ISSN 1948-9366 (online)

World Journal of

Gastrointestinal Surgery

World J Gastrointest Surg 2022 February 27; 14(2): 78-210

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Surgery

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

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastrointestinal Surgery

ISSN
ISSN 1948-9366 (online)

LAUNCH DATE
November 30, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Peter Schemmer

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

PUBLICATION DATE
February 27, 2022

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World J Gastrointest Surg 2022 February 27; 14(2): 78-106

DOI: 10.4240/wjgs.v14.i2.78

ISSN 1948-9366 (online)

FRONTIER

Therapeutic strategies for gastroenteropancreatic neuroendocrine neoplasms: State-of-the-art and future perspectives

Elettra Merola, Andrea Michielan, Umberto Rozzanigo, Marco Erini, Sandro Sferrazza, Stefano Marcucci, Chiara Sartori, Chiara Trentin, Giovanni de Pretis, Franca Chierichetti

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Ramirez RA, Wang WQ

Received: March 20, 2021
Peer-review started: March 20, 2021
First decision: October 3, 2021
Revised: October 18, 2021
Accepted: January 25, 2022
Article in press: January 25, 2022
Published online: February 27, 2022

Elettra Merola, Andrea Michielan, Sandro Sferrazza, Giovanni de Pretis, Department of Gastroenterology, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari (APSS), Trento 38122, Italy

Umberto Rozzanigo, Department of Radiology, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari (APSS), Trento 38122, Italy

Marco Erini, Franca Chierichetti, Department of Nuclear Medicine, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari (APSS), Trento 38122, Italy

Stefano Marcucci, Department of Surgery, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari (APSS), Trento 38122, Italy

Chiara Sartori, Department of Pathology, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari (APSS), Trento 38122, Italy

Chiara Trentin, Department of Medical Oncology, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari (APSS), Trento 38122, Italy

Corresponding author: Elettra Merola, MD, PhD, Department of Gastroenterology, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari (APSS), Largo Medaglie D'Oro 9, Trento 38122, Italy. elettra.merola@apss.tn.it

Abstract

Although gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) have always been considered rare tumors, their incidence has risen over the past few decades. They represent a highly heterogeneous group of neoplasms with several prognostic factors, including disease stage, proliferative index (Ki67), and tumor differentiation. Most of these neoplasms express somatostatin receptors on the cell surface, a feature that has important implications in terms of prognosis, diagnosis, and therapy. Although International Guidelines propose algorithms aimed at guiding therapeutic strategies, GEP-NEN patients are still very different from one another, and the need for personalized treatment continues to increase. Radical surgery is always the best option when feasible; however, up to 80% of cases are metastatic upon diagnosis. Regarding medical treatments, as GEP-NENs are characterized by relatively long overall survival, multiple therapy lines are adopted during the lifetime of these patients, but the optimum sequence to be followed has never been clearly defined. Furthermore, although new molecular

markers aimed at predicting the response to therapy, as well as prognostic scores, are currently being studied, their application is still far from being part of daily clinical practice. As they represent a complex disease, with therapeutic protocols that are not completely standardized, GEP-NENs require a multidisciplinary approach. This review will provide an overview of the available therapeutic options for GEP-NENs and attempts to clarify the possible approaches for the management of these patients and to discuss future perspectives in this field.

Key Words: Gastroenteropancreatic neuroendocrine neoplasms; Therapeutic strategies; Radical surgery; Medical treatments; Overview; Future perspectives

Core Tip: Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) have shown an increasing incidence over the past few decades. Although International Guidelines propose algorithms aimed guiding therapeutic strategies, the need for personalized treatment continues to increase. Radical resection is always the best option when feasible; however, up to 80% of cases are metastatic upon diagnosis. Several medical therapies are available for unresectable cases: Somatostatin analogs, peptide receptor radionuclide therapy, targeted drugs (primarily everolimus and sunitinib), chemotherapy and immunotherapy. This review provides an updated overview of the available therapeutic options for GEP-NENs and attempts to discuss future perspectives in this field.

Citation: Merola E, Michielan A, Rozzanigo U, Erini M, Sferrazza S, Marcucci S, Sartori C, Trentin C, de Pretis G, Chierichetti F. Therapeutic strategies for gastroenteropancreatic neuroendocrine neoplasms: State-of-the-art and future perspectives. *World J Gastrointest Surg* 2022; 14(2): 78-106
URL: https://www.wjgnet.com/1948-9366/full/v14/i2/78.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i2.78

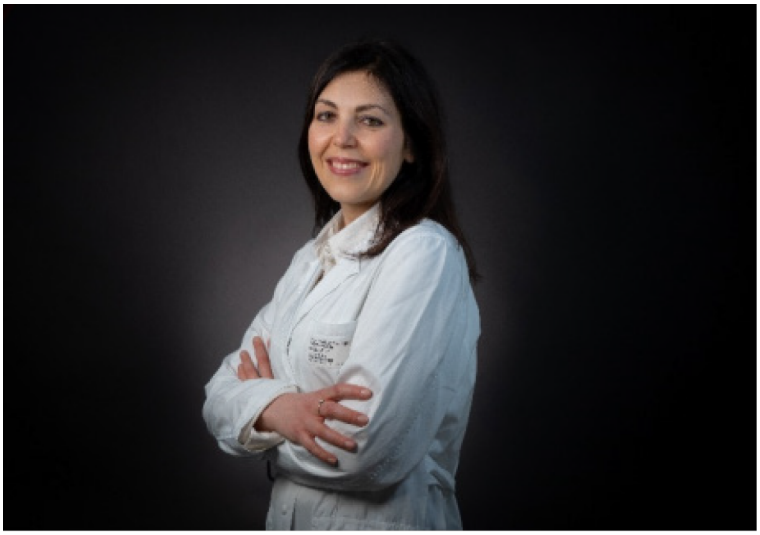
BIOGRAPHY

Elettra Merola, MD, PhD: She is a gastroenterologist and researcher currently working at the Department of Gastroenterology of Santa Chiara Hospital (APSS), Trento (Italy). She received her MD degree with honors in 2005 from Campus Bio Medico University, Rome (Italy), and during medical school she was visiting student and researcher at the University of Illinois in Chicago (United States) and at Temple University in Philadelphia (United States). In 2009, she completed her residency in Gastroenterology and in 2013 her PhD in Digestive Oncology at Sant'Andrea Hospital, Sapienza University, Rome (Italy), where she developed a particular interest in neuroendocrine neoplasms (NENs). Her experience in this field grew, joining as a visiting researcher the European Neuroendocrine Tumor Society (ENETS) center of excellence of Charité University, Berlin (Germany) (2015-2017), and then working as an NEN specialist at the NEN center of FAU Erlangen University, Erlangen (Germany) (2017-2018). Dr. Merola is internationally recognized for her expertise in NENs and she has led several cooperative studies aimed at improving the clinical management of these patients. In March 2017 she was awarded the ENETS Center of Excellence Academy Fellowship Grant for an international, cooperative research project regarding curative surgery in neuroendocrine tumors. She moved to Santa Chiara Hospital (APSS) in Trento (Italy) in 2018, where she promoted the management of NEN patients in a multidisciplinary setting, coordinating a dedicated NEN tumor board. She is also responsible for the outpatient clinic of neuroendocrine neoplasms in the Gastroenterology Department (Figure 1).

INTRODUCTION

Although gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) have always been considered rare tumors, their incidence has risen in recent decades, up to 3-5 cases *per* 100000 persons *per* year[1,2]. They represent a highly heterogeneous group of neoplasms with varying biological behavior. Several prognostic factors have an impact on GEP-NEN survival, including the proliferative index (Ki67)[3], disease stage according to the European Neuroendocrine Tumor Society (ENETS) tumor-node-metastasis (TNM) staging system[4,5], and the World Health Organization (WHO) classification[6].

In particular, if the definition of NENs is adopted for all neoplasms with a neuroendocrine differentiation in general, based on immunolabeling for chromogranin A and synaptophysin, the novel WHO 2019 classification[6] distinguishes two different subgroups in terms of morphology, genetics, response



DOI: 10.4240/wjgs.v14.i2.78

Figure 1 Elettra Merola, MD, PhD, Department of Gastroenterology, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari (APSS), Largo Medaglie D'Oro 9, Trento 38122, Italy

to therapy, and prognosis: NETs and neuroendocrine carcinomas (NECs). NETs are well-differentiated neuroendocrine neoplasms, characterized by a population of cells with uniform nuclear features, "salt and pepper" chromatin, organoid architecture and sometimes minimal necrosis. NETs are classified according to proliferation fraction in G1 (mitotic count < 2 *per* 2 mm^2 and/or < 3% Ki-67 index), G2 (mitotic count 2-20 *per* 2 mm^2 and/or 3%-20% Ki-67 index), and G3 (mitotic count > 20 *per* 2 mm^2 and/or > 20% Ki-67 index). Instead, NECs are highly aggressive poorly differentiated neoplasms that grow in sheets, usually with abundant necrosis. They are further classified into small cell NECs or large cell NECs, based on the cell morphology. NECs are high grade by definition; grading for these neoplasms is not assigned to avoid confusion regarding the NET G3 category.

The expression of somatostatin receptors (SSTRs) also has an important role in therapy selection and characterizes nearly 90% of NENs. This feature is mainly identified by functional imaging tests, which are pivotal in diagnosis, disease staging, and the therapeutic management of NENs. They include octreotide scintigraphy with radiolabeled somatostatin analogs (SSAs) (Octreoscan®), limited by the low accuracy in detecting small lesions (< 1 cm in diameter) and by a difficult semiquantitative analysis[7]. The subsequent development of different radiolabeled DOTA-conjugated peptides (DOTANOC, DOTATOC, DOTATATE) for positron emission tomography/computed tomography (PET/CT) has changed the landscape of nuclear medicine. Following the first published paper introducing ^{68}Ga-DOTATOC-PET/CT, a series of further papers showed that this test could detect no less than 30% more neuroendocrine lesions than Octreoscan® and conventional CT[8].

Although International Guidelines propose algorithms aimed at guiding therapeutic strategies[9-13], NEN patients are still very different from one another and the need for personalized treatments continues to increase. Although radical surgery is always the best option when feasible, up to 80% of cases are metastatic upon diagnosis and data on adjuvant treatments are still insufficient for this disease. Regarding medical treatments, as NENs are characterized by a relatively long overall survival (OS), multiple therapy lines are adopted for these patients during their lifetime, but the best sequence to be followed has never been clearly defined. Furthermore, new molecular markers aimed at predicting therapy response and prognostic scores[14,15] are currently being studied, but their application is still far from being part of daily clinical practice. A recent network meta-analysis including only phase-III randomized controlled trials (RCTs) has attempted to identify the best therapeutic strategy for controlling tumor growth, proposing the combination of peptide receptor radionuclide therapy (PRRT) and SSAs as the option with the best progression-free survival (PFS). However, this analysis seems very speculative and hard to apply to real-life settings.

This review will explore the available antiproliferative therapeutic options for GEP-NENs, based on evidence reported in the literature and on many years of experience in the field. It also includes the contribution of the specialists working in the multidisciplinary setting dedicated to NEN patients at Santa Chiara Hospital (APSS) in Trento (Italy). A separate session will be dedicated to new frontiers in the therapy landscape. Genetic syndromes and management of clinical syndrome (*i.e.* carcinoid syndrome) will not be discussed in this manuscript.

RESECTABLE DISEASE

Endoscopic treatment

The incidence of GEP-NENs has increased in the last two decades also due to the extensive use of endoscopy, particularly following the worldwide implementation of bowel cancer screening programs. Endoscopic resection is reserved to small, localized NETs, mainly located in the rectum, stomach and duodenum. The endoscopist must have extensive knowledge of the macroscopic appearance of these lesions and perform endoscopic ultrasound (EUS) for staging when an invasive NET is suspected, and perform a biopsy when lesions arise from the deep mucosal layer and then extend into the submucosa [16]. A thorough evaluation of tumor location, size, and depth of invasion are mandatory and a multidisciplinary consultation is recommended prior to resection even in case of small and low-grade lesions[17,18].

In this session, the endoscopic approach for gastrointestinal NETs will be discussed according to site, and our proposal for endoscopic management is reported in Table 1.

Colorectal NETs: Colonic NETs are located in the right colon in 70% of cases, can reach a very large size without obstructive symptoms, and are usually aggressive[19]. Given their advanced stage at the time of diagnosis, endoscopic treatment has only been reported in case series, with a significant burden of complications and incomplete resections[17].

Rectal NETs (r-NETs) appear as small, sessile lesions, located within 5-10 cm of the anal verge, with overlying normal or yellowish mucosa. Larger lesions may also be semi-pedunculated or have central depression or ulceration[19].

Staging with EUS is not required for lesions < 10 mm in size due to the negligible risk of invasion[16,20]. The endoscopist may be tempted to perform a standard snare resection but must bear in mind that the complete removal rate for polypectomy is approximately 30%, and for conventional endoscopic mucosal resection (EMR) it is highly variable (17%-90%) due to the submucosal nature of these nodules [19,21,22].

Modified EMR techniques have been employed to obtain a deeper resection. Cap-assisted EMR (EMR-C) uses a dedicated cap with a circumferential rim that can lodge a crescent snare. After saline injection of the submucosa, the lesion is suctioned within the cap and cut. Band-ligation EMR (EMR-L) also requires saline injection. Once the lesion has been adequately captured by the deployment of an elastic band (usually employed for variceal ligation), a snare resection is performed below the band.

The rate of histologically complete resection by modified EMR is high, particularly for EMR-L (93%-100% *vs* 71%-100% for EMR-C) and comparative studies and a meta-analysis confirmed a higher complete resection rate than conventional EMR[20,23,24]. Resection by EMR-C and EMR-L are both used for r-NETs, and the only comparative retrospective study available to date demonstrated similar effectiveness[23]. The higher *en bloc* resection rate for EMR-L was explained by the authors by the larger quantity of submucosa captured by the thickness of the elastic band.

Another technique for advanced endoscopic resection is endoscopic submucosal dissection (ESD). This technique is superior in terms of radical histologic resection in r-NETs ≥ 10 mm[17], but has similar outcomes to EMR-C and EMR-L for small r-NETs (< 10 mm) despite a longer procedure time[20,25].

Gastric NETs: Gastric NENs (g-NENs) usually arise from enterochromaffin-like (ECL) cells and are divided into three types. More specifically, Type I arises in the setting of a chronic atrophic gastritis, Type II is associated with gastrinomas, and Type III is sporadic and independent from gastrin levels. Two additional categories of g-NENs have been recently described and are currently being investigated: Type IV lesions arise from non-ECL endocrine cells, whereas another subtype of g-NETs might be determined by the chronic use of proton pump inhibitors[19,26,27].

Type I and II g-NETs have a highly variable endoscopic aspect (red or yellow, depending on the vascular supply) and are sometimes characterized by a central depression. They usually appear as smooth and rounded multiple polypoid lesions, with size < 20 mm and located in the gastric body and fundus[19,28,29]. As Type I g-NETs are mainly characterized by indolent behavior, conservative management with endoscopic surveillance +/- resection is safe and effective also in the case of recurrent lesions[17,30,31].

Disease staging by EUS prior to resection is not required for small Type I g-NETs (< 10 mm) but it is mandatory when lesions are ≥ 10 mm, when Ki67 is > 3% or in the case of Type II g-NETs[17]. The data regarding ESD show complete resection achieved in 75%-100% of cases, with a lower rate of positive vertical margins at histology compared to standard EMR[32-34]. Modified EMR techniques (EMR-L or EMR-C) are currently being used for Type I g-NETs, and should be considered for small lesions (≤ 10 mm) that can be completely suctioned within the cap in order to obtain the *en bloc* resection (Figure 2).

Type II lesions are extremely rare, and in the absence of high-quality level data, their management is generally similar to Type I[27]. However, considering their size upon presentation (≥ 10 mm) they usually require ESD for complete *en bloc* resection that is better than EMR.

Type III g-NENs are larger, solitary lesions located anywhere in the stomach, sometimes with a broad fixed base and ulceration indicating deeper invasion[17,28,29]. They require a complete disease staging, including EUS. As lymph node involvement is present in more than 50% of cases upon diagnosis and

Table 1 Proposed endoscopic management for gastrointestinal neuroendocrine tumors

	r-NETs	g-NETs	d-NETs	e-NETs
Prevalence (% of GI-NETs)	8-30	4.6-7	1-3	0.2
Indications to EUS	≥ 10 mm	(1) Type I ≥ 10 mm; and (2) Type II-III	Always	Always
Indications to endoscopic resection	< 20 mm, no signs of deep invasion or lymphadenopathy	G1/G2, 10-20 mm, no signs of deep invasion or lymphadenopathy	(1) < 10 mm, no signs of deep invasion or lymphadenopathy; (2) 10-20 mm, G1/G2, no signs of deep invasion or lymphadenopathy (debated); and (3) Periampullary region: G1, no signs of deep invasion or lymphadenopathy(debated)	≤ 10 mm, confined to submucosa, no ulceration
Resection techniques	(1) EMR-C, EMR-L (< 10 mm); and (2) ESD (10-20 mm)	(1) EMR-C, EMR-L (Type I < 10 mm); and (2) ESD (Type I 10-20 mm, Type II-III)	(1) EMR, EMR-C, EMR-L, ESD; and (2) Endoscopic papillectomy in referral centers	EMR-C, EMR-L, ESD

d-NETS: Duodenal neuroendocrine tumors; EMR-C: Cap-assisted endoscopic mucosal resection; EMR-L: Band-ligation endoscopic mucosal resection; e-NETs: Esophageal neuroendocrine tumors; ESD: Endoscopic submucosal dissection; EUS: Endoscopic ultrasound; GI: Gastrointestinal; g-NETs: Gastric neuroendocrine tumors; r-NETs: Rectal neuroendocrine tumors.

liver metastases is in 22%-75%, an endoscopic approach is not frequent in these cases[18,27]. A recent systematic review included 121 patients from eight studies with small localized Type III g-NETs who underwent endoscopic resection. The complete resection rate varied from 72% to 87%, but details about the endoscopic technique were often not reported, preventing comparisons of the EMR and ESD outcomes[18].

Type IV g-NENs are described as aggressive lesions, with a size of > 40 mm upon diagnosis, and in the case of localized disease, surgical resection is preferable[19].

Small bowel NETs: Jejunal and ileal NETs are usually > 20 mm, multifocal in 40% of cases, and with lymphatic involvement upon diagnosis in 70% of cases[19]. Due to these features, and as they are often beyond the reach of a device-assisted enteroscopy, a surgical approach is recommended for localized disease. Endoscopy may instead be helpful for diagnosis, in the case of bleeding, or for tattooing of the lesion[19].

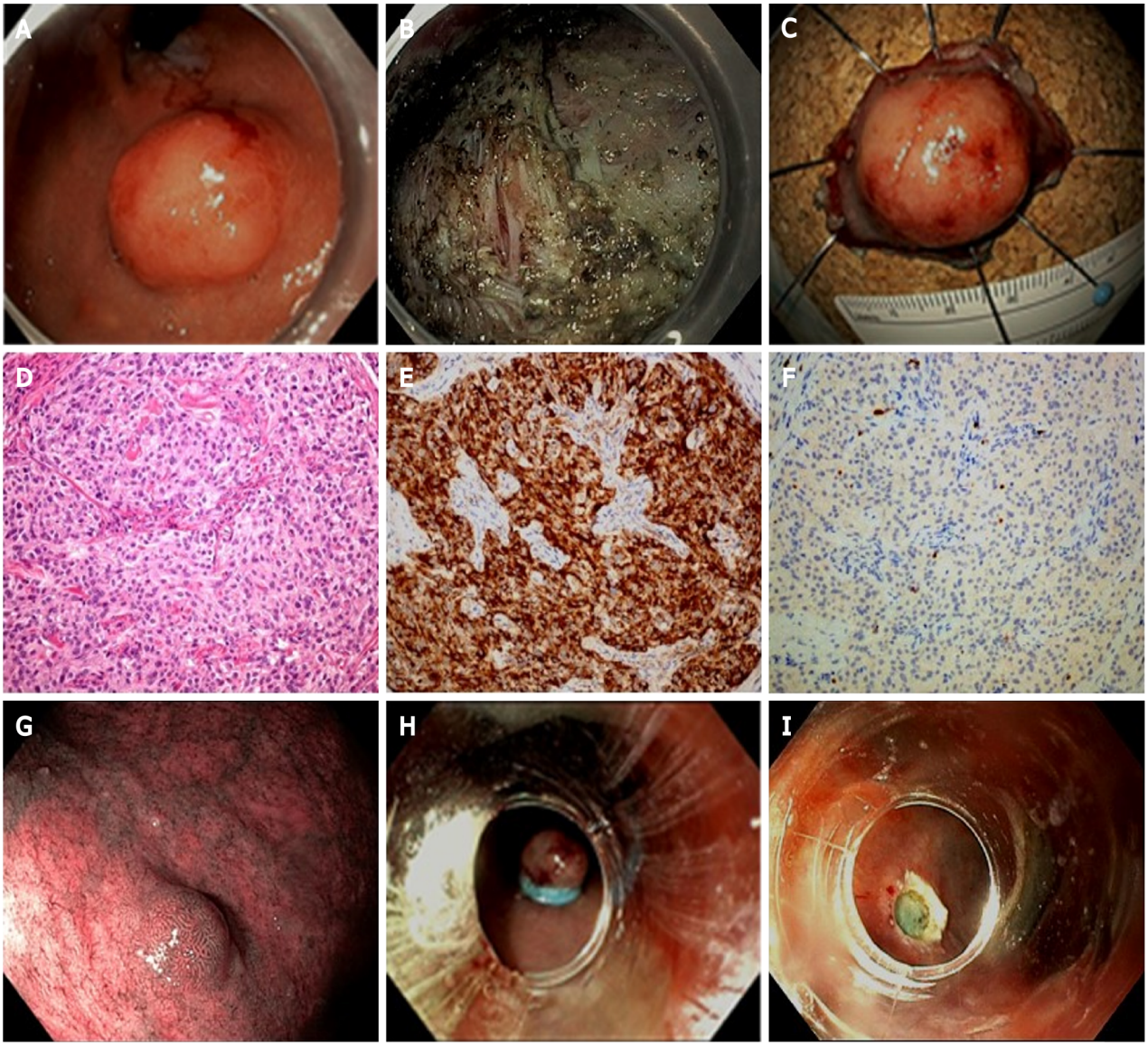
Duodenal NETs (d-NETs) are usually small, sessile and solitary lesions, mainly located in the duodenal bulb or second part[28]. As even sub centimetric tumors present lymphatic spread in 40%-60% upon diagnosis, EUS is mandatory, and resection by EMR or ESD is reserved to submucosal lesions < 10 mm with no lymphatic involvement[17,19]. The management of intermediate (10-20 mm) lesions is controversial and based on local expertise[28]. Considering the thin duodenal wall, some authors prefer to use standard EMR rather than modified EMR[29]. Standard EMR has indeed shown outcomes that are comparable to EMR-C and EMR-L, although higher rates of complete histological removal (70%-92%) has been reported for EMR-L in a small case series[35-38]. Some authors even suggest the autoamputation of small d-NETs using band ligation without snare resection[39].

The rate of radical resection by ESD in the duodenum is variable (67%-100%), due to the technical challenge of scope maneuvering in this anatomical district and the scarce submucosal lifting[36,40]. Moreover, the complication rate may be higher than in other gastrointestinal districts, especially perforation (13%-67% in small case series)[36,41,42]. Based on these considerations, ESD may be offered depending on local expertise and preferentially reserved to poor surgically-suited candidates.

Endoscopic full-thickness resection (EFTR) is usually reserved for subepithelial tumors originating from the muscularis propria. It has only been described for NETs in small case series and ideally should not provide a clear advantage compared to ESD as most NETs remain submucosal[17,43]. The ability of EFTR to secure the intestinal wall with an over-the-scope clip under the cutting plane may overcome the risks of endoscopic resection in the duodenum[40]. However, this advantage may be hampered by the technical drawbacks of operating this unwieldy device in the already difficult duodenal anatomy.

Duodenal NETs originate from the periampullary region in 20% of patients. In these cases, current guidelines recommend surgical resection because they have a more aggressive biology and their metastatic potential is independent of tumor size[18,28,30,35]. Nevertheless, a growing body of evidence favors a prior attempt with endoscopic papillectomy[21,44]. Prospective data are needed to evaluate the efficacy of this approach.

Esophageal NETs: Esophageal NETs (e-NETs) account for only 0.2% of total gastrointestinal NETs. Their appearance is similar to other gastrointestinal NETs, but they tend to have a central ulceration and may sometimes be multiple[29]. Endoscopic resection can be considered in low-risk cases: Lesions ≤ 10 mm, without ulceration and confined to the submucosa according to EUS evaluation. Both *en bloc* EMR and ESD have been effectively used for complete removal. However, the exceptionally rare incidence of e-NETs does not allow high level comparative studies for these techniques[17]. Regarding EMR, EMR-C



DOI: 10.4240/wjgs.v14.i2.78

Figure 2 Endoscopic management of gastric neuroendocrine tumors presentation of a clinical case referred to our hospital. A 78-year-old female patient was referred to our Endoscopy Unit for resection of a lesion of the gastric fundus. Staging by endoscopic ultrasound showed hypoechoic lesion of 19 mm × 12 mm, with well-defined margins, originating from the third hyperechoic layer. Fine-needle cytology diagnosed a NET G1 (Ki67 < 2%). The lesion was then resected by endoscopic submucosa dissection (ESD). Histological evaluation described a gastric NET (g-NET) G1, associated with autoimmune gastritis (Type I). During follow-up, another minor lesion (< 10 mm) suspected for NET was reported along the greater curvature, and resected by Band-ligation endoscopic mucosal resection (EMR-L). Histological report confirmed a Type I g-NET. A: Cardial area reflexed view; B: Resection base after ESD; C: Oriented and pinned specimen; D: Hematoxylin-eosin stain showing monomorphic cells in a nested architecture without necrosis; E: Corresponding Chromogranin A immunostain (20 × magnification); F: Corresponding Ki67 immunostain (20 × magnification); G: Endoscopic appearance of the lesion detected during follow-up; H: EMR-L: Rubber band release; I: Resection base after EMR-L.

and EMR-L are advocated to obtain a deeper submucosal resection than standard EMR.

Future perspectives and open questions: The available data regarding the use of SSAs in the management of Type I g-NETs derive from small, retrospective cohorts, resulting in controversial conclusions[45]. Prospective trials exploring this approach would be useful in understanding the indications and the potential benefit of this alternative option which is currently considered only experimental. A prospective study describing the endoscopic appearance of gastrointestinal NETs and proposing an endoscopic classification would help recognize these lesions and select the suitable technique for endoscopic resection.

Surgery with radical intent

Surgery with radical intent is the preferred option in the management of all GEP-NENs, when feasible. Preoperative work should include complete disease staging with both morphological and functional

imaging tests. We will discuss the surgical approach of these patients according to the tumor primary site and focusing on the main critical issues regarding this therapeutic option.

NETs of the appendix: Appendiceal NETs are usually incidental found during surgery for acute appendicitis. For this reason, radicality of the intervention and the indications to right hemicolectomy with lymphadenectomy still represent critical issues in the management of these patients. The European Guidelines for NETs have established, based on the literature, certain criteria aimed at guiding this decision according to the features of the tumor[46]. More specifically, appendicectomy is considered sufficient when the tumor is < 1 cm and resection is R0. Right hemicolectomy is instead recommended when the tumor is > 2 cm. Regarding the "grey zone" of intermediate tumor size (1-2 cm), additional risk factors indicating a surgical re-intervention are represented by a G2 histology, signs of histological vascular or lymphatic invasion (V1 and/or L1) or a mesoappendiceal infiltration > 3 mm.

Small bowel NETs: Pre-operative tests to be performed in the case of small bowel NETs (Sb-NETs) should also include echocardiography (to evaluate carcinoid heart disease) and colonoscopy. The surgical procedures for resection should include the intraoperative exploration of all abdominal cavities and extensive lymphadenectomy, as one-third of the cases (regardless of primary tumor size) have lymph node metastases upon diagnosis. As these lesions are in almost 80% of cases small, multiple nodules, undetectable by conventional imaging tests, palpation of the entire jejunum and ileum is mandatory to achieve radical resection. These tumors are often characterized by mesenteric fibrosis, and in 5% of cases by small peritoneal implants. For this reason, Sb-NETs are sometimes diagnosed for acute intestinal obstruction. Resection of mesenteric metastases is usually feasible, unless in cases of complete vascular encasement or retroperitoneal involvement[12,47].

Pan-NETs: Regarding pre-operative evaluation for Pan-NETs, vascular involvement (superior mesenteric vein, superior mesenteric artery, coeliac axis and common hepatic artery) must be accurately assessed in order to discuss the feasibility of a curative resection. When patients are candidate to enucleation, EUS or magnetic resonance cholangiopancreatography help evaluate the relationship of the tumor with the pancreatic duct[12]. There is an open debate about the management of non-functioning Pan-NETs < 2 cm and with no involvement of the main pancreatic duct. The two possible proposals are surgical resection *vs* follow-up. As long-term data concerning safety of the conservative management are insufficient, surgery can be considered in young, healthy patients. Parenchyma-sparing pancreatic resections (enucleation or central pancreatectomy) can be performed in these cases; however, complete surgery with these techniques is uncertain because lymphadenectomy is crucial to reach the radicality. In fact, recent data report that 12% of resected small Pan-NETs have lymph nodal metastases at surgery, with poorer recurrence-free survival (RFS) rates in the case of tumors of 15-20 mm[12,48]. The decision to operate or just observe these patients also needs to be based on the general conditions of patients, as the benefit of surgery can be counterbalanced by significant morbidity and mortality rates compared to conservative management[49].

