicators showed that LTG offered benefits of less blood loss ($P = 0.003$), shorter days to first flatus, and shorter postoperative hospitalization dasy ($P < 0.001$) compared with OTG, which illuminated specific superiority of minimally invasive surgery. LTG also could achieve adequate lymph nodes dissection with a comparable number of retrieved lymph nodes between LTG and OTG (33.38 ± 13.26 *vs* 34.75 ± 16.69, $P = 0.603$). Meanwhile, an interesting phenomenon was found that LTG cost more on operation and less on total hospitalization than OTG, which was similar to the results of the studies by Tegels *et al*[27] and Hoya *et al*[28]. Gosselin-Tardif *et al*[29] also found that the application of laparoscopic gastrectomy was more cost-effective compared with open gastrectomy in Canadians. We reckon that the fact that expensive disposable surgical instruments mostly relied on import might elevate surgical cost in LTG, but fast postoperative recovery could offset deviations by reducing other costs, which suggested LTG as a probable cost-effective alternative surgical approach after NACT.

In terms of perioperative complications, CLASS-02 trial conducted in China demonstrated that LTG performed by experienced surgeons had acceptable postoperative morbidity (19.1%) for clinical stage I GC[13]. STOMACH trial showed no significant difference in the rate of postoperative complications between OTG (42.9%) and LTG (34.0%) in LTG after NACT in Western countries ($P = 0.408$). Wang *et al*[30] demonstrated that LTG had comparable safety to OTG after NACT in the perioperative period and patients in the LTG group could benefit from less intravenous patient-controlled analgesia (IV-PCA) use [30]. Back to our study, we found that LTG did not significantly increase or decrease 30-d postoperative complications compared with OTG after NACT (overall morbidity of LTG *vs* OTG: 23.0% *vs* 28.0%, $P = 0.503$; severe morbidity of LTG *vs* OTG: 3.3% *vs* 2.7%, $P = 1.000$), which was similar to the results of the studies mentioned above. These results still existed in different ypTNM stage patients. Thus, we consider that the application of LTG after NACT could be safe and feasible whatever tumor stage was and we recommend to initiate prospective studies to give high-grade evidence in East Asia.

Long-term outcomes were inevitable to evaluate oncological benefit caused by different surgical approaches. The studies by Gambhir *et al*[14] and Komatsu *et al*[31] both pointed out a comparable long-term survival between LTG and OTG, nevertheless it remained uncertain between the LTG and OTG group after NACT. Our results of follow-up focused on 3-year OS and DFS rates showed no significant difference between the two groups (LTG compared to OTG: 3-year OS: 60.6% *vs* 64.6%, $P = 0.546$; 3-year DFS: 54.5% *vs* 51.8%, $P = 0.823$). Subgroup analysis according to different ypTNM stages also showed no significant difference in 3-year OS or DFS rate. These findings suggested that patients with LTG after NACT had similar oncological benefits compared with those in the OTG group irrespective of stage, and LTG after NACT could be regarded as an alternative surgical approach with acceptable short and long-term outcomes.

Our study has several limitations. Principally, this is not a prospective study which lacked of authentic evidence-based support and existed selection bias. Under the trend of climbing application of NACT as a promising treatment for AGC in East Asia[32], large-scale retrospective or even multi-institutional RCT studies are required to better understand the association between LTG and OTG after NACT. Moreover, small sample size increased the probability of type II error and reduced the power of test. To decrease such impact, we combined patients with adjacent ypTNM stages into one group to ensure enough sample size in subgroup analysis. Third, although SOX regimen was the main NACT treatment in our study, other regimens like XELOX and DCF were also used for a small portion of appropriate patients, which may slightly influence short or long-term outcomes. In addition, even the baseline characteristics of patients included in this study were comparable between the LTG and OTG groups, some potential imbalance caused by unknown indicators may affect the validity of results.

CONCLUSION

To sum up, this study suggested that there are no significant disparities between LTG and OTG in postoperative complication rates, 3-year OS rates, and 3-year DFS rates after NACT for AGC patients. LTG performed by experienced surgeons after NACT has several advantages including less blood loss, faster postoperative recovery, and less hospitalized cost, which could be regarded as an alternative surgical approach with its safety, feasibility, and comparable oncological benefits at any ypTNM stage.

Table 8 Univariate and multivariate analyses for disease-free survival

Factor	Univariate analysis		*P* value	Multivariate analysis		*P* value
	HR	95%CI		HR	95%CI	
Sex			0.259			
Male	1.000					
Female	0.851	0.642-1.127				
Age			0.267			
< 65	1.000					
≥ 65	1.326	0.806-2.181				
BMI (kg/m2)			0.706			
< 25	1.000					
≥ 25	0.706	0.403-1.237				
Surgical approach			0.825			
Laparoscopy	1.000					
Open	0.947	0.582-1.539				
CCI score			0.707			
0-2	1.000					
≥ 2	1.104	0.660-1.847				
pTNM stage			0.000			0.022
0-II	1.000			1.000		
III-IV	2.418	1.471-3.973		1.854	1.095-3.140	
Tumor diameter (cm)			0.022			0.200
≤ 3	1.000			1.000		
> 3	1.954	1.100-3.470		1.484	0.812-2.710	
Operation time (min)			0.710			
≤ 240	1.000					
> 240	1.095	0.679-1.765				
Estimated blood loss (mL)			0.024			0.204
≤ 200	1.000			1.000		
> 200	1.730	1.075-2.785		1.379	0.840-2.263	
Vascular invasion			0.001			0.020
No	1.000			1.000		
Yes	2.245	1.378-3.659		1.824	1.101-3.022	
Nerve invasion			0.203			
No	1.000					
Yes	1.387	0.838-2.295				
Differentiation			0.283			
Well/moderate	1.000					
Poor/undifferentiated	1.311	0.800-2.148				
Complications			0.751			
No	1.000					
Yes	1.093	0.631-1.894				
Historical factor			0.691			

2012-2015	1.000	
2016-2019	1.102	0.683-1.779

HR: Hazard ratio; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; CCI: Comprehensive complication index; BMI: Body mass index.

ARTICLE HIGHLIGHTS

Research background

Neoadjuvant chemotherapy (NACT) combined with surgery is regarded as an effective treatment for advanced gastric cancer (AGC). Laparoscopic surgery represents the mainstream of minimally invasive surgery.

Research motivation

Currently, surgeons focus more on surgical safety and oncological outcomes of laparoscopic gastrectomy after NACT.

Research objectives

We sought to evaluate short- and long-term outcomes between laparoscopic total gastrectomy (LTG) and open total gastrectomy (OTG) after NACT.

Research methods

We retrospectively collected the clinicopathological data of 136 patients who accepted gastrectomy after NACT from June 2012 to June 2019, including 61 patients in the LTG group and 75 patients in the OTG group. Clinicopathological characteristics between the LTG and OTG groups showed no significant difference. We compared the perioperative indexes and long-term outcomes between the LTG and OTG groups after NACT. SPSS 26.0, R software, and GraphPad PRISM 8.0 were used to perform statistical analyses.

Research results

In this study, we found that LTG had longer operation time, less blood loss, shorter days to first flatus, and shorter postoperative hospitalization days compared with OTG. LTG showed comparable 30-d postoperative morbidity as well as 3-year OS and DFS rate to OTG.

Research conclusions

This study suggested that there are no significant disparities between LTG and OTG in postoperative complication rates, 3-year OS rates, and 3-year DFS rates after NACT for AGC patients. LTG performed by experienced surgeons after NACT has several advantages including less blood loss, faster postoperative recovery, and less hospitalized cost, which could be regarded as an alternative surgical approach with its safety, feasibility, and comparable oncological benefits at any ypTNM stage.

Research perspectives

We recommend that experienced surgeons could select LTG for proper patients after NACT. Large-scale retrospective or even multi-institutional RCT studies are required to better understand the association between LTG and OTG after NACT.

FOOTNOTES

Author contributions: Cui H, Zhang KC, Cao B, Chen L, and Wei B designed the study; Cao B, Deng H, and Zhao RY collected the data; Liu Y analyzed and interpreted the data; Cui H and Zhang KC prepared the manuscript; all the authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Are laparoscopic cholecystectomy and natural orifice transluminal endoscopic surgery gallbladder preserving cholecystolithotomy truly comparable? A propensity matched study

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Abstract

BACKGROUND

Cholecystectomy is the preferred treatment option for symptomatic gallstones. However, another option is gallbladder-preserving cholecystolithotomy which preserves the normal physiological functions of the gallbladder in patients desiring to avoid surgical resection.

AIM

To compare the feasibility, safety and effectiveness of pure natural orifice transluminal endoscopic surgery (NOTES) gallbladder-preserving cholecystolithotomy *vs* laparoscopic cholecystectomy (LC) for symptomatic gallstones.

METHODS

We adopted propensity score matching (1:1) to compare trans-rectal NOTES cholecystolithotomy and LC patients with symptomatic gallstones. We reviewed 2511 patients with symptomatic gallstones from December 2017 to December 2020; 517 patients met the matching criteria (NOTES, 110; LC, 407), yielding 86 pairs.

RESULTS

The technical success rate for the NOTES group was 98.9% *vs* 100% for the LC group. The median procedure time was 119 min [interquartile ranges (IQRs), 95-

175] with NOTES *vs* 60 min (IQRs, 48-90) with LC ($P < 0.001$). The frequency of post-operative pain was similar between NOTES and LC: 4.7% (4/85) *vs* 5.8% (5/95) ($P = 0.740$). The median duration of post-procedure fasting with NOTES was 1 d (IQRs, 1-2) *vs* 2 d with LC (IQRs, 1-3) ($P < 0.001$). The median post-operative hospital stay for NOTES was 4 d (IQRs, 3-6) *vs* 4 d for LC (IQRs, 3-5), ($P = 0.092$). During follow-up, diarrhea was significantly less with NOTES (5.8%) compared to LC (18.6%) ($P = 0.011$). Gallstones and cholecystitis recurrence within a median of 12 mo (range: 6-40 mo) following NOTES was 10.5% and 3.5%, respectively. Concerns regarding the presence of abdominal wall scars were present in 17.4% ($n = 15/86$) of patients following LC (mainly women).

CONCLUSION

NOTES provides a feasible new alternative scar-free treatment for patients who are unwilling or unable to undergo cholecystectomy. This minimally invasive organ-sparing procedure both removes the gallstones and preserves the physiological function of the gallbladder. Reducing gallstone recurrence is essential to achieving widespread clinical adoption of NOTES.

Key Words: Gallstones; Trans-rectal; Natural orifice transluminal endoscopic surgery; Minimally invasive surgery; Gallbladder preservation; Cholecystolithotomy; Laparoscopic cholecystectomy

Core Tip: Laparoscopic cholecystectomy (LC) is the current gold standard for treating gallstones. However, long-term complications of LC such as duodenogastric reflux, post-cholecystectomy syndrome, bile duct injuries and an increase in colonic cancer remain largely unreported/unstudied. Some experts now advocate simple gallstone extraction with gallbladder preservation (cholecystolithotomy) in order to avoid post-cholecystectomy syndrome, bile duct injury, and its association with colon cancer. The authors' developed the pure natural orifice transluminal endoscopic surgery trans-rectal gallbladder preserving cholecystolithotomy technique for removal of gallbladder stones. This study compared trans-rectal gallbladder preserving cholecystolithotomy with traditional LC.

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INTRODUCTION

Approximately 25 million people in the United States have gallstones, resulting in more than one million hospitalizations each year[1-4]. Cholecystectomy is the gold standard treatment for symptomatic gallstones[5]. For the past three decades, laparoscopic cholecystectomy (LC) has been the treatment of choice[6-8] as it is minimally invasive. However, since Rao *et al*[9]'s description of the first human NOTES trans-gastric appendectomy in 2004, ultra-minimally invasive techniques have evolved including natural orifice transluminal endoscopic surgery (NOTES) cholecystectomy[9]. Some experts now advocate cholecystolithotomy without gallbladder excision in order to preserve gallbladder function and to avoid gallbladder resection-related complications[10-13]. In addition, cholecystectomy is associated with post-cholecystectomy syndrome, surgical incision complications, and bile duct injury [14-16]. The reasons given for gallbladder preservation include the reported associations of colon cancer, functional gastrointestinal and psychological conditions following cholecystectomy[15-17].

Experimental studies using flexible endoscopic trans-rectal NOTES have suggested this approach as an attractive alternative option for intra-abdominal procedures[18-21]. However, concern regarding peritoneal contamination with trans-rectal NOTES limited the adoption of trans-rectal NOTES as a routine clinical practice. The problem of peritoneal contamination during trans-rectal NOTES has now been largely overcome with the use of a detachable obstructive colonic balloon which prevents distal colonic contamination (Figure 1)[22-24].

No comparison of NOTES and LC for symptomatic gallstones has previously been reported. Therefore, we performed a comparative study of pure NOTES gallbladder preservation cholecystolithotomy and LC to examine relative effectiveness as well as differences in post-operative pain, infection, time to normal diet intake, hospital duration, short- and long-term complications.

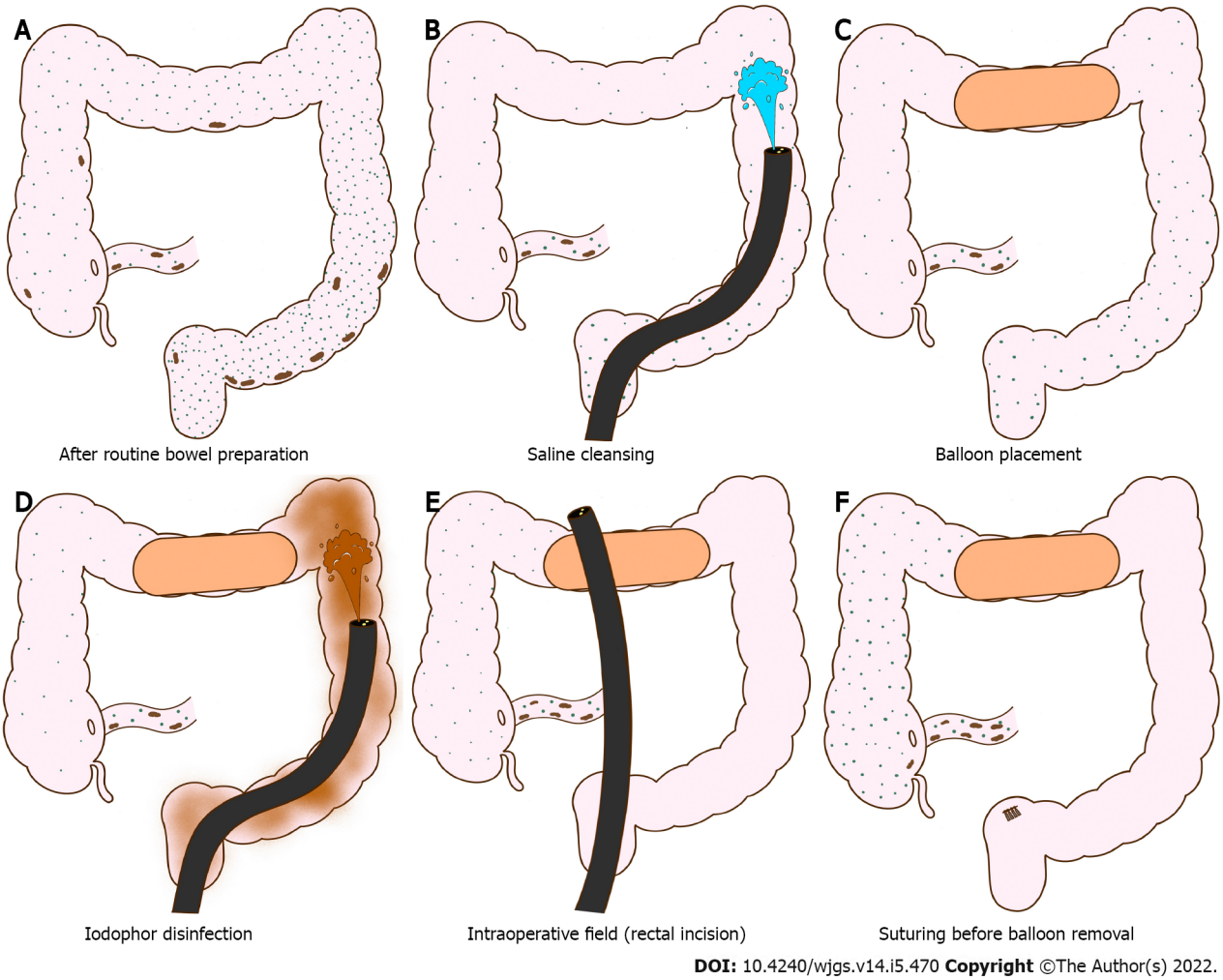

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Figure 1 Schematic of colonic cleansing, detachable balloon placement, and colonic disinfection. A: Colon after bowel preparations; B: Colon cleansing using saline solution; C: Placement of detachable balloon in the transverse colon; D: Distal colon disinfection using iodophor; E: Endoscopy insertion to peritoneal cavity *via* rectal incision; F: Suturing of rectal incision before balloon removal.

MATERIALS AND METHODS

Study design

The study protocol was approved by the independent ethics committee of the Second Affiliated Hospital of Harbin University. Written informed consent was obtained from all patients before the procedure. All NOTES procedures were performed by an expert gastroenterologist with experience of more than 150 NOTES procedures. The research was carried out in accordance with the Helsinki Declaration. All authors had access to the study data, and reviewed and approved the final manuscript.

Patient selection for NOTES

We extracted patient data from the inpatient database of the First Affiliated Hospital of Zhengzhou University who were treated for gallbladder disease from December 2017 to December 2020. The inclusion criteria were: (1) Patients over the age of 18 years and less than 80 years of age; (2) Patients with symptomatic cholelithiasis confirmed by B-ultrasound or other imaging examination (CT/MRI); (3) Patients with no history of major upper abdominal surgery; (4) A strong desire by the patient to retain the gallbladder; and (5) No absolute surgical contraindications, including severe hepatic, renal, cardiac and pulmonary insufficiency, history of cerebral coma and allergy to anesthesia *etc*. Exclusion criteria included: (1) Patients younger than 18 years or older than 80 years of age; (2) Patients with acute cholecystitis, chronic atrophic cholecystitis, atrophy of the gallbladder due to any reason and suspicion of gallbladder cancer; (3) Unable to undergo endoscopic surgery for various reasons such as associated other diseases or age factor; and (4) Could not be contacted or loss of information.