Locally advanced or metastatic disease: Regarding advanced Sb-NETs, surgery can be considered when patients suffer from symptoms due to mesenteric involvement but must be performed in specialized centers. In fact, radical resection or debulking surgery can significantly improve the quality of life of these patients[12]. Encouraging results of curative resection are also available for GEP-NEN patients with TNM stage IV disease, but after ruling out the presence of extra-abdominal disease. When radical resection is feasible, survival rates are indeed better than debulking or medical treatments. For Pan-NETs, median OS for these three options accounts for 97, 89, and 36 mo, respectively[50]. However, careful patient selection is mandatory in order to reduce the risk of complications. The data regarding the use of neoadjuvant treatment associated with radical surgery are scarce. The RMPanNET trial will compare the survival outcomes of metastatic Pan-NETs treated with resection on the primary tumor and metastases after neoadjuvant systemic treatment (SSAs, targeted therapy or chemotherapy) *vs* continuing only systemic treatment (Supplementary Table 1). The NEONEC trial will instead investigate the role of neoadjuvant treatment in terms of RFS in patients with localized NECs, adopting a cisplatin (or carboplatin)/etoposide regimen (Supplementary Table 1).

Role of adjuvant treatments: Unlike other cancers, the data regarding adjuvant treatments in GEP-NENs after curative surgery are scarce, and this approach is not routinely applied in clinical practice. This limitation is probably due to the relatively long survival rates after radical resection without any other treatments (especially for GEP-NETs G1-G2) and to the lack of validated risk scores aimed at identifying patients at high risk of disease recurrence.

A recent retrospective, multicenter study from the United States has reported survival outcomes of 91 GEP-NETs treated with adjuvant treatments (chemotherapy or SSAs) after curative-intended surgery, compared to patients receiving surgery only[51]. The results showed that adjuvant therapy had negative impact on RFS rates, with no benefit in terms of OS. Another piece of analysis from the Surveillance, Epidemiology, and End Results-Medicare (SEER) database included 318 colorectal NENs treated with radical surgery. Focusing on stage I-III TNM disease, no benefit in terms of OS or RFS was observed when adopting adjuvant chemotherapy compared to surgery only[52]. These data discourage the use of

adjuvant treatments, but might be read with caution due to the inevitable selection bias of retrospective studies. In fact, patients receiving post-surgical treatment, in a retrospective analysis, are characterized by more aggressive tumor features, and should not be compared to patients with theoretically less aggressive tumors.

Focusing on NENs G3, the available data concerning the use of adjuvant treatments after curative surgery are derived from retrospective cohorts and provide controversial results. In a series of 73 digestive NECs, with the majority having a colorectal primary tumor site, 43 received chemotherapy, either neoadjuvant and/or adjuvant. The median OS and RFS for patients receiving chemotherapy were 62 and 13 mo, respectively, showing the potential prognostic impact of chemotherapy on survival outcomes[53]. Another study compared the survival rates of 394 radically resected non-metastatic colorectal NECs receiving adjuvant chemotherapy *vs* 412 undergoing radical surgery only. The median OS was significantly longer for patients treated with adjuvant therapy [57.4 *vs* 38.2 mo for patients treated with surgery only; hazard ratio (HR): 0.73, $P < 0.01$], especially in the subgroup of patients with left-sided NECs[54]. Discouraging results were reported by Lin *et al*[55], who analyzed the data of 804 gastric NECs or MiNENs treated with radical surgery +/- adjuvant therapy. The study showed no statistically significant different OS between the two groups. In another retrospective series of 60 GEP-NENs G3 with TNM stage I-III disease receiving radical surgery, the 2-year OS of the total population was 64.5% and the median RFS was 14 mo. Adjuvant therapy, adopted in 20 patients, did not improve either the OS or RFS rates[56].

Future perspectives and open questions: The ASPEN study is prospectively assessing clinical outcomes of patients with Pan-NENs < 2 cm managed by radical surgery *vs* follow-up[57] (Supplementary Table 1). The validation of risk scores in prospective cohorts might help stratify resected GEP-NENs according to the risk of disease recurrence. Patients at high risk might be enrolled in RCT evaluating the potential benefit of adjuvant therapies compared to curative surgery only. Studies evaluating response to adjuvant treatments should also include NETs, as data showing a potential benefit of this therapeutic option so far available were mainly obtained in the setting of NEC patients.

ADVANCED OR METASTATIC DISEASE

Surgical resection of the primary tumor

Beyond the need for debulking in uncontrolled functioning syndrome, resection of the primary tumor is another possible surgical indication in metastatic disease. Some series have recently proved that, in addition to symptomatic relief (for example, for obstruction due to the mesenteric involvement in Sb-NETs), this approach has also a prognostic impact. In fact, in a retrospective series of 14510 GEP-NETs, a benefit in terms of survival has been observed for G1 and G2 patients[58]. A very recent publication from the SEER Registry, including 2219 GEP-NETs, confirms these results for all sites excluding the rectum, with an overall HR of 0.65. In addition, the study highlights the importance of a careful patient selection in a multidisciplinary setting[59]. These conclusions may however be limited by a selection bias, as in retrospective analysis the surgical approach might be reserved to patients with a better performance status or more localized disease[60].

Future perspectives and open questions: Prospective studies comparing the survival outcomes of patients with metastatic GEP-NENs treated with primary tumor resection *vs* patients not undergoing this option would assess the potential prognostic impact of this surgical approach.

Locoregional treatments

Indications, efficacy, and safety: Up to 80% of GEP-NETs present liver metastases at the time of initial diagnosis. Current guidelines recommend vascular and ablative locoregional treatments only for NETs G1-G2 in the case of metastases involving only or predominantly the liver with stable extrahepatic disease. The goals are the relief of symptoms caused by hormone secretion or mass effect in order to improve quality of life, and survival prolongation by slowing the growth of liver lesions. In very select cases, locoregional treatments can be bridging therapies to liver transplantation[61,62]. These treatments should be offered after discussion in a multidisciplinary team consultation, in the case of hepatic disease progression (DP), and might be also considered in conjunction with other systemic therapies or combined with surgery. The choice is based on liver tumor burden, patient symptoms, general clinical condition, but also on the local expertise and availability of the various procedures.

Liver-directed therapies for metastatic GEP-NETs include thermal ablation, transarterial embolization (TAE) or transarterial chemoembolization (TACE) and transarterial radioembolization (TARE), also known as selective internal radiation therapy (SIRT). The data regarding their anti-tumor efficacy primarily comes from retrospective studies using heterogeneous protocols, and consequently it is currently unclear which technique is preferable.

Ablation techniques (radiofrequency ablation, microwave ablation, and cryotherapy) require imaging guidance, and are only applied in the case of limited liver disease: Less than three lesions ≤ 3 cm, or a

single lesion < 5 cm, or even in association with liver surgery[61]. When feasible, thermal ablation shows lower complication rates than surgery (3.9% *vs* 20%, respectively) and a good clinical response (with relief of symptoms in up to 92%)[63]. Unfortunately, the benefits of ablation alone in terms of survival rates are difficult to demonstrate, due to the influence of subsequent lines of therapy in the calculation.

Vascular treatments are based on the rationale that neuroendocrine liver metastases are hypervascular, deriving all their blood supply from the hepatic artery, whereas the normal hepatic parenchyma is mainly supplied by the portal vein (75%). Arterial embolization makes it possible to deliver a tumoricidal dose of chemotherapy (TACE) or β-radiation (SIRT) in association with the ischemic effect on the lesions, thereby reducing systemic adverse effects (AEs) and limiting toxicity for the normal liver parenchyma through the use of a selective technique. The feared carcinoid crisis due to massive release of serotonin or vasoactive peptides in the case of secreting GEP-NETs is prevented by octreotide premedication and by scheduling the presence of the anesthesiologist during the procedure [11]. A multicenter retrospective study showed better results for catheter-based therapies in terms of OS and hepatic PFS for lower grade NETs and for liver tumor burden ≤ 50%, regardless of the primary tumor site (Pan-NETs or Sb-NETs)[64]. Previous studies have instead reported a higher morphological response rate (RR) and/or better OS for non-pancreatic cases[65].

The TACE uses a mixture of chemotherapy drugs and a temporary embolic agent (degradable starch microspheres of 50 μm, with a half-life of approximately 35–50 min), with the aim of preserving arterial patency for further cycles of treatment (Figure 3). Negative predictive factors for response to TACE treatment in GEP-NETs are represented by impaired liver function (ascites, bilirubin ≥ 2 mg/dL, albumin ≤ 3.5 mg/dL), tumor burden ≥ 70% and previous treatment with three or more systemic lines of therapy[61]. In the case of bilobar liver involvement, a sequential approach with multiple selective or lobar TACE treatment sessions is recommended, usually at a 6-8 wk interval, with assessments for patient tolerance and response after each course. Possible complications include portal vein narrowing or thrombosis, bile duct dilatation leading to biloma formation, and liver necrosis with the possible development of abscesses. Caution is therefore recommended especially in the case of bilio-enteric anastomoses, when initial bile duct dilatation or segmental portal vein thrombosis is detected by pretreatment imaging, representing relative contraindications to the performing of TACE.

Another technique, TARE with ^{90}Y-loaded microspheres, has a more favorable safety profile than TACE or TAE, with fewer AEs (pain, post-embolization syndrome, liver/biliary toxicity) in the early post-treatment period; however, hepatic cirrhosis with portal hypertension may appear as a long-term complication, especially in the case of bilobar treatment[66]. Patients should undergo preprocedural evaluation for hepatopulmonary shunts to ensure that no more than 20% of the blood flow is diverted to the lungs to avoid radiation pneumonitis.

A recent meta-analysis revealed that patients treated with TACE had significantly better OS than those treated with TARE[67]. TARE proved to be more effective than TAE/TACE when Ki67 ≥ 3%, whereas Ki67 < 3% predicts a greater benefit with TACE[68]. TARE is indicated in the case of TACE failure or in patients at risk for TACE including major portal vein thrombosis, bilio-enteric anastomoses, and heart problems contraindicating doxorubicin administration. The cost *per* procedure for TARE is nearly double that of TACE; however, there is usually no need for multiple treatment sessions[61]. The ArTisaN study will provide data on the efficacy of TARE in metastatic NETs in a phase II-designed study (Supplementary Table 1).

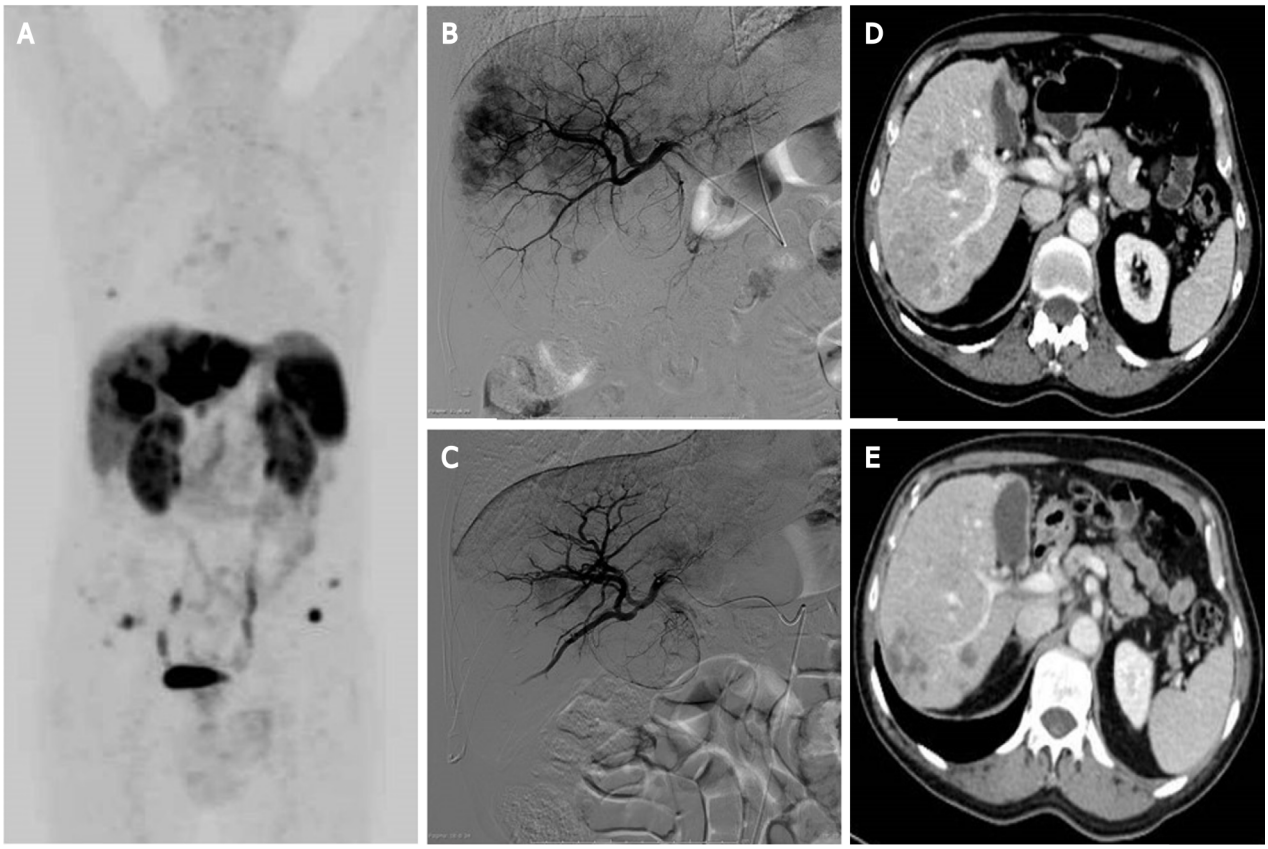
Future perspectives and open questions: Studies also including GEP-NETs G3 might explore the efficacy of locoregional treatments for liver metastases in these patients, especially cases with a lower proliferative index (*e.g.*, Ki67 < 55%). The LUTIA trial will investigate the efficacy of the intraarterial administration of ^{177}Lu-DOTATATE in patients with neuroendocrine liver metastases, and the impact on intra-hepatic biodistribution (Supplementary Table 1). The synergistic effect of liver directed-therapies with immunotherapy represents a further interesting approach to be investigated[69].

SSAs

Indications, efficacy, and safety: The expression of SSTRs is the prerequisite for benefiting from SSAs. These drugs bind with high affinity to the G protein-coupled transmembrane SSTR2 and with moderate affinity to SSTR5. They are usually adopted at the first-line stage in advanced GEP-NETs, with good tolerability. They have a double effect: Clinical syndrome control in functionally active NENs (*i.e.* carcinoid syndrome or duodenopancreatic functioning tumors), and antiproliferative effect[13].

Different formulations are available. The short-acting Octreotide is administered subcutaneously, usually to test the tolerability of the therapy. Long-acting formulations for antiproliferative treatment include Octreotide LAR (10, 20, or 30 mg) with intramuscular injection, and Lanreotide autogel (60, 90, or 120 mg) with deep subcutaneous injection. Pasireotide will not be discussed in this review, due to the limited and controversial results regarding its role as an antineoplastic treatment.

The antiproliferative effect of SSAs compared to placebo has been proved by two double-blind RCTs: The PROMID study[70] for Octreotide LAR and the CLARINET trial[71] for Lanreotide. Thanks to these publications, Octreotide LAR was registered for intestinal NETs and NETs of unknown primary tumor site, whereas Lanreotide autogel for intestinal NETs, Pan-NETs, or for cases with unknown primary tumor site. The recommended dosage for the antiproliferative use is the maximum available (Octreotide



DOI: 10.4240/wjgs.v14.i2.78

Figure 3 Locoregional treatments for neuroendocrine liver metastases-presentation of a clinical case referred to our hospital, with progressive liver disease after multiple systemic treatments. A: ^{68}Ga-DOTATOC-positron emission tomography/computed tomography (CT) whole-body maximum intensity projection image reveals multiple liver metastases involving both hepatic lobes, the left lobe being almost completely replaced by tumor. Bone and lymph nodal small metastases are also evident; B: Selective angiography of the right hepatic artery performed before lobar chemoembolization shows multiple hypervascular liver lesions; C: Selective angiography of the right hepatic artery performed 1 mo after two sessions of degradable starch microsphere transarterial chemoembolization (DSM-TACE). A marked reduction of the liver metastases enhancement is visible, preserved patency of the arterial intra-hepatic branches; D: Portal-phase CT scan before arterial chemoembolization: Multiple confluent hypodense lesions compared to liver parenchyma are detected in the right liver lobe; E: Portal-phase CT scan control after two DSM-TACE: Partial response of the liber metastases, which appear reduced in size and without contrast enhancement. Right portal vein branch narrowing represents an initial sign of liver/biliary toxicity.

LAR 30 mg or Lanreotide autogel 120 mg, administered every 4 wk)[13].

The cumulative antineoplastic effect of Octreotide and Lanreotide compared to placebo has been assessed by a meta-analysis with an overall population of 289 patients, showing a reduction of DP risk of 41% by adopting SSAs compared to placebo [HR: 0.41; 95% confidence interval (CI): 0.29-0.58, $P < 0.01$][72]. The meta-analysis also showed no statistically significant difference in terms of serious AEs (SAEs) between the two arms. However, a higher frequency of biliary stones occurred in the treatment arm (10.5% *vs* 2.7%, respectively)[72]. The elective prophylactic cholecystectomy in advanced GEP-NETs undergoing primary tumor resection represents a possible, but still debated, option in case SSAs are required.

Other possible side effects observed during treatment with SSAs are hypo/hyperglycemia, gastrointestinal symptoms (abdominal pain and diarrhea), and pancreatic insufficiency, which can be confirmed by fecal elastase test, and treated by pancreatic enzyme supplementation[73].

SSAs for highly proliferating Pan-NETs: Focusing on Pan-NETs, the available data regarding the efficacy of SSAs as antineoplastic treatment are limited to the CLARINET study, which however included only G2 cases with Ki67 < 10%[71]. Thus the question regarding their use in the case of higher proliferative index remains open. A recent cooperative real-world study analyzed the antiproliferative effect of SSAs when adopted at the first-line stage for non-functioning, metastatic Pan-NETS with Ki67 ≥ 10%[74]. The total population of 73 patients also included five Pan-NETs G3. The median PFS was 11.9 mo (95%CI: 8.6, 14.1), but a higher efficacy was shown in G2 patients and with limited hepatic tumor involvement. In detail, the median PFS was 12.4 mo in G2 patients *vs* 4 mo in G3 cases ($P < 0.01$). Patients with liver load ≤ 25% had a median PFS of 15 mo *vs* 9.7 mo in the case of higher hepatic tumor load ($P = 0.04$).

Dose escalation: After the occurrence of DP during the treatment with SSAs, GEP-NET patients receive more aggressive and less tolerable drugs. A possible alternative option to this approach is a dose escalation of SSAs. A recent systematic review regarding this therapeutic strategy has reported a disease control rate (DCR) of 30%-100%, and a median PFS of 6.8-32 mo. These wide ranges are probably due to the heterogeneity of the included studies, as they are both retrospective and prospective and they adopt different SSA formulations and at different disease statuses[75].

The NETTER-1 study evaluated the administration of Octreotide 60 mg every 4 wk, but in clinical practice, the dose increase is usually performed by shortening the time interval between injections[76]. The CLARINET FORTE study recently investigated, for the first time in a prospective setting, the potential benefit of this strategy in a series of Sb-NETs G1-G2 or Pan-NETs (NCT02651987)[77]. After experiencing DP during monthly injections of Lanreotide 120 mg, patients were treated with the same dosage but every 2 wk, respectively for 48 and 24 cycles. The results were presented at the last ESMO Conference 2020, showing a duration of stable disease of 13.8 mo for Sb-NETs and 8.3 mo for Pan-NETs. The DCR after 48 wk was 33.3% and 22.9%, respectively. Toxicity was similar to the data observed in the CLARINET trial[71], additionally highlighting the good safety profile of SSAs also after dose escalation, with rare Grade 3 side effects. Considering the efficacy, the good safety profile and the absence of deterioration of quality of life with SSA dose escalation, this approach might represent a valid option for progressive NENs, as it can delay the switch to other potentially more toxic drugs.

Novel biomarkers: Measuring the transcript profile of blood in NET patients is more sensitive and specific than chromogranin A or other blood tests available, and might overcome the limits of imaging tests in assessing the tumor response. The "NETest" represents a transcriptomic signature of NETs, being a multianalyte algorithm analysis PCR-based test. It evaluates, using peripheral blood real-time PCR, the tumor biological activity by measuring the expression of 51 genes, which are associated with neoplastic behavior. In a prospective study, its role in predicting tumor progression during SSAs for GEP-NETs was assessed, showing an earlier prediction of DP than chromogranin A, with an accuracy of 80%-100%[15]. Besides the potential applications of the NETest both for NET diagnosis and follow-up, this test is currently only experimental and it is unavailable in daily clinical practice[78].

Future perspectives and open questions: Besides the use of SSAs at the first-line stage in advanced GEP-NETs G1-G2, the role of these drugs in maintaining therapy is being explored. The REMINET trial is assessing whether Lanreotide 120 mg can maintain a stable disease in duodenopancreatic NETs G1-G2, after response to first-line chemotherapy. The preliminary results were presented at the last ENETS Conference 2021, but a phase III trial is needed for their validation (Supplementary Table 1). The TNE-IDC-COLE trial is evaluating, in a prospective randomized setting, the potential benefit of prophylactic cholecystectomy in advanced GEP-NETs receiving SSAs (Supplementary Table 1). The indication of SSAs in G3 cases needs to be further investigated, as well as the potential benefit of SSAs in cases with low or heterogeneous expression of SSTRs. Prospective studies assessing the role of NETest in predicting response to SSAs, as well as other therapeutic options, are needed for validation of this test in clinical practice.

Interferon

Interferon alpha (IFN-α) is licensed in Europe for functioning GEP-NETs, but it can also control tumor growth. This latter function is based both on a direct antiproliferative effect (influencing the cell cycle, the production of growth factors, and angiogenesis), and an indirect immunomodulatory effect. Several prospective studies have investigated its efficacy as antineoplastic therapy, with conflicting results.

Bajetta *et al*[79] prospectively enrolled 53 patients affected by progressive, metastatic NETs. Patients received IFN-α-2a with the following scheme: 3 × 10^6 IU for the first 3 d, progressively increased to 6 × 10^6 IU for 8 wk, and then three times *per* week. After a median treatment duration of 6 mo, 64% of patients showed partial or complete tumor regression, lasting 1-11 mo. Less enthusiastic results were reported by Faiss *et al*[80], showing no benefit in terms of PFS adopting in naïve GEP-NETs the association of IFN-α/Lanreotide alone. Regarding comparison with chemotherapy, a study showed, in naïve patients with functioning tumor, a better DCR with IFN-α than with streptozotocin (STZ)/5-fluorouracil (5-FU) ($P < 0.01$)[81].

The most common clinical AEs that occur during IFN-therapy (nearly 50% of the patients) are: Flu-like syndrome (fatigue, fever), which can be prevented by paracetamol, neurological disorders (depression), weight loss, abdominal pain, alopecia, pain at the injection site, and headache. Biochemical toxicity includes: Impaired liver functional test (one third of patients), leukopenia, autoimmune diseases (thyroiditis) in 20% of cases, anemia (31%), thrombocytopenia, hyper/hypoglycemia, and the production of neutralizing interferon antibodies. Considering the balance of pros and cons, and the fact that we currently have several alternative options for unresectable GEP-NENs, IFN therapy is currently reserved for only very select cases, mostly syndromic[13]. Regarding the increase in dosage of IFN at DP, as well as its use in G3 patients, no consistent data are available in the literature.

PRRT

Indications, efficacy, and safety: PRRT is based on radiolabeled somatostatin receptor agonists binding SSTRs on tumor cells. After binding, they are internalized and stored in lysosomes, thereby delivering the radioactivity to the tumor cells. The target of PRRT is DNA damage induced by radiation and suboptimal repair, and this effect is more active during mitosis. Before PRRT begins, a basal Octreoscan®, ^{68}Ga-DOTA-PET/CT or ^{64}Cu-DOTA-PET/CT is mandatory in order to obtain *in vivo* mapping of all lesions expressing SSTRs. Suitable patients for PRRT have strong SSTR expression, whereas extensive hepatic and/or bone disease, as well as decreased renal function, may limit its indication. According to ENETS Consensus Guidelines "PRRT is a therapeutic option in progressive SSTR-positive NET with homogenous SSTR expression (all lesions are positive)"[82].

Radiolabeled DOTA pharmaceuticals include ^{90}Y- or ^{177}Lu-DOTATOC, and currently, ^{177}Lu-DOTATATE (LutaThera®), which was approved for GEP-NETs by the United States Food and Drug Administration in 2018. Due to the high renal toxicity, ^{90}Y is now used for the locoregional treatments of liver metastases. The usual schedule for PRRT comprises four cycles of ^{177}Lu-DOTATATE over 6-8 mo, achieving total radioactivity of 25-30 GBq. Toxicity includes myelotoxicity, which can be mitigated with extracorporeal affinity adsorption treatment. This side effect is usually mild and reversible; however, up to 10% of patients may develop WHO Grade 3/4 hematotoxicity, and rarely myelodysplastic syndrome or leukemia[10,83]. Nephrotoxicity may also be caused by PRRT, as the radiopeptides accumulate in the renal interstitium; however, this AE can be reduced by administering a positively charged amino acid infusion. Nausea, vomiting, or (rarely) carcinoid crisis may also occur with PRRT[10].

After a long series of retrospective studies investigating PRRT and proving its ability to inhibit tumor growth in 50%-70% of GEP-NETs[84], the first phase III RCT (the NETTER-1 study)[76] was published. It included 229 patients affected by progressive, unresectable, Sb-NETs G1-G2, and showed an improved outcome with Lutathera® + best supportive care (including Octreotide 30 mg) than with Octreotide 60 mg administered every 4 wk. More specifically, PFS rates at month 20 were 65.2% in the ^{177}Lu-DOTATATE group and 10.8% in the control group, and a benefit was also observed in terms of quality of life[85]. Based on this trial, Lutathera® has been registered for advanced, progressive GEP-NETs (although Pan-NETs had not been included in this RCT). Further analysis of the NETTER-1 results showed that in the PRRT arm, PFS was not significantly affected by tumor shrinkage, suggesting that this treatment prolonged PFS even when tumor objective response was not detected at imaging[86]. A delayed response to PRRT was indeed observed 3 years after PRRT in a patient participating in this trial [87]. These encouraging results have been strengthened by a meta-analysis of 22 RCTs investigating the efficacy of Lu-DOTATATE/DOTATOC in a cumulative population of 1758 advanced/inoperable NETs [88]. The pooled disease RR was 25.0%-35.0%, while the pooled DCR was around 80.0%, proving the efficacy of PRRT as an antineoplastic treatment in these patients.

In a recent consensus, the indication for PRRT was confirmed as a second-line treatment for GEP-NETs with ^{68}Ga-DOTA-SSA-uptake in all lesions, in NET G1-G2 at DP, and in a subset of NETs G3 when all lesions are positive at ^{68}Ga-DOTA-PET/TC[89]. Regarding the efficacy of PRRT in improving OS, the data are still scarce. A new analysis from the NETTER-1 trial, presented at the American Society of Clinical Oncology conference 2021, has however observed no significant benefit from PRRT compared to high-dose SSAs in terms of OS[90].

PRRT for G3 patients: The data regarding the use of PRRT in GEP-NENs G3 are derived from retrospective series, suggesting the potential active role of this treatment for highly proliferating cases. A recent review of the literature with the same topic has shown a median PFS of 19 mo when adopting PRRT in NETs G3 patients *vs* 11 mo for NECs with Ki67 < 55%, and only 4 mo for NECs with higher Ki67[91]. Based on these results, PRRT can be considered for patients with increased uptake on somatostatin-based imaging tests, both in GEP-NETs G3 and NECs, but with a Ki67 < 55%, inoperable disease, life expectancy of at least 3–6 mo, and reasonable performance status (Karnofski Score > 50%) [82]. A potential role for highly proliferating NEC patients might be reserved to very selected cases, and probably a dual tracer using somatostatin-based imaging tests and ^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG) PET/CT might be necessary for these patients.

Novel biomarkers and potential role of ^{18}F-FDG-PET/CT: DP during PRRT is reported in 15%–30% of patients, and the lack of predictive biomarkers helping identify responders *vs* non-responders represents an open issue for NEN management. Proposed tests are the PRRT prediction quotient (PPQ), which is a blood-based assay for eight genes useful to predict PRRT efficacy with an accuracy of 97%, and the NETest, showing an accuracy of 98% in assessing response to PRRT. Trends of NETest correlate with PPQ prediction, but no tests can predict toxicity[92,93]. The ^{18}F-FDG-PET/CT might also help select patients who are candidate for PRRT. It is commonly used in many tumors, but its value for NENs had been initially reserved only for poorly differentiated cases. The recent International Consensus regarding the role of theragnostic in NENs considered it suitable to employ ^{18}F-FDG PET/CT in NECs, in NETs G3 and also in NETs G1-G2, in order to identify the mismatched (^{18}F-FDG-PET/CT-positive/^{68}Ga-DOTA-SSA-negative) lesions[89]. Indeed, as up to 45% of patients referred to PRRT may present heterogeneous SSTR expression, ^{18}F-FDG PET/CT might differentiate GEP-NETs G1-G2 disease into low- and high-risk patients of poor response to PRRT[94].