Interventions

Description of trans-rectal NOTES technique: After routine bowel preparation, all procedures were

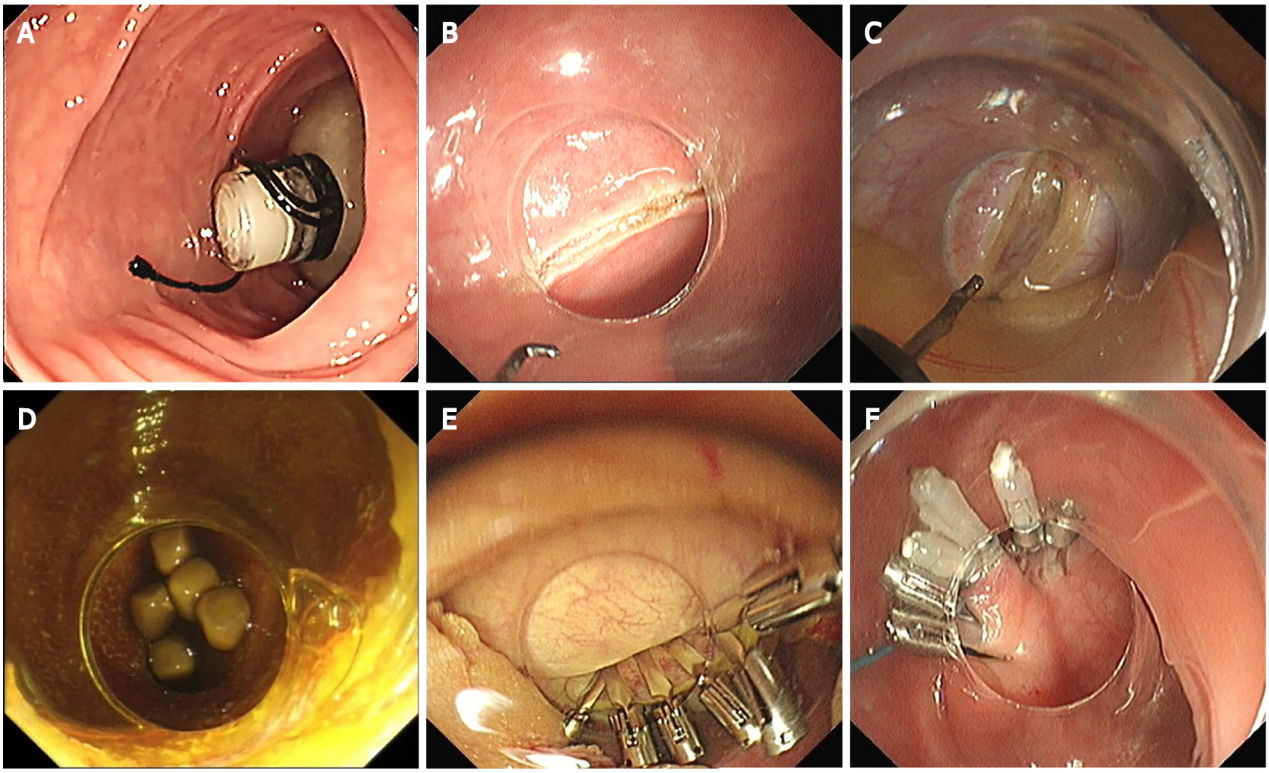

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Figure 2 Natural orifice transluminal endoscopic surgery trans-rectal gallbladder preserving cholecystolithotomy. A: Detachable balloon placement in the colonic lumen; B: Rectum incision for trans-rectal access; C: Gallbladder incision; D: Visualization of gallbladder stones; E: Closure of the gallbladder wall with endoclips; F: Closure of the rectal incision with endoclips and endoloops.

performed under general anesthesia. With the patients in the lithotomy position, a colonoscope (EVIS GIF-Q260J, Olympus, Tokyo, Japan) was advanced into the transverse colon for colonic cleansing. A detachable colonic exclusion balloon was placed into the transverse colon with help of the colonoscope and inflated to 3.0-3.5 cm in diameter by injecting 120 to 140 mL of air into the balloon to occlude the transverse colonic lumen (Figure 2A). Cleansing and disinfection of the distal colonic and rectal lumen was then completed with a 0.1% povidone-iodine solution. A disinfected (a low temperature ethylene oxide processed) gastroscope with a transparent cap attached to the tip of the endoscope was inserted and an incision was made on the right anterior wall of the rectum 15 to 20 cm from the anal verge using Hook and IT knives (Figure 2B). The endoscope was advanced upward through the inter-bowel space into the upper peritoneal cavity where the liver and gallbladder were identified. A full-thickness longitudinal incision was created in the gallbladder wall using the Hook and IT knifes (Figure 2C). The tip of the endoscope was inserted into the gallbladder cavity and the bile was aspirated. The lumen was then cleansed with normal saline and the gallstones were extracted from the gallbladder using a biliary stone extractor (E151186, GMBH FLEX, Germany) and removed *via* the trans-rectal incision (Figure 2D). The gallbladder incision was closed with endoclips (longclip, HX-610-090, Olympus, Tokyo, Japan) (Figure 2E). The endoscope was then withdrawn and the stomal opening in the rectum was closed with endoclips and endoloops (HX-20L-1, Olympus, Tokyo, Japan) (Figure 2F). The colon occlusion balloon was deflated and removed and the colonic mucosa at the site of balloon occlusion was inspected (Videos 1 and 2
).

Description of laparoscopic technique: LC was performed by expert gastroenterology surgeons with experience of more than 500 cholecystectomies. LC was performed using a standard laparoscopic approach.

Outcomes

The two methods of therapy were compared with regard to treatment success, procedure time, post-operative pain, time to normal diet intake, duration of hospital stay, and post-operative short- and long-term complications, and recurrence rate.

Follow-up

The median follow-up period was one year (range: 6-40 mo). The primary outcome was treatment

success. In the NOTES-treated group, treatment success was defined as successful if the procedure was completed using endoscopic surgery without conversion to laparoscopic or open surgery. In the LC group, treatment success was identified as a successful cholecystectomy without converting to open surgery.

Secondary outcomes included procedure time, post-operative pain, duration of post-operative hospital stay, duration of fasting, and post-operative short-term (within 2 wk) and long-term complications, and recurrence rate. In the NOTES group, short-term complications included biliary peritonitis, fever, nausea and vomiting, bleeding and systemic complications (pulmonary embolism, stroke, cardiac events, acute renal failure, and sepsis). Long-term complications included recurrent gallstone, recurrent cholecystitis, diarrhea, constipation, and malignant tumors of the gallbladder. In the LC group, short-term complications included incisional infection, incisional pain, bile duct injury, anesthesia-related complications, and systemic complications. Long-term complications included abdominal pain, hernia, and digestive symptoms. All enrolled patients were followed up by telephone and/or medical records.

Statistical analysis

We used logistic regression models for the calculation of propensity scores. We used a 1:1 propensity score matching (PSM) with the NOTES and LC groups and the caliper value fixed at 0.1 for the propensity matching score. The study matched clinical baseline indicators including age, sex, bilirubin levels, gallbladder stones, temperature, white blood cell count, and hemoglobin. An absolute standard difference of less than 0.1 was considered negligible between both groups. Categorical variables were expressed as frequency and percentages with 95%CI, and continuous variables (operative time, post-operative hospital stay, fasting time, and recurrent time) were expressed as medians with interquartile ranges (IQRs). The Pearson × 2 and Fisher's exact tests were used for categorical variables, and the Mann-Whitney test was applied for continuous variables. Gender, age, baseline leukocytes, total bilirubin, and number of gallbladder stones were analyzed by univariate Cox proportional risk regression for the 1-year recurrence-free outcome. PSM and all calculations were conducted with Stata/SE 15.0 (Stata Corp., College Station, TX, United States). A two-sided P value less than 0.05 was considered statistically significant.

RESULTS

Population characteristics before and after PSM

We extracted data from 2511 patients from the inpatient database of patients treated for gallbladder disease. We excluded 15 patients younger than 18 years of age, 201 patients older than 80 years of age, 55 patients with malignant gallbladder tumor, 112 patients with open surgery, 1281 patients with chronic atrophic cholecystitis and/or atrophy of the gallbladder, 159 patients unable to undergo endoscopic surgery, and 171 patients who could not be contacted (lost to follow-up). Consequently, there were 517 patients eligible for matching (NOTES, 110; LC, 407), and yielded 86 patient pairs (Figure 3). Table 1 shows the characteristics of the patients before and after PSM.

Short-term complications

In the NOTES group, one patient (n = 85/86) was referred to open surgery for removal of the gallbladder due to adhesions between the gallbladder and surrounding tissue. The overall success rate was 98.9% (95%CI: 94.3%-99.8%; n = 85/86). All the patients in the LC group successfully underwent LC with a success rate of 100%. Subsequent pathology confirmed chronic cholecystitis in all. The median operative time was 119 min (IQRs, 95-175) in the NOTES group which was longer than the LC group with a median time of 60 min (IQRs, 48-90), (difference, 59 min; P < 0.001). The median duration of fasting in the NOTES group was 1 d (IQRs, 1-2) *vs* 2 d (IQRs, 1-3) in the LC group, (difference, 1 d; P < 0.001). The median post-operative hospital stay was 4 d (IQRs, 3-6) in the NOTES group *vs* 4 d in the LC group (IQRs, 3-5), (P = 0.092).

In the NOTES group, 2.3% (95%CI: 0.6%-8.9%; n = 2/85) of patients developed post-operative biliary peritonitis. All the peritonitis patients recovered with abdominal irrigation (percutaneous flushing of the peritoneal cavity with saline solution) and combined antibiotic treatment. In the LC group, 2.3% (95%CI: 0.6%-7.4%; n = 2/86) of patients developed lung infections, 5.8% (95%CI: 2.3%-11.7%; n = 5/86) of patients had severe abdominal pain, 1 (1%, 95%CI: 0.2%-5.7%) patient had a wound infection with fever, and one patient had urinary retention. The mortality rate in both groups was 0%.

Long-term complications (post-cholecystectomy syndrome)

During the follow-up period, all patients in the two groups are alive. In the LC group, 18.6% (95%CI: 10.6%-25.6%; n = 16/86) of patients developed diarrhea, of which 8 (8.4%, 95%CI: 4.3%-15.7%) had frequent diarrhea, 5 (5.3%, 95%CI: 2.3%-11.7%) patients were prone to diarrhea after eating fatty foods, 3 (3.3%, 95%CI: 1.1%-8.9%) patients had occasional diarrhea, and diarrhea symptoms were not relieved by symptomatic treatment. In comparison, 5.8% (95%CI: 2.3%-11.8%; n = 5/85) of NOTES patients

Table 1 Baseline patient characteristics after propensity score matching

Variable	NOTES group (*n* = 86)	LA group (*n* = 86)	*P* value
Age, *n* (%)			0.88
≤ 60 yr	51 (59.3)	50 (58.1)	
> 60 yr	35 (40.7)	36 (41.2)	
Sex, *n* (%)			0.53
Male	55 (63.9)	51 (59.3)	
Female	31 (36.1)	35 (40.7)	
Total bilirubin levels[1], *n* (%)			0.72
0-25	83 (96.5)	81 (94.2)	
> 25	3 (3.5)	5 (5.8)	
Temperature[2], *n* (%)			0.75
≤ 37.2°C	6 (6.9)	5 (5.8)	
> 37.2°C	80 (93.1)	81 (94.2)	
Gallbladder stones, *n* (%)			0.75
≤ 3	6 (6.9)	5 (5.8)	
> 3 (or Mud-like gallstones)	80 (93.1)	81 (94.2)	

[1]Total bilirubin levels, reference: 0-25 μmol/L.
[2]Baseline temperature, reference: 36.3-37.2 °C.
The data are presented in the form *n* (%). NOTES: Natural orifice transluminal endoscopic surgery.

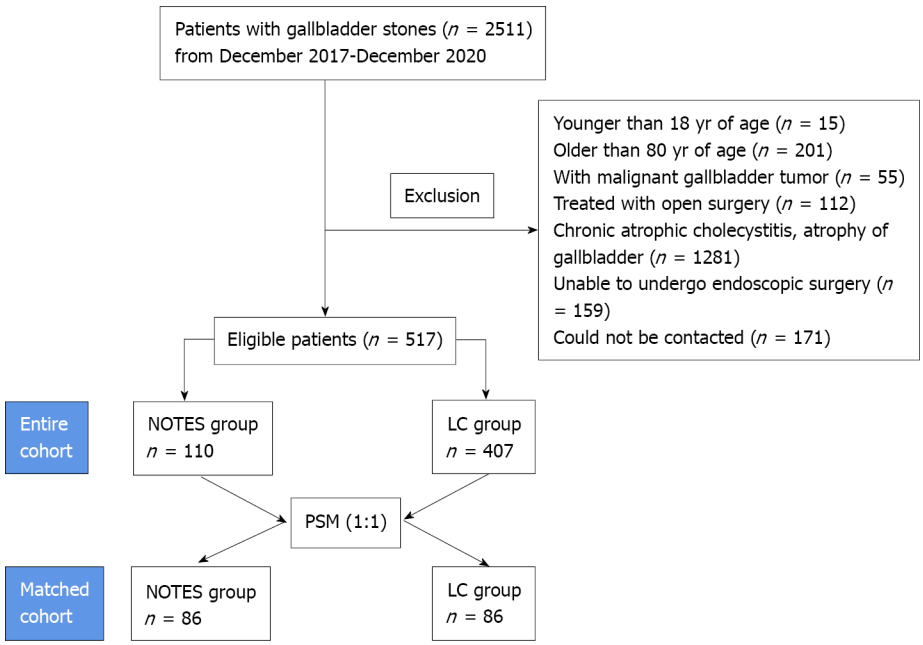

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Figure 3 Flow chart of the entire and matched cohort. NOTES: Natural orifice transluminal endoscopic surgery.

presented with diarrhea, 3 of them after undergoing cholecystectomy which was significantly less frequent than after LC [difference, 11.5 percentage points (95%CI: 2.5-20.8); *P* = 0.011]. 2.3% (95%CI: 0.6%-7.4%; *n* = 2/85) of NOTES patients presented with constipation *vs* 3.5% (95%CI: 1.1%-8.9%; *n* = 3/86) of LC patients [difference, 1.03 percentage points (95%CI: -0.5-7); *P* = 0.663].

In the LC group, 5.8% (95%CI: 2.3%-11.7%; *n* = 5/86) of patients had pain in the surgical area with anxiety; 17.4% (95%CI: 9.8%-24.4%; *n* = 15/86) of patients were concerned about scars on the abdominal wall (mainly women). 11.6% (95%CI: 5.8%-18.3%; *n* = 10/86) of patients had decreased appetite and

reduced their diet compared to their preoperative status. Only 2.3% (n = 2/85) of NOTES patients had decreased appetite [difference, 8.4 percentage points (95%CI: 1.3-16.3); P = 0.018]. Two (2.3%, 95%CI: 0.6%-7.4%) patients had back pain after exertion, and one (1.06%, 95%CI: 0.2%-5.7%) patient had chest tightness. One (1.06%, 95%CI: 0.2%-5.7%) patient developed renal calculi (Table 2).

Risk factors for patients with recurrent gallbladder stones

Nine NOTES patients had recurrence of gallbladder stones suggested by abdominal ultrasound. The recurrent gallbladder stones were all mud-like stones with a median recurrence time of 210 d (IQRs, 165-255). The recurrence rate was 10.5% (95%CI: 5.1%-17.2%; n = 9/85); 5 underwent cholecystectomy; 4 patients were asymptomatic and they did not wish to undergo further therapy with either NOTES or LC. We recommended re-NOTES or LC for recurrent cases. The post-operative pathology revealed chronic cholecystitis; 3.5% (95%CI: 1.1%-9%; n = 3/85) of patients had pain in the right upper abdomen and the diagnosis of cholecystitis recurrence was made by ultrasound and CT examination, of which 1 (1.1%, 95%CI: 0.2%-5.8%) patient had gallbladder stones combined with cholecystitis. In patients with recurrence who did not receive surgical treatment, symptoms were significantly reduced after antibiotic treatment. Figure 4A shows the cumulative incidence of recurrent gallbladder stones and Figure 4B shows recurrent cholecystitis in the NOTES patients. To identify risk factors for recurrence of gallbladder stones, we performed univariate Cox regression analysis of gender, baseline leukocytes, number of gallstones, and age, and none of these factors were statistically significant for recurrence of gallbladder stones.

DISCUSSION

Symptomatic gallstones are common and cholecystectomy remains the 'gold standard' for their management[25,26]. In 1987, the first LC was conducted which ushered in the age of cholecystectomy with minimal trauma and rapid recovery. This approach demonstrated superiority and created a precedent for minimally invasive operations. Subsequently, with improved technology, many patients with cholelithiasis worldwide have undergone LC and this technique has become the standard treatment for cholelithiasis. However, simple gallstone extraction with gallbladder preservation (cholecystolithotomy) has been proposed in order to preserve the normal physiological function of the gallbladder, avoid post-cholecystectomy syndrome, bile duct injury, complications due to abdominal wall incisions, bile reflux gastritis, and reduce the incidence of gastrointestinal cancer[27-29]. The justification for this practice includes considerations regarding safety, reduced short- and long-term complications as well as cosmetic results and patient satisfaction. Besides this, in clinical practice, we have found that many Chinese patients express a strong desire for preservation of their gallbladder. In response to the clinical desires and importance of gallbladder preservation in a large number of patients, we developed pure NOTES trans-rectal gallbladder preserving cholecystolithotomy as an ultra-minimally invasive technique for removal of gallbladder stones and gallbladder preservation.

Both LC and NOTES approaches have advantages and disadvantages. The advantages of NOTES cholecystolithotomy include: (1) Organ retention and preserved biological function; (2) No incision on the body surface; (3) Early diet intake (*e.g.*, 6 h after the procedure patients are able to take a liquid diet); (4) Reduced post-operative pain; and (5) Fewer long-term complications compared to LC.

The problem with this approach is the current longer procedure time than that for LC and the potential for recurrence of gallstones. Long operative time is expected during the early clinical stage. During initial laparoscopic surgery, a 2-3 h operation was common. With experience and improved techniques, the operative time for NOTES cholecystolithotomy is expected to decrease.

Gallstone recurrence remains a concern. A recent report showed that the average recurrence risk for percutaneous cholecystolithotomy was 3% in 4 years and 10% in 15 years[30]. In China, a long-term analysis of the gallstone recurrence rate after laparoscopic cholecystolithotomy over more than 15 years reported a rate of 10.1% within both 10 and 15 years[31]. In our study, the recurrence risk of gallstones was 9.8% (9/94) during 6 to 40 mo of follow-up. Widespread use of NOTES cholecystolithotomy may require development of a reliable method to prevent recurrence of gallstones. A randomized, double-blind placebo-controlled multicenter clinical trial reported that ursodeoxycholic acid is a safe and effective drug for the prevention of gallstone recurrence[32]. In an another meta-analysis Li *et al*[33] noted that not taking oral ursodeoxycholic acid after gallbladder preserving therapy increased the rate of stone recurrence[33]. Therefore, we recommend that patients who undergo cholecystolithotomy take ursodeoxycholic acid orally to prevent the recurrence of stones. However, further studies are needed to explore the mechanism, dosing and duration of therapy to prevent recurrence of gallstones before final recommendations are made.

The advantage of LC is a shorter procedure time than with NOTES. Disadvantages include: (1) The organ is resected so the loss of its biological function may result in long-term complications; (2) A scar on the body surface; (3) Diet intake is delayed (*e.g.* on day 2); (4) Risk of incision-related complications; and (5) More short- and long-term complications than that with NOTES (abdominal pain, nausea, diarrhea, constipation, fatty food intolerance, indigestion, association with colon cancer, functional

Table 2 Short- and long-term complications in the laparoscopic cholecystectomy and natural orifice transluminal endoscopic surgery cholecystolithotomy treatment groups

	NOTES group, *n* (%), (95%CI)	Laparoscopic group, *n* (%), (95%CI)	Differences
Short-term complications			
Biliary peritonitis	2 (2.3), 0.6-8.9	0 (0), -	< 0.497
Post-operative pain (Abdominal or incisional)	4 (4.7), 1.8-11.4	5 (5.8), 2.5-12.9	0.740
Lung infection	0 (0), -	2 (2.3), 0.6-9.9	
Incisional infection	0 (0), -	1 (1.2), 0.2-6.3	
Urinary retention	0 (0), -	1 (1.2), 0.2-6.3	
Long-term complications			
Diarrhea	5 (5.8), 2.5-12.9	16 (18.6), 11.8-28.1	0.011
Constipation	2 (2.3), 0.6-8.9	3 (3.5), 1.2-9.8	0.063
Decreased appetite	2 (2.3), 0.6-8.9	10 (11.6), 6.4-20.1	0.018
Pain with anxiety in surgical area	-	5 (5.8), 2.5-12.9	
Concerned about scars	-	15 (17.4), 10.9-26.8	
Gallstones recurrence	9 (10.5), 5.6-18.7		
Cholecystitis recurrence	3 (3.5), 1.2-9.8		

NOTES: Natural orifice transluminal endoscopic surgery.

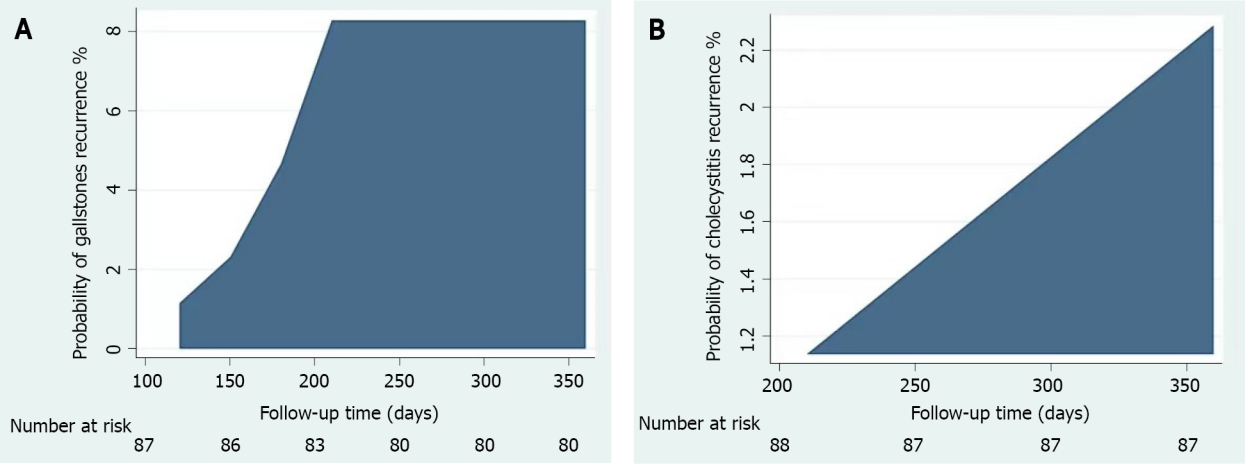

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Figure 4 The cumulative incidence of recurrent gallbladder stones and recurrent cholecystitis in the natural orifice transluminal endoscopic surgery group. A: Cumulative incidence of recurrent gallbladder stones in natural orifice transluminal endoscopic surgery (NOTES) patients; B: Cumulative incidence of recurrent cholecystitis in the NOTES patients.

gastrointestinal and psychological conditions)[14-18].

There was no significant difference in duration of hospital stay between the two groups. Initially, we admitted patients after undergoing NOTES procedure for a longer than usual time as this was a preliminary study with a limited sample size. Post-operative stay ranged between 3 and 5 d *vs* same day surgery for LC in the United States and western world, which might raise questions. The explanation for this is that in China the standard of post-operative care is different, and after all types of abdominal surgery (laparoscopic or open surgery) patients remain in hospital under observation for 3-5 d.

In our study, the most significant differences between the two groups were long-term complications and no wound infections. Although, LC seems to be a 50 min procedure with a good outcome, its long-time complications are largely unstudied including post-cholecystectomy syndrome and a possible association with colon cancer. On the other hand, the only long-term reported (10-15 years of follow-up) complication of percutaneous cholecystolithotomy has been gallstones recurrence. The main reported factors associated with the recurrence of gallstones are a family history of cholelithiasis, a preference for

greasy food and gallbladder dysfunction prior to cholecystolithotomy[29-33].

Compared with LC, NOTES is more than a cosmetic technique to perform surgery as it also has the potential to reduce anesthesia requirements, accelerate patient recovery, and, above all, provide minimally invasive access to organs that are otherwise difficult to access with conventional open or laparoscopic approaches. In addition, some patients refuse surgery and some older patients are not considered candidates for surgical procedures. NOTES provides an alternative option to treat gallstone disease. Although we found short-term complications and recurrences, overall, the safety and efficacy were good with NOTES. With time and improved technology these complications will likely be reduced.

This study has some limitations, including NOTES is a new technique, a retrospective study design, small cohort, and absence of a control group which makes the study prone to attrition and possible loss of clinical data. The same limits the generalizability of the study. Additional studies especially larger multi-center trials are needed to confirm the advantages shown here, and to understand the future for this innovative new approach in the treatment of symptomatic gallstones.

CONCLUSION

In conclusion, NOTES appears to be a minimally invasive and feasible alternative technique for the management of patients with symptomatic gallstones. In our study more than 85% of patients showed good results without complications. Its advantages include no skin wound, organ retention, quick recovery, fewer post-operative complications, and patient satisfaction. Although, this procedure is unlikely to immediately replace LC, it proved useful for patients wishing to avoid surgical resection, and produced good results. Reducing the recurrence of gallstones is essential to achieve widespread clinical adoption of NOTES.

ARTICLE HIGHLIGHTS

Research background

Laparoscopic cholecystectomy (LC) remains the preferred option for symptomatic gallstones. However, the gallbladder functions in regulating bile flow and storing bile, and cholecystectomy may disrupt the whole biliary system and induce subsequent complications. Simple gallstone extraction with gallbladder preservation (cholecystolithotomy) has been proposed in order to preserve gallbladder function and to avoid gallbladder resection-related complications.

Research motivation

In response to the clinical desires and importance of gallbladder retention in a large number of patients, we developed pure natural orifice transluminal endoscopic surgery (NOTES) trans-rectal gallbladder preserving cholecystolithotomy as an ultra-minimally invasive technique for removal of gallbladder stones and gallbladder preservation.

Research objectives

To compare the feasibility, safety and effectiveness of pure NOTES gallbladder-preserving cholecystolithotomy *vs* LC for symptomatic gallstones.

Research methods

We extracted patient data from the inpatient database and adopted propensity score matching (1:1) to compare trans-rectal NOTES cholecystolithotomy and LC in patients with symptomatic gallstones.

Research results

The technical success rate for the NOTES group *vs* the LC group was 98.9% *vs* 100%. Post-operative pain was similar between NOTES and LC; however, the median duration of fasting was less in NOTES patients. During the follow-up period, diarrhea was significantly less with NOTES (5.8%) compared to LC (18.6%). The recurrence rate of stones and cholecystitis within a median of 12 mo (range: 6-40 mo) following NOTES was 10.5% and 3.5%, respectively. Concerns regarding the presence of abdominal wall scars were present in patients following LC.

Research conclusions

NOTES appears to be a minimally invasive and feasible alternative scar-free technique for the management of patients with symptomatic gallstones. Reducing the recurrence of gallstones is essential to achieve widespread clinical adoption of NOTES.

Research perspectives

Although cholecystectomy remains the mainstay in gallstones treatment due to its unique merits, it may not be feasible in surgical patients at high-risk or with biliary deformity. In addition, since post-operative adverse events after removal of the gallbladder are inevitable in some patients, more and more endoscopists are interested in preservation of gallbladder function during the management of gallstones. Therefore, in our opinion NOTES cholecystolithotomy may be an alternative treatment for symptomatic gallstones, especially for patients wishing to avoid surgical resection.

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FOOTNOTES

Author contributions: Liu BR, Saif U and Yang BH contributed to the design of the study, collected data and drafted the manuscript; Yang BH, Lu XY performed the data analyses and revised the manuscript; Zhao LX, Liu D, and Liu ZZ helped perform the analysis with constructive discussions; Zhang JY and Saif U contributed to manuscript preparation data for the work; Liu BR conceived the work that led to the submission and approved the final version; all authors issued final approval for the version to be submitted.

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ORIGINAL ARTICLE

Observational Study

Application of omental interposition to reduce pancreatic fistula and related complications in pancreaticoduodenectomy: A propensity score-matched study

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Abstract

BACKGROUND

The life-threatening complications following pancreatoduodenectomy (PD), intra-abdominal hemorrhage, and postoperative infection, are associated with leaks from the anastomosis of pancreaticoduodenectomy. Although several methods have attempted to reduce the postoperative pancreatic fistula (POPF) rate after PD, few have been considered effective. The safety and short-term clinical benefits of omental interposition remain controversial.

AIM

To investigate the safety and feasibility of omental interposition to reduce the POPF rate and related complications in pancreaticoduodenectomy.

METHODS

In total, 196 consecutive patients underwent PD performed by the same surgical team. The patients were divided into two groups: An omental interposition group (127, 64.8%) and a non-omental interposition group (69, 35.2%). Propensity score-matched (PSM) analyses were performed to compare the severe complication rates and mortality between the two groups.

RESULTS

Following PSM, the clinically relevant POPF (CR-POPF, 10.1% *vs* 24.6%; $P = 0.025$) and delayed postpancreatectomy hemorrhage (1.4% *vs* 11.6%; $P = 0.016$) rates were significantly lower in the omental interposition group. The omental inter-

position technique was associated with a shorter time to resume food intake (7 d *vs* 8 d; $P = 0.048$) and shorter hospitalization period (16 d *vs* 21 d; $P = 0.031$). Multivariate analyses showed that a high body mass index, nonapplication of omental interposition, and a main pancreatic duct diameter < 3 mm were independent risk factors for CR-POPF.

CONCLUSION
The application of omental interposition is an effective and safe approach to reduce the CR-POPF rate and related complications after PD.

Key Words: Pancreaticoduodenectomy; Pancreatic fistula; Complication; Omental interposition

Core Tip: Postoperative pancreatic fistula (POPF) is a life-threatening complication after pancreaticoduodenectomy. Multiple methods have been described in the literature to prevent POPF; however, few trials have demonstrated that a certain method can achieve good clinical outcomes. In this study, we proved that the application of omental interposition can reduce the incidence of clinically relevant POPF, which is associated with a trend towards accelerated recovery.

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INTRODUCTION

Pancreaticoduodenectomy is the gold standard for benign or malignant tumors in the periampullary region. Despite advances in surgical techniques and perioperative care, the postoperative morbidity rate remains high (20-50%), even in high-volume comprehensive hospitals[1-3]. Postoperative pancreatic fistula (POPF) is a life-threatening complication because of its interrelationship with delayed postpancreatectomy hemorrhage (PPH) and postoperative intraabdominal infection[4]. POPF is responsible for erosion of the gastroduodenal artery stump (GDAS), skeletonized hepatic artery (HA), or other adjacent abdominal vessels due to activated pancreatic enzymes.

During the last quarter of the 20th century, multiple methods have been described in the literature to prevent POPF and subsequent complications, including the usage of somatostatin or octreotide, introduction of pancreatic duct stenting, creation of various anastomosis techniques (*e.g.*, duct-to-mucosa, pancreatogastrostomy, invagination), use of polyethylene glycolic acid mesh to reinforce around the pancreatojejunostomy (PJ) site, and use of fibrin glue over the PJ site[5-9]. However, few trials have demonstrated that a certain method will reinforce the PJ site in PD with favorable clinical outcomes.

Currently, the greater omentum has been widely used to reinforce anastomoses and compensate for tissue defects in the fields of thoracic, urinary, and general surgery[10-12]. Recently, some centers have shown that fixing the omental interposition behind the anastomotic site of the PJ to protect the GDAS and nearby HA from erosive pancreatic juices is the most promising approach to reduce the incidence of severe complications[13,14], but they did not have control group data.

Our study investigated whether the application of the omental interposition could effectively reduce the incidence of POPF and its related complications after pancreaticoduodenectomy.

MATERIALS AND METHODS

Patients

Between January 2015 and December 2019, 196 consecutive patients underwent pancreaticoduodenectomy performed by the same surgical team at our institution. The first 69 consecutive patients did not use omental interpositions, and the remaining 127 used omental interpositions. According to whether the omental interposition was applied, the patients were divided into two groups: the omental group (79 males, 48 females; mean age: 64.8 years) and the non-omental interposition group (44 males, 25 females; mean age: 62.1 years). Propensity score matching (PSM) was used to minimize bias from the

nonrandomized treatment assignments. We summarized the data on the general clinical characteristics, short-term surgical outcomes, and recovery. Moreover, the laboratory data on the drain fluid amylase obtained on the first postoperative day (DFA1) were pooled. All data were prospectively collected in our electronic media database. This study was approved by the ethics review committee of Huadong Hospital Affiliated to Fudan University (2019K087; Shanghai, China).

Surgical technique

At our institution, PD was accomplished with a standard approach. After the head of the pancreas had been removed, intestinal reconstruction was achieved with a modified version of the method described by Child. A reconstruction PJ was performed (by duct-to-mucosa, end-to-side reconstruction) and a pancreatic drainage tube was placed. (1) Insert the pancreatic juice drainage tube into 3-5 cm and use 4-0 polydioxanone suture to insert the needle from the ventral side of the pancreatic duct, penetrate the anterior and posterior walls of the pancreatic juice drainage tube, and suture from the back of the pancreatic duct to fix the drainage tube; (2) Place the pancreatic juice drainage tube into the distal end of the jejunal loop, and purse suture of the jejunal incision; and (3) Use 3-0 prolene to suture of seromuscular layer of pancreas and jejunum. Hepaticojejunostomy (HJ) was performed with continuous barbed sutures or interrupted sutures. Gastrojejunostomy (GJ) was performed with interrupted 3-0 polypropylene monofilament sutures.

In the omental interposition group, following complete anastomosis, we routinely placed a pedicled omental interposition in front of the adjacent vessels (HA, PV, and GDAS) and behind the anastomosis where the pancreas stump was fixed to the jejunum[15]. The omental interposition was fixed to the hepatic portal and hepatogastric ligament with several sutures to prevent postoperative mobilization (Figure 1). Generally, the upper boundary of the omental interposition was the level of the hepatogastric ligament, the left boundary was the level of the pancreatic body, and the right boundary was the right margin of the inferior vena cava, so that the omental interposition could separate skeletonized vessels from a possible anastomotic leakage. Then two double catheterization cannulas (PJ tube and HJ tube) were placed at the left anterior of the PJ anastomosis site and right posterior of the HJ anastomosis site, respectively. The blood flow of the omental interposition was reconfirmed before the abdominal cavity was closed. The application of the omental interposition in PD is shown in Figure 2.

In the non-omental interposition group, we simply placed the two drainage tubes at the aforementioned positions after completing the anastomosis. After the operation, the amylase concentration from the drainage fluid was measured daily. If the drain fluid amylase obtained on DFA1 exceeded 2000 U/L, abdominal irrigation was used to dilute the concentration of pancreatic juice around the anastomosis as soon as possible. Approximately 3000 mL normal saline was irrigated every day, with a flow rate of 200 mL/h. The flow of irrigation was modulated frequently according to the character of the secretion. The suction pressure was set with low-pressure suction between 20 and 30 cm water. Once the amylase level of the dilution fluid was lower than 30 U/L, the use of abdominal irrigation was stopped. The drainage tubes were removed until the amylase concentration was less than three times the upper limit of the normal serum level. All patients underwent routine postoperative computed tomography (CT) examinations before the drain tubes were removed to assess the presence of potential complications and peritoneal effusion.

Definitions

POPF was defined and graded according to the modified definition by the International Study Group of Pancreatic Fistula (ISGPF)[16]. Clinically relevant POPF (CR-POPF) was considered grades B and C. Delayed gastric emptying (DGE) and PPH were defined and classified by the International Study Group for Pancreatic Surgery[17,18]. Intra-abdominal infections were diagnosed according to the definition proposed by the Surgical Infection Society and the Infectious Diseases Society of America[19].

Statistical analysis

All statistical analyses were conducted using SPSS 23.0. The χ^2 test or Fisher's exact test was used for categorical variables, whereas the Student's *t*-test or Wilcoxon rank-sum test (whether the variables were normally distributed) were used for continuous variables. $P < 0.05$ was considered statistically significant. After matching, each patient who received an omental interposition was matched to a patient in the non-omental interposition group by using nearest-neighbor matching in a 1:1 ratio. A PSM analysis was used to reduce the impact of the treatment selection bias when estimating the omental interposition values using original observational indicators. Multivariable logistic regression was performed with adjustments for the propensity scores using the associated covariates.

RESULTS

Analyses of all unmatched patients

The demographic and clinically related variables of all patients including age, sex, body mass index

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Figure 1 Omental interposition was placed in front of the adjacent vessels and behind the anastomosis where the pancreas stump was fixed to the jejunum. 1: Liver; 2: Portal vein; 3: Hepatic artery; 4: Common bile duct; 5: Hepaticojejunostomy; 6: Gastrojejunostomy; 7: Celiac artery; 8: Pancreaticojejunostomy site; 9: Gastrojejunostomy. site; 10: Omental interposition; 11: Transverse colon.

(BMI), American Society of Anesthesiologists score, serum albumin content, main pancreatic duct size and pathology were similar between the two groups ($P > 0.05$). However, patients in the omental interposition group had a higher median serum bilirubin than those in the non-omental interposition group (96.5 [17.9-107.0] *vs* 20.5 [9.6-148.5]; $P = 0.015$). Laparoscopic pancreaticoduodenectomy (LPD) was more frequently performed in the omental interposition group than in the non-omental interposition group (69, 54.3% *vs* 19, 27.5%; $P < 0.001$). The details are shown in Table 1.

Regarding postoperative complications, a comparison revealed that the rates of CR-POPF (13, 10.2% *vs* 17, 24.6%; $P = 0.028$), biliary fistula (BF, 2,1.6% *vs* 5, 7.2%; $P = 0.041$), delayed PPH associated with POPF (1, 0.8% *vs* 8, 11.6%; $P = 0.002$), and postoperative transfusion (18,14.2% *vs* 20, 29.0%; $P = 0.012$) were significantly lower in the omental interposition group than in the non-omental interposition group. The rates of other surgery-related complications, including DGE, intra-abdominal abscess, and reoperation, did not significantly differ between the two groups. Regarding mortality, there was no significant difference between the two groups (2, 1.6% *vs* 5, 7.2%; $P = 0.101$). However, the CR-POPF-related mortality in the omental interposition group was significantly lower than the mortality in the non-omental interposition group (1, 0.8% *vs* 5, 7.2%; $P = 0.021$). The details on the deaths that occurred are shown in Table 2 and Figure 3. Fewer complications in the omental group may be related to passing the laparoscopic learning curve. However, among the 108 cases of OPD, 58 cases applied the omental interposition technique, and the omental interposition group had lower incidence of complications (6, 10.3% *vs* 9, 18%; $P = 0.008$) and lower mortality rate (0, 0% *vs* 4, 8%; $P = 0.007$).

When comparing relevant data on the enhanced recovery after surgery between the two groups, the HJ and PJ drainage tubes were removed earlier in the omental interposition group than in the non-omental interposition group (both $P < 0.05$). The omental interposition group of patients had significantly shorter postoperative durations of restarting their diet and shorter length of hospital stay than the non-omental interposition group patients (both $P < 0.01$). Based on the laboratory test results, the DFA1 around the HJ in the omental interposition group was dramatically lower than that in the non-omental interposition group (300.0 [74.3-893.0] *vs* 599.8 [171.1-2064.7]; $P = 0.002$). In the omental interposition group, the drain amylase values from the tube around the HJ were lower than those around the PJ (300.0 [74.3-893.0] *vs* 546.8 [76.4-3094.0]; $P < 0.001$). However, the difference disappeared in the non-omental interposition group. The details are shown in Table 2 and Figure 4A.

Analyses of all matched patients

To reduce the impact of selection bias and the role of the procedure (LPD and OPD), PSM was performed using nine selected baseline characteristics. After PSM, the patient demographic and clinically related characteristics, including preoperative serum bilirubin and operation methods, were similar between the two groups. The rates of CR-POPF (7, 10.1% *vs* 17, 24.6%; $P = 0.025$), delayed PPH associated with POPF (1, 1.4% *vs* 8, 11.6%; $P = 0.016$) and postoperative transfusion (9, 13.0% *vs* 20, 29.0%; $P = 0.022$) remained significantly lower in the omental interposition group than in the non-

Table 1 Comparisons of patients' characteristics between the two groups

	Before PSM			After PSM		
	Omental interposition group (127)	Non-omental interposition group (69)	*P* value	Omental interposition group (69)	Non-omental interposition group (69)	*P* value
Male/female	79/48	44/25	0.919	46/23	44/25	0.721
Age (yr)	64.8 ± 10.5	62.1 ± 9.9	0.083	64.2 ± 9.5	62.1 ± 9.9	0.210
BMI (mean ± SD, kg/m^2)	21.9 ± 3.0	22.0 ± 2.8	0.844	21.9 ± 3.2	22.0 ± 2.9	0.933
ASA score, *n* (%)			0.126			0.168
I	65 (51.2)	42 (60.9)		34 (49.3)	42 (60.9)	
II	60 (47.2)	24 (34.8)		34 (49.3)	24 (34.8)	
III	2 (1.6)	3 (4.3)		1 (1.4)	3 (4.3)	
Serum ALB [*n* (%), g/L]			0.152			1.00
< 35	13 (10.2)	12 (17.4)		12 (17.4)	12 (17.4)	
≥ 35	114 (89.8)	57 (82.6)		57 (82.6)	57 (82.6)	
Serum bilirubin (μmol/L)	96.5 (17.9-107.0)	20.5 (9.6-148.5)	0.015	29.8 (12.4-153.7)	20.5 (9.6-148.5)	0.753
Main pancreatic duct size [*n* (%), mm]			0.080			0.173
< 3	57 (44.9)	40 (58.0)		32 (46.4)	40 (58.0)	
≥ 3	70 (55.1)	29 (42.0)		37 (53.6)	29 (42.0)	
Operation method, *n* (%)			0.005			0.708
LPD	69 (54.3)	19 (27.5)		21 (30.4)	19 (27.5)	
OPD	58 (45.7)	50 (72.5)		48 (69.6)	50 (72.5)	
Pathology, *n* (%)			0.009			0.151
PDAC	53 (41.7)	25 (36.2)		36 (52.2)	25 (36.2)	
Bile duct cancer	10 (7.9)	13 (18.8)		4 (5.8)	13 (18.8)	
Ampulla of Vater cancer	18 (14.2)	15 (21.7)		10 (14.5)	15 (21.7)	
Duodenal cancer	11 (8.7)	2 (2.9)		2 (2.9)	2 (2.9)	
Other carcinoma	19 (15.0)	2 (2.9)		3 (4.3)	2 (2.9)	
Benign tumor	16 (12.6)	12 (17.4)		14 (20.3)	12 (17.4)	

ALB: Albumin; ASA: American Society of Anesthesiologist score; BMI: Body mass index LPD: Laparoscopic pancreaticoduodenectomy; OPD: Open pancreaticoduodenectomy.

omental interposition group after PSM. The operation time in the omental interposition group was slightly longer both before (388.3 ± 68.8 *vs* 365.2 ± 75.0) and after (392.6 ± 74.1 *vs* 365.2 ± 75.0) the match, which may be related to the selection, cutting, and fixing of the omental interposition. Moreover, the omental interposition group of patients had a significantly shorter postoperative duration to restart their diet (7 [5-8] *vs* 8 [6-15]; $P = 0.048$) and shorter hospital stays (16 [12-24] *vs* 21 [13-32]; $P = 0.031$] than the non-omental interposition group of patients. The non-omental interposition group had greater mortality related to POPF than the omental interposition group (5 [7.2%] *vs* 1 [1.4%]), but there was no significant difference, which may be related to the small number of cases. The details are shown in Table 2.