Re-treatment with PRRT: The opportunity to perform a second PRRT regimen, in patients already undergoing this therapy, is currently being discussed. Rudisile *et al*[95] re-treated 35 patients, who had previously received four cycles with ^{177}Lu-DOTATATE, obtaining a stable disease in 26 patients (81.3%). They concluded that salvage therapy with ^{177}Lu-DOTATATE is safe and effective, even in patients with extensive previous multimodal therapies during DP. The experience from Denmark reports a better response for G1-G2 cases than G3, but shorter survival outcomes upon retreatment (median PFS 19 mo, median OS 54 mo)[96]. In 2021, a meta-analysis of seven studies regarding PRRT re-treatment in 414 patients with advanced NETs showed a median PFS of 12.52 mo, with a safety profile similar to the initial PRRT treatment[97]. These encouraging data have been recently supported by a consensus on theragnostic in NENs, proposing PRRT rechallenge in patients with a stable disease for at least 1 year following therapy completion[89].

Neoadjuvant PRRT: The use of pre-surgical PRRT, aimed at obtaining disease downstaging, primarily derives from small retrospective series. The largest series includes 57 GEP-NETs with unresectable primary tumor due to vascular involvement, with or without liver metastases. After receiving pre-operative ^{177}Lu-DOTATATE, resectable primary tumor was observed in 15 (26.3%) cases. The estimated PFS rate at 2 years was 90%-95%, and OS accounted for 92.1%. A better response was observed in the case of: Duodenal NETs, GEP-NETs with no regional lymph node involvement, primary tumor < 5 cm, liver lesions ≤ 1.5 cm, number of liver lesions ≤ 3, and ^{18}FDG-uptake as a maximum standard uptake value < 5 in the primary tumor[98]. Regarding Pan-NETs, neoadjuvant PRRT seems to reduce the size of the primary tumor, the size of metastatic lymph nodes, and the risk of pancreatic fistula, maintaining the same post-operative survival outcomes[99].

Future perspectives and open questions: Besides the available data supporting PRRT as a second-line treatment after SSA-failure, the efficacy of PRRT at first line will be evaluated by the NETTER-2 study, which adopts Lutathera® in combination with long-acting Octreotide in advanced GEP-NETs G2-G3 compared to high-dose (60 mg) long-acting Octreotide (Supplementary Table 1). The RCT is including both naïve patients and cases previously treated with SSAs in the absence of DP. The study will also provide more data regarding the use of PRRT in the treatment of GEP-NETs G3, probably also at first line. The identification of novel biomarkers helping select the right candidates for PRRT from the NENs would pave the way for the application of precision medicine in this field. The NeoLuPaNET trial will assess the role of neoadjuvant PRRT in resectable Pan-NETs at high risk of disease recurrence. The study endpoints will include post-operative 90-d morbidity and mortality rates, and objective RRs (Supplementary Table 1). Somatostatin receptor antagonists rather than agonists, labeled with radionuclides, are being investigated and seem to provide a longer tumor residence time of the administered dose. New alpha, beta, gamma, and Auger electron-emitting radionuclides are being investigated. In particular, ^{212}Pb-DOTAMTATE seems to be a possible alternative to ^{177}Lutethium (NCT03466216). The first results from a dose-escalation study on 6 patients were presented at the NANETS 2020 Conference[100], and the results are promising.

Targeted therapies: Everolimus

Indications, efficacy, and safety: Everolimus is an inhibitor of the mammalian target of rapamycin, which is an intracellular protein kinase downstream of the phosphoinositide 3-kinase (PI3K)/Akt pathway involved in tumorigenesis. It has been approved as an antineoplastic drug for progressive GEP-NETs as a result of several trials and also "real-life" experiences. It is usually prescribed at a standard dosage of 10 mg/d as continuous oral intake, but in the case of toxicity it can be reduced to 5 mg/d or interrupted (in the case of Grade 3 or 4 side effects).

Focusing on metastatic Pan-NETs, the phase II trial RADIANT-1 proved the efficacy in tumor control after chemotherapy failure of both everolimus alone (10 mg/d) and combined with Octreotide LAR, led to a median PFS of 9.7 mo and 16.7, respectively[101]. The subsequent phase III RADIANT-3 study assessed tumor control by everolimus in 140 progressive Pan-NETs, and showed a significantly different median PFS compared to placebo: 11.0 mo *vs* 4.6 mo, respectively ($P < 0.01$)[102].

Regarding non-pancreatic NETs, the RADIANT-4 RCT evaluated the efficacy of everolimus 10 mg/d compared to placebo in progressive, well-differentiated, non-functioning lung and non-pancreatic digestive NETs[103]. A significantly higher PFS was observed in the treatment arm compared to placebo (11 mo *vs* 3.9 mo; $P < 0.001$), with a rate of disease stabilization respectively of 81% *vs* 64%. The efficacy of everolimus was also proved in terms of OS, with a 36% reduction in the risk of death (HR: 0.64; $P = 0.037$). However, a recent meta-analysis of all available trials adopting everolimus for NENs confirmed the benefit in terms of PFS, but not in terms of OS[104].

The efficacy of everolimus and the good safety profile in advanced progressive GEP-NETs were also confirmed in the real-world setting. In 169 patients receiving this drug for compassionate use, the median PFS was 12 mo and the median OS was 32 mo. The results of the study also suggested the use of everolimus before chemotherapy and PRRT, as the subgroup of patients previously treated with these therapies had suffered due to higher toxicity[105].

Reported toxicity during treatment with everolimus includes: Stomatitis (up to 67% of cases), skin rash (29%–49%), fatigue (33%), infections (20%), diarrhea (30%), cytopenias (< 20%), pulmonary toxicity (10.4%), metabolic impairment (hyperglycemia 5%-13%, increased triglyceride and cholesterol levels 39%-66%, hypophosphatemia 40%), peripheral oedema (13%-20%), and renal impairment (rare and transient)[13,106,107]. Regarding stomatitis, a systematic review observed a longer PFS when it occurs within 8 wk from the start of therapy[106].

Everolimus for G3 patients: A potential antiproliferative effect of everolimus in NENs G3 far been reported in well-differentiated cases. A median PFS of 6 mo and a median OS of 28 mo were observed in a small, retrospective cohort of 15 cases with Ki67 20%-55%[108]. In this series, disease stabilization was maintained in 40% of cases for at least 1 year. Focusing on prospective studies, the NECTOR study (a phase II multicenter trial) has evaluated the safety and efficacy of everolimus after failure of platinum-containing chemotherapy in Pan-NECs, providing discouraging results[109]. In the enrolled 25 patients, the median PFS was only 1.2 mo and median OS was 7.5 mo. Disease control was obtained in 39.1% of cases, with no objective response.

Resistance to everolimus: The antiproliferative effect of everolimus may be limited by primary and secondary drug resistance. In detail, patients showing DP at their first evaluation after starting treatment are primary refractory, whereas cases facing DP after an initial tumor response are patients with acquired resistance[110]. Several strategies are being investigated to overcome the resistance to everolimus. Retreatment after a pause might be an option, but this strategy is only supported by clinical experience and not by published data. A possibility reported in the literature is represented by BEZ-235, which is a dual inhibitor for PI3K and mammalian target of rapamycin (mTOR) (PI3K/mTOR kinase inhibitors), and has a potential synergistic effect when adopted in combination with everolimus. Passing from preclinical to clinical studies, about 250 patients affected by several tumor types were treated with this drug. Since the patients experienced high toxicity of the gastrointestinal tract and bone marrow, as well as early progression, the trials including Pan-NETs were prematurely stopped[111,112].

Future perspectives and open questions: The EVINEC study is currently enrolling patients with G3 neuroendocrine disease, after platinum-based chemotherapy failure, to be treated with everolimus (Supplementary Table 1). This trial will provide further data regarding the use of this therapy in NEC patients. The possibility to retreat patients with everolimus, alone or in combination with other drugs, has never been investigated but may represent another option to be evaluated in future studies. This strategy might also help overcome the resistance to everolimus.

Targeted therapies: Sunitinib

Indications, efficacy, and safety: Sunitinib is an oral multikinase inhibitor competing with ATP for binding within the intracellular domain of various wild-type and/or mutated receptor tyrosine kinases. This antiangiogenetic drug acts against vascular endothelial growth factor receptors, platelet-derived growth factor receptors, KIT, fms-like tyrosine kinase 3, and RET. It has been registered for advanced progressive Pan-NETs at a standard oral daily dose of 37.5 mg, based on a double-blind phase III RCT including 171 well-differentiated, advanced, progressive Pan-NETs receiving sunitinib or placebo[113]. The trial was interrupted early due to the significantly different outcomes and toxicity observed in the two arms: Median PFS 11.4 mo with sunitinib *vs* only 5.5 mo in the placebo arm ($P < 0.01$), OS at 6 mo 92.6% *vs* 85.2%, respectively ($P = 0.02$). A re-analysis of this study[114] showed no significant difference in terms of quality of life between the two arms, with the exception of a worsening of diarrhea observed in the treated patients ($P < 0.05$). Reported toxicity observed during treatment with sunitinib generally includes gastrointestinal symptoms (diarrhea, nausea, vomiting) in 33%-59% of cases, and fatigue (41% of patients). Other possible side effects can be hypertension, headache, the hand-foot syndrome, and neutropenia (Grade 3-4 in 12%). Treatment discontinuation due to side effects occurs in 15% of patients, and 31% require a dose reduction[13]. Experiences from the real-world setting reported, in 62 Pan-NETs receiving Sunitinib for a median time of 165 d, objective response in 13.7% of patients, but the need for dose reduction in 41.9%[115]. In an Italian retrospective study[116] of 80 pre-treated Pan-NETs receiving sunitinib, the median PFS was very close to the results of the trial by Raymond *et al*[113] (10 mo), with 7.5% of patients stopping the treatment due to toxicity. The data concerning the efficacy of sunitinib in non-pancreatic NENs are scare and disappointing. One study from Korea[117] adopted sunitinib in 10 non-pancreatic patients, observing a disease stabilization in 50% of the series, but a poorer median PFS than in cases treated with everolimus: 1.7 mo *vs* 14.7 mo, respectively ($P < 0.01$).

Sunitinib for G3 patients: Regarding G3 disease, data regarding the use of sunitinib are scarce. Mizuno *et al*[118] observed, in 15 unresectable Pan-NENs G3 receiving sunitinib, a significantly better outcome for Pan-NETs G3 than Pan-NECs ($P < 0.05$), and no significant difference between Pan-NETs G3 and G1-G2 cases. A tumor response in G3 cases treated with sunitinib was also observed by Pellat *et al*[119] in an open-label study, who described in 31 GEP-NENs G3 a median PFS of 42 d, and median OS of 181 d. However, this study was primarily focused on biomarkers, and did not report further details regarding survival.

Future perspectives and open questions: Prospective studies should assess the efficacy of sunitinib in non-pancreatic, digestive NENs, as well as in GEP-NENs G3.

Targeted therapies: Surufatinib

Surufatinib is an oral tyrosine kinase inhibitor targeting immune cells and angiogenesis. To date, few data are available on its efficacy in GEP-NENs, but they are encouraging. Results of the SANET-ep RCT [120] enrolling 198 patients with progressive, unresectable or metastatic, well differentiated, extra-pancreatic NETs showed a better median PFS for the surufatinib arm compared to placebo (9.2 mo *vs* 3.8 mo, respectively, $P < 0.01$). The SANET-p trial included 172 progressive, advanced, Pan-NETs, receiving surufatinib or placebo. The median PFS rates were 10.9 mo *vs* 3.7 mo, respectively ($P < 0.01$)[121]. Based on these results, surufatinib might represent a possible further therapeutic option for advanced GEP-NENs, but it also needs to be evaluated in a real-life setting to draw definitive conclusions, especially if we consider the reported toxicity. The two available trials[120,121], in fact, showed more frequent AEs, the occurrence of Grade 3 or worse hypertension, proteinuria, and hypertriglyceridemia. SAEs were reported in 22%-25% of cases in the surufatinib group, and death was observed in 3 patients in both trials.

Chemotherapy

According to the ENETS Guidelines[9], chemotherapy in general represents a valid option for progressive or advanced Pan-NETs and GEP-NENs G3. Besides these indications, it may also be considered in other particular situations, such as GEP-NENs G2 with high Ki67, in the case of rapidly progressive disease, after the failure of other treatments, or even in cases not expressing SSTRs.

Chemotherapy: STZ

Indications, efficacy, and safety: STZ is generally adopted in advanced/metastatic Pan-NETs G1-G2 with high tumor burden, with the aim of obtaining an objective response. STZ is an alkylating agent, usually administered intravenously as a daily regimen for a 6-wk schedule, by rapid injection or short (15–30 min) infusion with a maximum single dose of 1500 mg/m^2. The data concerning its efficacy are controversial, and this drug is not available in some European countries (including Italy). A retrospective study from Germany adopted STZ/5-FU in 96 Pan-NETs, including 56.3% naïve patients, and 6.3% G3. Objective response was reached in 42.7% of patients and stable disease in 40.6%. The median time to progression and OS were 19.4 and 54.8 mo, respectively. A better outcome was observed for Pan-NETs with Ki67 < 15%[122]. Besides the association with 5-FU, an alternative combination of STZ with doxorubicin (or even the STZ/5-FU/doxorubicin regimen) has been investigated, and a better response was observed compared to STZ/5-FU; however, the application of these regimens was limited by a significant cardiotoxicity[123,124].

The most frequent AEs caused by STZ are renal toxicity (dose-related and cumulative), gastrointestinal symptoms (nausea, vomiting, diarrhea), glucose intolerance, liver dysfunction, and hematotoxicity. STZ is mutagenic and carcinogenic and its extravasation causes necrotic tissue lesions [9]. With regard to toxicity, a Japanese retrospective, multicenter study[125] reported in 110 patients the same efficacy adopting a daily *vs* weekly administration of STZ-based chemotherapy, and with monotherapy *vs* combination therapy, but with a significantly better tolerability when STZ was adopted as a monotherapy. The objective response observed in the overall population was 21.8%, with median PFS of 9.8 mo. Schrader *et al*[126] proposed maintaining therapy with STZ/5-FU, using an extended cycle protocol. After the 6-wk protocol, resulting in a median PFS of 21 mo and a median OS of 69 mo, 13 of the 28 included patients were switched to an extended 3-mo cycle protocol for maintaining therapy. This treatment provided an additional median PFS of 23 mo.

Future perspectives and open questions: The use of STZ for non-pancreatic GEP-NETs needs to be further investigated, and might represent a potential option as a neoadjuvant treatment. There are a few studies that evaluate a potential role of STZ in the management of G3 cases and these provided conflicting results[122,127,128]. This option should be further investigated in a prospective setting. Therapy combination with PRRT might be explored as a possible additional therapeutic option for GEP-NETs.

Chemotherapy: Temozolomide and capecitabine

Indications, efficacy, and safety: Temozolomide is an oral alkylator, whereas capecitabine is an oral prodrug for 5-FU. Their association (CAPTEM) usually follows a scheme consisting of capecitabine 750 mg/m^2 twice daily (days 1–14) and temozolomide 200 mg/m^2 once daily at bedtime (days 10–14) every 28 d[129]. Chemotherapy with CAPTEM has been initially adopted in advanced Pan-NETs G1-G2, based on retrospective studies showing a synergistic effect of these two drugs against tumor proliferation. A randomized phase II study (NCT01824875) including Pan-NETs has definitely proved its superiority in disease control compared to only temozolomide, observing a median PFS of 22.7 mo *vs* 14.4 mo, respectively ($P = 0.023$), whereas median OS was not reached *vs* 38 mo[130].

The cumulative antineoplastic effect of CAPTEM regimen has been calculated by a recent meta-analysis including 15 studies and a total population of 384 NENs: Median OS was at least 12 mo and DCR was 72.89%[131]. The efficacy of CAPTEM has also been assessed at first line for Pan-NETs, resulting in an objective response in 70% of patients and median PFS of 18 mo[129]. Regarding toxicity, most frequent AEs due to temozolomide are gastrointestinal symptoms (vomiting, mild nausea, constipation, anorexia), rash, headache, and fatigue, but convulsions may also occur. Grade 3-4 events have been observed in more than 40% of cases after 4 mo of therapy, and may remain in more than 30% for 12 mo following the stopping of treatment. They include thrombocytopenia (3.36%), neutropenia (0.69%), lymphopenia (0.65%), anemia (0.59%), mucositis (0.57%), and transaminase elevation (0.13%)[9,131]. Capecitabine is associated with hand-foot syndrome and liver toxicity (usually hyperbilirubinemia). Less frequently, hematological toxicity may also occur. Side effects are usually reversible and do not require permanent drug discontinuation, but only a dose reduction[9].

CAPTEM for non-pancreatic GEP-NETs and G3 patients: Some series report the use of CAPTEM regimen also for non-pancreatic GEP-NETs. Ostwal *et al*[132] included in their series of 29 NENs G2-G3 also 12 Sb-NENs, obtaining a median PFS for the overall cohort of 33.7 mo. Spada *et al*[133] analyzed data regarding 170 NETs treated with temozolomide-based chemotherapy, including 21 gastrointestinal primary cases and G1 cases. Objective response of the overall population was 28%, median OS 35.6 mo, and median PFS 14.7 mo. The efficacy and safety of CAPTEM regimen have also been proven after prolonged administration in a retrospective study from Israel[134] including 79 NENs with median treatment duration of 12.1 mo (range 0.6-55.6). The median PFS was 10.1 mo and median OS 102.9 mo, with DCR achieved in 59.5% patients. SAEs were rare, with a low discontinuation rate. Regarding the use of temozolomide-based therapy for NENs G3, data from the literature describes CAPTEM as the most commonly used treatment for NETs G3, with a DCR of 65% (35% objective response) and a median PFS of 9.4-12 mo[135]. Instead, the few data available regarding the use of this temozolomide-based regimen in GEP-NECs report poorer disease control in this subset of patients compared to all NETs (HR: 2.70)[136], with a median PFS of 1.8 mo and a median OS of 7.8 mo observed in unresectable extra-pulmonary NECs after platinum-based chemotherapy failure[137].

Neoadjuvant use of TEMCAP: Only two series sought to exploit the downstaging effect of TEMCAP as a neoadjuvant treatment. In a series of 30 Pan-NETs with advanced disease or hepatic metastases, partial response after CAPTEM was achieved in 43% of cases[138]. Another report from the United States adopted in six Pan-NETs with borderline criteria for resectability the CAPTEM regimen +/- radiotherapy before surgery, and obtained in all the patients a radiologic response, and a R0 resection in four[139].

Future perspectives and open questions: Alkylating agents (temozolomide, dacarbazine, DTZ) transfer methyl adducts on DNA bases. Of these, O6-methylguanine accounts for many of their cytotoxic effects and can be repaired by the O6-methylguanine-methyltransferase (MGMT). Approximately half of Pan-NETs are MGMT-deficient, as determined by impaired tumor MGMT expression or by MGMT promoter methylation[133]. An open issue is whether the MGMT deficiency may be a relevant biomarker for increased response and improved survival in these patients. Prospective studies evaluating this possibility and attempting to standardize the assessment of MGMT status are needed. Prospective studies investigating the potential benefit from neoadjuvant CAPTEM for advanced GEP-NETs would provide data regarding a possible further cytotoxic role of this chemotherapy regimen.

Chemotherapy: Platinum-based regimens

Indications, efficacy, and safety: Platinum-based chemotherapies are considered the standard of care for unresectable GEP-NECs[9]. Sorbye *et al*[140] showed a better outcome for advanced GEP-NENs G3 adopting palliative chemotherapy compared to best supportive care. Median OS was indeed 11 mo *vs* 1 mo, respectively. Patients with Ki67 < 55% had a lower RR to the treatment (15% *vs* 42%, $P < 0.001$) but a better OS than cases with higher Ki67 (14 mo *vs* 10 mo, $P < 0.001$). Furthermore, the analysis identified negative prognostic factors for survival a poor performance status, a primary tumor colorectal site, and elevated platelets or lactate dehydrogenase levels.

A recent study performed a reclassification of G3 patients previously treated with platinum-based chemotherapy based on the new WHO classification[6]. In this analysis, a higher RR was observed for NECs with Ki67 ≥ 55% (44%) than NECs with Ki67 < 55% (25%) or NETs G3 (24%). Median PFS was instead 5 mo for all the subgroups[141]. The cisplatin-etoposide regimen (or alternatively carboplatin-etoposide, or irinotecan-cisplatin) is usually adopted at first line in these neoplasms, with an expected RR of 30%-70% and high toxicity. An adequate organ function and performance status are thereby required to receive this systemic treatment[9,142,143].

Cisplatin is usually administered by intravenous infusion, after intensive pre- and post-treatment intravenous hydration +/- osmotic diuretic (to prevent renal toxicity)[9]. Etoposide is usually administered by intravenous infusion, but oral formulation is also available[144]. Regarding toxicity, cisplatin is contraindicated in the case of renal impairment or allergic reactions against platinum compounds, whereas dose reduction is not needed in the case of liver function impairment. Side effects (involving at least 10% of patients) include gastrointestinal symptoms (anorexia, nausea, vomiting, and

diarrhea), hematotoxicity (leukopenia, thrombocytopenia, and anemia), renal disorders, hearing impairment, fever, and peripheral sensory neurotoxicity (transient or permanent)[9]. The data concerning the possibility to adopt carboplatin in the case of renal failure as an alternative to cisplatin are still scarce; however, AEs, including liver failure, may occur also with carboplatin[9]. Etoposide is carcinogenic and mutagenic. The dose-limiting effect of etoposide is myelosuppression. Impaired hepatic or renal function may increase etoposide concentration in tissue. Gastrointestinal symptoms may also occur, as well as stomatitis and temporary hair loss[9]. The association of oxaliplatin-based chemotherapy with 5-FU, leucovorin, and oxaliplatin (FOLFOX) or with capecitabine (XELOX) are usually adopted for NECs as a second or further line of therapy, with an expected DCR of 62%-84%[145,146]. Some series have shown activity also in GEP-NENs G1-G2[145,147], and a retrospective series has reported promising results with FOLFOX also adopted at first line for GEP-NETs G2 and GEP-NENs G3 [148]. Toxicity from FOLFOX includes hematotoxicity (84.1%), chemotherapy-induced peripheral sensory neuropathy, renal toxicity, and infections[148].

Platinum-based chemotherapy for GEP-NETs G3: The efficacy of platinum-based chemotherapy in unresectable GEP-NETs G3 is uncertain. A recent retrospective series analyzed the efficacy of platinum-based treatment, regardless of tumor differentiation and grading[149]. The data regarding 50 Pan-NETs and 29 Pan-NECs were collected, observing partial response in 20% and 41%, respectively. Median OS was 10.9 mo *vs* 29.2 mo, respectively, and no statistically significant difference in terms of PFS was observed. A potential role of cisplatin-etoposide and FOLFOX-regimens in NETs G3 have been suggested, but with a short-lived response[135]. These data also suggest a potential role of platinum-based regimen in Pan-NETs, but patient selection still represents a critical issue. Some molecular markers have been proposed to help select patients (*e.g.*, retinoblastoma protein, KRAS, and TP53 mutations), but the data are still scarce and only based on retrospective series[150-152].

Future perspectives and open questions: Prospective studies investigating new biomarkers predicting tumor response to platinum-based chemotherapy would help select the right candidates for this treatment, including a subgroup of GEP-NETs G3.

Prospective studies adopting FOLFOX at first line in GEP-NENs G3 would definitely assess the potential efficacy of this regimen in these aggressive neoplasms.

Chemotherapy: Fluorouracil, leucovorin, and irinotecan

Regarding GEP-NECs, chemotherapy with fluorouracil, leucovorin, and irinotecan (FOLFIRI) is a possible second-line option for GEP-NENs after cisplatin-etoposide failure. The series published to date are small and retrospective[153]. A randomized, non-comparative, multicenter phase II trial (the SENECA study) will assess the efficacy of CAPTEM *vs* FOLFIRI in GEP-NECs as a second-line treatment after failure of platinum-based therapy (Supplementary Table 1).

Immunotherapy

Indications, efficacy, and safety: In the last decade, immunotherapy has revolutionized the prognosis of many solid tumors, such as melanoma and non-small cell lung cancer. However, the efficacy of immune checkpoint inhibitors (ICIs) in NENs is disappointing. The reasons for this failure might be related to their tumor biology, since NETs are usually characterized by a slow growth rate, a relatively low tumor mutational burden and a rare microsatellite instability[154,155]. Instead, although NECs are highly aggressive neoplasms with high tumor mutational burden, ICIs have not achieved the expected results with these patients[154,156,157].

One of the first ICIs tested in NENs is pembrolizumab, a highly selective, humanized monoclonal antibody blocking the interaction of programmed cell death protein 1 (PD-1) with its ligands [programmed death-ligand 1 (PD-L1) and PD-L2]. The multicohort, single-arm, phase 1 KEYNOTE-028 basket trial evaluated the safety and efficacy of pembrolizumab monotherapy across 20 tumor cohorts, including a cohort of 25 non-pancreatic NETs and a cohort of 16 Pan-NETs. Patients had a PD-L1-positive tumor and were mostly heavily pre-treated. The median follow-up was 20 mo and the overall RR 12.0% in non-pancreatic NETs and 6.3% in Pan-NETs, respectively. The range of response duration was 6.9-17.6 mo. No complete response was observed[158]. In the subsequent phase II KEYNOTE-158 basket trial, pembrolizumab was administered in a cohort of 107 progressive NETs. Patients were enrolled regardless of PD-L1 expression. Objective (only partial) response was achieved in 3.7% of patients, and they all had PD-L1-negative neoplasms. The treatment provided disease stabilization se in 57% of cases, a median PFS of 4.1 mo and a median OS of 24.2 mo. Although these results seem encouraging, they need to be read with caution, as NETs are characterized by a slow growth[159].

ICI for G3 patients: The role of ICIs was also analyzed in NENs G3. Vijayvergia *et al*[160] published a joint analysis of two prospective, non-randomized trials with pembrolizumab in 29 advanced NENs G3 after failure of platinum-based treatment. In 1 patient (3.4%), an objective response was observed, while 6 (20.7%) achieved stable disease. The median PFS was 8.9 wk, with no significant differences between the PD-L1-positive and PD-L1-negative groups. Similar and no clinically relevant results were obtained with avelumab[161]. Another humanized anti-PD-1 antibody, spartalizumab, was evaluated in a phase

II, multicenter, single-arm study of 95 patients including 55 GEP-NETs and 21 GEP-NECs[162]. All patients were progressive at study entry and had received prior treatment for advanced disease. The DCR was 64.2% in the NET group and 19% in the GEP-NEC group, with a better outcome observed for thoracic NETs. However, this study was formally negative because the primary endpoint (objective response > 10%) was not reached.

Combination immunotherapy: Studies of combination immunotherapy with dual blockade of PD-1 and cytotoxic T-lymphocyte antigen 4 (CTLA-4) have shown more promising results. In the DART SWOG 1609 basket trial, ipilimumab was adopted in combination with nivolumab[163]. The cohort of rare tumors also included 32 extra-pancreatic NENs (18 with high-grade disease). One patient obtained complete response (3%), whereas 7 (22%) achieved a partial response, with a better outcome achieved by NECs than NETs (P = 0.004). The combination of durvalumab with tremelimumab in patients with progressive NETs was investigated in the phase II DUNE trial. This study recruited 123 patients, including GEP-NENs after the failure of standard therapies. The immune-related RECIST objective response was 0% for gastrointestinal NETs, 6.3% for Pan-NETs, and 9.1% for GEP-NENs G3[164].

Future perspectives and open questions: Considering the poor results obtained by adopting immunotherapy in NENs, compared to other solid cancers, new biomarkers able to identify the right candidates for immunotherapy are needed. New prospective trials investigating further immunotherapy combination are also needed to provide further therapeutic options to progressive, heavily pretreated patients. More data concerning immunotherapy for GEP-NECs are also needed, as therapeutic options for these aggressive cases are still scarce.

NEW FRONTIERS

The concept of new frontiers in the field of therapy for GEP-NENs can have several interpretations. Besides the introduction of novel medications, new perspectives also include: Endoscopic ablation for Pan-NETs, medical therapy combination, and the optimization of therapy sequences.

Endoscopic ablation for Pan-NETs

The development of specifically designed accessories and suitable technologies for locoregional treatments with EUS guidance has made it possible to perform tumor ablations in Pan-NETs not eligible for surgery, resulting in a lower morbidity rate.

These treatments include EUS-guided radiofrequency ablation (EUS-RFA), which is utilized for the treatment of small functional Pan-NETs to improve symptoms without serious complications[165]. The same technique has also been used to treat non-functional asymptomatic Pan-NETs, with complete response obtained in 71.4%-85.7%[166].

Another technique that has demonstrated good safety and reproducible results is ablation by ethanol injection. Multiple case reports and case series have been published with a procedure success rate ranging from 50% to 60% for non-functioning Pan-NETs and 93% for functioning Pan-NETs[167]. Similar results were achieved in a larger cohort by Choi *et al*[168], treating 33 Pan-NETs with a mixture of 1:1 ethanol and lipidiol. Complete ablation was observed in 60% of the lesions, with complete necrosis at the 3-year follow-up in 41%.

The RAPNEN trial is currently recruiting patients with Pan-NENs to be treated with EUS-RFA, and will investigate the efficacy of this treatment in both functioning and non-functioning cases, including G3 patients (Supplementary Table 1).

Therapy combination

Several studies have investigated the antiproliferative effect of therapy combinations, thereby exploiting the potential synergistic effect of the different treatments. This approach must however be investigated with caution, also considering the possible superior toxicity compared to single treatments.