Following PSM, the omental interposition group had dramatically lower DFA1 around the HJ than the non-omental interposition group (200.0 [58-610.6] *vs* 599.8 [171.1-2064.7] $P = 0.003$). In the omental interposition group, the DFA1 around the HJ was lower than the DFA1 around the PJ (200.0 [58-610.6] *vs* 325.0 [75.3-2869], $P < 0.001$). The details on DFA1 are shown in Table 2 and Figure 4B.

Table 2 Comparisons of the postoperative outcomes between the two groups

	Before PSM			After PSM		
	Omental interposition group (127)	Non-omental interposition group (69)	*P* value	Omental interposition group (69)	Non-omental interposition group (69)	*P* value
CR-POPF	13 (10.2%)	17 (24.6%)	0.028	7 (10.1%)	17 (24.6%)	0.025
Operation time (mean ± SD, min)	388.3 ± 68.8	365.2 ± 75.0	0.031	392.6 ± 74.1	365.2 ± 75.0	0.033
BF, *n* (%)	2 (1.6)	5 (7.2)	0.041	1 (1.4)	5 (7.2)	0.208
DGE, *n* (%)	4 (3.1)	6 (8.7)	0.178	1 (1.4)	6 (8.7)	0.115
PPH, *n* (%)	1 (0.8)	8 (11.6)	0.002	1 (1.4)	8 (11.6)	0.016
Intra-abdominal abscess, *n* (%)	15 (11.8)	12 (17.4)	0.286	8 (11.6)	12 (17.4)	0.333
Reoperation, *n* (%)	3 (2.4)	6 (8.7)	0.096	2 (2.9)	6 (8.7)	0.274
Mortality in 30 d, *n* (%)	2 (1.6)	5 (7.2)	0.101	2 (2.9)	5 (7.2)	0.438
Mortality related to POPF, *n* (%)	1 (0.8)	5 (7.2)	0.038	1 (1.4)	5 (7.2)	0.210
DFA1 around the HJ site (U/L)	300.0 (74.3-893.0)	599.8 (171.1-2064.7)	0.002	200.0 (57.5-659.8)	599.8 (171.1-2064.7)	0.003
DFA1 around the PJ site (U/L)	546.8 (76.4-3094.0)	350.0 (50.0-2577.4)	0.255	325.0 (69.5-2972.5)	350.0 (50.0-2577.4)	0.951
Duration until removal of the tube around the HJ site (d)	7 (5-9)	9 (7-14)	0.000	8 (6-11)	9 (7-14)	0.115
Duration until removing the tube around the PJ site (d)	7 (6-11)	10 (7-15)	0.004	8 (6-12)	10 (7-15)	0.100
Required blood transfusions, *n* (%)	18 (14.2)	20 (29.0)	0.012	9 (13.0)	20 (29.0)	0.022
Length of hospital stay (d)	15 (11-22)	21 (13-32)	0.004	16 (12-24)	21 (13-32)	0.031
Duration until restarting diet (d)	6 (5-8)	8 (6-15)	0.001	7 (5-8)	8 (6-15)	0.048

BF: Biliary fistula; CR-POPF: Clinically relevant postoperative pancreatic fistula; DFA1: Drain fluid amylase obtained on the first postoperative day; DGE: Delayed gastric emptying; HJ: Hepaticojejunostomy; PJ: Pancreaticojejunostomy; PPH: Postpancreatectomy hemorrhage.

Factors associated with CR-POPF after PD

Table 3 shows the univariate and multivariate analyses of the PSM data to evaluate the risk factors associated with CR-POPF after PD. Male sex, BMI ≥ 23 kg/m^2, nonapplication of omental interposition, DFA1 around HJ ≥ 1000 U/L, and main pancreatic duct size < 3 mm were significantly associated with the development of CR-POPF after PD. Multivariate logistic regression analyses showed that a high BMI (odds ratio [OR] = 6.094, 95% confidence interval [CI]: 2.021-18.374; P = 0.001), nonapplication of omental interposition (OR = 3.145, 95%CI: 1.040-9.509; P = 0.042), and main pancreatic duct diameter < 3 mm (OR = 5.663, 95%CI: 1.456-22.033; P = 0.012) were independent factors that were significantly associated with the development of CR-POPF after PD.

DISCUSSION

To date, POPF remains the most fatal complication after PD. Pancreatic fistula, especially clinically related postoperative fistula, is the most common cause of delayed PPH and intra-abdominal infections after PD[1-4]. Leaked activated pancreatic juice is highly corrosive. Once the drainage tubes fail to effectively work, pancreatic juice accumulates in the potential cavity gap around the anastomosis. This condition may erode the vulnerable anastomosis and adjacent vascular wall. Various efforts[5-8] have been tested for their ability to reduce the incidence of CR-POPF after PD, such as improved anastomosis and the use of somatostatin. However, few randomized control trials have significantly prevented CR-POPF.

Table 3 The univariate and multivariate analyses of the propensity score-matched data to evaluate the risk factors associated with clinically relevant postoperative pancreatic fistula after pancreaticoduodenectomy

	CR-POPF (24)	No CR-POPF (114)	*P* value	Multivariate analysis		
				OR	95%CI	*P* value
Age (mean ± SD, yr)	63.5 ± 7.9	63.1 ± 10.1	0.829			
Sex, *n* (%)			0.040			
Male	20 (83.3%)	70 (61.4%)		2.436	0.692-8.574	0.165
Female	4 (16.7%)	44 (38.6%)		Reference		
Operation method, *n* (%)			0.143			
LPD	4 (16.7%)	36 (31.6%)				
OPD	20 (83.3%)	78 (68.4%)				
BMI (kg/m^2)			0.000			
≥ 23	18 (75.0%)	33 (28.9%)		6.094	2.021-18.374	0.001
< 23	6 (25.0%)	81 (71.1%)		Reference		
Serum bilirubin (μmol/L)	96.6 (16.1-180.4)	67 (13.8-111.2)	0.185			
Serum ALB (g/L)			0.843			
≥ 35	21 (87.5%)	98 (86.0%)				
< 35	3 (12.5%)	16 (14.0%)				
ASA score, *n* (%)			0.122			
Grade I	11 (45.8%)	66 (57.9%)				
Grade II	11 (45.8%)	47 (41.2%)				
Grade III	2 (8.3%)	1 (0.9%)				
Pathology, *n* (%)			0.196			
Malignancy	23 (95.8%)	96 (84.2%)				
Benign	1 (4.2%)	18 (15.8%)				
Omental interposition, *n* (%)			0.025			
Yes	7 (29.2%)	62 (54.4%)		Reference		
No	17 (70.8%)	52 (45.6%)		3.145	1.040-9.509	0.042
Operating time (mean ± SD, min)	387.1±82.5	377.7±71.2	0.609			
HJ DFA1 (U/L)			0.010			
≥ 1000	13 (54.2%)	31 (27.2%)		1.000	1.000-1.000	0.834
< 1000	11 (45.8%)	83 (72.8%)		Reference		
PJ DFA1 (U/L)			0.115			
≥ 1000	13 (54.2%)	42 (36.8%)				
< 1000	11 (45.8%)	72 (63.2%)				
Main pancreatic duct size [*n* (%), mm]			0.000			
≥ 3	3 (12.5%)	64 (56.1%)		Reference		
< 3	21 (87.5%)	50 (43.9%)		5.663	1.456-22.033	0.012

ALB: Albumin; ASA: American Society of Anesthesiologist score; BMI: Body mass index; DFA1: Drain fluid amylase obtained on the first postoperative day; HJ: Hepaticojejunostomy; LPD: Laparoscopic pancreaticoduodenectomy; OPD: Open pancreaticoduodenectomy; PJ: Pancreaticojejunostomy.

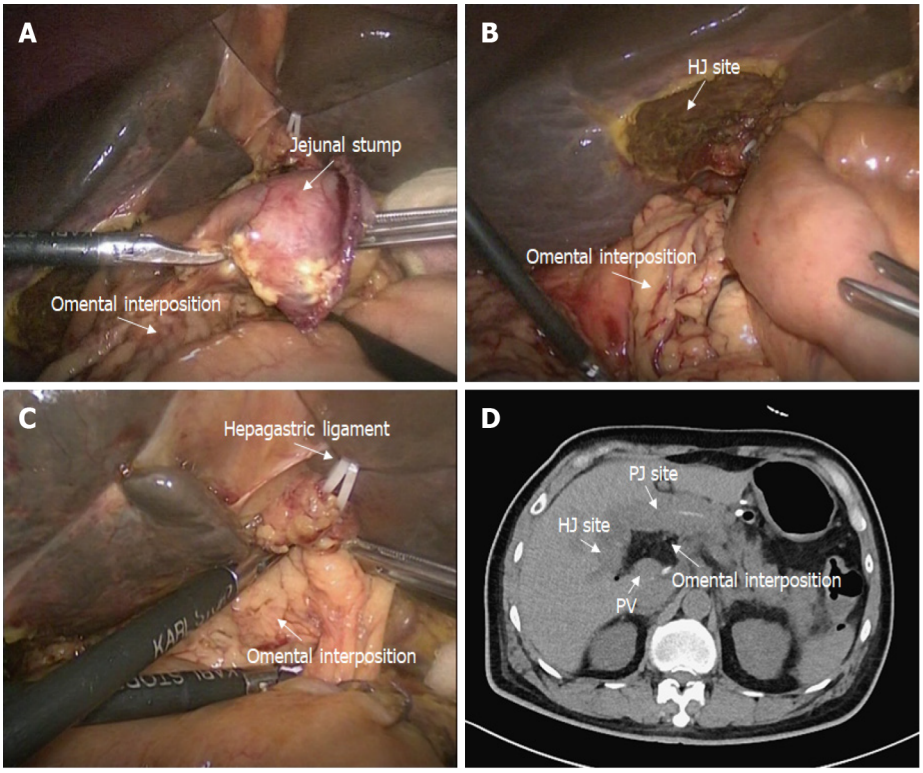

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Figure 2 Application of the omental interposition in pancreaticoduodenectomy. A: The pedicled omental interposition was placed in front of the adjacent vessels (hepatic artery, portal vein, and gastroduodenal artery stump) and behind the pancreaticojejunostomy site; B: The right boundary of the omental interposition was the right margin of the inferior vena cava; C: The upper boundary of the omental interposition was the hepatogastric ligament; the omental interposition was fixed to the hepatic portal and hepatogastric ligament with several sutures to prevent postoperative mobilization; D: Postoperative computed tomography images. The omental interposition elevated the hepaticojejunostomy site and filled the potential cavity.

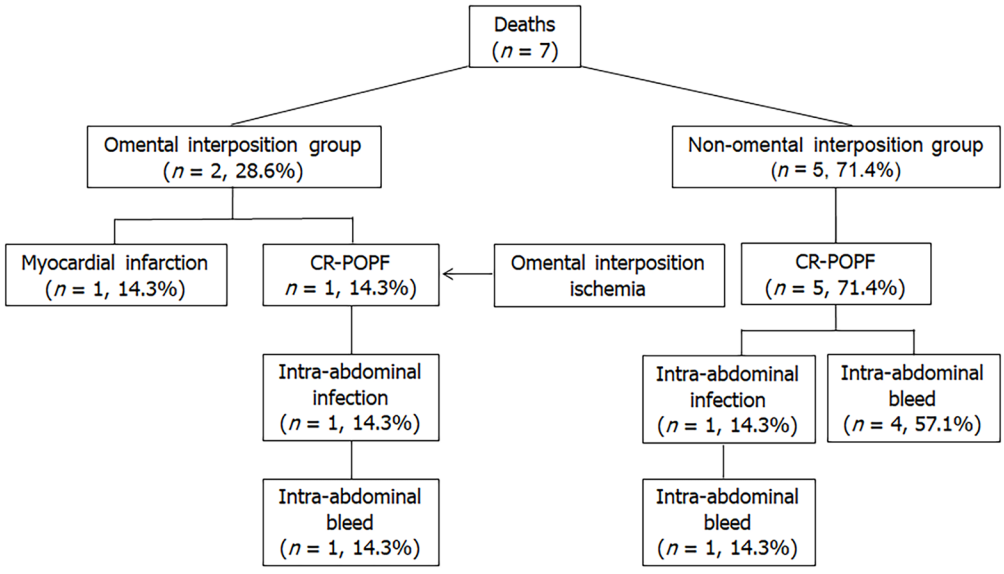

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Figure 3 Causes of death in the two groups.

Since pancreatic fistulas are almost inevitable after PD, it is necessary to improve the surgical techniques and accelerate the healing process of fistulas to strive for "harmless" pancreatic fistulas. Experimental results have shown that the greater omentum can resist corrosion, provide anti-infection properties, absorb the peritoneal effusion, regenerate blood vessels and repair tissue defects. Thus, we hypothesized that the omental interposition could seal the posterior wall of the PJ anastomosis, fill the potential cavity to avoid effusion at the surgical site, cover the skeletonized vessels to avoid erosion and

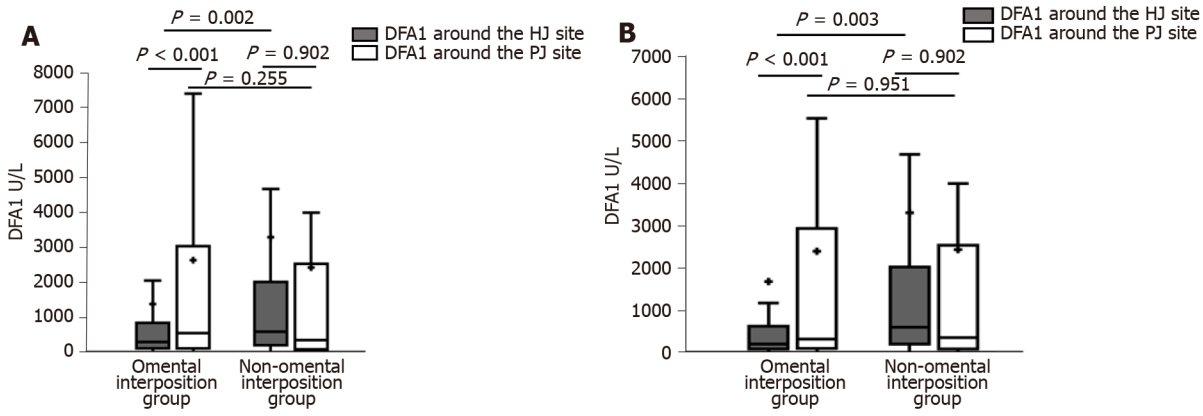

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Figure 4 Differences between the two groups. A: Drain fluid amylase obtained on the first postoperative day (DFA1) before propensity score-matching (PSM); B: DFA1 after PSM.

accelerate the regeneration of blood vessels to improve the blood supply of the anastomosis. The study shows that the incidence of CR-POPF and delayed PPH were lower in the omental interposition group than in the non-omental interposition group. As a result of the reduced complications, the average duration to restart diet and the length of hospital stay were shorter in the omental interposition group. Previous studies on OPD have reached similar conclusions. Maeda[14] covered the major splanchnic arteries and the PV with an omental flap in 100 patients. Although the author concluded that the incidence of POPF (20%) was not significantly different from that in other articles, he did not rule out biochemical fistulas based on the modified definition by the ISGPF. Matsuda *et al*[20] emphasized the preventive effect of omental flaps in PD against postoperative pseudoaneurysm formation. Shah *et al*[21] wrapped the omental flap around the PJ site in 101 patients and showed that it could reduce the incidence of POPF (4.0% *vs* 17.4%), PPH (0% *vs* 6.5%), BF (1.0% *vs* 13.0%), and DGE (4.0% *vs* 17.4%) compared to those in the non-omental interposition group.

In addition to the physiological function of the omental interposition, our method could elevate the height of the anastomosis and fill the potential cavity due to the physical characteristics. Because the omental interposition can elevate the position of the HJ anastomosis (Figure 2D), the erosive pancreatic fluid will flow to the left instead of remaining around the skeletonized vessels in the right upper quadrant of the abdomen. The difference in DFA1 between HJ and PJ sites confirm these physical characteristics in the omental interposition group. This finding also confirms that the application of the omental interposition, by preventing leakage from the anastomosis, reduces the incidence of delayed PPH. Because of the effective control of serious complications, the omental interposition group had their drainage tubes removed earlier, required fewer postoperative transfusions, restarted their diet earlier and had a shorter hospital stay than the non-omental interposition group. These findings are highly consistent with the aforementioned studies showing the efficacy of the omental interposition in PD.

PSM of nine baseline characteristics was performed to reduce selection bias and potential confounding factors between the two groups. After matching, the incidences of CR-POPF and delayed PPH remain significantly lower in the omental interposition group. Similarly, the difference in median DFA1 values between HJ and PJ sites in the omental interposition group remained observable. However, in the non-omental interposition group, the DFA1 around the PJ site was significantly higher than the DFA1 around the HJ site. Due to the physical characteristics of the omental interposition, the corrosive pancreatic juice would flow to the left upper quadrant of the abdomen because of gravity. Obviously, these details matter tremendously.

Previous studies[22-24] have reported that the risk factors for POPF include a high BMI, soft pancreatic texture, and small pancreatic duct size. In our study, univariate and multivariate analyses revealed that a high BMI, nonapplication of omental interposition, and main pancreatic duct diameter < 3 mm were independent factors significantly associated with the development of CR-POPF after PD. The developed statistical model had a c-index of 0.848. These findings were partially consistent with previous POPF risk scores.

Only one patient in the omental group died of delayed PPH caused by ischemic infection due to poor blood supply of the omental interposition, which resulted in delayed hemorrhage. This was the eighth case in which we applied the omental interposition with insufficient emphasis on ensuring good blood supply to the omental interposition. Since then, we detached the gastrocolic ligament along the gastric wall to ensure good blood supply to the omental interposition.

This study had several limitations, including its design as a single-center, retrospective observational study. However, all clinically related data were prospectively collected, and all operations were performed by the same surgical group with the same surgical technology. Thus, the majority of the

potential confounding factors were controlled.

CONCLUSION

In conclusion, we believe that the application of the omental interposition is technically simple and may help prevent CR-POPF and the associated complications following PD.

ARTICLE HIGHLIGHTS

Research background

Postoperative pancreatic fistula (POPF) is a life-threatening complication after pancreaticoduodenectomy (PD).

Research motivation

Several methods have attempted to reduce the POPF after PD, few have been considered effective. The safety and short-term clinical benefits of omental interposition remain controversial.

Research objectives

To investigate the safety and feasibility of omental interposition to reduce the POPF rate and related complications in PD.

Research methods

In total, 196 consecutive patients underwent PD performed by the same surgical team, the patients were divided into two groups: an omental interposition group (127, 64.8%) and a non-omental interposition group (69, 35.2%). Propensity score-matched analyses were performed to compare the severe complication rates and mortality between the two groups.

Research results

The clinically relevant POPF (CR-POPF; 10.1% *vs* 24.6%; $P = 0.025$) and delayed postpancreatectomy hemorrhage (1.4% *vs* 11.6%; $P = 0.016$) rates were significantly lower in the omental interposition group. The omental interposition technique was associated with a shorter time to resume food intake (7 *vs* 8 d; $P = 0.048$) and a shorter hospitalization period (16 *vs* 21 d; $P = 0.031$).

Research conclusions

The application of the omental interposition is an effective and safe approach to reduce the CR-POPF rate and related complications after PD.

Research perspectives

Prospective studies are needed on the role of omental interposition in reducing CR-POPF.

FOOTNOTES

Author contributions: Li Y, Liang Y, and Deng Y contributed equally to this manuscript; Jiang CY participated in the conception and design of this study; Deng Y, Cai ZW, Ma MJ, Wang LX, Liu M, and Wang HW participated in the data collection; Li Y participated in the data collection, analysis, and drafting of the article; Liang Y participated in the design of the study and data analyses; All authors have read and approved the final manuscript.

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SCIENTOMETRICS

Global research production pertaining to gastrointestinal involvement in COVID-19: A bibliometric and visualised study

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) is a global pandemic that can cause diarrhoea, nausea/vomiting, and abdominal pain, among other gastrointestinal (GI) symptoms.

AIM

To perform a bibliometric analysis of the global research production pertaining to GI involvement in COVID-19.

METHODS

The Scopus database was used to search the global literature on GI involvement in COVID-19 during 2020. A bibliometric review of these publications was also performed using VOSviewer.

RESULTS

Scopus had published 95615 documents on COVID-19 in all areas of research at the time of data collection. In total, 1267 publications on the topic of GI and

COVID-19 were identified. Research articles (n = 606; 47.83%), letters (293; 23.13%), and reviews (186; 14.68%) were the most popular types of documents. The most productive countries and institutions in this field were the United States and Huazhong University of Science and Technology. The most cited paper was Xiao *et al*, which was published in *Gastroenterology* as a brief communication, with 798 citations. This paper provides evidence for GI infection of COVID-19 and its possible faecal–oral transmission route. In the term cluster analysis, there were two frontiers in this field: GI manifestations among COVID-19 patients and the implications of COVID-19 for the gastroenterologist.

CONCLUSION

GI manifestations among COVID-19 patients and implications of COVID-19 for gastroenterologists were of interest, especially in the early stages of the pandemic.

Key Words: COVID-19; Gastrointestinal; Symptoms; Bibliometric; Scopus

Core Tip: This bibliometric analysis provides the first concise summary of global gastrointestinal (GI) publications related to coronavirus disease 2019 (COVID-19). It highlights the benefits of bibliometric analysis in a systematic and structured way to measure the productivity of studies. GI manifestations among COVID-19 patients and the implications of COVID-19 for gastroenterologists were of interest, especially in the early stage of the pandemic. The results will form the basis for future research and guide decision-making in research related to GI symptoms and treatments in COVID-19.

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INTRODUCTION

In December 2019, coronavirus disease (coronavirus disease 2019, COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spread quickly from China to nearly every country in the world, and is now considered the world's most significant public health threat, causing a massive crisis for global health[1-3]. The 2019 new coronavirus was named SARS-CoV-2 by the World Health Organization (WHO), with COVID-19 being given as the disease name[4]. As of March 13, 2021, there were over 118 million confirmed cases worldwide, with more than 2.6 million associated global deaths, according to a WHO report[5].

In most studies, patients with COVID-19 have gastrointestinal (GI) manifestations, such as diarrhoea, nausea, anorexia, vomiting, abdominal pain, and GI bleeding[6-11], in addition to fever and common respiratory symptoms including cough, and shortness of breath[3,12]. However, some patients have developed various fatal complications including severe pneumonia, pulmonary oedema, acute respiratory distress syndrome, septic shock, and organ failure[13-15]. Several studies have shown that SARS-CoV-2 can interact with angiotensin-converting enzyme 2 (ACE2) receptors on ileal enterocytes and colon epithelial cells, implying a trophism for the GI tract[7]. The pathophysiology of GI symptoms is unclear, but it appears that SARS-CoV-2 binds to ACE2, which regulates amino acid homeostasis and microbiome balance in the intestine, causing a change in physiological function that leads to GI symptoms[16-18].

Several systematic reviews and meta-analyses have indicated that during the pandemic, there was an increase in the number of publications discussing the impact of COVID-19 on the GI system in several countries[6,9-11,19-27]. To date, there has not been a global bibliometric review of research related to GI and COVID-19. Bibliometrics aims to determine the depth of information in a given field[28]. In other areas of COVID-19, this approach has been used to quantify and categorise research output, allowing for mapping the area in question based on the most involved authors, institutions, countries, citations, journals, and hot topics in this field[29-32]. Therefore, the purpose of this study was to report a bibliometric analysis of the global research production pertaining to GI involvement in COVID-19 to determine the most widely cited papers and most prolific countries, institutions, and journals related to this topic. Our results will help to guide priority setting and policy formulation for long-term strategies to improve the outcomes of COVID-19 patients with GI manifestations.

MATERIALS AND METHODS

Data sources

The publications were retrieved on the same day from the Scopus on March 20, 2021, to prevent bias due to the daily database updates. Since Scopus is the most commonly accepted and regularly used database for analysing scientific articles in the field of bibliometrics, it was chosen as the search engine. Although we recognise the existence of other databases, we acted in accordance with the methodological approach of previous research[33,34].

Search strategies

The search was restricted to publications between January 1 and December 31, 2020. The following search strategy was used in this bibliometric study to retrieve data.

Step 1: To achieve the goals of this bibliometric review, the terms related to COVID-19 entered into the Scopus engine were chosen from the literature related to COVID-19[35-38]. All of the following terms were used as Article Title/Abstract/Keyword: "COVID 19" OR "2019 novel coronavirus" OR "coronavirus 2019" OR "SARS-CoV-2" OR "SARS-CoV 2" or "coronavirus disease 2019" OR "2019-novel CoV" OR "2019 ncov" OR "COVID 2019" OR "corona virus 2019" OR "nCoV-2019" OR nCoV2019 OR "nCoV 2019" OR 2019-ncov OR COVID-19 OR "Severe acute respiratory syndrome coronavirus 2" OR Novel Coronavirus.

Step 2: We confined the publications that we obtained in Step 1 to those with the terms gastrointestinal and related words in their title. The terms relevant to GI that were entered into the Scopus engine were selected from previous GI meta-analyses[6,39]. All of the following terms were entered as Article Title: gastrointestinal OR "GI tract" OR gastr* OR Diarrh* OR Constipation OR Vomiting OR *intestin* OR dysphagia OR "Abdominal pain" OR Nausea OR heartburn OR Bowel OR Gut OR digest* OR stomach OR duodenal OR colon OR colorectal anorectum. The asterisk (*) was used as a truncator or wildcard to capture all of the term variants that shared a core.

Bibliometric analysis

The data collected included the following bibliometric parameters: type of documents, number of publications, citation count, country, institution, and journals. The impact index per article is presented for the top ten most-cited papers as determined by *Reference Citation Analysis* (RCA). Baishideng Publishing Group Inc. owns RCA, an open, multidisciplinary citation analysis database (Pleasanton, CA, United States) (https://www.referencecitationanalysis.com/).

Visualise analysis

VOSviewer version 1.6.16 (Leiden University, Leiden, The Netherlands) was used for bibliometric visualisation[40]. In this study, VOSviewer was used for collaborative patterns between countries and term co-occurrence analysis. As a result, we decided to build and visualise the network terms used in the title/abstract of publications to define the hot topics in this field. The relationship between terms is based on the number of publications in which they appear together, according to co-occurrence analysis [40]. Therefore, the aim of this study was to identify research areas as hot topics, and it is a valuable indicator for tracking scientific progress[41].

RESULTS

Volume and types of publications

Scopus had published 95615 documents on COVID-19 in all areas of research at the time of data collection. In total, 1267 publications on the topic of GI and COVID-19 were identified during the period of study (January 1 to December 31, 2020). A total of 1267 documents (1.33%) were used in this study. Research articles (n = 606; 47.83%), letters (293; 23.13%), and reviews (186; 14.68%) were the most popular types of documents.

Active countries and international research collaboration

The United States was the leader in this field, with 278 publications (21.94%). Other top countries were China (222, 17.52%), Italy (184, 14.52%), and the United Kingdom (159, 12.55%) (Table 1). Several studies reported the symptoms of GI to be present in 2.6% and 75% patients with COVID 19 infection (Table 1). There were 33 countries included (the minimum number of publications for each country was 10), and their network collaboration maps were visualised by VOSviewer (Figure 1). The top four countries by centrality were the United States, China, Italy, and the United Kingdom. According to their centrality, these countries showed close collaboration with each other and a strong research influence with other countries.

Table 1 List of the top 10 countries pertaining to gastrointestinal publications involvement in coronavirus disease 2019

Ranking	Country	No. of documents	%	Study population	Sample size	Prevalence of GI symptoms (%)	Common GI symptoms
1st	United States	278	21.94	Multicentre Cohort Study [48]	318	61.3	Loss of appetite, diarrhoea, and nausea
2nd	China	222	17.52	Retrospective study[51]	1320	14.5	Diarrhoea, anorexia, and nausea and vomiting
3rd	Italy	184	14.52	Prospective case-control study[47]	34	8.8	Diarrhoea, abdominal pain, and nausea
4th	United Kingdom	159	12.55	Prospective observational cohort study[42]	20, 133	23	Diarrhoea, nausea/vomiting, and abdominal pain
5th	Spain	61	4.81	Retrospective study[49]	76	75	Diarrhoea, nausea/vomiting, and abdominal pain
6th	France	59	4.66	Retrospective study[45]	114	2.6	Diarrhoea
7th	Germany	56	4.42	Retrospective study[43]	50	> 16	Diarrhoea, nausea/vomiting
8th	India	51	4.03	Prospective study[44]	252	10.3	anorexia, nausea, vomiting, abdominal pain
9th	Australia	37	2.92	Epidemiological study[50]	295	> 16	Diarrhoea, nausea/vomiting, and abdominal pain
10th	Iran	33	2.60	Retrospective study[46]	611	25.4	Nausea/vomiting, diarrhoea, and abdominal pain

GI: Gastrointestinal.

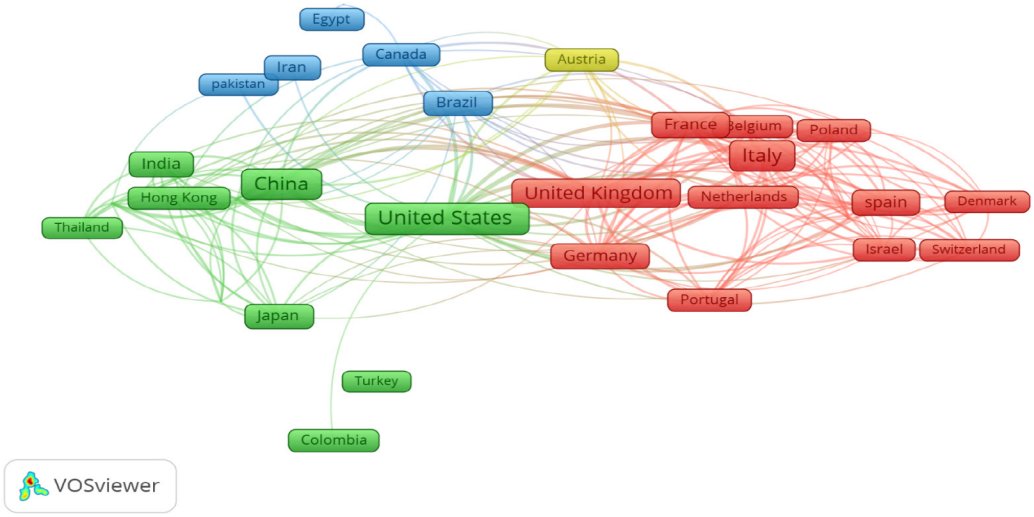

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Figure 1 Network visualisation map of international research collaborations among the top 33 active countries with at least 10 articles published each.

Active institutions/organisations

Table 2 shows the top 10 institutions in terms of publication numbers. The Huazhong University of Science and Technology, China (n = 33 publications), Humanitas Research Hospital, Italy (n = 23 publications), the Humanitas University, Italy (n = 30 publications), and the Tongji Medical College, China (n = 29 publications) were the top four productive and influential institutions, indicating that they have achieved significant scientific achievements and research capability.

Active journals

Regarding journals, *Gastroenterology* ranked first with 457 publications (4.50%), followed by *American Journal of Gastroenterology* (n = 34; 2.68%), *Inflammatory Bowel Diseases* (n = 34; 2.68%), and *Lancet Gastroenterology and Hepatology* (n = 34; 2.68%). Table 3 presents the top 10 most popular journals with

Table 2 List of the top 10 institutions pertaining to gastrointestinal publication involvement in coronavirus disease 2019

Ranking	Institution	Country	*n*	%
1st	Huazhong University of Science and Technology	China	33	2.60
2nd	Humanitas Research Hospital	Italy	32	2.53
3rd	Humanitas University	Italy	30	2.37
4th	Tongji Medical College	China	29	2.29
5th	INSERM	France	27	2.13
6th	Chinese University of Hong Kong	China	26	2.05
7th	Fondazione Policlinico Universitario Agostino Gemelli IRCCS Università Cattolica del Sacro Cuore	Italy	25	1.97
8th	Università degli Studi di Roma La Sapienza	Italy	22	1.74
9th	Università degli Studi di Milano	Italy	21	1.66
10th	Università degli Studi di Padova	Italy	20	1.58
10th	University Hospitals Birmingham NHS Foundation Trust	United Kingdom	20	1.58

Table 3 List of the top 10 journals pertaining to gastrointestinal publications involvement in coronavirus disease 2019

Ranking	Journal	*n*	%	Impact factors
1st	*Gastroenterology*	57	4.50	17.373
2nd	*American Journal of Gastroenterology*	34	2.68	10.171
2nd	*Inflammatory Bowel Diseases*	34	2.68	4.261
2nd	*Lancet Gastroenterology and Hepatology*	34	2.68	14.789
5th	*Digestive and Liver Disease*	33	2.60	3.570
6th	*British Journal of Surgery*	29	2.29	5.676
7th	*Alimentary Pharmacology and Therapeutics*	25	1.97	7.515
8th	*Clinical Gastroenterology and Hepatology*	21	1.66	8.549
9th	*Colorectal Disease*	20	1.58	2.769
10th	*Journal of Gastroenterology and Hepatology*	18	1.42	3.437

Impact factors were retrieved from the 2019 Journal Citation Reports (Clarivate Analytics).

the highest number of global research productions pertaining to GI involvement in COVID-19.

Top cited documents

The number of citations is an important measure of the impact and recognition that a paper has received from the scientific community. Table 4 presents the 10 most cited studies found in the Scopus database. The top 10 most cited publications had citation counts ranging from 269 to 798. Furthermore, the ten most cited articles have an impact index per article of 189 to 617.5 (Table 4).

Most frequent terms (research themes)

Using VOSviewer, we examined the term occurrence from 1267 publications. As seen in Figure 2, 270 words were identified and grouped into two clusters based on the number of times they appeared in the titles and abstracts of all publications. The red cluster involved GI manifestations including terms such as “gastrointestinal”, “symptoms”; “nausea”, “vomiting”, and “diarrhoea”. The green cluster involved implications of COVID-19 for the gastroenterologist including terms such as “recommendations”, "procedure”, “impact”, “surgery”, “endoscopy”, “strategy”, “practice”, and “prevention”.

DISCUSSION

The use of bibliometric analysis to review the patterns and development of various fields and areas of

Table 4 List of the top 10 cited articles for gastrointestinal publications involvement in coronavirus disease 2019

Ranking	Ref.	Title	Source title	Cited by	Impact index per article[1]
1st	Xiao *et al* [58], 2020	"Evidence for Gastrointestinal Infection of SARS-CoV-2"	*Gastroenterology*	798	617.5
2nd	Xu *et al*[59], 2020	"Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding"	*Nature Medicine*	525	384.0
3rd	Gu *et al*[52], 2020	"COVID-19: Gastrointestinal Manifestations and Potential Fecal–Oral Transmission"	*Gastroenterology*	507	342.5
4th	Pan *et al*[55], 2020	"Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: A descriptive, cross-sectional, multicenter study"	*American Journal of Gastroenterology*	464	352.5
5th	Wu *et al*[57], 2020	"Prolonged presence of SARS-CoV-2 viral RNA in faecal samples"	*Lancet Gastroenterology and Hepatology*	451	374.5
6th	Jin *et al*[53], 2020	"Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms"	*Gut*	362	277.0
7th	Cheung *et al* [10], 2020	"Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis"	*Gastroenterology*	356	269.5
8th	Lamers *et al* [54], 2020	"SARS-CoV-2 productively infects human gut enterocytes"	*Science*	338	317.5
9th	Yeo *et al*[60], 2020	"Enteric involvement of coronaviruses: is faecal–oral transmission of SARS-CoV-2 possible?"	*Lancet Gastroenterology and Hepatology*	323	202.0
10th	Tian *et al* [56], 2020	"Gastrointestinal features in COVID-19 and the possibility of faecal transmission"	*Alimentary Pharmacology and Therapeutics*	269	189.0

[1]The impact index per article is presented based on *Reference Citation Analysis* [source: Baishideng Publishing Group Inc. (Pleasanton, CA 94566, United States)].

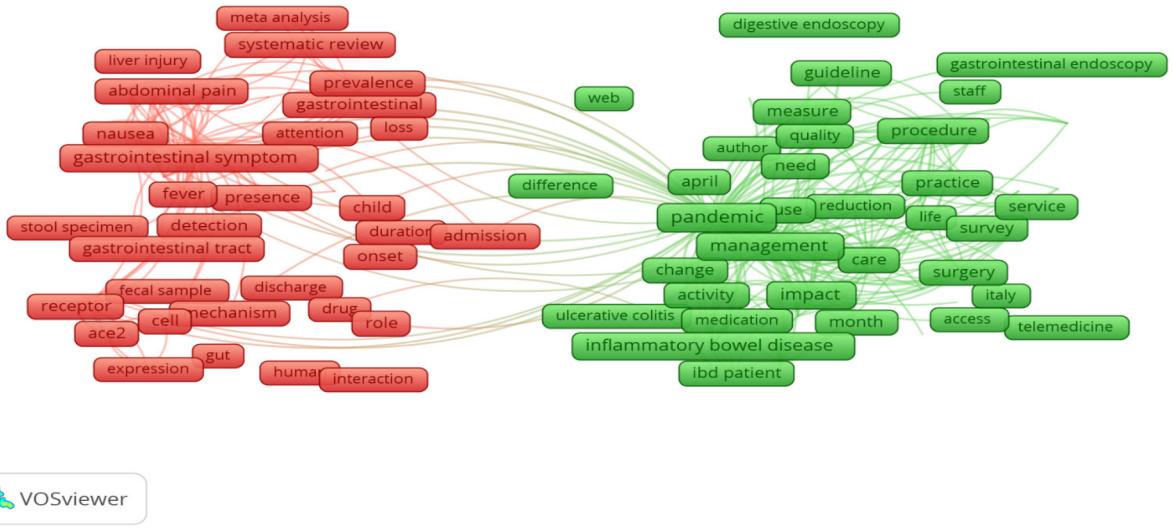

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Figure 2 Network visualisation map of the most frequent terms in titles/abstracts of the retrieved literature pertaining to gastrointestinal publications involvement in coronavirus disease 2019. The terms were divided into two clusters based on the various colours created by default, namely, gastrointestinal manifestations coronavirus disease 2019 (COVID-19) patients (red), and implications of COVID-19 for gastroenterologists (green). The large icon indicates the terms that appeared at a high frequency. Among the 13932 terms, only 270 (defined as terms that occurred > 15 times) appeared in titles and abstracts in all publications.

research is becoming more common. The current data analysis reflects various facets of GI publication involvement in COVID-19, including the top countries, institutions, cited articles, journals generating COVID-19 publications, and hot topics in this field. It is critical to determine scientific output through bibliometric analysis to guide researchers on what has already been developed and what is currently

being researched so that future research can resolve information gaps.