Therapy combination with PRRT: In one phase II clinical trial[169], ^{177}Lu-DOTATATE PRRT was implemented with capecitabine and temozolomide in advanced low-grade NETs, achieving DCR in 71% of patients, a median PFS of 31 mo and median OS not reached. AEs were mild to moderate, and most frequently represented by nausea, thrombocytopenia and neutropenia. In another phase II study[170], the efficacy and toxicity of PRRT with ^{177}Lu-DOTATATE were assessed in combination with metronomic capecitabine, as a radio-sensitizer agent, in advanced, progressive ^{18}FDG-positive GEP NETs with Ki67 < 55%. The DCR was obtained in 85% of cases, with a median PFS of 31.4 mo, and a median OS not reached. No renal toxicity was observed in this series.

The combination with CAPTEM was also investigated as a sandwich chemo-PRRT treatment. More specifically, within 2 wk after PRRT, CAPTEM was administered followed by a 2-wk rest period; the next cycle of CAPTEM was repeated similarly and followed by 1 mo break, and the next cycle of PRRT was administered at about 3 mo. Two cycles of CAPTEM were therefore sandwiched between two

cycles of PRRT. With this treatment schedule, DCR was observed in 84% of cases, while the median PFS and OS were not reached at a median follow-up of 36 mo[171]. Regarding first-line PRRT, a series from India investigated its efficacy in association with Capecitabine in 45 consecutive unresectable NETs, with favorable outcomes. In detail, partial response was observed in 30% of cases, and the median PFS was 48 mo[172].

Therapy combination with everolimus: Bajetta *et al*[173] adopted the everolimus + LAR Octreotide combination regimen in naïve advanced NETs, and obtained positive conclusions. More specifically, 18% and 74% of the cases showed objective response and disease stabilization for at least 6 mo, respectively. The EVERLAR study[174] reported prospective data on everolimus in combination with SSAs in non-functioning gastrointestinal NETs, with encouraging results in terms of both safety and efficacy. Indeed, the 24-mo PFS rate was 43.6%, with objective response achieved in 2.3% and stable disease in 58.1%. The median OS was not reached after 24 mo. Focusing on chemotherapy, the combination of everolimus and temozolomide offered interesting results in advanced Pan-NETs. In 40 patients treated with these two therapies for 6 mo, no synergistic toxicities were observed and 40% of patients experienced a partial response. The median PFS rate was 15.4 mo, whereas the median OS was not reached[175]. A single-arm trial (NCT02248012) will show the potential synergy of everolimus and temozolomide in NET G3 patients with Ki67 ranging from 20% to 55% (Supplementary Table 1).

Therapy combination with sunitinib: The combination of sunitinib and SSAs adopted in 50 NET patients lead to a "not reached" median PFS, with DCR of 86%. These results come from real-world studies and may be limited by retrospective design and heterogeneous population[176]. Sunitinib was also investigated to potentiate tumor control after TAE in 23 NETs, administered for 1 year after the procedure, achieving a median PFS of 15.2 mo and RR of 72%[177].

Chemotherapy combination: A recent retrospective study has evaluated response to treatment with 5-FU, doxorubicin and STZ (FAS) in Pan-NETs. Median PFS was 20 mo and median OS 63 mo. A better outcome was observed when adopting the FAS regimen at first line, without significant safety concerns [178]. The BEVANEC trial is currently recruiting GEP-NEC patients, after failure of platinum-based chemotherapy, to receive a combination of bevacizumab with FOLFIRI *vs* FOLFIRI alone (Supplementary Table 1)[179].

Therapy sequence

Although the therapeutic landscape for NENs offers several options, the correct therapy sequence to be adopted is so far unknown. Several trials are attempting to compare different sequences in order to understand, on the basis of benefit and toxicity, which alternative option should be preferred. The safety and efficacy of everolimus after prior treatment with PRRT was investigated in a multicenter study including 24 GEP-NETs[180]. Major clinical AEs during treatment with everolimus were hyperglycemia (20.8%), thrombocytopenia (8.3%), fatigue (8.3%) and elevated alanine transaminase levels (8.3%). The median PFS was 13.1 mo, longer than observed in previous trials, suggesting that pretreatment with PRRT might not affect response to everolimus. A retrospective series of Pan-NETs pretreated with chemotherapy followed by PRRT showed that previous treatment with more than one chemotherapy line was a negative prognostic factor for survival outcome, whereas resection of the primary tumor had a positive impact on survival[181]. The COMPETE trial is currently recruiting unresectable, progressive GEP-NETs G1-G2 to receive treatment by PRRT with ^{177}Lu-Edotreotide *vs* everolimus (Supplementary Table 1). The SEQTOR study, which has been developed in Europe, aims instead to investigate the optimal sequence for everolimus and chemotherapy (Supplementary Table 1).

CONCLUSION

In summary, as GEP-NENs represent a highly heterogeneous disease treated with therapeutic protocols that are not fully standardized, a multidisciplinary approach is mandatory for their management. Great advances have been made in the last decade in terms of treatments. Current trials will help answer the open questions regarding therapies for these patients, offering new perspectives in terms of novel drugs, therapy sequence and therapy combination. These data, together with molecular profiling and the application of radiomics in the understanding of tumor features and behavior, will also pave the way for precision medicine in this oncological field.

FOOTNOTES

Author contributions: All authors performed the literature research, wrote the manuscript, and read and approved the final manuscript.

Conflict-of-interest statement: All Authors declare no conflict of interest related to this publication.

Country/Territory of origin: Italy

ORCID number: Elettra Merola 0000-0001-9553-7684; Andrea Michielan 0000-0003-1353-0935; Umberto Rozzanigo 0000-0002-9541-2555; Marco Erini 0000-0002-6314-0196; Sandro Sferrazza 0000-0002-7595-0129; Stefano Marcucci 0000-0001-9144-9038; Chiara Sartori 0000-0003-3137-0082; Chiara Trentin 0000-0002-5213-0208; Giovanni de Pretis 0000-0001-7636-0422; Franca Chierichetti 0000-0002-1898-4736.

S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Fan JR

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World J Gastrointest Surg 2022 February 27; 14(2): 107-119

DOI: 10.4240/wjgs.v14.i2.107

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Surgical strategies for Mirizzi syndrome: A ten-year single center experience

Wei Lai, Jie Yang, Nan Xu, Jun-Hua Chen, Chen Yang, Hui-Hua Yao

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Balakrishnan DS, Kotelevets SM

Received: September 3, 2021
Peer-review started: September 3, 2021
First decision: October 2, 2021
Revised: October 13, 2021
Accepted: January 14, 2022
Article in press: January 14, 2022
Published online: February 27, 2022

Wei Lai, Jie Yang, Nan Xu, Jun-Hua Chen, Chen Yang, Hui-Hua Yao, Department of Hepatobiliary-Pancreatic-Splenic Surgery, Chengdu First People's Hospital (Chengdu Integrated TCM & Western Medicine Hospital), Chengdu 610044, Sichuan Province, China

Corresponding author: Wei Lai, MD, Associate Professor, Attending Doctor, Department of Hepatobiliary-Pancreatic-Splenic Surgery, Chengdu First People's Hospital (Chengdu Integrated TCM & Western Medicine Hospital), No. 18 Wanxiang North Road, High Tech District, Chengdu 610044, Sichuan Province, China. laiwei119@163.com

Abstract

BACKGROUND

Mirizzi syndrome (MS) remains a challenging biliary disease, and its low rate of preoperative diagnosis should be resolved. Moreover, technological advances have not resulted in decisive improvements in the surgical treatment of MS. Complex bile duct lesions due to MS make surgery difficult, especially when the laparoscopic approach is adopted. The safety and long-term effect of MS treatment need to be guaranteed in terms of preoperative diagnosis and surgical strategy.

AIM

To analyze preoperative diagnostic methods and the safety, effectiveness, prognosis and related factors of surgical strategies for different types of MS.

METHODS

The clinical data of MS patients who received surgical treatment from January 1, 2010 to December 31, 2020 were retrospectively reviewed. Patients with malignancies, choledochojejunal fistula, lack of data and lost to follow-up were excluded. According to preoperative imaging examination records and documented intraoperative findings, the clinical types of MS were determined using the Csendes classification. The safety, effectiveness and long-term prognosis of surgical treatment in different types of MS, and their interactions with the clinical characteristics of patients were summarized.

RESULTS

Sixty-six patients with MS were included (34 males and 32 females). Magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) showed specific imaging features of MS in 58 cases (87.9%), which was superior to ultrasound scan (USS) in the diagnosis of MS and more sensitive to subtle biliary

lesions than USS. The overall laparoscopic surgery completion rate was 53.03% (35/66), where the completion rates of MS type I, II and III were 69.05% (29/42), 42.86% (6/14) and zero (0/10), respectively. Thirty-one patients (46.97%) underwent laparotomy or conversion to laparotomy including 11 cases of iatrogenic bile duct injury which occurred in type I patients, and 25 of these patients underwent bile duct exploration, repair and T-tube drainage. In addition, 25 patients underwent intraoperative choledochoscopy and T-tube cholangiography. Overall, 21 cases (31.8%) were repaired by simple suturing, and 14 cases (21.2%) were repaired using the remaining gallbladder wall patch in the subtotal cholecystectomy. The ascendant of the Csendes classification types led to an increase in surgical complexity reflected by increased operation time, bleeding volume and cost. Gender, acute abdominal pain and measurable stone size had no effect on Csendes type of MS or final surgical approach. Age had no effect on the classification of MS, but it influenced the final surgical approach, hospital stay and cost. A total of 66 patients obtained a relatively high preoperative diagnostic rate and underwent surgery safely without serious complications, and no mortality was observed during the follow-up period of 36.5 ± 26.5 mo (range 13-76, median 22 mo).

CONCLUSION

MRI/MRCP can improve the preoperative diagnosis of MS. The Csendes classification can reflect the difficulty of treatment. The surgical strategies including laparoscopic surgery for MS should be formulated based on full evaluation and selection.

Key Words: Mirizzi syndrome; Surgical strategy; Diagnosis; Classification; Surgical approach; Laparoscope

Core Tip: Accurate preoperative diagnosis is a prerequisite for rational selection of surgical strategies for Mirizzi syndrome (MS). Preoperative images combined with findings during intraoperative exploration to determine the classification of MS is the basis for confirming the surgical approach. The present study revealed that magnetic resonance imaging is an effective and reliable preoperative diagnostic method for MS. Laparoscopic surgery can be used in most patients with MS type I and II following detailed evaluation, while type III and IV patients require laparotomy or conversion surgery. Our results verified that disease classification can reflect the difficulty of MS surgery.

Citation: Lai W, Yang J, Xu N, Chen JH, Yang C, Yao HH. Surgical strategies for Mirizzi syndrome: A ten-year single center experience. *World J Gastrointest Surg* 2022; 14(2): 107-119
URL: https://www.wjgnet.com/1948-9366/full/v14/i2/107.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i2.107

INTRODUCTION

Mirizzi syndrome (MS) is a special clinical complication of cholecystolithiasis. It refers to a series of symptoms caused by compression of the common bile duct (CBD) or hepatic duct with or without varying degrees of cholecystobiliary fistula, which results from the impaction of stones in the Hartmann pouch or cystic duct of the gallbladder and/or tissue inflammation and edema[1].

According to the clinical manifestations, pathophysiological changes and imaging features, MS is divided into different types. The Csendes classification is most commonly used in classification of clinical types of MS[2]. This classification divides MS into four main types. Type I: The Hartmann pouch or cystic duct is impacted by gallstones accompanied by compression of the CBD, without fistula formation. Type II: A fistula is formed and the eroded circumference of the CBD is less than one third of that in type I. Type III: The fistula erodes two thirds of the circumference of the CBD. Type IV: Cholecystobiliary fistula involves the whole circumference of the CBD.

Advances in medical technology, such as laparoscopy and robotic surgery, have brought hepatobiliary surgery into a new era. Even so, MS is still a dilemma for surgeons because the low incidence rate leads to difficulty in accumulating personal experience, and is associated with a high conversion rate, and a high risk of operative complications, particularly bile duct injury (BDI)[3,4].

Accurate diagnosis is a prerequisite for the correct treatment of MS. An inaccurate diagnosis usually results in misjudgment during surgery, increases the incidence of BDI, and finally leads to worse clinical consequences. MS has long been a dilemma for surgeons, especially when laparoscopic surgery is performed[5,6]. The diagnosis and management of MS are still challenging[7,8].

Even in patients with a definite diagnosis, many difficulties and risks still need to be overcome in dealing with MS. The erosion of structures, changes in anatomy, dense adhesions and fibrotic lesions caused by stone incarceration and local inflammation increase the difficulty of surgery, the risk of bleeding and the probability of BDI[9]. In view of the above reasons, it is believed that laparoscopic surgery is not the best treatment method for MS, even if it is not a contraindication[10,11].

Endoscopic retrograde cholangiopancreatography (ERCP) can provide more accurate biliary images, and establish diagnosis before operation, and intervene on the combined CBD stones simultaneously. However, its inherent disadvantages limit its application in the comprehensive treatment of MS[1,12,13], such as the treatment of the diseased gallbladder, and cholecystectomy still needs to be performed at the same time or delayed.

Due to the high cost and low popularization, requirements for the operating skills of surgeons, and complications similar to laparoscopic surgery, robotic surgery is not a practical means to treat MS[14-16]. Moreover, it is usually performed in combination with ERCP when dealing with MS, which increases the requirements for facilities and personnel[17,18].

This study retrospectively reviewed the experience of the surgical treatment of MS in our hospital over the past ten years. This experience is mainly based on the strategy that magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) is used as an essential preoperative diagnostic method, combined with the findings of intraoperative exploration to determine the surgical plan in MS patients, without ERCP preoperatively or intraoperatively. The strategy was safe and effective, even though ERCP was not routinely performed. It can be implemented in hospitals with basic facilities and medical qualifications. It is especially suitable for promotion in areas with insufficient medical resources.

MATERIALS AND METHODS

Study design and setting

We conducted a retrospective study involving patients diagnosed with MS who were treated by surgery at the Chengdu First People's Hospital. Data were collected from the case database in our hospital.

Patients and data collection

All patients diagnosed with MS from January 1, 2010 to December 31, 2020 were enrolled in this study. The inclusion criteria were: (1) Over 18 years old; (2) MS patients without intrahepatic bile duct stones and choledocholithiasis; and (3) The results of related imaging and detailed intraoperative exploration were recorded. The exclusion criteria were: (1) Patients with hepatobiliary malignancies; (2) Patients complicated by choledochojejunal fistula; (3) Data were missing and could not be classified; and (4) Patients lost to follow-up.

According to preoperative imaging examination and intraoperative findings, the clinical types of MS was determined using the Csendesclassification[2].

Ethical concerns

The study was reviewed and approved by the Institutional Review Board of Chengdu First People's Hospital(Chengdu Integrated TCM & Western Medicine Hospital). All patients and/or their guardians signed an informed consent before surgery, which met the ethical requirements. Due to the retrospective design of the study, informed consent was waived by the ethics committee for this study.

Follow-up

All patients were followed up in the outpatient department until to June 30, 2021. At least one liver function and ultrasound scan (USS) examination of the hepatobiliary system was completed during the follow-up period after discharge. Before extubation, T-tube cholangiography was performed routinely in patients with T-tube placement, and MRI/MRCP was adopted if necessary. The patients with a percutaneous transhepatic cholangio pancreatic drainage (PTCD) tube were treated in the same way as those with a T-tube. Whether the patients would receive subsequent treatment was determined according to the review results.

Statistical analysis

Continuous variables are presented as mean ± SD, and categorical variables are presented as frequencies and percentages. The comparison of rates among different groups was based on counting data χ^2 test. The mean number of different groups was compared by variance analysis. Statistical analyses were performed using SPSS 19 (IBM Corp., Armonk, NY, United States). A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

General information

Sixty-six patients with MS were included, 34 males (51.5%) and 32 females (48.5%), which is approximately 0.6% of the patients who underwent cholecystectomy in our hospital during the same period. Their age ranged from 18 to 83 years (48.1 ± 15.0, median 47 years). Forty-eight patients (72.7%) with acute abdominal pain and 18 patients (27.3%) without acute abdominal pain were admitted through different routes.

Thirty-nine patients (59.1%) had at least one previous admission according to the available medical records. The upper limit of the normal reference value for total bilirubin detection in our hospital is 28 μmol/L. According to this standard, 35 patients (53.0%) also had jaundice at the time of admission, and 6 of these patients (1 with type II and 5 with type III) underwent preoperative PTCD because of severe comorbidities (hypertension in 1, diabetes in 2 and lung disease in 3) and received general anesthesia surgery after their comorbidities were controlled. The demographic data of the MS patients included in this study are shown in Table 1.

Imaging examinations

ERCP was not performed in any of the 66 MS patients, and USS and MRI/MRCP were performed in all the patients. USS showed bile duct dilatation in 13 cases (19.7%), bile duct compression in 11 cases (16.7%), and the others showed no specific signs. All patients underwent MRI/MRCP at the same time. The results showed that 58 cases (87.9%) had special imaging features of MS, including stones in the Hartmann pouch or cystic duct, extrinsic compression of the bile duct, dilatation of the bile duct and obvious inflammatory changes in Calot's triangle. MRI/MRCP was superior to USS in the diagnosis of MS (Fisher's exact test, $\chi^2 = 5.873$, $P = 0.023$). It seemed that serious biliary changes (type II and type III) could be easily identified by USS, especially when combined with higher bilirubin levels. MRI/MRCP was more sensitive to subtle biliary lesions than USS, even without jaundice (Table 2).

Clinical type and surgical method, hospitalization time, treatment cost

According to preoperative imaging examinations and intraoperative findings, 42 patients were classified as Csendes type I, 14 patients were classifies as type II, and 10 patients were classified as type III. None of the patients had type IV disease. Taking laparoscopic surgery as the standard, the overall completion rate was 53.03% (35/66), where the completion rates in type I, II and III were 69.05% (29/42), 42.86% (6/14) and zero (0/10), respectively. Different Csendes types had different degrees of jaundice ($\chi^2 = 51.417$, $P = 0.000$), and the different types ultimately required different surgical methods, as laparoscopic surgery alone could not be performed in all MS patients (Table 3). The ascendant in the type of Csendes classification led to increased surgical complexity (Table 3). Thus, the higher the classification degree, the more difficult the surgery. This was reflected in increased operation time, bleeding volume and treatment cost, which were statistically significant (Table 3). The hospitalization time increased in different Csendes types, but the differences were not statistically significant.

Gender, acute abdominal pain and the measurable stone size had no effect on Csendes type of MS and final surgical method. Preoperative treatment time did not affect the final surgical method ($\chi^2 = 5.950$, $P = 0.295$). However, the longer the preoperative treatment time, the longer the overall length of hospital stay ($F = 19.70$, $P = 0.000$) and the higher the overall cost ($F = 6.778$, $P = 0.002$).

Age had no effect on the classification of MS, but it did influence the final surgical method. The laparoscopic surgery completion rates in different age groups (< 45 year, 45-60 year and > 60 year) were 58.06% (18/31), 52.94% (9/17) and 47.06% (8/17), respectively ($\chi^2 = 16.06$, $P = 0.042$). In addition, hospital stay ($F = 5.654$, $P = 0.002$) and hospitalization cost ($F = 7.400$, $P = 0.008$) in patients over 60 years old were both significantly higher than those in patients under 60 years old.

Intraoperative data and technical details

Three-port laparoscopic surgery was used routinely. Four-port laparoscopic surgery as an alternative technique was performed when necessary. The right subcostal incision was the standard approach for laparotomy or conversion. Impacted stones varied in size from 0.5 cm to 6 cm, resulting in different fistulas accompanied by local inflammation and fibrotic adhesions. The upper and lower bile ducts of these lesions were dilated to varying degrees (Table 4). Six patients with preoperative PTCD underwent intraoperative cholangiography through the PTCD tube to achieve the correct anatomical identification. Thirty-six patients underwent retrograde cholecystectomy to obtain correct anatomical identification. Due to improper operation when separating Calot's triangle, such as vigorous tearing, 11 cases of iatrogenic BDI occurred in type I patients. Twenty-one cases (31.8%) were repaired by simple suturing, and 14 cases (21.2%) were repaired using the remaining gallbladder wall patch in subtotal cholecystectomy (STC). The excess gallbladder wall can be resected after satisfactory repair to avoid the formation of residual gallbladder. A T-tube should be placed in patients with obvious compression of the bile duct, severe scar fibrosis and unsatisfactory repair. The T-tube was generally placed below the bile duct repair site, one short arm placed upward to the repair site to play a supporting role, and the PTCD tube placed above the repair site. T-tubes were placed in 25 patients (37.9%), including 3 type III

Table 1 Demographic data of Mirizzi syndrome patients, *n* (%), (mean ± SD), (range and median)

Category		
Male/Female		34/32
Age (yr)		48.1 ± 15.0, 18-83, 47
Admission route (Emergency/Outpatient)		48/18
Previous admissions		2.24 ± 0.96, 1-3, 3
Months from discovery of gallstone to this admission		17.8 ± 4.51, 9-22, 21
Confirmed episodes of abdominal pain		2.15 ± 1.04, 1-6, 2
Total bilirubin (μmol/L)	≤ 28	31 (47.0%)
	28-56	27 (40.9%)
	> 56	8 (12.1%)
Postoperative pathologicalresults ofgallbladder	Acute inflammation	24 (36.4%)
	Acute inflammation and gangrene	8 (12.1%)
	Acute suppurative inflammation	9 (13.6%)
	Chronic inflammation	12 (18.2%)
	Chronic suppurative inflammation	5 (7.6%)
	Xanthogranuloma	8 (12.1%)
Preoperative PTCD		6 (9.1%)
Preoperative treatment time (d)		6.35 ± 3.28, 2-20, 6
Postoperative treatment time (d)		7.36 ± 3.66, 3-19, 6.5
Total hospitalization time (d)		13.76 ± 5.41, 6-31, 13
Hospitalization cost (CNY Yuan)		24549 ± 6536, 13596-40815, 23044

PTCD: Percutaneous transhepatic cholangio pancreatic drainage.

Table 2 Diagnosticclues of Mirizzi syndrome by ultrasound scan and magnetic resonance imaging/magnetic resonance cholangiopancreatography in different cases

Imaging examination		Type I	Type II	Type III	Statistics	Total bilirubin (μmol/L)			Statistics
						≤ 28	28-56	> 56	
USS	+	10	8	6	$\chi^2 = 12.00$; $P = 0.002$	11	9	4	$\chi^2 = 0.760$; $P = 0.684$
	-	32	6	4		20	18	4	
MRI/MRCP	+	34	14	10	$\chi^2 = 5.202$; $P = 0.074$	23	27	8	$\chi^2 = 10.28$; $P = 0.006$
	-	8	0	0		8	0	0	

USS: Ultrasound scan; MS: Mirizzi syndrome; MRI: Magnetic resonance imaging; MRCP: Magnetic resonance cholangiopancreatography.

patients through the fistula, and in the other 22 cases through the bile duct incision. Twenty-five patients underwent intraoperative choledochoscopy and T-tube cholangiography to further clarify the condition of the bile duct and ensure no residual stones before the end of surgery. A Winslow foramen drainage tube was also routinely placed in all patients before the end of surgery. The operation time varied, but the total bleeding volume was acceptable and no patients required intraoperative blood transfusion (Table 4).

Follow up, postoperative complications and prognosis

A total of 66 patients were followed up for 36.5 ± 26.5 mo (range 13-76, median 22 mo). All Winslow foramen drainage tubes were removed 3-25 d after surgery according to the recovery, drainage characteristics, combined with liver function and USS results. If a T-tube was placed, it was removed 1.5 to 6 mo after cholangiography if liver function tests were normal.

Table 3 Effects of Csendes classification on surgical methods, operative time, bleeding volume, hospitalization time and cost (*n* = 66), (mean ± SD), (range, median)

		Type I	Type II	Type III	Type IV	Statistics
n (%)		42 (63.64%)	14 (21.21%)	10 (15.15%)	0	
Total bilirubin (μmol/L)	≤ 28	29	2	0	-	χ^2 = 51.42; *P* = 0.000
	28-56	13	11	3	-	
	> 56	0	1	7	-	
Surgical methods	LC	29	6[2]	0	-	χ^2 = 29.91; *P* = 0.000
	LC convert to OC	2	3[2]	0	-	
	LC convert to OC + BDER + T-tube	7[1,2]	4[3]	8[3]	-	
	OC	0	1[2]	0	-	
	OC + BDER + T-tube	4[1,2]	0	2[3]	-	
Hospitalization time (d)		12.8 ± 4.8; 6-25, 12.5	15.1 ± 6.2; 8-26, 13.5	15.9 ± 6.1; 8-31, 15	-	*F* = 1.981; *P* = 0.146
Treatment cost (CNY Yuan)		23037 ± 5522; 13596-40815, 21963	24916 ± 7146; 15108-36557, 23593	30387 ± 6865; 17161-40568, 28624	-	*F* = 5.909; *P* = 0.004
Operative time (minutes)		154.4 ± 91.1; 50-395, 122.5	230.4 ± 133.7; 80-480, 175	219.0 ± 122.2; 95-520, 177.5	-	*F* = 3.486; *P* = 0.037
Bleeding volume (mL)		96.6 ± 81.5; 20-340, 60	191.4 ± 123.3; 30-390, 180	163.5 ± 114.3; 25-400, 140	-	*F* = 5.919; *P* = 0.004

[1]Bile duct exploration and repair due to intraoperative iatrogenic bile duct injury (BDI).
[2]Simple suture due to small fistula or slight BDI.
[3]Repaired with remaining gallbladder wall patch following subtotal cholecystectomy.
LC: Laparoscopic cholecystectomy; OC: Open cholecystectomy; BDER: Bile duct exploration and repair.

Incision infection occurred in 7 patients, mainly in those who underwent open surgery or conversion. Overall, incision infection was mild and healed after local drainage and oral antibiotic treatment. Bile leakage occurred in 9 cases during the perioperative period accompanied by different degrees of localized peritonitis, which were resolved by strengthening drainage, delayed extubation and symptomatic treatment. Postoperative bleeding occurred in 4 patients, mainly manifested as bloody drainage (2 cases of abdominal bloody drainage and 2 cases of bloody bile), which lasted three to four days in the week after surgery. It was estimated that the average daily volume did not exceed 60 mL, and the patients recovered following conservative hemostasis treatment without reoperation or interventional therapy. Five patients were considered to have acute cholangitis due to abnormal liver function and fever. These patients recovered after liver protection and anti-infection treatment. Fourteen patients had a transient elevation in transaminase and/or bilirubin based on preoperative liver function, they gradually recovered and were discharged after symptomatic treatment. One patient with preoperative Csendes type III had elevated transaminase repeatedly with normal bilirubin after discharge. USS showed dilation of the right intrahepatic bile duct and MRI/MRCP showed slight constriction of the right hepatic duct with dilation of the right intrahepatic bile duct, which was considered to be compression caused by inflammation and edema. The transaminase level and imaging results gradually returned to normal after oral liver protective drug treatment. Five patients had residual or recurrent stones in the CBD during the follow-up period, and the stones were successfully removed (3 cases by choledochoscopy*via* the T-tube sinus, and 2 cases by ERCP). Postoperative pneumonia occurred in 3 patients who had preoperative lung diseases, these patients recovered after treatment according to advice provided by the Respiratory Department. Seven cases had different degrees of gastrointestinal dysfunction which normalized after symptomatic treatment.

By the end of the follow-up period, no residual gallbladder was confirmed by imaging examination and no reoperations were necessary. No patients died during the follow-up period (Table 5).

DISCUSSION

The first accurate description and report of MS was by the Argentine surgeon Mirizzi in 1948[1]. Since

Table 4 Intraoperative data and technical details (*n* = 66)

Category		*n* = 66
Final surgical approach	3-port laparoscopic surgery	24, 36.4%
	4-port laparoscopic surgery	11, 16.7%
	Right subcostal incision	31, 46.9%
Maximum diameter of stone (cm)		2.15 ± 1.17, 0.5-6, 2
Fistula size (mm)	Longitudinal diameter	4.1 ± 1.0, 2-6, 4
	Transverse diameter	4.5 ± 1.4, 2-8, 4
Diameter of extra hepatic bile duct (mm)		Maximum 14 ± 2.8, 10-22, 14
		Minimum 8.4 ± 1.8, 6-12, 8
Iatrogenic BDI		11, 16.7% (11 in type I)
Retrograde resection of gallbladder		36, 54.5%
BDER (35, 53%)	Simple suture repair	21, 31.8% (11 in type I, 10 in type II)
	STC and repair using gallbladder wall	14, 21.2% (4 in Type II,10 in type III)
T-tube (25, 37.9%) (14-22 Fr, 18 Fr)		Transfistula 3 (in type III)
		Transbiliary incision 22
Cholangiography (25, 37.9%)	Trans-PTCD	6[1]
	Trans-T-tube	25
Choledochoscopy (25, 37.9%)	Trans-fistula	3
	Trans-cystic duct	2
	Trans-biliary incision	20
Operative time (min)		180 ± 110, 50-520, 140
Bleeding volume (mL)		127 ± 104, 87.5, 20-400

[1]At the beginning of operation, cholangiography was performed using the percutaneous transhepatic cholangio pancreatic drainage tube to confirm the anatomical structure of the biliary duct.
BDER: Bile duct exploration and repair; STC: Subtotal cholecystectomy; PTCD: Percutaneous transhepatic cholangio pancreatic drainage; BDI: Bile duct injury.