Following the COVID-19 pandemic, high-income countries such as the United States, China, Italy, the United Kingdom, Spain, France and Germany are the world leaders in GI publications in COVID-19. A potential reason for these findings is the high prevalence of COVID-19 in countries that experienced the initial outbreak[61-66]. In the most recent studies, nearly 60% of the COVID-19 publications in the Web of Science come from the United States, China, Italy and the United Kingdom[67]. According to the research, the United States contributed the most scientific papers published during the COVID-19 pandemic. This is due to the fact that it has the most academic journals on the search sites in use, as well as being a country where researchers from all over the world want to publish their findings[68]. China was second in the ranking. This is demonstrated by the fact that China has over 3.61 million licensed doctors[13]. Furthermore, Chinese institutions contributed various papers to the COVID-19 research initiative and played a crucial role in the pandemic response[69].

This study found that many publications focused on GI manifestations among COVID-19 patients and implications of COVID-19 for gastroenterologists. So far, COVID-19-related research has involved disease transmission, virology and immunology, epidemiology, clinical characteristics, nonpharmaceutical interventions, detection and diagnosis, treatment, vaccines, and other categories including the psychological status of the medical staff and public during the pandemic[67,70].

The current study used a bibliometric review to discuss the top 10 cited publications about GI involvement in COVID-19. Just three articles addressed GI intervention in COVID-19 patients, while the rest of the widely cited literature centred on GI characteristics and disease features in COVID-19 patients. The most-cited paper was Xiao *et al*[58], which was published in *Gastroenterology* as a brief communication, with 798 citations. This paper provides evidence for GI infection in COVID-19 and its possible faecal-oral transmission route. The second most-cited paper was by Xu *et al*[59] from *Nature Medicine* as a brief communication. According to the results of that study, rectal swab testing may be more helpful than nasopharyngeal swab testing in assessing the efficacy of management and timing of quarantine termination. However, replication-competent virus in faecal swabs was not demonstrated in the study, and this is necessary to confirm the possibility of faecal-oral transmission. The third most-cited paper was by Gu *et al*[52] in *Gastroenterology* as a commentary, which stated that COVID-19 could be present in the oral cavity and faeces of infected people. Moreover, that study recommended that the initial digestive symptoms of COVID-19 should be an alert for early isolation, detection, diagnosis and intervention.

Therefore, our study provides an understanding of the research on GI symptoms in COVID-19, and citation rates can indicate important research topics, development trends in COVID-19 and GI-related research, and provide a reference for research cooperation. However, the mechanism of intestinal infection, its relationship to cytokine release syndrome, and the probability of faecal-oral transmission all require further research in larger populations, especially prospective validation studies with well-designed questions.

This bibliometric analysis provides the first concise summary of global GI publications related to COVID-19. It highlights the benefits of bibliometric analysis in a systematic and structured way to measure the productivity of studies. However, no search strategy is flawless, and the dropout of false-positive or false-negative results is also expected. We attempted to be as comprehensive as possible, using all terms related to GI and COVID-19 listed in the literature. However, there was a possibility of missing some terms. Therefore, we did our best to retrieve all GI publications concerning COVID-19 and sought to verify their study approach using techniques introduced in previously published bibliometric studies. Furthermore, the number of citations will fluctuate over time due to the rapidly changing existence of COVID-19 science. The final limitation is that the authors did not search all scientific databases; however, this limitation is present in almost all bibliometric studies.

CONCLUSION

This research offers a detailed overview of the position of GI publications in COVID-19 research evolution during the early stages of the outbreak. In a short timespan (1 year) following the start of the COVID-19 pandemic, high-income countries such as the United States, China, Italy, the United Kingdom, Spain, France and Germany became the global leaders of GI-related publications, and were responsible for the bulk of the literature written in this field. This study has found that many publications focused on GI manifestations among COVID-19 patients and the implications of COVID-19 for gastroenterologists. While GI symptoms play an important role in COVID-19, there are still many knowledge gaps about their pathophysiology and prognostic value. Prospective studies with well-designed questions can be used to perform further research. The results of this bibliometric study will act as a basis for future research and guide decision-makers for research related to GI symptoms and treatment in COVID-19.

ARTICLE HIGHLIGHTS

Research background

Fever and respiratory symptoms are common in coronavirus disease 2019 (COVID-19) patients. Gastrointestinal (GI) symptoms such as diarrhoea, vomiting, and stomach pain may also occur in some patients.

Research motivation

There was an increase in the number of publications addressing the effect of COVID-19 on the GI system in a variety of countries during the outbreak, according to several systematic reviews and meta-analyses. There has not been a comprehensive bibliometric analysis of research on GI and COVID-19. The aim of bibliometrics is to determine the depth of knowledge in a given area.

Research objectives

The purpose of this study was to report a bibliometric analysis of the global research pertaining to GI involvement in COVID-19 to determine the most widely cited papers and most prolific countries, institutions, and journals related to this topic.

Research methods

We searched Scopus for publications during 2020, and selected articles focused on GI and COVID-19.

Research results

The current data analysis reflects various facets of GI-related publications in COVID-19, including the top countries, institutions, cited articles, journals generating COVID-19 publications, and hot topics in this field. It is critical to determine scientific output through bibliometric analysis to guide researchers on what has already been developed and what is currently being researched so that future research can resolve information gaps.

Research conclusions

COVID-19 GI manifestations and implications for gastroenterologists were of increasing concern, especially in the early stages of the pandemic. As a result, it is suggested that research on this subject be focused on the connection between GI manifestations and potential COVID-19 outcomes.

Research perspectives

Our results will help to guide priority setting and policy formulation for long-term strategies to improve the outcomes of COVID-19 patients with GI manifestations.

FOOTNOTES

Author contributions: Zyoud SH designed the study, collected the data, analyzed the data, made major contributions to the manuscript's existing literature search and interpretation, and drafted the manuscript; Al-Jabi SW participated in the study design, was involved in interpretation of the data, made revisions to the initial draft, and answered the reviewers' comments; Jairoun AA and Shahwan MJ corrected the manuscript and answered the reviewers' comments; all authors provided a critical review and approved the final manuscript before submission.

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CASE REPORT

Aorto-oesophageal fistula after corrosive ingestion: A case report

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Abstract

BACKGROUND

Aorto-oesophageal fistula (AOF) are uncommon and exceedingly rare after corrosive ingestion. The authors report a case of AOF after corrosive ingestion that survived. A comprehensive literature review was performed to identify all cases of AOF after corrosive ingestion to determine the incidence of this condition, how it is best managed and what the outcomes are.

CASE SUMMARY

A previously healthy 30-year-old male, presented with a corrosive oesophageal injury after drain cleaner ingestion. He did not require acute surgical resection, but developed long-segment oesophageal stricturing, which was initially managed with cautious dilatation and later stenting. An AOF was suspected at endoscopy performed two months after the ingestion, when the patient represented with massive upper gastrointestinal bleeding. The fistula was confirmed on computerised tomographic angiography. The initial bleeding at endoscopy was temporised by oesophageal stenting; a second stent was placed when bleeding recurred later the same day. The stenting successfully achieved temporary bleeding control, but resulted in sudden respiratory distress, which was found to be due to left main bronchus compression caused by the overlapping oesophageal stents. Definitive bleeding control was achieved by endovascular aortic stent-grafting. A retrosternal gastroplasty was subsequently performed to achieve gastrointestinal diversion to reduce the risk of stent-graft sepsis. He was subsequently successfully discharged and remains well one year post injury.

CONCLUSION

AOF after corrosive ingestion is exceedingly rare, with a very high mortality. Most occur weeks to months after the initial corrosive ingestion. Conservative management is ill-advised.

Key Words: Aorto-oesophageal fistula; Corrosive/caustic injury; Corrosive ingestion; Case report

Core Tip: Aorto-oesophageal fistula (AOF) after corrosive ingestion is exceedingly rare, but is usually catastrophic. We present a case of AOF after corrosive ingestion which was successfully managed with a combination of oesophageal stenting to achieve temporary bleeding control, and endovascular aortic stent-grafting with retrosternal gastroplasty as definitive management. Including this case, only 16 individual cases of this rare condition are found in the literature, with only two survivors prior to this case. Fistula formation usually only occurs weeks to months after the ingestion incident and as such a high level of suspicion is needed to diagnose this illusive and difficult to manage condition.

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INTRODUCTION

Aorto-oesophageal fistula (AOF) is a rare, but deadly entity. Chiari's classic triad of midthoracic pain, a herald bleed, followed by exsanguinating haemorrhage was initially described for AOF after foreign body ingestion but has since been applied to any AOF[1]. The most common causes include complicated thoracic aortic aneurysms, oesophageal foreign bodies and oesophageal carcinoma[1]. Confirming the diagnosis can be challenging and in most cases is only made at post-mortem examination. Management remains controversial and overall survival is low. AOF after corrosive or caustic ingestion are exceedingly rare and only a few cases have been described in the literature. We report a case of an AOF survivor after corrosive ingestion. A comprehensive literature review was performed to identify all cases of AOF after corrosive ingestion to assess how common the condition is, how it is best managed and what the outcomes are.

A comprehensive search of the literature up to March 31, 2021 was performed with the help of a clinical librarian in the following databases: PubMed, PubMed Central, Scopus, Web of Science Core Collection and Cochrane Library. No language or time constraints were set. The following keyword search terms were used: [(Aorta OR aorta OR aortas OR aortic) AND (oesophagus OR esophagus OR oesophageal OR esophageal) AND (fistula OR fistulae OR fistulas) AND (corrosive OR corrosion OR corroding OR caustic OR caustics OR lye OR abrasive OR abrasives OR acid OR acids OR alkaline)]. The following MESH terms were also included in the search: ["Aorta" (Mesh) OR "Aortic Diseases" (Mesh)] AND [Esophageal Fistula (Mesh)] AND ["Caustics" (Mesh)] (Supplementary Table 1).

A total of 2460 studies were identified after the initial search, of which only 11 publications met the final inclusion criteria, rendering a total of 15 individual cases of AOF after corrosive ingestion (not including our own case, reported in this publication).

CASE PRESENTATION

Chief complaints

A 30-year-old male, known with a long-segment oesophageal stricture two months after corrosive ingestion, underwent an urgent gastroscopy for an upper gastrointestinal bleed. During the procedure he was noted to have massive bleeding from the oesophagus and an AOF was suspected.

History of present illness

The patient initially presented to our institution five days after accidentally consuming a corrosive substance, later identified as drain cleaner (sodium hydroxide). He was dared to consume the substance at a party and was unaware that it contained a corrosive. Except for a mild tachycardia, vital signs and routine blood work on initial admission were normal. He had an inflamed oropharyngeal mucosa and careful early upper gastrointestinal endoscopy indicated a severe corrosive injury with extensive necrosis of almost the entire oesophageal mucosa, but with viable visible underlying oesophageal

muscle (Zargar grade IIb[2]). He also had a milder gastric injury, with superficial focal ulceration but no necrosis, limited to the gastric antrum (Zargar grade IIa[2]). With no features of full thickness gastric or oesophageal necrosis, an endoscopic nasojejunal feeding tube was placed and he was admitted for continued observations and nutritional support.

Contrast swallow examination on day nine post injury (Figure 1) confirmed the extensive oesophageal injury with irregular mucosa and already showed early long-segment stricturing. The feeding tube was removed fourteen days later after successful early cautious serial bougie dilatation to 14 mm. He was discharged home three days later tolerating a soft diet.

At his two-weekly review, he again complained of near-complete dysphagia. Upper gastrointestinal endoscopy with fluoroscopy now confirmed an established high-grade, long oesophageal stricture extending from 25 cm from the front incisors to the oesophagogastric junction. Due to the risk of perforation associated with pneumatic or repeat bougie dilatation, a more gradual dilatation with temporary stenting was opted for. Two overlapping 120 mm × 20 mm fully covered self-expanding metal stents were placed (Taewoong Medical Company, Gojeong, South Korea). He remained well after this, tolerating a soft diet at home.

He returned three weeks later reporting a single episode of haematemesis, but was haemodynamically and generally well. He did not complain of dysphagia. Gastroscopy was again performed, which revealed both stents in-situ and patent. However, the most proximal stent had migrated distally by some 2 cm with an area of stricturing above this. The scope was passed beyond this with complete endoscopic examination down to the second part of the duodenum revealing no signs of gastrointestinal bleeding or pathology. On pulling back the proximal stent to cover the area of developing stricturing, brisk bleeding occurred which was controlled after placement of a third oesophageal stent.

History of past illness

The patient was previously healthy, with no known prior medical or surgical history.

Personal and family history

There was no other relevant personal history or family history of note. Other than social alcohol use he denied any other substance use.

Physical examination

After the bleeding from the suspected AOF was temporised, his vital signs showed a blood pressure of 105/67 mmHg, a heart rate of 150 beats/minute, a respiratory rate of 18 breaths/minute with oxygen saturation of 97% on room air and a normal Glascow Coma Scale of 15/15. His general examination was normal with no signs of pallor or other abnormalities.

Laboratory examinations

Full blood count showed a formal haemoglobin of 9.3 g/dL and a mild leukocytosis of 11.59 × 10^9/L. Urea, creatinine and electrolytes were normal.

Imaging examinations

On suspicion of an AOF, an urgent computerised tomographic angiogram (CTA) was performed, which confirmed the fistula in the region of the proximal thoracic oesophagus with an aberrant right-sided aortic arch (Figure 2).

FINAL DIAGNOSIS

AOF after corrosive ingestion.

TREATMENT

After the bleeding was stopped, the patient was resuscitated with intravenous fluids and admitted. After CTA confirmation of the AOF, an endovascular aortic repair was planned but another massive bleed occurred which was temporised with a fourth oesophageal stent. This was followed by transient respiratory distress and chest X-ray showed a near-complete "white-out" of the left chest (Figure 3). A thoracic endovascular aortic repair *via* a right femoral approach using a 28 mm (proximal diameter) × 28 mm (distal diameter) × 157 mm (covered length) Valiant thoracic stent graft (Medtronic, Dublin, Ireland) was then successfully performed.

To prevent endovascular stent contamination, an oesophageal exclusion with a retrosternal gastric conduit was performed five days after the endovascular procedure. On-table bronchoscopy showed extrinsic compression with near-complete occlusion of the left main bronchus. On-table oesophagoscopy with successful retrieval of the four oesophageal stents was performed. Repeat bronchoscopy now

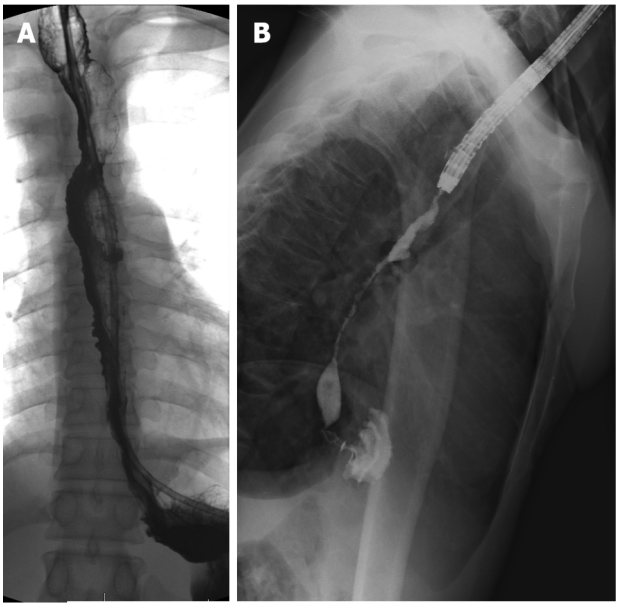

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Figure 1 Contrast swallow examination on day nine post injury. A: Contrast swallow study performed 9 d post injury, already confirming early long-segment stricturing of the oesophagus; B: Fluoroscopic study during endoscopy performed 4 wk post injury, showing high-grade, long-segment oesophageal stricturing.

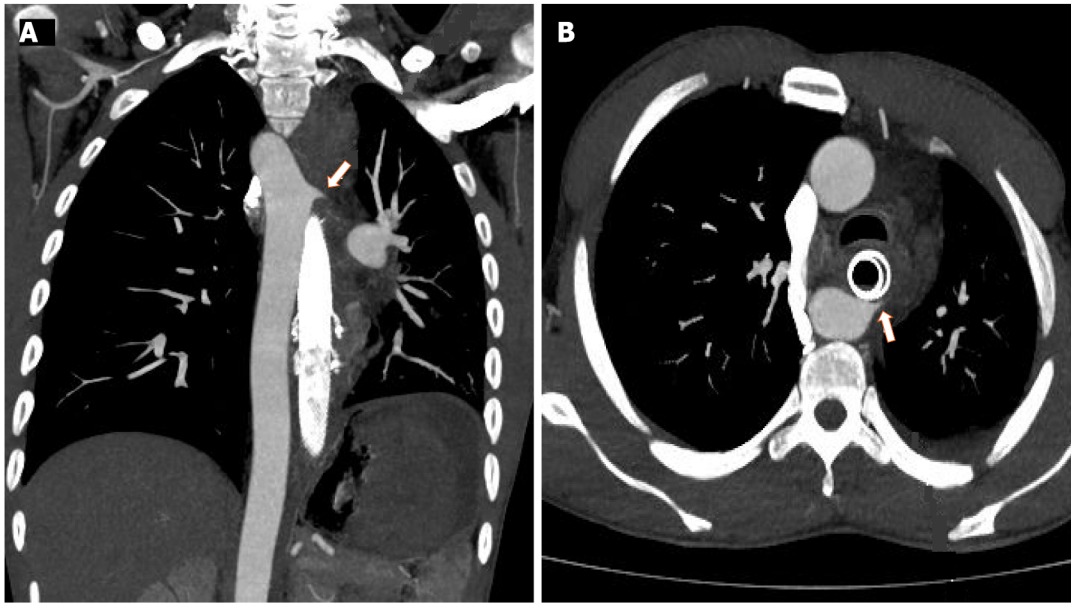

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Figure 2 Computed tomography angiogram images confirming the site of the proximal aorto-oesophageal fistula (arrows). A: Coronal image; B: Axial image.

revealed a patent left main bronchus, confirming that the extrinsic bronchial occlusion was due to the radial pressure of the oesophageal stents. The oesophageal exclusion was then performed, leaving the native, severely strictured and adherent oesophagus in-situ.

OUTCOME AND FOLLOW-UP

The patient was discharged 13 d later without complication. He subsequently developed mild stricturing of the proximal oesophagogastric anastomosis, which was successfully treated with serial dilatations. At one year post the initial corrosive injury the patient is well and dysphagia-free.

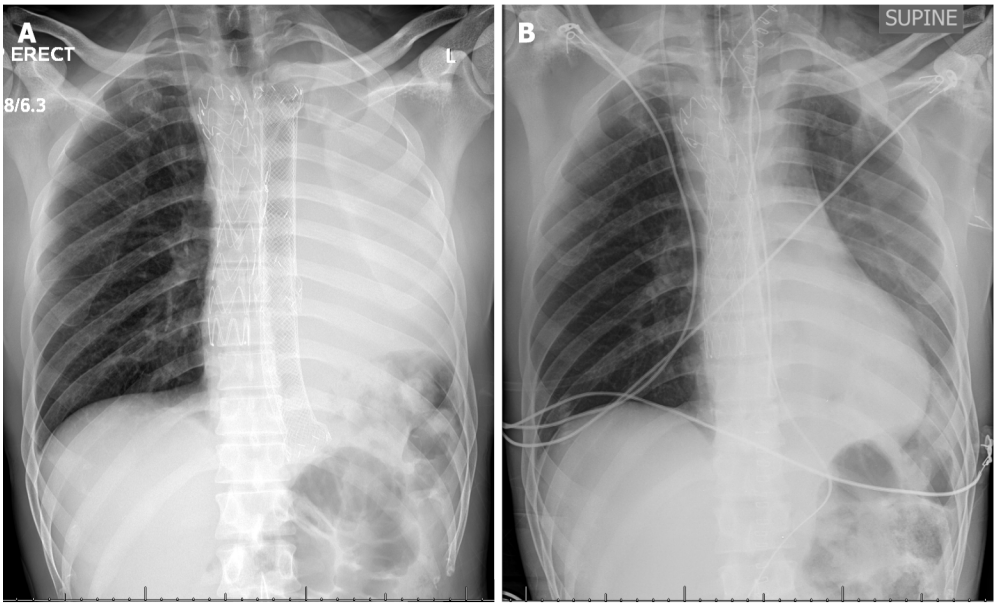

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Figure 3 Chest X-ray. A: Chest X-ray post aortic endovascular repair, showing aortic stent-graft, multiple overlapping stents in the oesophagus and white-out of the left lung, caused by left main bronchus compression by the oesophageal stents; B: Chest X-ray immediately post-operative after retrosternal gastric pull-up and removal of oesophageal stents showing good left lung re-expansion.

DISCUSSION

AOF are uncommon. In an extensive literature review in 1991 Hollander and Quick[1] identified a total of only 500 AOF cases of all aetiologies, with 51% being related to thoracic aortic aneurysms, 19% related to foreign body ingestion and 17% related to oesophageal malignancy[1]. Aorta-oesophageal fistula after corrosive ingestion is exceedingly rare. Our own comprehensive literature review on AOF after corrosive ingestion yielded only 15 cases other than our own, with only two other reported survivors. Table 1 outlines numerous characteristics of the entire cohort of 16 cases. Unfortunately, as most cases pre-date 2000, missing data was common in many cases. In the 13 cases where the mode of diagnoses was specified, the diagnosis was only made on imaging in two patients, at surgical exploration in two patients and in the remaining nine at post-mortem examination. The time from corrosive ingestion to AOF formation ranged from 2–62 d, with a median time of 14 d (IQR: 11.5–35.5 d). In only four cases (25%) was a herald bleed prior to massive haemorrhage reported. Five cases had a concomitant fistula between the oesophagus and respiratory tract (four tracheo-oesophageal fistulae and one broncho-oesophageal fistula), while in seven cases a concomitant gastric injury was described. Of the 16 described cases, 13 died resulting in a mortality rate of 81.2%. In four patients (25%) management of the AOF was attempted, of whom three survived.

Diagnosis remains challenging. Chiari's triad is of limited diagnostic value with only a minority of patients in this review having evidence of a herald bleed. Although endoscopy may be useful in suspecting the injury, vascular imaging with angiography or CTA is required to make a definitive diagnosis. Fistulae following corrosive ingestion typically occur more than two weeks post injury. In the context of the case reported the significant radial force exerted by self-expanding oesophageal stents needs to be considered. We postulate that the AOF likely formed due to a combination of factors, including the initial corrosive injury, but cannot exclude that the radial force of the stents placed was contributory. This force was also responsible for bronchial compression, which has previously been described in the literature[3,4]. It needs to be highlighted that using oesophageal stenting in the early management of the corrosive stricture is controversial, but was made by the treating team in light of the severity and length of the corrosive stricture where the risk of perforation using bougie or balloon dilatation was considered too high. Using an oesophageal stent to temporise bleeding was performed as the patient was present in the endoscopy suite where fluoroscopy was readily available, but using balloon tamponade to achieve haemostasis is another option and may be more suitable in other settings.

Conservative management of AOF is invariably fatal and should be reserved for patients not fit for intervention. Effective management of any AOF requires management of the fistula from both the oesophageal and aortic sides. The decision between open and endovascular management of the aorta is controversial and although contemporary guidelines consider open repair the gold standard, this is mostly based on fistulae secondary to thoracic aortic aneurysms, where the primary pathology is vascular[5]. With corrosive ingestion the primary pathology is in the oesophagus. Attempted definitive repair using an endovascular stent-graft leaves the significant concern of oesophageal content gaining

Table 1 Summary of all aorto-oesophageal fistula after corrosive ingestion publications and individual patient cases (total cases *n* = 16)

Ref.	Age (yr)	Sex	Corrosive agent	Ingestion intent	Days to presentation	Herald bleed	Diagnosis	Management of AOF	Outcome	Associated corrosive injuries
Schranz[9], 1934	16	F	Alkali	[1]	7	N	Autopsy	-	D	BOF
Singh *et al* [10], 1976	[1]	[1]	[1]	[1]	[1]	[1]	Autopsy	-	D	-
Waller and Rumler[11], 1963	10	M	Alkali	A	10	N	Autopsy	-	D	TOF, gastric (necrosis)
Rabinovitz *et al*[12], 1990	23	F	[1]	[1]	12	Y	Autopsy	-	D	TOF, gastric and duodenal injuries
Singh *et al* [10], 1976	54	M	Alkali	[1]	27	N	Autopsy	-	D	TOF, diaphragm (necrosis, perforation)
Ottosson [13], 1981	14	M	Alkali	A	44	N	Surgery	Primary repair of the oesophagus and aorta	D	-
Sarfati *et al* [14], 1987	[1]	[1]	[1]	[1]	14	[1]	[1]	[1]	D	[1]
	[1]	[1]	[1]	[1]	14	[1]	[1]	[1]	D	[1]
	[1]	[1]	[1]	[1]	14	[1]	[1]	[1]	D	[1]
Rabinovitz *et al*[12], 1990	34	M	Alkali	S	23	Y	Autopsy	-	D	TOF, gastric (necrosis with perforation)
Marone *et al* [7], 2006	20	M	Acid	S	25	N	Surgery	Open local aortic repair, then endovascular stent repair. Oesophageal bypass (colon conduit)	S	Gastric necrosis with perforation
Yegane *et al* [15], 2008	37	M	Acid	S	11	N	Autopsy	-	D	-
	40	M	Acid	[1]	2	N	Autopsy	-	D	-
	67	M	Acid	[1]	60	Y	Autopsy	-	D	Gastric (di Constanzo grade II injury)
Lee *et al*[8], 2011	75	F	Alkali	[1]	60	N	CT	Open aortic repair, total oesophago-gastrectomy	S	Gastric (total gastrectomy)
This study[2]	30	M	Alkali	A	62	Y	CT, Endoscopy	Oesophageal stenting endovascular aortic repair, oesophageal bypass (gastric conduit)	S	Gastric (Zargar IIa injury)

[1]Not mentioned.

[2]Authors own case report, not previously published.

F: Female; M: Male; A: Accidental; S: Suicidal; N: No; Y: Yes; CT: Computed tomography; D: Deceased; S: Survived; AOF: Aorto-oesophageal fistula; BOF: Broncho-oesophageal fistula; TOF: Trachea-oesophageal fistula.

access to the synthetic graft *via* the fistula, with the risk of prosthetic sepsis. For this reason, management of the fistula from the oesophageal side is mandatory. Although oesophageal stenting could facilitate temporizing the bleeding and divert content away from the fistula, long-term results in terms of preventing graft infection are lacking. While a surgical conduit will effectively divert luminal content, leaving the native oesophagus in-situ is associated with a risk of mucocoele formation and possible future risk of malignant transformation[6]. However, this must be weighed up against a difficult oesophageal resection due to extensive mediastinal fibrosis with a high risk of associated surgical morbidity[6].

The patient described in this case report was managed with minimally invasive interventions for temporizing control using oesophageal stenting and definitive management of the aortic defect with endovascular stenting. Surgical management was reserved for the oesophageal reconstruction. Marone *et al*[7] reported the first successfully managed patient with AOF after corrosive, which involved initial local closure of the fistula *via* open surgical access followed by endovascular stent repair of the aorta and oesophageal replacement with a retrosternal colonic conduit. Lee *et al*[8] reported a patient that was

successfully managed with surgical repair of the aorta, followed by oesophagogastrectomy.

In view of the extreme rarity of this condition, with only five other cases described in the last 30 years, creating evidence-based management algorithms or follow-up protocols is truly challenging. We do however advise clinicians treating patients after corrosive ingestion to ensure there is regular, planned patient follow-up in all those who sustain significant oesophageal corrosive injuries (Zargar IIb and above) who survive the initial management period. This should be done primarily due to the very high incidence of subsequent stricture formation frequently requiring long term endoscopic treatment. The common scenario of multi-level or long-segment stricturing seen with severe corrosive injuries poses challenging management problems[6]. Clinicians should be alerted to the fact that any reported gastro-intestinal bleeding in these patients, even months after the initial injury, may represent an AOF. We recommend CT angiography as the diagnostic modality of choice and strongly advocate that all diagnosed fistulae be treated on an individualised basis in a multi-disciplinary environment *via* combined approaches from the vascular and gastro-intestinal sides of the fistula.

CONCLUSION

Outcomes for AOF after corrosive ingestion remain dismal. Although a rare cause of upper gastrointestinal bleeding, it should be considered as a cause following corrosive injury and requires a high level of suspicion as fistula formation often occurs in a delayed fashion after the ingestion event. Management should be individualised as guidelines to aid decision-making are lacking. Optimal outcomes are best achieved with multimodality therapy in a multidisciplinary setting.

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FOOTNOTES

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CASE REPORT

Castleman disease of the pancreas mimicking pancreatic malignancy on ^{68}Ga-DOTATATE and ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography: A case report

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Abstract

BACKGROUND

Castleman disease is an uncommon nonclonal lymphoproliferative disorder, which frequently mimics both benign and malignant abnormalities in several regions. Depending on the number of lymph nodes or regions involved, Castleman disease (CD) varies in diagnosis, treatment and prognosis. It rarely occurs in the pancreas alone without any distinct clinical feature and tends to be confused with pancreatic paraganglioma (PGL), neuroendocrine tumors (NETs), and primary tumors, thus impeding proper diagnosis and treatment.

CASE SUMMARY

A 28-year-old woman presented with a lesion on the neck of the pancreas, detected by ultrasound during a health examination. Physical examination and laboratory findings were normal. The mass showed hypervascularity on enhanced computed tomography (CT), significantly increased ^{18}F-fluorodeoxyglucose uptake on positron emission tomography (PET)/CT, and slightly increased somatostatin receptor (SSTR) expression on ^{68}Ga-DOTATATE PET/CT, suggesting no distant metastases and subdiagnoses such as pancreatic PGL, NET, or primary tumor. Intraoperative pathology suggested lymphatic hyperplasia, and only simple tumor resection was performed. The patient was diagnosed with the hyaline vascular variant of CD, which was confirmed by postoperative immuno-

histochemistry. The patient was discharged successfully, and no recurrence was observed on regular review.

CONCLUSION
High glucose uptake and slightly elevated SSTR expression are potentially new diagnostic features of CD of the pancreas.

Key Words: Castleman disease; Pancreatic malignancy; Pancreatic neuroendocrine tumors; Pancreatic paraganglioma; Positron emission tomography; Case report

Core tip: Some rare tumors with high blood supply to the pancreas, such as Castleman disease (CD), paraganglioma, and neuroendocrine tumors are difficult for clinicians to differentially diagnose based on conventional imaging and clinical presentation. In our case, CD of the pancreas had no obvious clinical features as previously reported but showed higher glucose uptake and mildly increased somatostatin receptor expression on positron emission tomography/computed tomography, which might help in the diagnosis.

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INTRODUCTION

Castleman disease (CD), a rare nonclonal lymphoproliferative disorder of unknown etiology, is alternatively known as giant lymph node hyperplasia or angiofollicular lymph node hyperplasia, first described by Dr. Benjamin Castleman in 1954[1]. Variably manifested and capable of influencing any region in the body, CD largely imitates both benign and malignant tumors in the neck, thorax, abdomen and pelvis[2]. Despite increasing reports on CD, the condition remains difficult to diagnose, particularly when it appears as a pancreatic mass[3]. With the ability to collect structural and metabolic information, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) plays a pivotal role in the early diagnosis, robust characterization, and therapeutic evaluation of CD[4]. However, no ^{18}F-FDG PET/CT images of pancreatic CD have thus far been reported. ^{68}Ga-DOTATATE PET/CT is the first choice for evaluating the well-differentiated histologic subtypes of neuroendocrine tumors (NETs), but its diagnostic value for identifying CD has yet to be determined[5].

CASE PRESENTATION

Chief complaints

A 28-year-old woman presented to our department with the complaint of a pancreatic lesion, which was detected by ultrasound during a physical examination conducted 1 wk earlier.

History of present illness

The patient showed a feel-good self-report without abdominal pain, distension, diarrhea, fever, and other discomforts.

History of past illness

The patient had good health history.

Personal and family history

The personal and family history of the patient was unremarkable.

Physical examination

The vital signs of the patient were within the normal range. No yellow staining of skin and sclera was

observed. Abdominal physical examination revealed no positive signs without tenderness and lumps in the abdomen.

Laboratory examinations

Blood analysis revealed mild anemia, with low hemoglobin concentration (102 g/L), normal leukocyte count, and normal platelet count. All liver function indexes were normal. The following were also normal: levels of serum amylase, lipase and alkaline phosphatase; plasma or urinary metanephrine levels; and tumor markers for alpha-fetoprotein (1.97 ng/mL), carcinoembryonic antigen (3.63 ng/mL), carbohydrate antigen (CA) 153 (16.40 U/mL), and CA199 (19.66 U/mL). Endoscopic results suggested chronic nonatrophic gastritis with erosion. Fasting and postprandial insulin levels were within the normal range.

Imaging examinations

A plain CT scan (Figure 1A) showed a hyperdense lesion (arrow) measuring 3.0 cm × 2.0 cm × 2.5 cm in the neck of the pancreas. On contrast-enhanced CT, the lesion (arrow) showed significant enhancement in the arterial phase (Figure 1B), evenly distributed with smooth and well-defined boundaries, and gradually washed out in the venous phase (Figure 1C). ^{18}F-FDG PET/CT images (Figure 2) showed glucose hypermetabolism with an standardized uptake value $(SUV)_{max}$ of 3.6 in the pancreatic mass. ^{68}Ga-DOTATATE PET/CT images (Figure 3) revealed minimally increased expression of somatostatin receptor (SSTR) on the pancreatic mass (arrows) with a SUV_{max} of 5.8.

FINAL DIAGNOSIS

The final diagnosis of the presented case was pancreatic hypervascular malignancy, not excluding CD, paraganglioma (PGL), and NETs.

TREATMENT

On the basis of neoplastic etiology, we intended to perform pancreaticoduodenectomy. During exploratory laparotomy, we found that the mass had a rich blood supply. We completely separated it from the pancreatic tissue. The size of the tumor was 3.5 cm × 3 cm with a complete envelope (Figure 4A). Intraoperative frozen section examination (hematoxylin–eosin staining) suggested lymphatic hyperplasia, germinal centers with regressive transformation, and expanded mantle with "an onion skin" rimming of small lymphocytes (Figure 4B). Given the high probability of a benign mass, we performed simple tumor resection.

OUTCOME AND FOLLOW-UP

Immunohistochemistry: CD3 and CD5 (T zone +), CD20 (B zone +), CD10 and BCL-6 (germinal center +), BCL-2 (low expression in the germinal center, high expression outside the germinal center), CD21 (Figure 4C) and CD23 (follicular dendritic cell proliferation in the germinal center), Ki-67 (Figure 4D, high expression in the germinal center, low expression outside the germinal center), and Cyclin D1(). The immunohistochemical profile was consistent with the hyaline vascular variant of CD. The patient showed no apparent discomfort after surgery and was discharged after 1 wk. No recurrence of abdominal ultrasonography was reported after half a year.

DISCUSSION

CD occurs throughout the body. Approximately 70% of the condition presents in the chest, 15% in the neck, and 15% in the abdomen–pelvis, principally involving lymphoid tissues. Castleman disease also occasionally occurs in extralymphatic sites, such as the larynx, lungs, pancreas, meninges, and muscles [6-8]. It is subclassified because of the number of enlarged lymph nodes[9]. The involvement of a single lymph node or region is referred to as unicentric CD (UCD), whereas that of multiple lymph nodes is known as multicentric CD (MCD). A battery of pathological variants includes the classic hyaline vascular type, the less common plasma cell variant and human-herpesvirus-8-associated type, and the multicentric type, not otherwise specified[10]. Moreover, 90% of the cases of hyaline vascular CD are unicentric[11]. UCD typically manifests as an asymptomatic mass with a benign growth, but MCD presents with diffuse lymphadenopathy, organ dysfunction, and systemic inflammation.

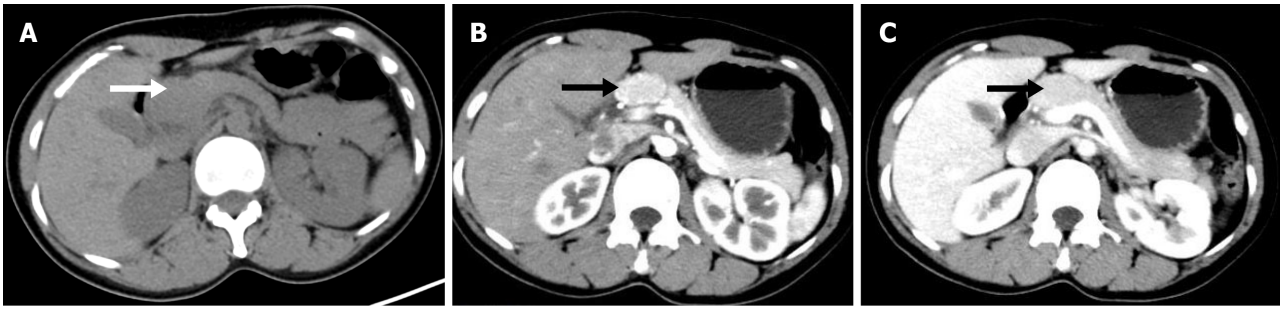

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Figure 1 Preoperative computed tomography of the abdomen. A: A plain computed tomography (CT) scan showed a hyperdense lesion measuring 3.0 cm × 2.0 cm × 2.5 cm in the neck of the pancreas; B: On enhanced CT, the lesion showed significant enhancement in the arterial phase, evenly distributed with smooth and well-defined boundaries; C: In the venous phase, the lesion was gradually washed out.

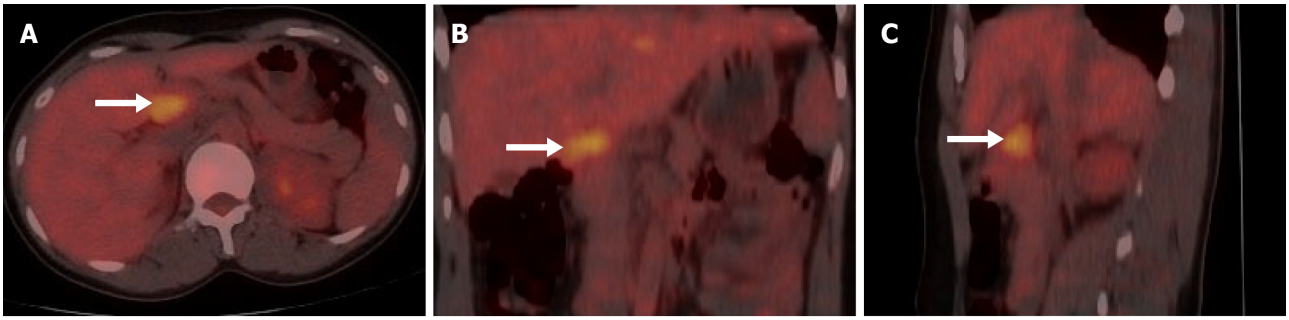

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Figure 2 ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography showing glucose hypermetabolism in the pancreatic mass. A: Axial positron emission tomography/computed tomography (PET/CT); B: Coronal PET/CT; C: Sagittal PET/CT.

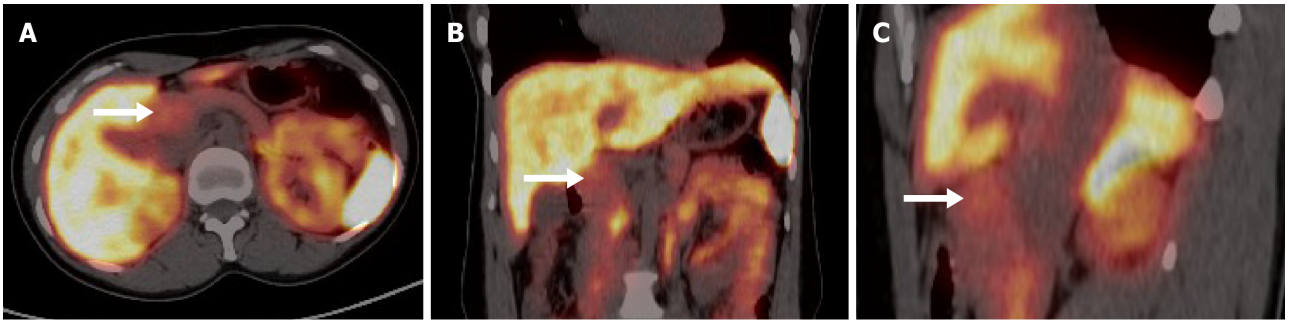

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Figure 3 ^{68}Ga-DOTATATE positron emission tomography/computed tomography revealing slightly elevated somatostatin receptor expression on the pancreatic mass. A: Axial positron emission tomography/computed tomography (PET/CT); B: Coronal PET/CT; C: Sagittal PET/CT.