Table 5 Postoperative complications (*n* = 66)

Postoperative complications	*n* (%)
Incision infection	7 (10.6)
Bile leakage	9 (13.6)
Bloody drainage	4 (6.1)
Cholangitis	5 (7.6)
Abnormal liver function	14 (21.2)
Biliary stricture	1 (1.5)
Residual or recurrent stone	5 (7.6)
Pneumonia	3 (4.5)
Gastrointestinal dysfunction	7 (10.6)

then, different MS classification criteria have emerged to aid surgical decision-making[3,19-23]. Among them, the Csendes classification with four types[2] is the most commonly used in clinical practice, which includes the presence or absence of gallbladder bile duct fistula and its degree.

The incidence of MS is relatively low, and usually accounts for less than 5% of gallstone patients[13,24,25]. The proportion of patients with each type of MS is also different, and gradually decreases from type I to type IV[23,26-29]. The proportion of patients with type I is 35% to 77%, and the proportion with type IV is usually less than 5%. Safioleas *et al*[26], Kwon and Inui[29] reported the diagnosis and treatment of 24 cases of MS in 8 years and 27 cases of MS in 20 years, respectively, and found no type IV patients. Cui *et al*[27] reported 198 cases of MS in 6 years, of which type I accounted for 59.1% and type IV accounted for 3.1%. Kamalesh *et al*[28] reported 20 cases in 7 years, of which type I accounted for 35% and type IV accounted for 5%.

As MS has no specific symptoms other than those observed in patients with gallstones, the preoperative diagnosis rate of MS is low, and it is confirmed by further exploration when iatrogenic BDI occurs during surgery. In various studies, the preoperative diagnosis rate of MS ranged from 30% to 83%[26,29].

At present, USS is still the first choice for the diagnosis of cholecystolithiasis, but the accuracy of USS for the diagnosis of MS is insufficient. As a basic and routine examination method, USS cannot objectively and comprehensively judge the condition of the bile duct preoperatively and most MS patients have no specific clinical manifestations other than the symptoms associated with gallstones; thus, the preoperative diagnosis of MS is not easy using USS[1,3,30]. Although Joseph *et al*[31] reported that the "Tri-duct sign" represented by the cystic duct, common hepatic duct and portal vein dilatation is helpful in the diagnosis of MS, the clinical typical "Tri-duct sign" is rare and it is affected by the experience of ultrasound examiners , limited understanding of MS and insufficient vigilance. Therefore, in order to improve the diagnostic accuracy, other methods such as CT, ERCP and MRI/MRCP are also used in the preoperative diagnosis of MS. Most studies have demonstrated that CT is not better than USS in the diagnosis of MS, and it is not a deterministic method. ERCP has been used to show the anatomical structure of the bile duct accurately, for removal of coexisting common duct stones and placement of a biliary stent, which is a great help for surgeons in managing MS. It is been considered the gold standard for MS diagnosis due to the above-mentioned advantages[32-35]. However, ERCP has certain equipment requirements and a technical threshold, and not every hospital can carry out ERCP routinely. ERCP is an invasive method of examination and treatment, and associated with some complications[1,12]. In clinical practice, ERCP is not usually performed in patients with simple gallstones, and is only performed if MS is suspected, rather than as a routine method. Therefore, a reliable routine preferred method to diagnose MS is required. As a result, ERCP cannot be popularized in the clinic, especially in hospitals with scarce resources. Due to the specific conditions of our hospital, we cannot conveniently and routinely perform ERCP; thus, ERCP was not included in the diagnosis and treatment of MS in this study. When ERCP is unavailable, the difficulties faced by surgeons cannot be reduced[13].

MRI/MRCP has beneficial characteristics such as it is noninvasive, repeatable, and provides multi-layer clear imaging. It can fully display the number, size and distribution of stones, the shape of the bile duct, the level and degree of obstruction, gallbladder lesions and other details, and help to screen tumors[12,13]. It has become the most suitable method for the preoperative diagnosis of MS, and has practical significance in helping surgeons to manage MS. In the present study, the diagnostic rate of preoperative MRI/MRCP for MS was 87.9% (58/66), while the detection rate of USS for MS was only 36.4% (24/66). However, MRI/MRCP is still insufficient in defining Csendes classification as it cannot accurately judge the presence and degree of the fistula[12,36], which should be further determined by combining with intraoperative findings.

Due to stone compression, biliary stricture, fistula formation, inflammatory edema, fibrotic adhesions, intraoperative bleeding and other difficult conditions, MS has become an important cause of BDI. It was also considered a taboo in laparoscopic surgery and open operation was suggested. In 2016, Kumar *et al*[3] reported 169 patients with MS, including 34 (20%) with type I, 97 (57%) with type II, 28 (17%) was type III and 10 (6%) with type IV MS, who were treated surgically. An open surgery was performed in 146 (86%) cases. Laparoscopic surgery was attempted in only 23 (14%) cases and was successful in only 1 patient with type II. Other scholars have also made considerable efforts to perform laparoscopic surgery for MS, but mainly for Csendes type I and type II patients[7-11]. The results of our study also showed that in most Csendes type I and in some type II MS patients, laparoscopic cholecystectomy (LC) can be completed safely with an overall success rate of 53% (35/66) under comprehensive evaluation and careful dissection. Generally, after relieving compression and inflammatory adhesion of type I MS, the diameter of the bile duct can be restored. However, BDI cannot be completely avoided. A total of 11 cases of BDI occurred in this study, all in type I patients, which may be related to the characteristics of local lesions and the failure of surgeons to treat with caution. Fortunately, BDI was not severe and did not lead to ischemia and disconnection of the bile duct. However, the occurrence of BDI will eventually lead to a change in classification, that is, patients with type I will at least upgrade to type II accompanied by an increase in the complexity of the operation. This is an important reason why our success rate of laparoscopic surgery is lower than those in other studies[7,9], even though our study had a relatively high preoperative diagnosis rate. Similarly, it is necessary to avoid fistula enlargement in Csendes type II and type III patients caused by iatrogenic injury.

From a technical perspective, small bile duct fistulas can be repaired with intermittent absorbable sutures. Such patients can usually undergo cholecystectomy and bile duct repair under complete laparoscopy without T-tube drainage. Larger fistulas can be repaired using the retained gallbladder wall patch following STC and a T-tube ought to be placed. STC is emphasized if bile duct repair is required, which can be used to repair the CBD fistula in difficult circumstances[37].

If the laparoscopic repair is not satisfactory or the operation is difficult, it should be converted to open surgery. For patients with Csendes type III MS, the surgical plan should be chosen based on the preoperative evaluation, combined with the technical level and clinical experience of the surgical team, and laparoscopic surgery should not be performed. According to our results, open surgery or timely conversion to open surgery was preferred in 31 cases (46.97%) including type I patients. Although the surgical trauma increased, the overall postoperative outcomes were good with no long-term morbidity or mortality.

Whether open or laparoscopic surgery for MS is chosen, correct anatomical identification is very important. Intraoperative biliary imaging can be used to clarify anatomy and avoid BDI[12]. We performed intraoperative cholangiography (6 of them *via* the PTCD and T tube) and choledochoscopy in 25 patients (37.9%). These methods can not only help us confirm the correct anatomical structure, but also judge whether there are complicated bile duct stones, strictures and satisfactory repair. We suggest that intraoperative cholangiography should be a mandatory adjunct in difficult situations.

In 2018, Seah *et al*[30] reported 64 patients with MS treated at Singapore General Hospital, including 43 with type I, 18 with type II, and 3 with type III. The diagnostic rate of MS was 88.9% by preoperative MRI and was 11.4% by USS, which were similar to our results (87.9% by MRI and 36.4% by USS). Our study also showed similar results to their studies in the frequency of intraoperative choledochoscopy (37.9% *vs* 44.6%) and cholangiography (37.9% *vs* 46.2%). However, in their study, 57 patients (57/64, 89.1%) chose direct open surgery or conversion surgery with a higher T-tube placement rate (63.1%) and an overall complication rate of approximately 43.8%. In addition, a total of 10 patients (10/64, 15.6%) needed hepaticoenteric anastomosis, including 3 patients with type I MS. They came to a conclusion on this basis that a trial of laparoscopic dissection with low threshold for open conversion is recommended if suspicion is high.

In our study, cholangiojejunostomy was avoided. However, according to the results of other studies [3,23,25,30], cholangiojejunostomy is still a necessary surgical method for patients with a large biliary fistula, especially those with obvious local scarring, ischemia or a large longitudinal defect. Therefore, patients who require cholangiojejunostomy are mainly some type III patients and almost all type IV patients. In addition, the surgical approach is usually open or laparoscopic converted to open surgery. Although surgical technology has made great progress in recent years, including endoscopy, minimally invasive technology and robotics, it has not directly improved the surgical treatment of type IV MS[14-16,29]. Our study did not include type IV patients; thus, we have no direct experience in the surgical treatment of type IV patients. It may take a little longer before technical progress can be routinely applied to the treatment of MS.

Thus, patients with MS should be evaluated comprehensively based on MRI/MRCP. Open surgery or timely conversion to open surgery should be selected when preoperative evaluation or LC intraoperative exploration shows that laparoscopic surgery is unsuitable. Based on this study, a flowchart of surgical strategies for MS is presented as Figure 1.

This study also found that the cost, operative time and bleeding volume in patients with Csendes type I, type II and type III showed an increasing trend with statistical significance (Table 3). Thus, the classification can reflect the difficulty of treatment, indicating that we should avoid increasing the risk to patients due to a change in classification caused by iatrogenic BDI.

Surgery for MS patients should be carried out as soon as the diagnosis and classification are determined. This study confirmed that prolonging preoperative treatment time does not increase the success rate of MS laparoscopic surgery. On the contrary, the longer the preoperative treatment time, the longer the overall length of hospital stay and the higher the overall cost. The reason for this may be that preoperative treatment cannot change the existing lesions and type of MS, and it is difficult to eliminate local inflammatory edema and fibrotic adhesions in a short time. This study also confirmed that the presence or absence of acute abdominal pain had no effect on the classification of MS and the final surgical technique, and suggested that the preoperative treatment time should not be prolonged until the symptoms disappear.This study also found that the success rate of laparoscopic surgery in elderly patients was lower and the treatment cost was higher, which may be related to the longer course of disease, more serious inflammatory scar adhesions and bile duct compression in elderly patients. In addition, it does not rule out the selection bias caused by the subjective will of both surgeons and patients in clinical practice. The size of stones has no effect on the classification of MS and the final surgical technique, which may be because the inflammation, edema, adhesions and compression induced by stones play important roles in the pathogenesis of MS.

The main limitations of our study are its retrospective nature and small sample size. The operations were completed by different surgeons, which inevitably resulted in heterogeneity of the treatment process and consequences. As the published studies adopted incompletely consistent classification standards of MS, the final conclusions have not reached a consensus. In view of this, we only provide our own experience in the surgical treatment of MS. The conclusions in our study should be confirmed

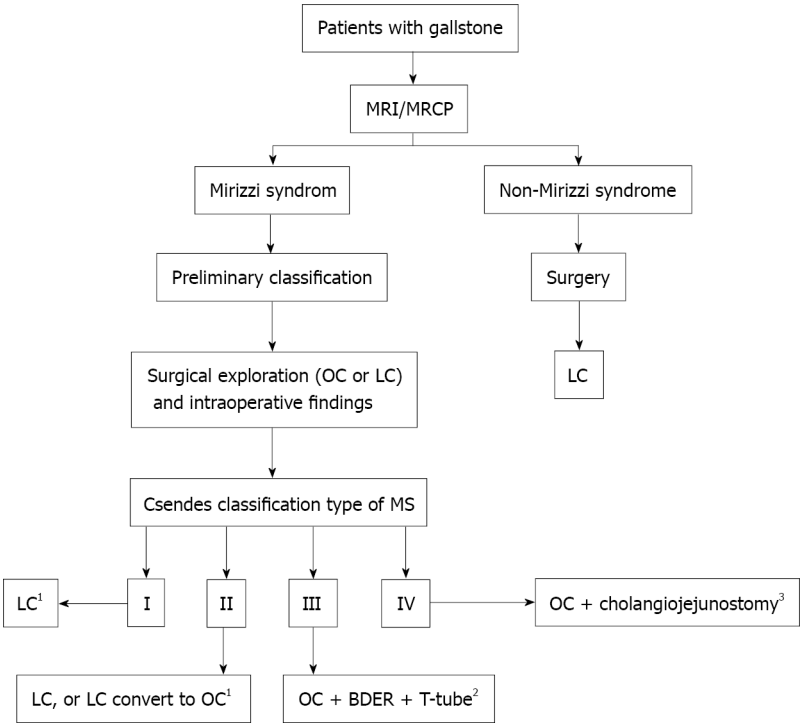

Figure 1 Flowchart of surgical strategies for Mirizzi syndrome. [1]If necessary, bile duct exploration and repair and T-tube drainage (BDER + T-tube) should be carried out using different methods according to different situations; [2]A part of type III patients need cholangiojejunostomy; [3]Cholangiojejunostomy is inevitable in almost all type IV patients. LC: Laparoscopic cholecystectomy; OC: Open cholecystectomy; BDER: Bile duct exploration and repair; MRI: Magnetic resonance imaging; MRCP: Magnetic resonance cholangiopancreatography; MS: Mirizzi syndrome.

by further large sample prospective research.

CONCLUSION

In this study, a relatively high preoperative diagnosis rate was obtained in 66 patients with MS who underwent surgery safely without serious long-term complications. Based on our limited experience, we recommend that MRI/MRCP should be considered a routine and necessary examination before laparoscopic surgery for MS. On the basis of a full evaluation and careful selection, MS patients can be treated by laparoscopic surgery, especially Csendes type I and type II patients, and timely conversion to open surgery may also be necessary. For patients with Csendes type III, the surgical technique requires careful decision-making. The Csendes classification can reflect treatment difficulty in MS patients, and increased risk due to a change in type grade caused by iatrogenic BDI should be avoided. These findings also suggest that active treatment should be carried out for gallbladder stones to reduce the risk of progression to MS, and surgery should be performed as soon as possible once MS is diagnosed. Use of the above strategies can reduce surgical complications, avoid cholangiojejunostomy and obtain a better clinical prognosis.

ARTICLE HIGHLIGHTS

Research background

Mirizzi syndrome (MS) has always been a challenge for surgeons and an important cause of bile duct injury (BDI). At present, this problem has still not been resolved. If we do not accurately understand the pathological characteristics and potential surgical risks of MS, this may lead to adverse clinical consequences.

Research motivation

The treatment methods and effects for MS are changeable according to the different classification types, and the risks are also variable. Whether laparoscopic surgery is suitable for the treatment of MS is also controversial.

Research objectives

This study is a retrospective analysis using data accumulated over a decade that aimed to summarize preoperative diagnostic methods and the safety, effectiveness, prognosis and related factors of surgical strategies including laparoscopic surgery for different types of MS.

Research methods

Sixty-six patients who met the inclusion criteria were included in the study. The diagnostic methods, clinical classification, surgical approach, complications and long-term prognosis were analyzed.

Research results

Magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) is superior to ultrasound scan in the diagnosis of MS. The overall laparoscopic surgery completion rate was 53.03% (35/66). Thirty-one patients (46.97%, 31/66) underwent laparotomy or conversion to laparotomy, including 11 cases of iatrogenic BDI which occurred in type I patients. Overall, 35 patients (53.03%, 35/66) needed bile duct repair using different methods. Twenty-five patients underwent intraoperative choledochoscopy and T-tube cholangiography. A total of 66 patients obtained a relatively high preoperative diagnosis rate and underwent surgery safely without serious complications and no mortality was observed during the follow-up period.

Research conclusions

MRI/MRCP can improve the preoperative diagnosis rate of MS. Laparoscopic surgery can be undertaken safely in some patients with MS, especially Csendes type I and type II patients, and the surgical technique should be carefully determined for Csendes type III patients. The Csendes classification can reflect treatment difficulty and was related to the length of hospital stay and cost. The risk to patients due to a change in Csendes classification caused by iatrogenic injury during surgery should be avoided.

Research perspectives

Sixty-six patients completed diagnostic and treatment procedures by different medical groups within 10 years, which may have led to significant heterogeneity. Accurate conclusions should be confirmed by further large sample prospective studies.

FOOTNOTES

Author contributions: Lai W designed the research protocol, wrote the paper analyzed the data, reviewed and revised the paper; Lai W, Yang J, Xu N, Chen JH, Yang C and Yao HH conducted the research and analyses; all authors have read and approved the final version to be submitted.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of Chengdu First People's Hospital(Chengdu Integrated TCM & Western Medicine Hospital).

Informed consent statement: Due to the retrospective design of the study, informed consent was waived by the ethics committee for this study.

Conflict-of-interest statement: The authors have no conflicts of interest to report.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Country/Territory of origin: China

ORCID number: Wei Lai 0000-0002-9763-5349; Jie Yang 0000-0001-7201-1858; Nan Xu 0000-0003-3898-6381; Jun-Hua Chen 0000-0002-3813-0842; Chen Yang 0000-0003-0225-5130; Hui-Hua Yao 0000-0002-7803-8565.

S-Editor: Fan JR
L-Editor: A

P-Editor: Fan JR

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2022 February 27; 14(2): 120-131

DOI: 10.4240/wjgs.v14.i2.120

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Long-term outcomes of postgastrectomy syndrome after total laparoscopic distal gastrectomy using the augmented rectangle technique

Suguru Yamauchi, Hajime Orita, Jun Chen, Hiroki Egawa, Yutaro Yoshimoto, Akira Kubota, Ryota Matsui, Yukinori Yube, Sanae Kaji, Shinichi Oka, Malcolm V Brock, Tetsu Fukunaga

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Cai ZL, Luo TH

Received: October 7, 2021
Peer-review started: October 7, 2021
First decision: December 4, 2021
Revised: December 15, 2021
Accepted: February 10, 2022
Article in press: February 10, 2022
Published online: February 27, 2022

Suguru Yamauchi, Hajime Orita, Jun Chen, Hiroki Egawa, Yutaro Yoshimoto, Akira Kubota, Ryota Matsui, Yukinori Yube, Sanae Kaji, Shinichi Oka, Tetsu Fukunaga, Department of Gastroenterology and Minimally Invasive Surgery, Juntendo University Hospital, Tokyo 113-8431, Japan

Malcolm V Brock, Department of Surgery, The Johns Hopkins University School of Medicine, Baltimore, MD 21205-2196, United States

Corresponding author: Suguru Yamauchi, MD, Doctor, Surgeon, Department of Gastroenterology and Minimally Invasive Surgery, Juntendo University Hospital, 3-1-3 Hongo, Bunkyo-ku, Tokyo 113-8431, Japan. s.yamauchi.gk@juntendo.ac.jp

Abstract

BACKGROUND

For total laparoscopic distal gastrectomies for gastric cancer, the reconstruction method is critical to the clinical outcome of the procedure. However, which reconstruction technique is optimal remains controversial. We originally reported the augmented rectangle technique (ART) as a reconstruction option for total laparoscopic Billroth I reconstructions. Still, little is known about its effect on long-term outcomes, specifically the incidence of postgastrectomy syndrome and its impact on quality of life.

AIM

To analyze postgastrectomy syndrome and quality of life after ART using the Postgastrectomy Syndrome Assessment Scale-37 (PGSAS-37) questionnaire.

METHODS

At Juntendo University, a total of 94 patients who underwent ART for Billroth I reconstruction with total laparoscopic distal gastrectomies for gastric cancer between July 2016 and March 2020 completed the PGSAS-37 questionnaire. Multidimensional analysis was performed, comparing those 94 ART cases from our institution (ART group) to 909 distal gastrectomy cases with a Billroth I reconstruction from other Japanese institutions who also completed the PGSAS-37 as part of a larger national database (PGSAS group).

RESULTS
Patients in the ART group had significantly better total symptom scores in all the symptom subscales (*i.e.*, esophageal reflux, abdominal pain, meal-related distress, indigestion, diarrhea, constipation, and dumping). The loss of body weight was marginally greater for those in the ART group than in the PGSAS group (-9.3% *vs* -7.9%, $P = 0.054$). The ART group scored significantly lower in their dissatisfaction of ongoing symptoms, during meals, and with daily life.

CONCLUSION
ART for Billroth I reconstruction provided beneficial long-term results for postgastrectomy syndrome and quality of life in patients undergoing total laparoscopic distal gastrectomies for gastric cancer.

Key Words: Laparoscopic distal gastrectomy; Postgastrectomy syndrome; Augmented rectangle technique; Billroth I; Postgastrectomy Syndrome Assessment Scale-37

Core Tip: Reducing the prevalence of postgastrectomy syndrome (PGS) and improving the quality of life (QOL) after gastrectomy for gastric cancer patients has become an important technical challenge for surgeons. We developed the augmented rectangle technique (ART) for Billroth I reconstruction after total laparoscopic distal gastrectomy. Our patient outcome results have been good in the short-term. Long-term patient outcomes have not been studied. Here, we evaluated PGS and QOL after gastrectomy with ART using the Postgastrectomy Syndrome Assessment Scale-37. Application of ART produced beneficial long-term PGS and QOL results in patients undergoing total laparoscopic distal gastrectomies.

Citation: Yamauchi S, Orita H, Chen J, Egawa H, Yoshimoto Y, Kubota A, Matsui R, Yube Y, Kaji S, Oka S, Brock MV, Fukunaga T. Long-term outcomes of postgastrectomy syndrome after total laparoscopic distal gastrectomy using the augmented rectangle technique. *World J Gastrointest Surg* 2022; 14(2): 120-131
URL: https://www.wjgnet.com/1948-9366/full/v14/i2/120.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i2.120

INTRODUCTION

The postgastrectomy syndrome (PGS) is an almost inevitable functional disorder after a radical gastrectomy for gastric cancer[1-3]. In addition to precipitating weight loss because of a reduction in the size (or loss) of the stomach, PGS can also induce systemic disturbances, such as dumping syndrome. These problems can lead to deterioration of a patient's long-term postoperative quality of life (QOL)[4, 5]. Determining if there is a correlation between an increased risk of PGS and certain gastrectomy reconstruction techniques will ensure the optimal selection of appropriate surgical approaches to prevent and treat PGS. Importantly, it is appropriate to question how widely employed contemporary minimally invasive surgeries, such as laparoscopic gastrectomy, contribute to the risk of developing PGS.

Total laparoscopic distal gastrectomy (TLDG) for gastric cancer has evolved from a conventional laparoscopic-assisted gastrectomy to a more complex procedure incorporating more sophisticated techniques and instruments. Fukunaga *et al*[6] originally described the augmented rectangle technique (ART) as a novel Billroth I reconstruction after TLDG. ART for Billroth I reconstruction has been reported to have good short-term results, but no long-term PGS and QOL results have been reported.

The Postgastrectomy Syndrome Assessment Scale-37 (PGSAS-37) was developed by the Japanese Postgastrectomy Syndrome Working Party (JPGSWP) in 2015 to serve as an integrated questionnaire designed to assess postgastrectomy-specific clinical symptoms and QOL[7]. JPGSWP also initiated a multi-institutional nationwide surveillance program to investigate medium to long-term symptoms, living status, and QOL following various types of gastrectomies. The JPGSWP felt that it was necessary to create a standard tool to assess postoperative QOL after any surgical procedure performed at any facility in Japan. This also allowed the statistical analysis of national data collected for each gastrectomy performed at numerous institutions throughout Japan. A "PGSAS statistical kit" was also created to allow free access that allowed individual institutions to compare their own patient outcomes to those PGS outcomes from patients undergoing gastrectomy procedures anywhere else in Japan.

This study investigated the impact on PGS and QOL in patients at Juntendo University in Japan who underwent ART for Billroth I reconstruction compared to a national database of patients who

underwent other reconstruction techniques from multiple institutions throughout Japan and who completed the PGSAS-37 form.

MATERIALS AND METHODS

Patients

From 238 patients who underwent gastrectomy for gastric cancer at Juntendo University Hospital from July 2016 to March 2020, 115 (48.3%) had received a TLDG using ART for Billroth I reconstruction. A PGSAS-37 questionnaire was administered to all patients. Completed or nearly completed questionnaires were retrieved from 94 (81.7%) patients, and these patients were selected for inclusion in this retrospective study (Figure 1). Clinical, perioperative, pathological, and PGSAS-37 questionnaire data were collected and analyzed. Clinicopathological variables included postoperative observation period, age, sex, preoperative body mass index, pathological stage, approach, extent of lymph node dissection, and combined resection. Pathological stage was described according to the Japanese Classification of Gastric Carcinoma[8]. Perioperative outcomes included operative time, intraoperative blood loss, and conversion to open surgery. Postoperative complications, stratified using the Clavien-Dindo classification system[9], included postoperative hospital stay and adjuvant chemotherapy. The study protocol was approved by the ethics committee of the Juntendo University Hospital (Approval No. 20-192). The need for informed consent was waived in view of the retrospective and observational nature of the study. An opt-out approach was used by accessing a written disclosure on the study's website (URL: https://www.gcprec.juntendo.ac.jp/kenkyu/files/6379827945f9a62a8f32ec.pdf).

ART

ART is an anastomosis technique that uses three linear staplers (LS) for TLDG. After gastrectomy, an insertion hole is made in the duodenum and the remnant stomach stump on the greater curvature side. The thinner and thicker 60-mm jaws of the LS are inserted into the greater curvature ends of both the duodenal and remnant gastric stump. The lesser curvature end of the stapled duodenal stump is rotated externally 90°, and the device is closed and fired. After the initial suturing of the stomach and duodenum, the posterior wall and cranial wall form a V-shape. A 30-mm LS is used to close the insertion holes up to the closest side of the duodenal resection margin. This suture creates the third side, which is the caudal wall. Finally, the entire stapled duodenal resection is removed, using a 60-mm LS to create the fourth side that makes up the rectangular anterior wall. This series of operations creates an augmented rectangular gastroduodenal anastomotic stoma.

PGS & QOL assessment

The PGSAS-37 is a multidimensional QOL questionnaire based on the Gastrointestinal Symptom Rating Scale[10,11]. The PGSAS-37 questionnaire consists of 37 questions with 15 items from the Gastrointestinal Symptom Rating Scale, and 22 clinically relevant items selected and added by the JPGSWP (Table 1). These additional items consist of eight assessing overall symptoms, two dumping syndrome, five meal quantity, three meal quality, one work status, and three life dissatisfaction. These items are aggregated into nine subscales, for a total of seventeen main assessable outcomes. Nine subscales are derived from the average score of the corresponding items and include an evaluation of esophageal reflux, abdominal pain, meal-related distress, indigestion, diarrhea, constipation, dumping, quality of ingestion, and dissatisfaction with daily life. The total symptoms score is calculated from the average of the seven symptoms subscale scores. The main outcome consists of three categories, namely symptoms, living status, and QOL (Table 2). In the PGSAS-37 questionnaire, high scores denote favorable outcomes regarding ingested amounts of food per meal, ingested amounts of food per day, appetite, hunger, satiety, the quality of food, and change in body weight. Low scores on most of the other items and for symptom subscales indicate favorable outcomes.

The questionnaire was distributed to all patients who underwent gastrectomy for gastric cancer by a doctor or nurse at the time of outpatient treatment. Questionnaires were conducted at 1 mo, 3 mo, 6 mo, 12 mo, and 24 mo after surgery. The most recent questionnaire data collected for each patient was used in this study. The questionnaire was collected and managed by a medical clerk, and the data were blindly scored.

Study method

This is a retrospective cohort study. We compared it to a national database of 909 patients with distal gastrectomies and Billroth I reconstructions who completed the PGSAS-37 questionnaire. The primary endpoint of our study was to compare the long-term patient outcomes between the two groups in terms of prevalence of PGS and QOL.

Statistical analysis

Continuous data are presented as average and standard deviations. Independent-sample *t*-tests were

Table 1 Postgastrectomy Syndrome Assessment Scale-37 evaluation items

	Item		Subscales
Symptom	1	Abdominal pains	Esophageal reflux subscale (items 2, 3, 5, 16)
	2	Heartburn	Abdominal pain subscale (items 1, 4, 20)
	3	Acid regurgitation	Meal-related distress subscale (items 17-19)
	4	Sucking sensations in the epigastrium	Indigestion subscale (items 6-9)
	5	Nausea and vomiting	Diarrhea subscale (items 11, 12, 14)
	6	Borborygmus	Constipation subscale (items 10, 13, 15)
	7	Abdominal distension	Dumping subscale (items 22, 23, 25)
	8	Eructation	
	9	Increased flatus	Total symptom score (more than seven subscale)
	10	Decreased passage of stools	
	11	Increased passage of stools	
	12	Loose stools	
	13	Hard stools	
	14	Urgent need for defecation	
	15	Feeling of incomplete evacuation	
	16	Bile regurgitation	
	17	Sense of foods sticking	
	18	Postprandial fullness	
	19	Early satiation	
	20	Lower abdominal pains	
	21	Number and type of early dumping symptoms	
	22	Early dumping, general symptoms	
	23	Early dumping, abdominal symptoms	
	24	Number and type of late dumping symptoms	
	25	Late dumping symptoms	
Living status	26	Ingested amount of food per meal[1]	
	27	Ingested amount of food per day[1]	
	28	Frequency of main meals	
	29	Frequency of additional meals	
	30	Appetite[1]	Quality of ingestion subscale (items 30-32)[1]
	31	Hunger feeling[1]	
	32	Satiety feeling[1]	
	33	Necessity for additional meals	
	34	Ability for working	
Quality of life	35	Dissatisfaction with symptoms	Dissatisfaction with daily life subscale (items 35-37)
	36	Dissatisfaction at the meal	
	37	Dissatisfaction with working	

[1]Higher scores indicate a better condition. In items or subscale without [1], higher scores indicate a worse condition. Each subscale and total symptom score is calculated as the average of its composite items or subscale score.