Complete removal of lymph nodes is an effective and usually curative treatment for UCD, and the recurrence rate is low. Chemotherapy and radiotherapy are alternative therapies when the mass cannot be completely removed surgically[9,12]. By contrast, MCD has a poor prognosis, with a high recurrence rate associated with clinicopathological features and a high risk of malignancy leading to possible transformation into malignant lymphoma, plasmacytoma and Kaposi's sarcoma, among others[4]. Meanwhile, treatment options for MCD are complex and include steroid therapy, chemotherapy, antiviral drugs, or the use of antiproliferative regimens[4,13]. Therefore, the clinical typing of CD determines the corresponding diagnosis and prognosis.

Conventional imaging [CT/magnetic resonance imaging (MRI)] is not widely used to guide typing because it fails to distinguish clearly between reactive hyperplasia and pathological enlargement of lymph nodes, nor does it sensitively detect the involvement of normal-sized lymph nodes[4]. However, ^{18}F-FDG PET/CT can be used to assess the metabolism of lymph node enlargement. Although lymph node biopsy is the only method for the definitive diagnosis of CD, available evidence suggests that previous FDG-PET/CT can help differentiate CD subtypes and guide subsequent treatment and

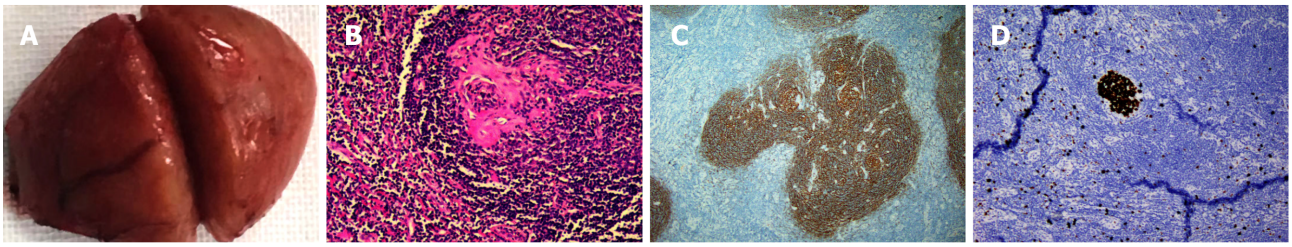

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Figure 4 Specimen photograph and pathological photographs. A: The pancreatic mass with an intact envelope, measuring approximately 3.5 cm × 3 cm; B: Photomicrograph (hematoxylin-eosin stain) suggesting a germinal center with the classic "onionskin" appearance (magnification × 200); C: Immunohistochemistry of CD21 (magnification × 200); D: Immunohistochemistry of Ki-67 (magnification × 200).

monitoring[13]. In our case, the ^{18}F-FDG PET/CT results showed that the mass was solitary in the pancreas with high glucose metabolism and no distant metastases, consistent with the diagnosis of UCD. CD is rarely reported on ^{68}Ga-DOTATATE PET/CT, and the ability and accuracy of its classification are unknown. In our case, UCD showed higher SSTR expression.

When the tumor is located in the pancreas and is highly vascularized, some rare conditions other than CD including PGL and NETs should also be considered[14].

PGL, a rare type of vascular NET, results from a paraganglial cell cluster that develops from the ectoderm of the neural crest[15]. The majority of the tumors are benign, and only 10% of the tumors are malignant. Although up to 77% of the tumors are commonly located retroperitoneally, the PGL is rarely located in the pancreas. A retrospective analysis of 15 cases diagnosed with PGL located in the pancreas summarized the clinical and imaging features of the disease[14]. Most patients exhibit no apparent symptoms or abdominal discomfort caused by compression. Enhanced CT suggests significant enhancement of the mass at the early stage. MR images reveal tumor isointensity for the T1-weighted image and hyperintensity, hypointensity, or mixed intensity for the T2-weighted image. PGL located in the chest and pelvis may overproduce some hormones, particularly catecholamine which causes sweating, palpitations, and hypertension. PGLs most commonly overexpress SSTR2. [^{68}Ga]-Somatostatin agonists (SSTas) target SSTR2 and are internalized into the cells. DOTA-coupled SSTas exhibit excellent affinity for SSTR2[16]. Owing to its ultrahigh detection rate, [^{68}Ga] DOTA-somatostatin analog PET/CT has become the preferred imaging approach to diagnosing retroperitoneal PGL[17]. However, [^{68}Ga] SSTas PET can inevitably lead to false-positive findings, including metastatic lymph nodes owing to various cancers, meningioma, the pituitary gland, inflammatory diseases, and some rare conditions, such as fibrous dysplasia[18] Focal pancreatic accumulation in the uncinate process may mimic pancreatic NETs.

Pancreatic NETs (pNETs) are heterogeneous epithelial neoplasms derived from pluripotent stem cells of the neuroendocrine system[19]. The tumor is malignant and classified as either functional or nonfunctional[14]. Nonfunctional pNETs are asymptomatic or manifest local compression, whereas functional pNETs cause clinical syndromes associated with hormone hypersecretion according to the cell of origin. In MRI, the tumor presents with hypointensity on T1-weighted imaging and mostly hyperintensity on T2-weighted imaging; however, few are isointense or hypointense. In enhanced CT images, the functional pNET shows a clear boundary and rich blood supply, and the diameter of the tumor is generally < 2 cm[14]. The nonfunctional pNET presents heterogeneous enhancement, necrosis, and cystic degeneration in enhanced CT images and often has a larger diameter (> 5 cm) than that of the functional pNET. ^{68}Ga-DOTATATE PET/CT, the first choice for evaluating well-differentiated histological subtypes of NETs, provides staging with improved accuracy and additional treatment choices[20].

CONCLUSION

CD rarely occurs in the pancreas. CD of the pancreas often presents with an abundant blood supply, which, together with the lack of specificity in the clinical presentation, further blurs the distinction of the disease from NETs and PGL. PET/CT is supposed to be selected to guide the typing and subsequent treatment choices for CD. In our case, PET/CT showed that CD was solitary in the pancreas, and complete surgical resection led to a good prognosis. In addition to abundant blood supply, high glucose uptake and slightly elevated SSTR expression are potentially new diagnostic features of CD of the pancreas.

ACKNOWLEDGMENTS

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FOOTNOTES

Author contributions: He K and Yang XL proposed the idea and supervised, revised the writing; Liu SL collected the data, analyzed the literature, and wrote the manuscript; Luo M assisted with data collection and imaging guidance; He K, Gou HX were the patient's surgeons and participated in the entire operation; all authors read and approved the manuscript.

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

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LETTER TO THE EDITOR

Applying refined pancreaticogastrostomy techniques in pancreatic trauma

Jake Krige, Marc Bernon, Eduard Jonas

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Abstract

We comment on a study titled "Feasibility and safety of "bridging" pancreaticogastrostomy for pancreatic trauma in Landrace pigs" in which ten pigs were randomized to either experimental "bridging" pancreaticogastrostomy (PG) or a control group with a routine mucosa-to-mucosa PG. At six months anastomoses had strictured and closed in both groups. The authors concluded that "bridging" PG is feasible and safe in damage control surgery during the early stage of pancreatic injury. In this letter we comment on the study design, specifically leaving a 2 cm gap between the pancreatic stump and the stomach and highlight the complexity of performing pancreatic anastomoses following trauma pancreaticoduodenectomy as to our experience in a high volume trauma centre. Our data emphasize that pancreatic anastomoses in trauma are complex procedures with significant postoperative morbidity and are best managed collaboratively by trauma and hepatopancreaticobiliary surgical teams with the required technical skills.

Key Words: Pancreatic trauma; Pancreatic anastomoses; Pancreaticogastrostomy; Complications

Core Tip: In the elective setting a number of different pancreatic anastomotic methods have been proposed with variations in the site of implantation (stomach or jejunum), the anastomotic technique and the use of pancreatic duct stenting. These techniques need to be adapted to the prevailing operative circumstances. We recommend a pancreaticogastrostomy rather than a pancreaticojejunostomy in the presence of severe shock, prolonged resuscitation and associated major vascular injuries. We routinely use a 5 Fr silastic intraluminal pancreatic duct stent through the anastomoses.

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TO THE EDITOR

We read with interest the research study by Feng *et al*[1] in the *World Journal of Gastrointestinal Surgery* entitled "Feasibility and safety of bridging pancreaticogastrostomy for pancreatic trauma in Landrace pigs" which was designed to simulate damage control surgery in pancreatic trauma[1]. In their study ten Landrace pigs were randomized into an experimental group in which a "bridging" pancreaticogastrostomy (PG) was performed while in a control group a routine mucosa-to-mucosa PG was constructed. Amylase levels in drainage fluid, fasting and two-hour postprandial blood glucose, insulin levels in peripheral blood, and insulin levels in portal vein blood were measured six months after the operation. Repeat surgery was undertaken one and six months to examine the condition of the abdominal cavity and pancreas and evaluate the patency of the PG.

After surgery, the authors found that the fasting and two-hour postprandial blood glucose levels were similar. There was also no difference in the fasting and two-hour insulin values of postprandial peripheral blood and portal vein blood six months after the operation between the two groups. One month after the operation, the tract in the bridging group and the conventional PG were patent. However, after six months both groups had strictured and closed with chronic pancreatitis present in both. The authors concluded that a "bridging" PG is a practical and secure method of damage control surgery during the initial management of a pancreatic injury.

The authors are to be congratulated on this innovative study evaluating a "bridging" PG in order to overcome the difficulties related to a PG after trauma. All pancreatic surgeons will concede that the pancreatic anastomosis is the Achilles' heel of pancreatic surgery, especially so when circumstances are unfavorable, as occurs in pancreatic trauma. The authors acknowledge that using this method the bridging tubes invariably became dislodged with time and that all the PG anastomoses eventually strictured with resultant chronic pancreatitis in both groups. We are however puzzled why the authors left a 2 cm gap between the pancreatic stump and the stomach bridged by the tube because this space will inevitably fibrose and stricture. Intuitively it makes more sense to create a sutured and stent-splinted apposition PG which provides a tight seal without a gap between the pancreas and stomach and would theoretically be less prone to fibrosis and stricturing. Two further observations which test the validity of their study are that the operations undertaken on the pigs were elective procedures which did not simulate a pancreatic trauma situation as occurs in reality, nor do the authors provide any evidence in their study that the bridging procedure is indeed quicker than a conventional anastomosis.

We, too, have grappled with the complexities of establishing a safe method for a pancreatic anastomosis in pancreatic trauma[2]. Our clinical experience is based on one of the largest active databases of complex pancreatic injuries in the world. We have shown that when a trauma pancreaticoduodenectomy has been completed, several important assessments are necessary with regard to the timing and type of reconstruction. The crucial factor in the eventual result is the quality of the pancreatic anastomosis. As is relevant during elective resections, the pancreatic to bowel anastomosis after a pancreaticoduodenectomy for trauma is the Achilles' heel of the operation and a leak from the pancreatic anastomosis failure is the most important reason for the considerable incidence of complications which may occur after the operation. Even when the pancreatic anastomosis is performed during elective operations the fistula rate is significant and the incidence is greatest in patients who have a soft pancreatic parenchyma when combined with a small main pancreatic duct. These important risk factors which are relevant when the pancreas is injured are further aggravated by a pancreas that is may be hemorrhagic, as well as a jejunal wall thickened by edema, which makes the circumstances even more difficult and hazardous for a sound anastomosis.

During elective surgery several techniques have been suggested to minimize the possibility of pancreatic fistulas occurring after the operation. These include the location of implantation (stomach or jejunum), the technique used for the anastomosis and whether a stent is used to splint the pancreatic duct and bowel. These techniques may need to be modified according to the existing conditions. PG and pancreaticojejunostomy each have their own benefits and disadvantages but neither are consistently appropriate after a serious pancreatic injury where edema and substantial damage to tissues are critical influences deciding whether a particular type or method should be used in the anastomotic reconstruction. In our clinical studies we routinely used a PG when prolonged hypotension, extended fluid resuscitation and associated venous injuries resulted in an edematous small bowel which jeopardized the anastomosis. Under these unfavorable conditions there are several rational and technical reasons for doing a PG in preference to a pancreaticojejunostomy. The posterior gastric wall is conveniently contiguous to the pancreatic remnant and approximation is never a problem. The

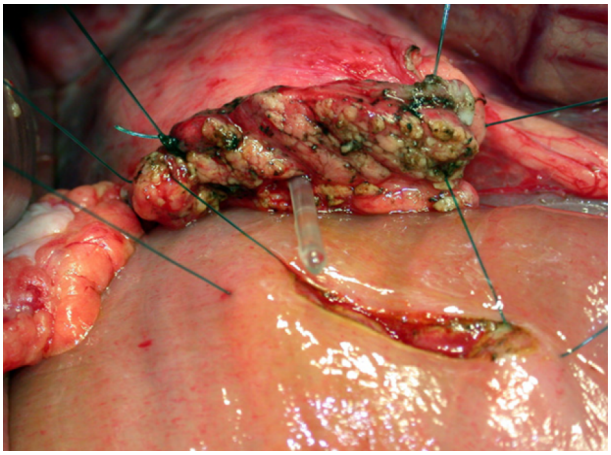

Figure 1 Construction of a single layer stented pancreaticogastrostomy. Citation: Feng J, Zhang HY, Yan L, Zhu ZM, Liang B, Wang PF, Zhao XQ, Chen YL. Feasibility and safety of "bridging" pancreaticogastrostomy for pancreatic trauma in Landrace pigs. *World J Gastrointest Surg* 2021; 13: 419-428. Copyright ©The Authors 2021. Published by Baishideng Publishing Group Inc.

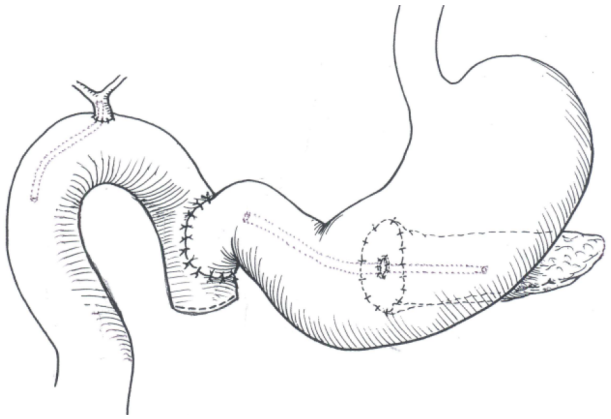

Figure 2 Stented pancreaticogastrostomy with an Imanaga configuration. Citation: Krige JE, Jonas E, Thomson SR, Kotze UK, Setshedi M, Navsaria PH, Nicol AJ. Resection of complex pancreatic injuries: Benchmarking postoperative complications using the Accordion classification. *World J Gastrointest Surg* 2017; 9: 82-91. Copyright ©The Authors 2021. Published by Baishideng Publishing Group Inc.

gastrostomy can be created to the precise dimension required without any difference in size to allow a tension-free anastomosis. In addition, the gastric wall is thick, sutures hold well, has a generous blood supply and is less likely than the jejunum to develop ischemic complications. Gastric and pancreatic secretions are easily drained *via* a well-placed nasogastric tube after a PG and the pancreatic exocrine enzymes remain inactivated with a low pH in the absence of enterokinase. We prefer to use a modified single layer interrupted suture technique which includes the pancreatic capsule and parenchyma and we routinely place a 5 Fr silastic intraluminal stent rather than to attempt a more complicated duct to mucosa technique which escalates the level of complexity (Figure 1). If circumstances dictate we apply the Imanaga method of reconstruction which, with minor modifications, allows endoscopic access to the biliary system subsequently if required for retrieval of biliary stents and balloon-enhanced cholangiography through the duodenojejunal anastomosis (Figure 2).

Our data emphasize that pancreatic anastomoses in trauma are technically complicated procedures which may have substantial sequelae postoperatively and are best treated collaboratively by trauma and hepatopancreaticobiliary surgical teams who have the requisite technical skills to recognize and deal with high-risk pancreatic anastomoses.

FOOTNOTES

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LETTER TO THE EDITOR

Providing higher value care for hepatocellular carcinoma rather than diagnosis: What can current radiologists do?

Shan Yao, Yi Wei, Bin Song

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Abstract

Medical imaging is of great value for the comprehensive evaluation of hepatocellular carcinoma from diagnosis to prognosis, which contributes to optimal clinical management making.

Key Words: Hepatocellular carcinoma; Medical imaging; Clinical management

Core Tip: Medical imaging plays a vital role in the accurate diagnosis and grading of hepatocellular carcinoma as clinical treatment decision-making. Moreover, it is of powerful value for noninvasively preoperative evaluation of the treatment outcomes, prognosis, and survival with high sensitivity and repeatability. The comprehensive assessment involving preoperative, perioperative, and postoperative indicators for treatment option selection will assist surgeons precisely and maximize the benefits for patients.

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TO THE EDITOR

In the current issue, we read with interest a retrospective study by Delvecchio *et al*[1], where liver resection (LR) and radiofrequency ablation (RFA) were evaluated as the

treatment of choice for single hepatocellular carcinoma (HCC) (≤ 30 mm) located in posterosuperior segments (PSS) in elderly patients. Based on operative time, hospital stay, and short- and long-term outcomes, RFA was recommended as a suitable option.

The critical value of tumor size for LR or RFA differs in various criteria and guidelines, most of which is 20 mm. Single HCC with a tumor size of ≤ 30 mm was mainly targeted in this study. Locations with difficulties in surgery (PSS) and age (for the elderly ≥ 70 years old) were considered while making the treatment decision. It offered an insightful perspective and a specific focus, providing a supplement to this field with certain guiding significance for clinical management practice.

As described in the study, all subjects underwent computed tomography (CT) or magnetic resonance imaging (MRI) before treatment to access the tumor location and size, which are the two key points of this study. The diagnosis and stage of HCC were based on the European Association for the Study of the Liver criteria[2], which also regard medical imaging manifestations as a dominant support. Thus, medical imaging plays a vital role in the accurate diagnosis and qualitative evaluation of HCC. Along with morphological features, such as tumor location and size, satellite nodules, portal vein embolus, and invasion of adjacent tissues can be evaluated using CT or MRI, which are also of prognostic significance for patients with HCC after treatment.

Apart from the abovementioned perioperative and postoperative indicators for selecting treatment option, preoperative evaluation can be performed using noninvasive medical imaging with high sensitivity and repeatability. In a study by Cha *et al*[3], pretreatment imaging was utilized to compare the outcomes of RFA and LR for HCC ≤ 30 mm, and a high positive predictive value was achieved. Burgeoning functional imaging technologies, such as gadoxetic acid-enhanced MRI, intravoxel incoherent motion, T1 mapping, have enabled insightful assessment of microvascular invasion, hepatocyte membrane function, hepatocyte density changes, tissue microcirculation, and liver reserve function. Meanwhile, artificial intelligence-imaging combining radiomics has been empowering deep data mining of CT or MRI images of HCC from diagnosis to prognosis. In prior studies, we found that preoperative CT imaging combined with clinical features could predict the rate of liver regeneration after right hepatectomy for HCCs with an accuracy of 0.78 and an area under the curve (AUC) of 0.84 [4]. Gadoxetic acid-enhanced MRI-derived features showed great potential for preoperative prediction of early recurrence of LR for HCCs, with the related model demonstrating a significant AUC of 0.841 (95%CI: 0.769-0.919)[5]. Taken together, medical imaging is closely related to optimal treatment decision-making and survival quality for patients. In future clinical practice, it is necessary to take full advantage of medical imaging to comprehensively evaluate tumor and liver conditions preoperatively as a treatment plan trade-off, so as to maximize the benefits for patients with HCC and meet the demands of precision medicine.

FOOTNOTES

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