Table 2 Main outcomes consisting of three categories

Category	Main outcome measure
Symptoms	
Subscale	Esophageal reflux subscale
	Abdominal pain subscale
	Meal-related distress subscale
	Indigestion subscale
	Diarrhea subscale
	Constipation subscale
	Dumping subscale
Total	Total symptom score
Living status	
Body weight	Change in body weight (%)[1]
Meals (amount)	Amount of food ingested per meal (%)[1]
	Necessity of additional meals
Meals (quality)	Quality of ingestion subscale[1]
Work	Ability for working
Quality of life	Dissatisfaction with symptom
Dissatisfaction	Dissatisfaction at the meal
	Dissatisfaction at working
	Dissatisfaction with daily life subscale

[1]Higher scores indicate a better condition. In items or subscale without [1], higher scores indicate a worse condition.

used to analyze continuous data while χ^2 or Fisher's exact tests were used to assess differences in categorical data. Statistical analysis was performed using the StatMate statistical software program (version V). $P < 0.05$ was considered significant. Cohen's d was calculated to determine the effect size. The value of Cohen's d reflects the effect of each casual variable, with 0.2 to < 0.5 denoting a small but clinically meaningful effect, while 0.5 to < 0.8 and ≥ 0.8 denote medium and large effects, respectively. The PGSAS statistic kit was used to compare our experimental data with Japanese national standard values for the Billroth I method from cases obtained from the PGSAS database.

RESULTS

Patient characteristics

Table 3 shows the patients' clinicopathological characteristics. There were 94 patients in the ART group and 909 patients in the PGSAS group. The postoperative observation period was significantly longer in the PGSAS group than in the ART group (40.7 ± 30.7 mo *vs* 27.1 ± 12.2 mo, respectively; $P < 0.001$). Age was significantly higher in the ART group than in the PGSAS group (70.0 ± 11.0 *vs* 61.6 ± 9.1, respectively; $P < 0.001$). Sex and preoperative body mass index showed no significant differences between the two groups. Patients in the ART group had significantly more advanced-stage cancer than those in the PGSAS group. The mean tumor size was 30.7±15.6 mm in the ART group. Laparoscopic surgery was performed in all cases in the ART group, but in only 45.6% of patients in the PGSAS group. Patients in the PGSAS group had a significantly higher rate of combined resection than those in the ART group.

Perioperative outcomes

Perioperative outcomes are shown in Table 4. The average operative time was 285 min, and the intraoperative blood loss was 21.1 mL. No cases were converted to open surgery. Postoperative complications included Clavien-Dindo ≥ 3 in 3 patients (3.1%), anastomotic leakage in 1 patient (1.0%), and anastomotic bleeding in 2 patients (2.1%). The average postoperative hospital stay was 14.5 d with adjuvant chemotherapy performed in 17 patients (18.1%).

Table 3 Patients' clinicopathological characteristics

	ART group	PGSAS group	*P* value
Number of patients	94	909	
Postoperative period in mo	27.1 ± 12.2	40.7 ± 30.7	< 0.001
Age in yr	70.0 ± 11.0	61.6 ± 9.1	< 0.001
Sex			0.333
Male	57	594	
Female	37	311	
Preoperative BMI in kg/m^2	22.7 ± 3.4	22.7 ± 3.0	1.000
Stage			< 0.001
I	70	909	
II	16	0	
III	8	0	
IV	0	0	
Approach			< 0.001
Open	0	489	
Laparoscopic	94	415	
Extent of lymph node dissection (D1 >/D1/D2)			0.135
D1 >	0	4	
D1	70	586	
D2	24	319	
Combined resection (absence/presence)			0.001
Absence	89	743	
Presence	5	166	

ART: Augmented rectangle technique; BMI: Body mass index; PGSAS: Postgastrectomy Syndrome Assessment Scale.

Main outcomes

A total of 17 main outcomes in three categories (symptoms, living status, and QOL) are shown in Tables 5 and 6, along with the results of the univariate analysis comparing the ART and the PGSAS groups. For the symptoms category, patients in the ART group had significantly lower scores (indicating a better physical condition) in all symptom subscales (esophageal reflux, abdominal pain, meal-related distress, indigestion, diarrhea, constipation, and dumping) and in the total symptoms score (1.6 ± 0.4 *vs* 2.0 ± 0.7; $P < 0.001$). Regarding the living status category, the loss of body weight was marginally greater for the ART group than the PGSAS group, (-9.3% *vs* -7.9%; $P = 0.054$). The ingested amount of food per meal was statistically lower (indicating a worse physical condition) in the ART group compared to the PGSAS group (6.3 ± 1.9 *vs* 7.1 ± 2.0; $P < 0.001$). Although the need for additional meals was not different between the two groups, the quality of ingestion subscale was significantly lower in the ART group compared to the PGSAS group (3.3 ± 1.0 *vs*3.8 ± 0.9; $P < 0.001$). Regarding the QOL category, the ART group was significantly lower (indicating a better physical condition) in the subscale of dissatisfaction with symptoms, meals, and daily life (except for the work related item). Furthermore, almost the same results were obtained if the same eligible patient criteria for PGSAS was applied (Supplementary Tables 1 and 2).

DISCUSSION

This is the first report to evaluate PGS and QOL after a TLDG reconstructed with the novel Billroth I method of ART. Importantly, we compared our results to patients from the Japanese national PGSAS study who did not receive ART. We analyzed PGS and QOL in patients who did and did not receive an ART and found that ART was beneficial. This is important because in Japan a distal gastrectomy is the

Table 4 Perioperative outcomes

	ART, *n* = 94
Operation time in min	285 ± 84
Intraoperative blood loss in mL	21.1 ± 16.4
Conversion to open surgery	0 (0%)
Postoperative complication CD ≥ 3	3 (3.1%)
Anastomotic-related complication	
Anastomotic leakage	1 (1.0%)
Anastomotic bleeding	2 (2.1%)
Anastomotic stenosis	0 (0%)
Delayed gastric emptying	0 (0%)
Non-anastomotic-related complication	
Pancreatic fistula	4 (4.2%)
Surgical site infection	4 (4.2%)
Pneumoniae	1 (1.0%)
Postoperative hospital stay in day	14.5 ± 14.9
Adjuvant chemotherapy	17 (18.1%)
Adjuvant radiation therapy	0 (0%)

ART: Augmented rectangle technique; CD: Clavien-Dindo.

Table 5 Main outcomes in symptoms categories

		ART group, *n* = 94		PGSAS group, *n* = 909		Cohen's d	*P* value
		mean	SD	mean	SD		
Symptom	Esophageal reflux subscale	1.4	0.6	1.7	0.8	0.30	< 0.001
	Abdominal pain subscale	1.5	0.5	1.7	0.7	0.26	0.003
	Meal-related distress subscale	1.7	0.7	2.1	0.9	0.35	< 0.001
	Indigestion subscale	1.6	0.6	2.0	0.8	0.43	< 0.001
	Diarrhea subscale	1.8	0.7	2.1	1.1	0.27	0.001
	Constipation subscale	1.9	0.7	2.2	1.0	0.32	< 0.001
	Dumping subscale	1.5	0.7	2.0	1.0	0.41	< 0.001
	Total symptoms score	1.6	0.4	2.0	0.7	0.45	< 0.001

ART: Augmented rectangle technique; PGSAS: Postgastrectomy Syndrome Assessment Scale; SD: Standard deviation.

most commonly performed surgical procedure for gastric cancer.

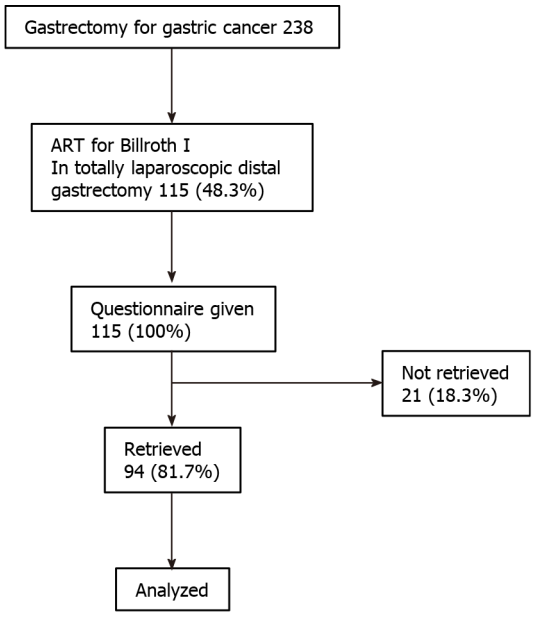
Billroth I is our preferred post-distal gastrectomy reconstruction method because of its technical simplicity and its restoration of normal anatomy[12]. Our patient questionnaire regarding reconstruction methods after distal gastrectomies in Japan showed that Billroth I was selected as the first choice in 77% of Japanese institutions[13]. In recent years, the number of laparoscopic gastrectomies performed in Japan has dramatically increased, resulting in the publication of multiple reports on various reconstruction techniques[14-17]. However, all of these reported techniques are technically challenging, requiring a certain degree of skill and experience and are associated with complications, such as obstruction due to torsion or stenosis at the anastomotic site.

In 2013, we developed ART as a simpler reconstruction technique after TLDG and currently utilize it for all Billroth I reconstruction methods. Importantly, we also reported a low rate of anastomotic-related complications in the short-term after surgery[6]. There was a concern, however, that in the long-term, there would be a high prevalence of esophageal reflux and dumping symptoms because of the large

Table 6 Main outcomes in living status and quality of life categories

		ART group, *n* = 94		PGSAS group, *n* = 909			
		mean	SD	mean	SD	Cohen's d	*P* value
Living status	Change in body weight (%)[1]	-9.3	6.4	-7.9	8.1	0.17	0.054
	Amount of food ingested per meal (%)[1]	6.3	1.9	7.1	2.0	0.41	< 0.001
	Necessity of additional meals	1.8	0.7	1.9	0.8	0.00	0.977
	Quality of ingestion subscale[1]	3.3	1.0	3.8	0.9	0.52	< 0.001
	Ability for working	1.8	0.9	1.8	0.9	0.13	0.261
Quality of life	Dissatisfaction with symptoms	1.6	0.7	1.8	0.9	0.21	0.022
	Dissatisfaction during meals	1.8	0.9	2.2	1.1	0.29	0.004
	Dissatisfaction during work	1.6	0.7	1.7	0.9	0.03	0.774
	Dissatisfaction with daily life subscale	1.7	0.6	1.9	0.8	0.21	0.016

[1]Higher scores indicate a better condition. In items or subscale without [1], higher scores indicate a worse condition. ART: Augmented rectangle technique; PGSAS: Postgastrectomy Syndrome Assessment Scale; SD: Standard deviation.



DOI: 10.4240/wjgs.v14.i2.120

Figure 1 Flow diagram for study inclusion. ART: Augmented rectangle technique.

rectangular anastomosis. Therefore, we evaluated long-term PGS and QOL after ART using the PGSAS-37 questionnaire and analyzed patients' postoperative functions in comparison to patients in a national database who did not receive ART. The PGSAS questionnaire, used by the national database, is designed specifically to evaluate functional parameters after gastrectomy. It is also freely accessible and is highly versatile since it observes a patient's condition during daily routine medical care.

Unexpectedly, patients in the ART group fared significantly better in all symptom subscales (esophageal reflux, abdominal pain, meal-related distress, ingestion, diarrhea, constipation, dumping) and in the total symptom scores than the patients in the PGSAS group. Symptoms such as regurgitation and dumping, presumably due to the large anastomosis, were significantly fewer than the national average. This result suggests that ART may be beneficial in reducing these symptoms after gastrectomy. It is not clear why the symptoms subscale and the total score categories both improved. Postoperative anastomotic complications cause a variety of complaints, so our low anastomotic complication rates associated with ART may have contributed to our better PGSAS-37 scores than the national average.

Moreover, the reason for this may not only be due to the anastomosis technique but also due to the fact that patients received postoperative continuous nutritional guidance (especially avoiding overeating), ready treatment for any complaint, life guidance as well as psychiatric care. At the very least, this study shows that the large rectangular anastomosis, which is a characteristic of ART, does not cause various complaints.

Focusing on the category of living status, the rate of weight loss in patients was marginally greater in the ART group than observed nationally (P = 0.054). Since the data suggest no additional meals consumed, a smaller amount of food per meal in the ART group may be one of the causes of weight loss. Another reason may be related to the shorter length of the postoperative observation period in our study. The average postoperative observation period was 40.7 mo in patients in the national PGSAS database but only 27.1 mo in patients with ART. In addition, the ART group included 17 patients (18.1%) who received postoperative adjuvant chemotherapy, which is also a factor that can lead to weight loss.

There are several reports on the relationship between PGS and the size of the gastric remnant after a distal gastrectomy with a Billroth I reconstruction. Nomura *et al*[18] reported that in cases of early gastric cancer patients who maintained half of their gastric remnant showed improved food intake, little postoperative weight loss, and few abdominal symptoms, such as diarrhea and abdominal pain, compared to those who only had one-third of their gastric remnant after a distal gastrectomy with a Billroth I reconstruction. On the other hand, there are reports that there is no relationship between the size of the gastric remnant and weight loss[19].

Japanese gastric cancer guidelines recommend at least two-thirds of the stomach be removed during a distal gastrectomy. We also follow the Japanese gastric cancer treatment guidelines and perform a complete gastric dissection. Misawa *et al*[19] evaluated PGS with and without a Kocher maneuver during distal gastrectomy with a Billroth I reconstruction. They reported that the Kocher maneuver resulted in poor PGSAS scores in the quality of ingestion subscale, which evaluates appetite, hunger, and satiety. We found the same result in our study. ART also slightly mobilizes the duodenum during reconstruction, although not to the same extent as a Kocher maneuver. This may be one of the reasons why this aspect of the PGSAS score in the quality of ingestion subscale was worse than the national average. The superior score for patients in the ART group, for the subscales of dissatisfaction with symptoms, diet, and with daily life, indicates that patients are in good shape physically. This also suggests that the lack of ART post-gastrectomy symptoms contributes to maintaining a good QOL on a daily basis. It is difficult to conclude that the infrequency of post-gastrectomy symptoms was due to an anastomosis technique alone but may also reflect appropriate decision making regarding the type of surgical procedure as well as the attentive postoperative management.

This study has several limitations. Specifically, this was a retrospective study in which there were substantial differences between the two groups making some direct comparisons problematic. For example, it is not possible to accurately match patients' preoperative physical conditioning. Also, since the data published by the PGSAS database are limited, it is again not possible to analyze certain variables that may have impacted outcome. However, almost the same results were obtained if the same eligible patient criteria for PGSAS were applied (Supplementary Tables 1 and 2). Further prospective research is needed to examine the effects of preoperative factors, including age, sex, body mass index, stage, *etc.* on PGS and QOL. Another limitation is that it was difficult to provide a rational explanation for all results. PGS varies widely among individuals and is influenced by a variety of physical and functional factors. There have been no studies of a specific Billroth I technique for TLDG that have examined as many symptoms as in this study. In particular, chronological changes are thought to be the most important issue in evaluating a patient's QOL after gastrectomy. However, we mainly focused on a certain variable, QOL, at the average postoperative observation period of 27.1 mo after gastrectomy. Kobayashi *et al*[20] reported that patients rarely had any subsequent changes in their QOL more than 1 year after gastrectomy. The average observation period in our study is, by definition, appropriate. At present, PGSAS-45, which is PGSAS plus SF-8, is often used for QOL evaluations after gastrectomy. SF-8 was not measured in this study, and further follow-up studies are needed with this instrument.

CONCLUSION

From this retrospective evaluation, we concluded that the results of an ART reconstruction produced beneficial long-term results with regards to PGS and postoperative QOL. Further investigation involving a larger number of patients comparing ART with other anastomotic techniques and evaluating long-term patient outcomes is needed to validate the benefits of ART reconstruction after TLDG.

ARTICLE HIGHLIGHTS

Research background

For total laparoscopic distal gastrectomies for gastric cancer, the reconstruction method is critical to the clinical outcome of the procedure. We originally reported the augmented rectangle technique (ART) as a reconstruction option for total laparoscopic Billroth I reconstructions. Yet, little is known about its effect on long-term outcomes, specifically the incidence of postgastrectomy syndrome (PGS) and its impact on quality of life (QOL).

Research motivation

Reducing the prevalence of PGS and improving the QOL after gastrectomy for gastric cancer patients has become an important technical challenge for surgeons. ART shows good short-term results, but long-term results in terms of PGS and quality of life should be reported.

Research objectives

To analyze PGS and QOL after ART using the Postgastrectomy Syndrome Assessment Scale-37 (PGSAS-37) questionnaire.

Research methods

At Juntendo University, 94 patients who underwent ART for Billroth I reconstruction with total laparoscopic distal gastrectomies for gastric cancer between July 2016 to March 2020 completed questionnaires. Multidimensional analysis was performed comparing those 94 ART cases from our institution (ART group) to 909 distal gastrectomy cases with a Billroth I reconstruction from other Japanese institutions who also completed the PGSAS as part of a larger national database (PGSAS group).

Research results

Patients in the ART group had significantly better total symptom scores in all the symptom subscales (esophageal reflux, abdominal pain, meal-related distress, indigestion, diarrhea, constipation, and dumping). The loss of body weight was marginally greater for those in the ART group than in the PGSAS group (-9.3% *vs* -7.9%; $P = 0.054$). The ART group scored significantly lower in their dissatisfaction of ongoing symptoms, during meals, and with daily life.

Research conclusions

The use of ART for Billroth I reconstruction produced beneficial long-term results with regards to PGS and QOL in patients undergoing total laparoscopic distal gastrectomies for gastric cancer.

Research perspectives

Further investigation of the mechanism underlying the usefulness of ART in terms of PGS and QOL is needed. Prospective studies are also needed on the involvement of factors other than the anastomotic method.

FOOTNOTES

Author contributions: Yamauchi S, Orita H Matusi R, Yube Y, Kaji S, Orita H, Brock MV and Fukunaga T contributed to writing of the manuscript; Yamauchi S, Orita H, Jun C, Egawa H, Yoshimoto Y, Yube Y, Kaji S and Oka S contributed to performing the procedures and analyzing the data; Yamauchi S and Yoshimoto Y contributed to statistical review; Orita H, Fukunaga T and Brock MV contributed to the conception and design of this work.

Institutional review board statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Juntendo University Hospital (Approval No. 20-192).

Informed consent statement: The study design was retrospective and a noninterventional study. Patients were not required to give informed consent to the study because the analysis used anonymized clinical data that were obtained after each patient agreed to treatment by written consent. We also applied an opt-out method to obtain consent for this study. The opt-out approach was used with website disclosure (URL: https://www.gcprec.juntendo.ac.jp/kenkyu/files/6379827945f9a62a8f32ec.pdf).

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

Data sharing statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. The data is not publicly available due to patient privacy and the General Data Protection Regulation.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Country/Territory of origin: Japan

ORCID number: Suguru Yamauchi 0000-0003-3185-3333; Hajime Orita 0000-0002-8263-7069; Jun Chen 0000-0003-1127-3824; Hiroki Egawa 0000-0003-1934-9918; Yutaro Yoshimoto 0000-0003-2354-5604; Akira Kubota 0000-0002-7869-4511; Ryota Matsui 0000-0003-3185-3332; Yukinori Yube 0000-0002-0289-8892; Sanae Kaji 0000-0002-1372-4468; Shinichi Oka 0000-0002-3820-3394; Malcolm V Brock 0000-0003-2961-851X; Tetsu Fukunaga 0000-0003-4802-8945.

S-Editor: Wang LL
L-Editor: A
P-Editor: Wang LL

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2022 February 27; 14(2): 132-142

DOI: 10.4240/wjgs.v14.i2.132

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Choledocholithiasis characteristics with periampullary diverticulum and endoscopic retrograde cholangiopancreatography procedures: Comparison between two centers from Lanzhou and Kyoto

Ke-Xiang Zhu, Ping Yue, Hai-Ping Wang, Wen-Bo Meng, Jian-Kang Liu, Lei Zhang, Xiao-Liang Zhu, Hui Zhang, Long Miao, Zheng-Feng Wang, Wen-Ce Zhou, Azumi Suzuki, Kiyohito Tanaka, Xun Li

Specialty type: Surgery

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Reddy NNR

Received: April 20, 2021
Peer-review started: April 20, 2021
First decision: June 13, 2021
Revised: June 24, 2021
Accepted: January 27, 2022
Article in press: January 27, 2022
Published online: February 27, 2022

Ke-Xiang Zhu, Ping Yue, Wen-Bo Meng, Lei Zhang, Xiao-Liang Zhu, Hui Zhang, Long Miao, Zheng-Feng Wang, Wen-Ce Zhou, Xun Li, Department of General Surgery, The First Hospital of Lanzhou University, Lanzhou 730000, Gansu Province, China

Ke-Xiang Zhu, Ping Yue, Hai-Ping Wang, Wen-Bo Meng, Lei Zhang, Xiao-Liang Zhu, Hui Zhang, Long Miao, Zheng-Feng Wang, Wen-Ce Zhou, Xun Li, Key Laboratory of Biological Therapy and Regenerative Medicine Transformation Gansu Province, The First Hospital of Lanzhou University, Lanzhou 730000, Gansu Province, China

Jian-Kang Liu, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02451, United States

Azumi Suzuki, Kiyohito Tanaka, Department of Gastroenterology, Kyoto Second Red Cross Hospital, Kyoto 602-8026, Japan

Corresponding author: Xun Li, PhD, Chief Doctor, Department of General Surgery, The First Hospital of Lanzhou University, No. 1 Donggang West Road, Chengguan District, Lanzhou 730000, Gansu Province, China. lxdr21@126.com

Abstract

BACKGROUND

Most of study regarding periampullary diverticulum (PAD) impact on endoscopic retrograde cholangiopancreatography (ERCP) therapy for choledocholithiasis based on data from one endoscopy center and lacked to compare the clinical characteristic of choledocholithiasis with PAD from different geographical patients.

AIM

To compare the choledocholithiasis clinical characteristics between two regional endoscopy centers and analyze impacts of clinical characteristics on ERCP methods for choledocholithiasis patients with PAD.

METHODS

Patients seen in two endoscopy centers (The First Hospital of Lanzhou University, Lanzhou, Gansu Province, China, and Kyoto Second Red Cross Hospital, Kyoto,

Japan) underwent ERCP treatment for the first time between January 2012 and December 2017. The characteristics of choledocholithiasis with PAD were compared between the two centers, and their ERCP procedures and therapeutic outcomes were analyzed.

RESULTS

A total of 829 out of 3608 patients in the Lanzhou center and 241 out of 1198 in the Kyoto center had choledocholithiasis with PAD. Lots of clinical characteristics were significantly different between the two centers. The common bile duct (CBD) diameter was wider, choledocholithiasis size was lager and multiple CBD stones were more in the Lanzhou center patients than those in the Kyoto center patients (14.8 ± 5.2 mm *vs* 11.6 ± 4.2 mm, 12.2 ± 6.5 mm *vs* 8.2 ± 5.3 mm, 45.3% *vs* 20.3%, $P < 0.001$ for all). In addition, concomitant diseases, such as acute cholangitis, gallbladder stones, obstructive jaundice, cholecystectomy, and acute pancreatitis, were significantly different between the two centers ($P = 0.03$ to < 0.001). In the Lanzhou center, CBD diameter and choledocholithiasis size were lower, and multiple CBD stones and acute cholangitis were less in non-PAD patients than those in PAD patients (13.4 ± 5.1 mm *vs* 14.8 ± 5.2 mm, 10.3 ± 5.4 mm *vs* 12.2 ± 6.5, 39% *vs* 45.3%, 13.9% *vs* 18.5%, $P = 0.002$ to < 0.001). But all these characteristics were not significantly different in the Kyoto center. The proportions of endoscopic sphincterotomy (EST), endoscopic balloon dilatation (EPBD), and EST+EPBD were 50.5%, 1.7%, and 42.5% in the Lanzhou center and 90.0%, 0.0%, and 0.4% in the Kyoto center, respectively. However, the overall post-ERCP complication rate was not significantly different between the two centers (8.9% in the Lanzhou and 5.8% in the Kyoto. $P = 0.12$). In the Lanzhou center, the difficulty rate in removing CBD stones in PAD was higher than in non-PAD group (35.3% *vs* 26.0%, $P < 0.001$). But the rate was no significant difference between the two groups in Kyoto center. The residual rates of choledocholithiasis were not significantly different between the two groups in both centers. Post-ERCP complications occurred in 8.9% of the PAD patients and 8.1% of the non-PAD patients in the Lanzhou Center, and it occurred in 5.8% in PAD patients and 10.0% in non-PAD patients in the Kyoto center, all $P > 0.05$.

CONCLUSION

Many clinical characteristics of choledocholithiasis patients with PAD were significantly different between the Lanzhou and Kyoto centers. The patients had larger and multiple stones, wider CBD diameter, and more possibility of acute cholangitis and obstructive jaundice in the Lanzhou center than those in the Kyoto center. The ERCP procedures to manage native duodenal papilla were different depending on the different clinical characteristics while the overall post-ERCP complications were not significantly different between the two centers. The stone residual rate and post-ERCP complications were not significantly different between choledocholithiasis patients with PAD and without PAD in each center.

Key Words: Clinical characteristics; Periampullary diverticulum; Endoscopic retrograde cholangiopancreatography; Choledocholithisasis

Core Tip: There were many studies on periampullary diverticulum (PAD) association with biliary stone and endoscopic retrograde cholangiopancreatography (ERCP) therapy. But many of them were from only single endoscopy center. In this article, the data from two centers of Lanzhou and Kyoto. We focused on comparing the choledocholithiasis characteristics with PAD, ERCP procedures and efficacy between the two centers. A total of 829 cases of choledocholithiasis with PAD in Lanzhou Center and 241 cases in Kyoto Center were involved. We find there are different characteristics of choledocholithiasis with PAD and different ERCP procedures to handle duodenal papilla between Lanzhou and Kyoto, and ERCP procedure depends on its own clinical characteristics.

Citation: Zhu KX, Yue P, Wang HP, Meng WB, Liu JK, Zhang L, Zhu XL, Zhang H, Miao L, Wang ZF, Zhou WC, Suzuki A, Tanaka K, Li X. Choledocholithiasis characteristics with periampullary diverticulum and endoscopic retrograde cholangiopancreatography procedures: Comparison between two centers from Lanzhou and Kyoto. *World J Gastrointest Surg* 2022; 14(2): 132-142

URL: https://www.wjgnet.com/1948-9366/full/v14/i2/132.htm

DOI: https://dx.doi.org/10.4240/wjgs.v14.i2.132

INTRODUCTION

Choledocholithiasis is a common disease of the biliary tract system, and its causes are not completely clear, but its occurrence is closely related to periampullary diverticulum (PAD). It was reported that the incidence of bile duct stones reached 51.3%-88.0% among PAD patients[1-4]. Our previous study also revealed that PAD is an important factor for the occurrence and reoccurrence of bile duct stones[5]. Endoscopic retrograde cholangiopancreatography (ERCP) is regarded as an effective method for the treatment of choledocholithiasis. However, the anatomy of the duodenal junction may change due to the presence of PAD and possibly make ERCP cumbersome in the treatment of choledocholithiasis[6-9]. Therefore, many studies have focused on the safety and success of ERCP for PAD patients with choledocholithiasis[6,9-13]. However, there were inconsistent results regarding the impact of PAD on the safety and success of ERCP for choledocholithiasis. Some studies have shown that PAD is a challenge in ERCP[6,14]. Other studies concluded that PAD was not considered an obstacle to ERCP cannulation[4,7,9]. Regarding efficacy, some studies have reported that therapeutic outcomes are not affected by the presence of PAD, and complication rates of ERCP were similar in patients with and without PAD[9]. However, other studies suggested that a high rate of ERCP-related complications was associated with PAD[14-15], and it is unknown what caused those differences. Hypothetically, one of the reasons for these inconsistent conclusions may be associated with the discrepancies in the clinical characteristics in different studies regarding PAD patients with choledocholithiasis.

Many previous studies were based on data from only one endoscopy center and lacked a comparison of the clinical characteristics of choledocholithiasis with PAD from different regions. Thus, little is known about the difference in the clinical characteristics of choledocholithiasis with PAD patients from different regions and the impact of the clinical characteristics on ERCP methods. Therefore, in this study, we compared the clinical characteristics of PAD patients with choledocholithiasis and identified the impact of PAD on the methods and efficacy of ERCP, involving two different regional endoscopy centers (The First Hospital of Lanzhou University, a University School of Medicine of Gansu, Lanzhou, Gansu Province, China, and the Kyoto Second Red Cross Hospital, Kyoto, Japan) over the same period.

MATERIALS AND METHODS

This study was performed in two endoscopy centers, the First Hospital of Lanzhou University, a University School of Medicine of Gansu, China, and the Kyoto Second Red Cross Hospital, Japan. PAD patients with choledocholithiasis were enrolled retrospectively from all patients with a naïve papilla who needed therapeutic ERCP between January 2012 and December 2017. Patient information included patient demographics, diagnosis with PAD or without PAD, diameter of the common bile duct (CBD), presence of choledocholithiasis, maximum diameter and number of choledocholithiasis, and concomitant diseases such as acute cholangitis, gallbladder stones, obstructive jaundice, cholecystectomy, and acute pancreatitis. The ERCP procedure, whether there was difficulty cannulating or not, the outcome of therapeutic ERCP for choledocholithiasis with PAD and the difficulty in removing the stones, residual stones in the CBD, and post-ERCP complications were all evaluated.

According to the above mentioned data, the comparative analysis was as follows: (1) comparison of the clinical characteristics of PAD patients with choledocholithiasis between the Lanzhou and Kyoto endoscopy centers and comparison of the clinical characteristics of patients with choledocholithiasis with and without PAD within each endoscopy center; (2) the ERCP procedures for PAD patients with choledocholithiasis between the two endoscopy centers and the ERCP curative efficacy with and without PAD within each center. The difficulty of removing biliary stones was defined by the presence of one or more of the following situations: the need for mechanical lithotripsy or another fragmented method; failure to remove the bile duct stones within 30 min; failure of stone extraction with a standard basket; and more than two endoscopic balloon dilatations (EPBDs). Residual stones in the common bile duct were defined as follows: Some choledocholithiasis was still in the bile duct or stones were suspected to still be in the bile duct through X-ray fluoroscopy at the end of ERCP and choledocholithiasis was again diagnosed within 3 mo after the first ERCP. Patients were placed under conscious sedation with meperidine and midazolam. ERCP was performed by experienced endoscopists who performed over 100 biliary interventions per year. Patients who initially planned to undergo diagnostic ERCP were not enrolled in this study. The follow-up was started as long as the ERCP was performed.

Statistical analysis

Categorical variables were analyzed with the chi-squared or Fisher's exact test, while continuous variables were expressed as the median and interquartile range and compared with the Wilcoxon rank sum test, or expressed as the mean and standard deviation and compared with *t*-test. All statistical assessments were 2-sided, and a *P* value less than 0.05 was considered significant. Statistical analysis was performed using the SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

In the cases of choledocholithiasis with PAD, 829 of 3608 patients in the Lanzhou center, and 241 of 1198 patients in the Kyoto center were enrolled in consecutive first session ERCP. Comparing the clinical characteristics between the Lanzhou center and the Kyoto center, patient age, diameter of the CBD, stone number and size in the CBD, comorbidities such as acute cholangitis, gallstones, obstructive jaundice, acute pancreatitis, and operation history of the bile duct were all significantly different, except for sex. In detail, compared with an average diameter (11.6 ± 4.2 mm) of the CBD in patients in the Kyoto center, the average diameter of the CBD was 14.8 ± 5.2 mm in patients in the Lanzhou center. Compared with the mean diameter of choledocholithiasis that was 8.2 ± 5.3 mm in patients in the Kyoto center, the mean diameter of choledocholithiasis was 12.2 ± 6.5 mm in Lanzhou. Regarding single or multiple choledocholithiasis, 45.3% of the patients had multiple stones and 54.7% of the patients had single stones in the Lanzhou center but 20.3% and 79.7% of patients had single and multiple stones in the Kyoto center, respectively. Each of those comparisons was significantly different ($P < 0.001$). Some comorbidities were also significantly different between the Lanzhou and Kyoto centers: acute cholangitis (18.5% *vs* 9.5%, $P = 0.001$); obstructive jaundice (13.8% *vs* 0.4%, $P < 0.001$); acute pancreatitis (4.7% *vs* 1.7%, $P = 0.03$); cholecystectomy (38.4% *vs* 3.7%, $P < 0.001$); and gallbladder stones (4.7% *vs* 12.5%, $P < 0.001$) (Table 1).

The failure rate of ERCP was not different between the two endoscopy centers, but the difficulty rate of deep cannulation of the bile duct was significantly different: 9.7% in Lanzhou *vs* 24.1% in Kyoto ($P < 0.001$). The proportions of endoscopic sphincterotomy (EST), EPBD, and EST+EPBD were 50.5%, 1.7%, and 42.5% in the Lanzhou center and 90.0%, 0.0%, and 0.4% in the Kyoto center, respectively. ERCP procedures to handle the duodenal papilla were significantly different between the two centers ($P < 0.001$). Regarding ERCP-related complications, the overall complication rate was 8.9% in Lanzhou and 5.8% in Kyoto. The results showed that the overall complications were not significantly different between the Lanzhou and Kyoto centers ($P = 0.12$) (Table 2).

Comparing PAD with non-PAD in each center, the results were as follows: The mean age of the PAD group was 56 years and was 65 years for non-PAD in Lanzhou, and it was 71 years and 76 with and without PAD in Kyoto, respectively. The mean age of PAD patients was significantly older than those without PAD in each center. In the Lanzhou center, the mean diameter of the CBD was 14.8 ± 5.2 mm in the PAD group and 13.4 ± 5.1 mm in the non-PAD group. The mean diameter of the CBD in the PAD group was significantly wider than that in the non-PAD group ($P < 0.001$). In the Kyoto Center, the mean diameter of the CBD was 11.6 ± 4.2 mm in the PAD group and 10.9 ± 3.6 mm in the non-PAD group. The mean diameter of the CBD was not significantly different between the two groups in Kyoto. Likewise, the mean diameter of the CBD stones was 12.2 ± 6.5 mm and 10.3 ± 5.4 mm in PAD group and non-PAD group in Lanzhou, respectively, and was 8.2 ± 5.3 mm and 7.5 ± 5.2 mm in PAD group and non-PAD group in Kyoto, respectively. The mean diameter of the CBD stones in the PAD group was higher than that in the non-PAD group in the Lanzhou center, whereas there was no significant difference in the diameter of the CBD stones in the Kyoto Center. The cases of multiple CBD stones were 45.3% and 39% in the PAD group and non-PAD group in the Lanzhou center and 20.3% and 19% in the PAD group and non-PAD group in the Kyoto center, respectively. The percent of patients with PAD with multiple CBD stones was significantly higher in Lanzhou but not in Kyoto. Concomitant diseases such as acute cholangitis, gallstones, and obstructive jaundice were significantly different between PAD and non-PAD patients in the Lanzhou center, but those comorbidities were not different between the PAD and non-PAD groups in the Kyoto center (Table 3).

The rate in the difficulty to cannulate aim tubes was 9.7% and 8.1% in the PAD group and non-PAD group in Lanzhou center, respectively, with no significant difference between the two groups ($P = 0.19$). Furthermore, in the Kyoto center, the rates were 24.1% and 32.5% in the PAD group and non-PAD group, respectively, with a significant difference between the two groups ($P = 0.02$) (Table 4). In the Lanzhou center, EST was performed in 57.9% and EST plus EPBD was performed in 33.5% of non-PAD patients, while EST was performed in 50.5% and EST plus EPBD was performed in 42.5% of PAD patients. The ERCP procedures to handle native duodenal papilla were different between the PAD and non-PAD groups in the Lanzhou center. In the Kyoto center, EST was performed in 87.6%, EST plus EPBD was performed in 1.1% of non-PAD patients, EST was performed in 90.0%, and EST plus EPBD was performed in only 0.4% of PAD patients. There were no differences in the ERCP procedures to handle native duodenal papilla between the PAD and non-PAD groups in Kyoto (Table 4).

Regarding the rate of difficulty in removing the stones, in the Lanzhou center, the ratio reached 35.3% and 26.0% in the PAD group and non-PAD group, respectively, with a significant difference between the two groups ($P < 0.001$), while it accounted for 53.8% and 53.3% in the PAD group and non-PAD group in the Kyoto center, respectively, with no significant difference between the two groups ($P = 0.89$) (Table 4).

The residual rate of choledocholithiasis in the Lanzhou center was 7.6% and 6.6% in the PAD group and non-PAD group, respectively, and it was 24.6% and 23.4% in the PAD group and non-PAD group in the Kyoto center, respectively. The residual rate of choledocholithiasis was not significantly different between the PAD group and the non-PAD group, both in the Lanzhou center ($P = 0.39$) and in the Kyoto center ($P = 0.73$) (Table 4).

Table 1 Comparison clinical characteristics of choledocholithiasis patient with periampullary diverticulum between Lanzhou and Kyoto

Clinical Item	Lanzhou (*n* = 829)	Kyoto (*n* = 241)	*P*
Age (mean ± SD, yr)	64.6 ± 13.6	75.7 ± 12.1	< 0.001
Gender			0.48
Male	448 (54.0)	124 (51.5)	
Female	381 (46.0)	117 (48.6)	
Diameter of CBD (mean ± SD, mm)	14.8 ± 5.2	11.6 ± 4.2	< 0.001
Cholecystectomy	15.5 ± 5.2	13.1 ± 4.8	0.18
Gallbladder in situ	14.4 ± 5.1	11.5 ± 4.2	< 0.001
Proportion of CBD stone, *n* (%)			< 0.001
Single-stone	449 (54.7)	188 (79.7)	
Multiple-stone	372 (45.3)	48 (20.3)	
Maximum diameter of CBD stone (mean ± SD, mm)	12.2 ± 6.5	8.2 ± 5.3	< 0.001
Diameter (< 2cm), *n* (%)	718 (86.6)	233 (96.7)	< 0.001
Diameter (≥ 2cm), *n* (%)	111 (13.39)	8 (3.3)	
Concomitant disease, *n* (%)			
Acute cholangitis	153 (18.5)	23 (9.5)	0.001
Gallbladder stone	39 (4.7)	30 (12.5)	< 0.001
Obstructive jaundice	114 (13.8)	1 (0.4)	< 0.001
Acute pancreatitis	39 (4.7)	4 (1.7)	0.03
Pancreatic duct stones	1 (0.1)	0 (0.0)	
Past medical history, *n* (%)			
Operation Billroth I	0 (0.0)	3 (1.2)	0.01
Operation Billroth II	5 (0.6)	1 (0.4)	1.00
Cholecystectomy	318 (38.4)	9 (3.7)	< 0.001
Billary tract surgery	34 (4.1)	0 (0.0)	0.001

CBD: Common bile duct.

Post-ERCP complications occurred in 8.9% of PAD patients and 8.1% of non-PAD patients in the Lanzhou center; furthermore, it was 5.8% in PAD patients and 10.0% in non-PAD patients in the Kyoto center. The post-ERCP complications between PAD and non-PAD patients in each center was not significantly different (Lanzhou, $P = 0.48$; Kyoto, $P = 0.07$) (Table 4).

DISCUSSION

PADs are extraluminal mucosal outpouchings of the duodenum that arise within a radius of 2-3 cm from the ampulla of Vater[6]. Patients with PAD often have slow biliary excretion and bile stasis due to mechanical pressure from the PAD to the distal end of the biliary tract. Additionally, PAD is often accompanied by duodenobiliary reflux and subsequent bacterial infection because of sphincter of Oddi dysfunction. These are potential reasons that PADs are clinically associated with biliary stones in many studies[16-20]. However, it is unknown what the characteristics of choledocholithiasis with PAD are from different regions. In our study, we found that the clinical characteristics of PAD patients with choledocholithiasis were significantly different between the Lanzhou center and Kyoto center.

The results showed that comorbid diseases, such as acute cholangitis, obstructive jaundice, and acute pancreatitis, were more common in the Lanzhou center than in the Kyoto center for PAD patients with choledocholithiasis. Our study showed that the average diameter of the CBD was 14.8 ± 5.2 mm in Lanzhou and 11.6 ± 4.2 mm in Kyoto, with a significant difference ($P < 0.001$), and the reasons are not entirely clear. However, one of the reasons for these different kinds of characteristics may be attributed to the larger stone size and multiple stone numbers in the CBD in patients in the Lanzhou center

Table 2 Comparison of endoscopic retrograde cholangiopancreatography related contents of choledocholithiasis with periampullary diverticulum between Lanzhou and Kyoto

ERCP Item	Lanzhou (*n* = 829)	Kyoto (*n* = 241)	*P*
Intubation failure, *n* (%)	8 (1.0)	1 (0.4)	0.69
Intubation difficulty, *n* (%)	80 (9.7)	58 (24.1)	< 0.001
Difficulty to remove stone out, *n* (%)	290 (35.3)	127 (53.8)	< 0.001
Residual stone, *n* (%)	62 (7.6)	58 (24.6)	< 0.001
Procedure to duodenal papilla, *n* (%)			
EST Only	419 (50.5)	217 (90.0)	< 0.001
EST + EPBD	352 (42.5)	1 (0.4)	< 0.001
EPBD only	14 (1.7)	0 (0.0)	0.049
Non-EST & non-EPBD	44 (5.3)	23 (9.5)	0.017
Post-complication (overall), *n* (%)	74 (8.9)	14 (5.8)	0.12
Acute cholangitis	22 (2.7)	1 (0.4)	0.035
Acute pancreatitis	49 (5.9)	8 (3.3)	0.11
Perforation	2 (0.2)	0 (0.0)	1.00
Bleeding	0 (0.0)	5 (2.1)	< 0.001

ERCP: Endoscopic retrograde cholangiopancreatography; EST: Endoscopic sphincterotomy; EPBD: Endoscopic balloon dilatation.

compared to the Kyoto center. Actually, the results revealed that the mean diameter of the stone size was 12.2 ± 6.5 mm in Lanzhou and 8.2 ± 5.3 mm in Kyoto, and the rate of multiple stones was 45.3% in Lanzhou, and only 20.3% in Kyoto, both with $P < 0.001$. Therefore, larger and multiple stones in the CBD would contribute to a dilated CBD, acute cholangitis and obstructive jaundice, and even to acute pancreatitis. Also, the reasons why the CBD stones were more abundant and larger in Lanzhou Center than in Kyoto Center are unknown. However, biliary duct stones are usually associated with the environment and metabolic diseases such as being overweight, obesity, diabetes and hyperlipidemia[21-23]. There are many different characteristics in dietary habits and geographical environments, even in metabolic diseases, between the Lanzhou center in China and the Kyoto center in Japan.

Non-PAD choledocholithiasis was used as a control, and the characteristics of choledocholithiasis with PAD within each center were further analyzed. We noticed that in the Lanzhou center, the clinical characteristics, including mean age, sex, mean size of the choledocholithiasis, single or multiple choledocholithiasis, diameter of the CBD, and concomitant diseases, such as acute cholangitis, obstructive jaundice, and gallbladder stones, differed significantly between the choledocholithiasis cases with PAD and without PAD. However, in the Kyoto center, excluding the mean age, the abovementioned clinical characteristics were not significantly different between choledocholithiasis cases with PAD and without PAD. These results indicated that PADs were associated with different clinical characteristics in patients with CBD stones in the Lanzhou center, but these characteristics were not seen in the Kyoto center. It was difficult to explain the outcome, but it confirmed that there is actually a difference in the characteristics of choledocholithiasis patients with PAD and without PAD from different regions. Ham JH *et al*[24] reported that PAD induces marked postcholecystectomy CBD dilatation. Kim CW *et al*[25] suggested that acute cholangitis patients with PAD had larger CBD stones and more severe cholangitis than those without PAD. However, Lee JJ *et al*[26] demonstrated that PAD alone does not lead to abnormal biliary dilatation in age- and sex-matched control groups. Therefore, choledocholithiasis with PAD had different clinical characteristics between Lanzhou and Kyoto. The different geographical environments, lifestyles, dietary habits, and health consciousness may contribute to the clinical characteristics.

ERCP is now a well-established standard method for removing choledocholithiasis, but it carries an 8%-12% risk of early complications, such as bleeding, duodenal perforation, and pancreatitis[17-18]. If the duodenal papilla opens intra-PAD or is very close to the PAD, the appearance, shape, and orifice of the duodenal papilla will be changed anatomically[25]. This kind of change likely leads to a higher risk and is more difficult to EST because the EST direction may deviate from the long axis of the CBD and the length available for EST is not enough. Under the condition of an insufficient length for the EST, the difficulty rate of removing large choledocholithiasis and residual rate of the stone will increase, and mechanical lithotripsy will probably be needed. In 2003, Ersoz G *et al*[27] first reported that EST followed by sequential EPBD using a 12-20 mm diameter balloon may be effective for difficult removals

Table 3 Comparison of clinical characteristics of choledocholithiasis patient with and without periampullary diverticulum in Lanzhou or Kyoto

Clinical Item	Lanzhou (*n* = 2702)			Kyoto (*n* = 613)		
	Non-PAD, *n* = 1873	PAD, *n* = 829	*P*	Non-PAD, *n* = 372	PAD, *n* = 241	*P*
Age, (median)	56.1 ± 16.9	64.6 ± 13.6	< 0.001	71.0 ± 15.0	75.7 ± 12.1	< 0.001
Gender, *n* (%)			< 0.001			0.22
Male	842 (45.0)	448 (54.0)		210 (56.4)	124 (51.4)	
Female	1031 (55.1)	381 (46.0)		162 (43.6)	117 (48.6)	
Proportion of CBD stone, *n* (%)			0.002			0.69
Single-stone	1131 (61.0)	449 (54.7)		298 (81.0)	188 (79.7)	
Multiple-stone	724 (39.0)	372 (45.3)		70 (19.0)	48 (20.3)	
Maximum diameter of CBD stone (mean ± SD, mm)	10.3 ± 5.4	12.2 ± 6.5	< 0.001	7.5 ± 5.2	8.2 ± 5.3	0.11
Diameter of CBD (mean ± SD, mm)	13.4 ± 5.1	14.8 ± 5.2	< 0.001	10.9 ± 3.6	11.6 ± 4.2	0.06
Cholecystectomy	14.5 ± 5.5	15.5 ± 5.2	0.008	11.3 ± 2.7	13.1 ± 4.8	0.25
Gallbladder in situ	12.7 ± 4.6	14.4 ± 5.1	< 0.001	10.9 ± 3.6	11.5 ± 4.2	0.07
Concomitant disease, *n* (%)						
Acute cholangitise	260 (13.9)	153 (18.5)	0.002	39 (10.5)	23 (9.5)	0.71
Gallbladder stone	129 (6.9)	39 (4.7)	0.03	43 (11.6)	30 (12.5)	0.74
Obstructive jaundice	311 (16.6)	114 (13.8)	0.06	0 (0.0)	1 (0.4)	
Past medical history, *n* (%)						
Operation Billroth I	6 (0.3)	0 (0.0)	0.19	8 (2.2)	3 (1.2)	0.54
Operation Billroth II	5 (0.3)	5 (0.6)	0.19	4 (1.1)	1 (0.4)	0.65
Cholecystectomy	738 (39.4)	318 (38.4)	0.61	16 (4.3)	9 (3.7)	0.73
Billary tract surgery	89 (4.8)	34 (4.10)	0.45	0 (0.0)	0 (0.0)	

PAD: Periampullary diverticulum.

of large bile duct stones, and the rate of early complications was acceptable. Weinberg BM *et al*[28] reported that an additional EST after EPBD was also required in 10%-19% of patients because the biliary opening was not sufficiently enlarged. After that report, several studies established that procedure as an effective and safe treatment for removing difficult-to-extract bile duct stones[29-31]. Kim HW *et al*[32] reported that the overall successful stone removal rate and the complication rate did not differ significantly between the PAD and control groups when applying limited EST plus large balloon dilation. Our previous study, a multicenter, randomized controlled trial, suggested that a balloon dilation time of 30 s for combined EST reduced the frequency of post-ERCP pancreatitis[33]. In addition, the Guideline of the European Society of Gastrointestinal Endoscopy strongly recommends EPBD as an alternative to EST for extracting choledocholithiasis < 8 mm in patients, especially in the presence of altered anatomy[34]. Therefore, there are now at least three methods (EST, EPBD, and EST plus EPBD) available to treat choledocholithiasis with PAD.

In our research, EST (50.5%), EST+EPBD (42.5%), and EPBD (1.7%) were adopted in the Lanzhou center, while EST (90.0%), EST+EPBD (0.4%), and EPBD (0.0%) were applied in the Kyoto center. Thus, the ERCP procedures were significantly different between the two centers. One of the main reasons for this distinction is the different clinical characteristics of choledocholithiasis with PAD mentioned above between Lanzhou and Kyoto. In other words, different ERCP methods are naturally based on patients' clinical characteristics.

Because of the different ERCP procedures between the Lanzhou and Kyoto centers, the efficacy of ERCP in each center needed to be compared. In the Kyoto center, owing to its own lack of different characteristics, such as the mean size of CBD stones (7.5 ± 5.2 mm, non-PAD; 8.2 ± 5.3 mm, PAD; P = 0.11), multiple stones (19.0%, non-PAD; 20.3% PAD; P = 0.69), there was no significant difference in efficacy between the patients with and without PAD (rate to remove choledocholithiasis difficulty, P = 0.89; residual rate of bile duct stones, P = 0.73). However, in the Lanzhou center, with differences in the clinical characteristics, such as the mean size of the CBD stones (10.3 ± 5.4 mm, non-PAD; 12.2 ± 6.5 mm,

Table 4 Comparison of endoscopic retrograde cholangiopancreatography related contents of choledocholithiasis patient with and without periampullary diverticulum in Lanzhou or Kyoto

ERCP Item	Lanzhou (*n* = 2702)			Kyoto (*n* = 613)		
	Non-PAD, *n* = 1873	PAD, *n* = 829	*P*	Non-PAD, *n* = 372	PAD, *n* = 241	*P*
ERCP method, *n* (%)						
EST Only	1084 (57.9)	419 (50.5)	< 0.001	326 (87.6)	217 (90.0)	0.36
EST and EPBD	627 (33.5)	352 (42.5)	< 0.001	4 (1.1)	1 (0.4)	0.65
EPBD only	47 (2.5)	14 (1.7)	0.19	4 (1.1)	0 (0.0)	0.16
Non-EST and non-EPBD	115 (6.1)	44 (5.3)	0.40	38 (10.2)	23 (9.5)	0.79
Curative effect, *n* (%)						
Intubation failure	18 (1.0)	8 (1.0)	0.99	1 (0.3)	1 (0.4)	
Intubation difficulty	152 (8.1)	80 (9.7)	0.19	121 (32.5)	58 (24.1)	0.02
Difficulty to remove stone out	482 (26.0)	290 (35.3)	< 0.001	196 (53.3)	127 (53.8)	0.89
Residual stone	123 (6.6)	62 (7.6)	0.39	86 (23.4)	58 (24.6)	0.73
Post ERCP complication, *n* (%)	152 (8.1)	74 (8.9)	0.48	37 (10.0)	14 (5.8)	0.07
Acute cholangitis	46 (2.5)	22 (2.7)	0.76	2 (0.5)	1 (0.4)	1.00
Acute pancreatitis	97 (5.2)	49 (5.9)	0.44	23 (6.2)	8 (3.3)	0.11
Perforation	4 (0.2)	2 (0.2)	1.00	3 (0.8)	0 (0.0)	0.28

ERCP: Endoscopic retrograde cholangiopancreatography; EPBD: Endoscopic balloon dilatation.

PAD; $P < 0.001$), multiple stones (39.0%, non-PAD; 45.3% PAD; $P = 0.002$), the difficulty rate of removing choledocholithiasis was significantly different ($P < 0.001$). However, if EST+EPBD was adopted, the residual rate of bile duct stones was not significantly different ($P = 0.39$) between choledocholithiasis patients with and without PAD. Therefore, to reach an appropriate efficacy, the ERCP procedure depends on the different clinical characteristics of choledocholithiasis patients with PAD. Interestingly, although different therapeutic ERCP procedures were employed in the Lanzhou and Kyoto centers, the overall post-ERCP complications were not significantly different for choledocholithiasis with PAD not only between Lanzhou and Kyoto centers ($P = 0.12$) but also within each center (Lanzhou, $P = 0.48$; Kyoto, $P = 0.07$). Thus, we confirmed that PAD did not increase ERCP-related complications when using an experienced endoscopist.

CONCLUSION

In conclusion, many clinical characteristics of choledocholithiasis patients with PAD were significantly different between the Lanzhou center and Kyoto center. Choledocholithiasis with PAD had more complexity with larger and multiple stones, wider diameter of the CBD, and more biliary duct comorbidities in the Lanzhou center compared to the Kyoto center. In the internal center analysis, the clinical characteristics mentioned above were also different between the PAD and non-PAD groups in the Lanzhou center but not in the Kyoto center. Different ERCP procedures to manage native duodenal papilla were adopted naturally depending on the clinical characteristics of choledocholithiasis with PAD to approve efficacy between the Lanzhou and the Kyoto centers. Although there was increased difficulty removing stones in the Lanzhou Center and an increased difficulty in removing deep cannulates in the Kyoto centers, the stone residual rate was not significantly different within each center for choledocholithiasis with PAD, and post-ERCP complications were also not significantly different between the two centers or within each center. Nevertheless, there are some shortcomings in this study, such as the role of different ERCP procedures in the recurrence of choledocholithiasis, which needs to be confirmed by further subsequent research.

ARTICLE HIGHLIGHTS

Research background

Most of study regarding periampullary diverticulum (PAD) impact on endoscopic retrograde cholangiopancreatography (ERCP) therapy for choledocholithiasis based on data from one endoscopy center and there were inconsistent conclusions of the PAD impacts on safety and post ERCP complications for choledocholithiasis.

Research motivation

What did cause the different conclusions of PAD impacts on post ERCP complications and safety for choledocholithiasis? UP to now, the real reason is little known and lacked to compare the clinical characteristic of choledocholithiasis with PAD from different geographical endoscopy centers.

Research objectives

To compare the clinical characteristics of choledocholithiasis with PAD between two regional endoscopy centers and analyze the efficacy of clinical characteristics on ERCP procedures for choledocholithiasis patients with PAD.

Research methods

Patients underwent ERCP treatment at first time between January 2012 and December 2017 were Involved. The clinical characteristics and ERCP related contents of choledocholithiasis with PAD were compared between Lanzhou center and Kyoto center. Furthermore, Choledocholithiasis without PAD as control, analyzed the clinical characteristic and ERCP therapy of Choledocholithiasis with PAD internal each center.

Research results

829 out of 3608 patients in Lanzhou center and 241 out of 1198 in Kyoto center suffered from choledocholithiasis with PAD. The overall clinical characteristics were significantly different excepting the gender between the two centers. Non-PAD choledocholithiasis as control, in Lanzhou center, many clinical characteristics of patients were significant difference between non-PAD and PAD (P = 0.03 - <0.001), but were no difference in Kyoto center (each with P > 0.05).

For choledocholithiasis with PAD patients, ERCP procedures to handle the duodenal papilla were significant different Lanzhou center and Kyoto center (P < 0.001). But the overall post-complication was no significant different between two centers (8.9% in Lanzhou center, 5.8% in Kyoto center. P = 0.12).

The difficult rate to remove stone, in Lanzhou center, was 35.3% and 26.0% in PAD group and non-PAD group, with a significant difference between two groups (P < 0.001), while it accounted for 53.8% and 53.3% in PAD group and non-PAD group in Kyoto center, with no significant difference between two groups. However, residual rate of choledocholithisasis was no significant difference between two groups in each center. Meanwhile, there were also no significant differences of post-ERCP complications between PAD and non-PAD patients within each center.

Research conclusions

Many clinical characteristics of choledocholithiasis patients with PAD were significant difference between Lanzhou and Kyoto. Patients carried characteristics with larger and multiple stones, wider diameter of CBD, and more possibility of acute cholangitis and obstructive jaundice in Lanzhou center than those in Kyoto. ERCP procedures to cope with native duodenal papilla were different between Lanzhou and Kyoto, depended on its own different clinical characteristics of choledocholithiasis with PAD. The efficacy and post-ERCP complications were no significant differences for choledocholithiasis with PAD in each own center. The overall post-ERCP complication was no statistics difference between two centers as well.

Research perspectives

The control study of multiple endoscopy centers from different region is worthy of conducting to uncover the characteristics of choledocholithiasis patients with PAD and their influences on therapy ERCP. The role of different ERCP procedures for recurrence of choledocholithiasis need to be confirmed through further subsequent research or prospective studies.

FOOTNOTES

Author contributions: Zhu KX, Yue P, Suzuki A, Tanaka K, Li X designed the research protocol; Zhu KX, Yue P, Meng WB, Zhang L, Zhu XL, Zhang H, Miao L, Wang ZF, Zhou WC, Suzuki A, Tanaka K, Li X were responsible for patient enrollment and data acquisition; Zhu KX, Yue P, Wang HP, Tanaka K contributed to data analysis and interpretation; Zhu KX, Yue P wrote the original manuscript; Zhu KX, Yue P, Meng WB, Liu JK, Li X contributed to critical revision

of the manuscript for important content; Wang HP, Liu JK contributed to statistical analysis for this study; Li X contributed to final approval of the article.

Institutional review board statement: The study was reviewed and approved by the First Hospital of Lanzhou University Institutional Review Board (Approval No. LDYYLL 2021-192).

Conflict-of-interest statement: The authors declare that they have no conflicts of interest to disclose.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Ke-Xiang Zhu 0000-0003-4272-5221; Ping Yue 0000-0001-8736-949X; Hai-Ping Wang 0000-0003-2055-8936; Wen-Bo Meng 0000-0002-9355-0225; Jian-Kang Liu 0000-0003-2454-8209; Lei Zhang 0000-0001-9320-304X; Xiao-Liang Zhu 0000-0002-5697-9583; Hui Zhang 0000-0003-0728-9188; Long Miao 0000-0002-7861-6134; Zheng-Feng Wang 0000-0002-4556-9247; Wen-Ce Zhou 0000-0002-0529-7777; Azumi Suzuki 0000-0002-6041-7719; Kiyohito Tanaka 0000-0002-9189-1755; Xun Li 0000-0001-6862-7692.

S-Editor: Chang KL
L-Editor: A
P-Editor: Chang KL

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2022 February 27; 14(2): 143-160

DOI: 10.4240/wjgs.v14.i2.143

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Nomograms predicting prognosis of patients with pathological stages T1N2-3 and T3N0 gastric cancer

Yu-Fei Wang, Xin Yin, Tian-Yi Fang, Yi-Min Wang, Dao-Xu Zhang, Yao Zhang, Xi-Bo Wang, Hao Wang, Ying-Wei Xue

Specialty type: Oncology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Kotelevets SM, Xue M

Received: June 6, 2021
Peer-review started: June 6, 2021
First decision: July 16, 2021
Revised: July 24, 2021
Accepted: January 6, 2022
Article in press: January 6, 2022
Published online: February 27, 2022

Yu-Fei Wang, Xin Yin, Tian-Yi Fang, Yi-Min Wang, Dao-Xu Zhang, Yao Zhang, Xi-Bo Wang, Hao Wang, Ying-Wei Xue, Department of Gastroenterological Surgery, Harbin Medical University Cancer Hospital, Harbin 150081, Heilongjiang Province, China

Corresponding author: Ying-Wei Xue, PhD, Chief Doctor, Professor, Department of Gastroenterological Surgery, Harbin Medical University Cancer Hospital, No. 150 Haping Road, Harbin 150081, Heilongjiang Province, China. xueyingwei@hrbmu.edu.cn

Abstract

BACKGROUND

Patients with pathological stages T1N2-3 (pT1N2-3) and pT3N0 gastric cancer (GC) have not been routinely included in the target population for postoperative chemotherapy according to the Japanese Gastric Cancer Treatment Guideline, and their prognosis is significantly different.

AIM

To identify the high-risk patients after radical surgery by analyzing biomarkers and clinicopathological features and construct prognostic models for them.

METHODS

A total of 459 patients with pT1N2-3/pT3N0 GC were retrospectively selected for the study. The Chi-square test was used to analyze the differences in the clinicopathological features between the pT1N2-3 and pT3N0 groups. The Kaplan–Meier analysis and log-rank test were used to analyze overall survival (OS). The independent risk factors for patient prognosis were analyzed by univariate and multivariate analyses based on the Cox proportional hazards regression model. The cutoff values of continuous variables were identified by receiver operating characteristic curve. The nomogram models were constructed with R studio.

RESULTS

There was no statistically significant difference in OS between the pT1N2-3 and pT3N0 groups (P = 0.374). Prealbumin (P = 0.040), carcino-embryonic antigen (CEA) (P = 0.021), and metastatic lymph node ratio (mLNR) (P = 0.035) were independent risk factors for prognosis in the pT1N2-3 group. Age (P = 0.039), body mass index (BMI) (P = 0.002), and gastrectomy (P < 0.001) were independent

risk factors for prognosis in the pT3N0 group. The area under the curve values of the nomogram models for predicting the 5-year prognosis of the pT1N2-3 group and pT3N0 group were 0.765 and 0.699, respectively.

CONCLUSION

Nomogram model combining prealbumin, CEA, and mLNR levels can be used to predict the prognosis of pT1N2-3 GC. Nomogram model combining age, BMI, and gastrectomy can be used to predict the prognosis of pT3N0 GC.

Key Words: Gastric cancer; Biomarker; Clinicopathological feature; Adjuvant chemotherapy; Prognosis; Nomogram

Core Tip: Patients with pathological stage T1N2-3 (pT1N2-3) and pT3N0 gastric cancer (GC) have not been routinely included in the target population for postoperative chemotherapy, and their prognosis is significantly different. The study aimed to identify the high-risk patients after radical surgery by analyzing biomarkers and clinicopathological features and construct prognostic models for them. Our results showed that the predictive models constructed by peripheral blood biomarkers and clinicopathological features can evaluate the prognosis of patients with pT1N2-3 and pT3N0 GC, which is worthy of further validation and promotion in clinical practice.

Citation: Wang YF, Yin X, Fang TY, Wang YM, Zhang DX, Zhang Y, Wang XB, Wang H, Xue YW. Nomograms predicting prognosis of patients with pathological stages T1N2-3 and T3N0 gastric cancer. *World J Gastrointest Surg* 2022; 14(2): 143-160

URL: https://www.wjgnet.com/1948-9366/full/v14/i2/143.htm

DOI: https://dx.doi.org/10.4240/wjgs.v14.i2.143

INTRODUCTION

Gastric cancer (GC) is the sixth most common cancer and the third leading cause of cancer-related death, with more than 860000 deaths annually[1]. The TNM staging system based on tumor infiltration, regional lymph node metastasis, and distant metastasis is considered as the conventional criterion for predicting prognosis and guiding treatment[2]. Adjuvant chemotherapy is recommended for patients with pathological stage II or III GC after radical resection to reduce recurrence probability. However, based on the results of the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC)[3], the Japanese Gastric Cancer Treatment Guidelines[4] recommend stage II/III disease as the standard target of adjuvant chemotherapy after surgery, with the exception of pathological stage T1N2-3 (pT1N2-3) and pT3N0. But, in these two groups, there is still a portion of high-risk patients with a poor prognosis. Therefore, the research of pT1N2-3 and pT3N0 GC patients with a poor prognosis may help clinicians carry out targeted and individualized treatment.

Although previous studies have discussed independent prognostic factors among patients with pT1N2-3 and pT3N0 GC, relevant results have not been consistent. Yura *et al*[5] suggested that pT1N2-3 patients with stage N3 or tumor diameter < 30 mm had a relatively poor prognosis, while pT3N0 patients had a good prognosis. Terada *et al*[6] suggested that patients with pT3N0/pT1N2-3 complicated with vascular infiltration might be at a high risk for disease recurrence and might be candidates for adjuvant chemotherapy. Other relevant studies have shown that lymphatic infiltration is an independent risk factor for poor prognosis in pT3N0 GC patients[7,8]. The above studies showed that the high heterogeneity of the same stage GC patients leads to significant differences in the risk for recurrence and death. Therefore, the search for effective diagnostic and monitoring tools for GC patients is a critical clinical goal. Many studies have shown that peripheral blood biomarkers and clinicopathological features can play an effective complementary role and have been widely used for the early diagnosis, therapeutic effect monitoring, and prognostic prediction of GC patients[9-11]. However, previous studies evaluated the prognostic value of only a limited number of clinicopathological features, and the results of these studies inevitably have some limitations. Therefore, this study aimed to determine peripheral blood biomarkers and clinicopathological features that influence the prognosis of patients with pT1N2-3 and pT3N0 GC, thereby more comprehensively identifying patients who may benefit from adjuvant chemotherapy.

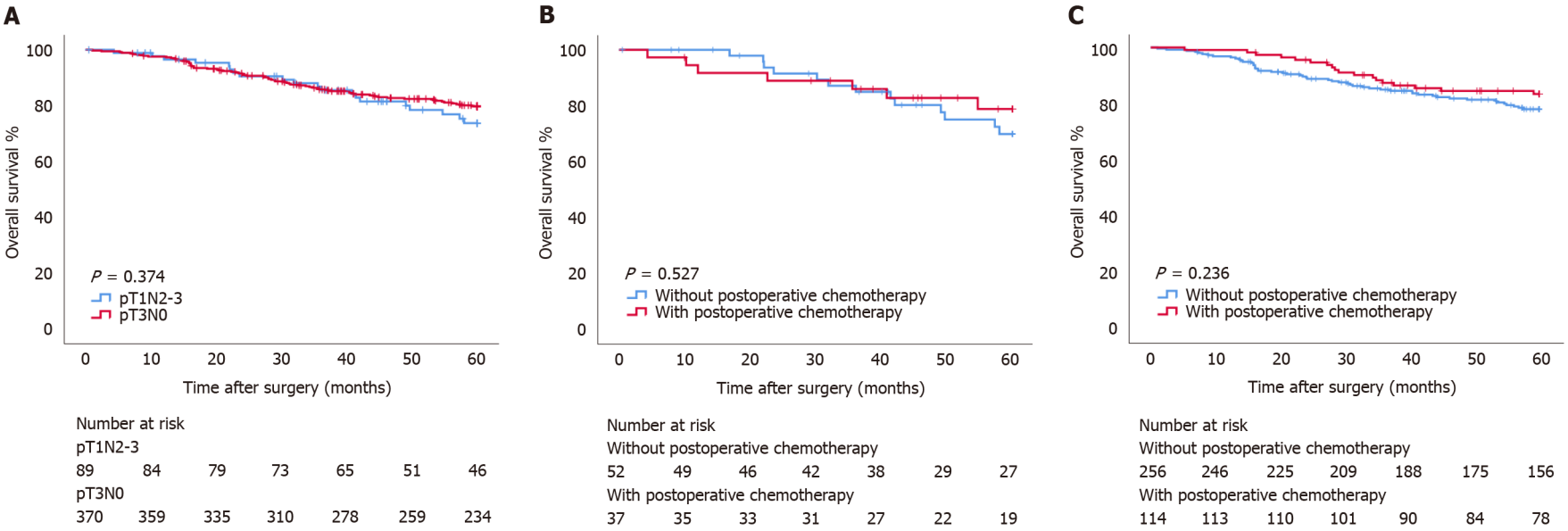


Figure 1 Survival curve analyses for patients with pT1N2-3 and pT3N0 GC. A: Overall survival curves for all patients; B: Overall survival curves for pT1N2-3 patients with and without postoperative chemotherapy; C: Overall survival curves for pT3N0 patients with and without postoperative chemotherapy.

In this study, we retrospectively analyzed patients who underwent radical gastrectomy at the Harbin Medical University Cancer Hospital between January 2000 and April 2016. The predictive models were constructed by combining the peripheral blood biomarkers and clinicopathological features which influence the prognosis of pT1N2-3b and pT3N0 GC patients.

MATERIALS AND METHODS

Patients

A total of 459 patients with pT1N2-3/pT3N0 GC were continuously selected for the study. All GC patients underwent radical gastrectomy according to the respective conditions[4]. The diagnosis of GC was based on tissue samples obtained during gastroscopy and further confirmed by pathologists through examination of postoperative pathological tissue. During hospitalization, the patients underwent routine preoperative examinations, including magnetic resonance imaging/gastric computed tomography (CT), abdominal ultrasonography, chest radiography, electrocardiography, hematological examination, and tumor marker examination. Some patients underwent positron emission tomography (PET)/CT if necessary. The patients were followed until the date of death or for 5

years, whichever came first.

The exclusion criteria were as follows: (1) Preoperative chemotherapy; (2) severe heart disease; (3) remnant gastric cancer; (4) postoperative confirmation of stage IV disease; (5) history of partial resection; (6) history of other malignant tumors; (7) esophagogastric junction tumor; and (8) endocrine carcinoma.

Postoperative chemotherapy regimens were based on the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology[12]. Oxaliplatin + capecitabine (XELOX) or oxaliplatin + S-1 (SOX) are the main treatment options for patients with stage II or III GC. To ensure the accuracy of the study, we included 166 patients who received complete postoperative chemotherapy at our institution. We did not include patients who did not undergo treatment at our institution or who returned to the local hospital after surgery and had incomplete chemotherapy records.

Clinicopathological data

Clinicopathological data of the patients were saved in the Gastric Cancer Information Management System v1.2 of the Harbin Medical University Cancer Hospital (Copyright No. 2013SR087424, http://www.sgihmu.com), including sex, age, body mass index (BMI), tumor diameter, tumor location, gastrectomy, histological type, metastatic lymph node ratio (mLNR), pT stage, pN stage, Borrmann type, vascular infiltration, nerve infiltration, postoperative chemotherapy, and laboratory examination. pTNM stage was consistent with the eighth edition of the American Joint Commission on Cancer (AJCC). Tumor marker or radiographic examinations (ultrasound, CT, and gastroscopy) were performed on all patients every 3-6 mo postoperatively. In addition, PET/CT examinations were performed as needed.

Blood sample collection

Blood samples were taken on an empty stomach the day after admission. Venous blood (2 mL) was collected from the cubital vein and sent to the blood laboratory to separate the serum and calculate the corresponding blood indexes.

Statistical analysis

The chi–square test was used to analyze the differences in clinicopathological factors between the two groups. Overall survival (OS) was defined as the date from surgery to death or the date of the last follow-up. The OS was shown as the mean and 95% confidence interval (CI). According to the receiver operating characteristic curve (ROC), the "Youden index" was calculated by sensitivity- (1-specificity). The maximum value of the Youden index was the optimal cutoff value for continuous variables. The log-rank test and Kaplan–Meier method were used to analyze survival curves. Univariate and multivariate analyses based on the Cox proportional hazards regression model were used to analyze the independent risk factors for prognosis. Hazard ratios (HRs) and 95%CIs were estimated for each factor. The nomogram models were drawn through R studio using the “SvyNom” and “rms” packages. Calibration plots were used to show the relationship between predicted probabilities and the actual outcome by using the Hosmer goodness-of-fit test. SPSS version 25.0 (SPSS Inc., Chicago, IL, United States) was used for statistical analyses, and $P < 0.05$ was considered statistically significant.

RESULTS

Clinicopathological characteristics

According to the postoperative pathology report, there were 89 and 370 patients in the pT1N2-3 group and pT3N0 group, respectively. In the pT1N2-3 group, the age range was 28-81 years (median, 55 years), and the male:female ratio was 44:45. In the pT3N0 group, the age range was 24-87 years (median, 58 years), and the male:female ratio was 269:101. There were statistically significant differences in the clinicopathological features between the two groups, including sex ($P < 0.001$), tumor diameter ($P = 0.002$), tumor location ($P = 0.007$), gastrectomy ($P = 0.001$), histological type ($P = 0.043$), vascular infiltration ($P = 0.021$), nerve infiltration ($P < 0.001$), and postoperative chemotherapy ($P < 0.001$). Table 1 shows the clinicopathological features of the two groups.

Comparison of prognosis between the two groups

The OS of patients with pT1N2-3 GC was 53.34 (95%CI: 50.369-56.317) mo, and the 5-year OS rate was 73.7%. The OS of patients with pT3N0 GC was 53.66 (95%CI: 52.179-55.149) mo, and the 5-year OS rate was 79.7%. There was no statistically significant difference in OS between the two groups (P=0.374) (Figure 1A). In the pT1N2-3 group, there was no significant difference in OS between patients with and without postoperative chemotherapy (OS: 53.20 mo *vs* 53.40 mo, $P = 0.527$; HR: 0.744, 95%CI: 0.297-1.865) (Figure 1B). Similarly, in the pT3N0 group, there was no significant difference in OS between patients with and without postoperative chemotherapy (OS: 55.08 mo *vs* 53.03 mo, $P = 0.236$; HR: 0.774, 95%CI: 0.430-1.393) (Figure 1C).

Table 1 Baseline characteristics of patients with pT1N2-3 and pT3N0 GC, *n* (%)

Characteristic	pT1N2-3b (*n* = 89)	pT3N0 (*n* = 370)	*P* value
Sex			**< 0.001**
Male	44 (49.4)	269 (72.7)	
Female	45 (50.6)	101 (27.3)	
Age (yr)			0.071
≤ 60	58 (65.2)	219 (59.2)	
> 60	25 (34.8)	151 (40.8)	
BMI (kg/m^2)			0.964
< 24	63 (70.8)	261 (70.5)	
≥ 24	26 (29.2)	109 (29.5)	
Borrmann type			**< 0.001**
0	89 (100.0)	0 (0.0)	
1	0 (0.0)	23 (6.2)	
2	0 (0.0)	126 (34.1)	
3	0 (0.0)	195 (52.7)	
4 or 5	0 (0.0)	26 (7.0)	
Tumor diameter (mm)			**0.002**
≤ 50	74 (83.1)	245 (66.2)	
> 50	15 (16.9)	125 (33.8)	
Tumor location			**0.007**
Upper	4 (4.5)	53 (14.3)	
Middle	11 (12.4)	66 (17.8)	
Lower	74 (83.1)	243 (65.7)	
Total	0 (0.0)	8 (2.2)	
Gastrectomy			**0.001**
Partial gastrectomy	83 (93.3)	289 (78.1)	
Total gastrectomy	6 (6.7)	81 (21.9)	
Histological type			**0.043**
Differentiated	32 (36.0)	177 (47.8)	
Undifferentiated	57 (64.0)	193 (52.2)	
pT stage			**< 0.001**
T1a	18 (20.2)	0 (0.0)	
T1b	71 (79.8)	0 (0.0)	
T3	0 (0.0)	370 (100.0)	
pN stage			**< 0.001**
N0	0 (0.0)	370 (100.0)	
N2	70 (78.7)	0 (0.0)	
N3a	18 (20.2)	0 (0.0)	
N3b	1 (1.1)	0 (0.0)	
Vascular infiltration			**0.021**
No	64 (71.9)	306 (82.7)	
Yes	25 (28.1)	64 (17.3)	

Nerve infiltration			**< 0.001**
No	82 (92.1)	224 (60.5)	
Yes	7 (7.9)	146 (39.5)	
Postoperative chemotherapy			**< 0.001**
Yes	52 (58.4)	114 (30.8)	
No	37 (41.6)	256 (69.2)	

Tumor location, histological type, pT stage, pN stage, pTNM stage, vascular infiltration, and nerve infiltration were according to the postoperative pathology report. Statistically significant *P* values are in bold ($P < 0.05$). BMI: Body mass index.

Prognosis of the pT1N2-3 group

Univariate and multivariate analyses based on the Cox proportional hazards regression model were performed to identify independent risk factors associated with the prognosis of patients with pT1N2-3 GC. Univariate analysis showed that age ($P = 0.044$), prealbumin ($P = 0.003$), carcino-embryonic antigen (CEA) ($P = 0.004$), and mLNR ($P < 0.001$) were statistically significant. Multivariate analysis showed that prealbumin ($P = 0.040$), CEA ($P = 0.021$), and mLNR ($P = 0.035$) were independent risk factors associated with prognosis (Table 2).

Subgroup analysis of independent risk factors associated with the prognosis of pT1N2-3 patients was performed. According to the Youden index, 222.35, 3.17, and 0.28 were the optimal cutoff values for prealbumin, CEA, and mLNR to evaluate the prognosis of patients with pT1N2-3 disease (Figure 2A). Subgroup analysis showed that there was a statistically significant difference in OS between patients with prealbumin > 222.35 mg/L and those with prealbumin ≤ 222.35 mg/L (OS: 57.11 mo *vs* 42.82 mo, $P < 0.001$; HR: 5.972, 95%CI: 2.430-14.681), between patients with CEA ≤ 3.17 ng/mL and those with CEA > 3.17 ng/mL (OS: 55.34 mo *vs* 43.19 mo, $P = 0.008$; HR: 3.497, 95%CI: 1.391-8.792), and between patients with mLNR ≤ 0.28 and those with mLNR > 0.28 (OS: 55.07 mo *vs* 45.72 mo, $P = 0.001$; HR: 4.430, 95%CI: 1.825-10.750). In addition, the combination of independent risk factors associated with the prognosis of pT1N2-3 patients was analyzed for survival. Patients with 0, 1, and 2-3 risk factors were defined as the low-risk group, moderate-risk group, and high-risk group, respectively, and there were statistically significant differences in OS among these groups (OS: 58.95 mo *vs* 48.91 mo *vs* 38.36 mo, respectively, $P < 0.001$) (Figure 3A-D).

Prognosis of the pT3N0 group

Univariate and multivariate analyses based on the Cox proportional hazards regression model were performed to identify independent risk factors associated with the prognosis of patients with pT3N0 disease. Univariate analysis showed that age ($P = 0.019$), BMI ($P = 0.004$), tumor diameter ($P = 0.003$), Borrmann type ($P = 0.018$), and gastrectomy ($P < 0.001$) were statistically significant. Multivariate analysis showed that age ($P = 0.039$), BMI ($P = 0.002$), and gastrectomy ($P < 0.001$) were independent risk factors associated with prognosis (Table 3).

Subgroup analysis of independent risk factors associated with pT3N0 patient prognosis was performed. According to the Youden index, 60.5 and 22.48 were the optimal cutoff values for age and BMI to evaluate the prognosis of patients with pT1N2-3 (Figure 2B). Subgroup analysis showed that there was a statistically significant difference in OS between patients aged ≤ 60 years and those aged > 60 years (OS: 55.07 mo *vs* 51.66 mo, $P = 0.003$; HR: 2.010, 95%CI: 1.252-3.228), between patients with BMI > 22.48 kg/m^2 and those with BMI ≤ 22.48 kg/m^2 (OS: 55.80 mo *vs* 51.81 mo, $P = 0.002$; HR: 2.165, 95%CI: 1.299-3.611), and between patients who underwent partial gastrectomy and those who underwent total gastrectomy (OS: 55.19 mo *vs* 47.92 mo, $P < 0.001$; HR: 3.378, 95%CI: 2.105-5.421). In addition, the combination of independent risk factors associated with the prognosis of pT3N0 patients was analyzed for survival. Patients with 0, 1, and 2-3 risk factors were defined as the low-risk group, moderate-risk group, and high-risk group, respectively, and there were statistically significant differences in OS among these groups (OS: 57.42 mo *vs* 55.02 mo *vs* 49.45 mo, respectively, $P < 0.001$) (Figure 3E-H).

Nomogram models

We combined the independent risk factors associated with prognosis to construct nomograms that were used to evaluate the prognosis of patients in the pT1N2-3 and pT3N0 groups (Figure 4A and D). The area under the curve (AUC) of the nomogram model in predicting the 3-year and 5-year prognosis of pT1N2-3 patients was 0.772 (95%CI: 0.617-0.926) and 0.765 (95%CI: 0.639-0.891), respectively; the sensitivity was 81.8% and 75.0%, respectively, and the specificity was 73.1% and 73.9%, respectively (Figure 4B and C). The AUC of the nomogram model for predicting the 3-year and 5-year prognosis of pT3N0 patients was 0.632 (95%CI: 0.547-0.837) and 0.699 (95%CI: 0.629-0.768), respectively; the sensitivity was 52.9% and 64.3%, respectively, and the specificity was 69.9% and 67.3%, respectively (Figure 4E and F). In addition, the calibration plots showed that the nomogram performed well for

Table 2 Univariate and multivariate analyses of clinicopathological factors of patients with pT1N2-3b GC

Characteristic	pT1N2-3b			
	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Sex		0.870	-	-
Male	1.000			
Female	0.929 (0.387-2.233)			
Age (yr)	1.044 (1.001-1.089)	**0.044**	1.022 (0.978-1.069)	0.335
BMI (kg/m^2)	0.924 (0.815-1.047)	0.216	-	-
Neutrophils (10^9/L)	1.034 (0.795-1.345)	0.802	-	-
Lymphocytes (10^9/L)	0.616 (0.297-1.278)	0.193	-	-
Platelets (10^9/L)	0.999 (0.992-1.006)	0.692	-	-
Fibrinogen (g/L)	1.277 (0.723-2.256)	0.399	-	-
ALT (U/L)	1.000 (0.973-1.029)	0.972	-	-
AST (U/L)	1.016 (0.968-1.067)	0.521	-	-
Albumin (g/L)	0.926 (0.833-1.028)	0.150	-	-
Prealbumin (mg/L)	0.986 (0.977-0.995)	**0.003**	0.990 (0.981-1.000)	**0.040**
CEA (ng/mL)	1.254 (1.074-1.464)	**0.004**	1.199 (1.028-1.399)	**0.021**
CA19-9 (U/mL)	1.000 (0.972-1.028)	0.992	-	-
Tumor diameter (mm)	0.986 (0.961-1.013)	0.307	-	-
Gastrectomy		0.683	-	-
Partial gastrectomy	1.000			
Total gastrectomy	1.356 (0.314-5.851)			
Histological type		0.324	-	-
Differentiated	1.000			
Undifferentiated	1.665 (0.605-4.581)			
pN stage		0.251	-	-
N2	1.000			
N3	1.752 (0.673-4.562)			
mLNR	47.797 (5.421-421.417)	**< 0.001**	17.488 (1.215-251.748)	**0.035**
Vascular infiltration		0.187	-	-
No	1.000			
Yes	1.865 (0.738-4.708)			
Nerve infiltration		0.989	-	-
No	1.000			
Yes	1.010 (0.234-4.359)			
Postoperative chemotherapy		0.528	-	-
Yes	1.000			
No	0.744 (0.297-1.865)			

CEA and CA19-9 were according to the tumor marker examination. Tumor location, histological type, mLNR, pTstage, pNstage, vascular infiltration, and nerve infiltration were according to the postoperative pathology report. Statistically significant *P* values are in bold ($P < 0.05$). HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index; ALT: Alanine transaminase; AST: A CEA: Carcino-embryonic antigen; CA19-9: Carbohydrate antigen 19-9; mLNR: Metastatic lymph node ratio.

Table 3 Univariate and multivariate analyses of clinicopathological factors of patients with pT3N0 GC

Characteristic	pT3N0			
	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Sex		0.087	-	-
Male	1.000			
Female	1.533 (0940-2.500)			
Age (yr)	1.029 (1.005-1.054)	**0.019**	1.025 (1.001-1.049)	**0.039**
BMI (kg/m^2)	0.890 (0.822-0.964)	**0.004**	0.881 (0.812-0.955)	**0.002**
Neutrophils (10^9/L)	0.947 (0.829-1.082)	0.421	-	-
Lymphocytes (10^9/L)	0.966 (0.719-1.298)	0.819	-	-
Platelets (10^9/L)	1.000 (0.997-1.003)	0.914	-	-
Fibrinogen (g/L)	1.048 (0.974-1.129)	0.210	-	-
ALT (U/L)	0.992 (0.969-1.015)	0.469	-	-
AST (U/L)	1.012 (0.986-1.037)	0.369	-	-
Albumin (g/L)	0.991 (0.949-1.034)	0.670	-	-
Prealbumin (mg/L)	1.657 (0.954-2.005)	0.087	-	-
CEA (ng/mL)	1.007 (0.985-1.030)	0.535	-	-
CA19-9 (U/mL)	1.002 (0.999-1.004)	0.214	-	-
Tumor diameter (mm)	1.011 (1.004-1.019)	**0.003**	1.000 (0.990-1.010)	0.981
Borrmann type		**0.018**		0.282
1	1.000		1.000	
2	0.368 (0.159-0.853)	**0.020**	0.473 (0.195-1.150)	0.099
3	0.520 (0.242-1.119)	0.095	0.620 (0.279-1.377)	0.240
4 or 5	1.110 (0.428-2.879)	0.830	1.051 (0.379-2.911)	0.924
Gastrectomy		**< 0.001**		**< 0.001**
Partial gastrectomy	1.000		1.000	
Total gastrectomy	3.378 (2.105-5.421)		3.222 (1.945-5.338)	
Histological type		0.380	-	-
Differentiated	1.000			
Undifferentiated	1.236 (0.771-1.980)			
Vascular infiltration		0.237	-	-
No	1.000			
Yes	1.142 (0.798-2.499)			
Nerve infiltration		0.373	-	-
No	1.000			
Yes	1.240 (0772-1.991)			
Postoperative chemotherapy		0.238	-	-
Yes	1.000			
No	0.774 (0.430-1.393)			

CEA and CA19-9 were according to the tumor marker examination. Tumor location, histological type, mLNR, pTstage, pNstage, vascular infiltration, and nerve infiltration were according to the postoperative pathology report. Statistically significant *P* values are in bold ($P < 0.05$). HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index; ALT: Alanine transaminase; AST: A CEA: Carcino-embryonic antigen; CA19-9: Carbohydrate antigen 19-9;

mLNR: Metastatic lymph node ratio.

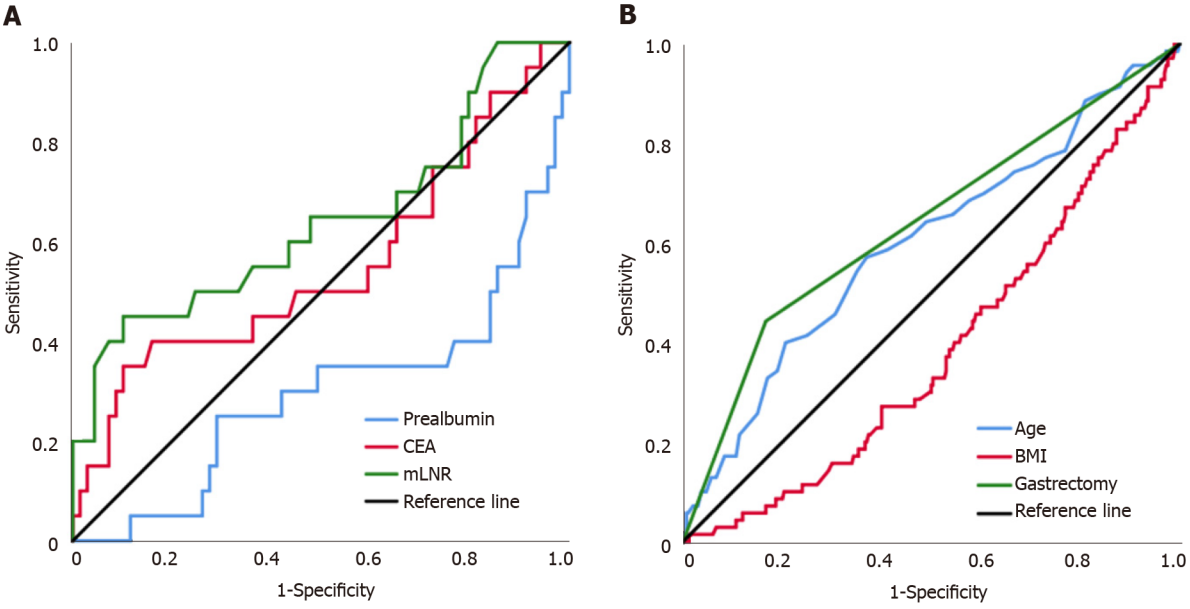


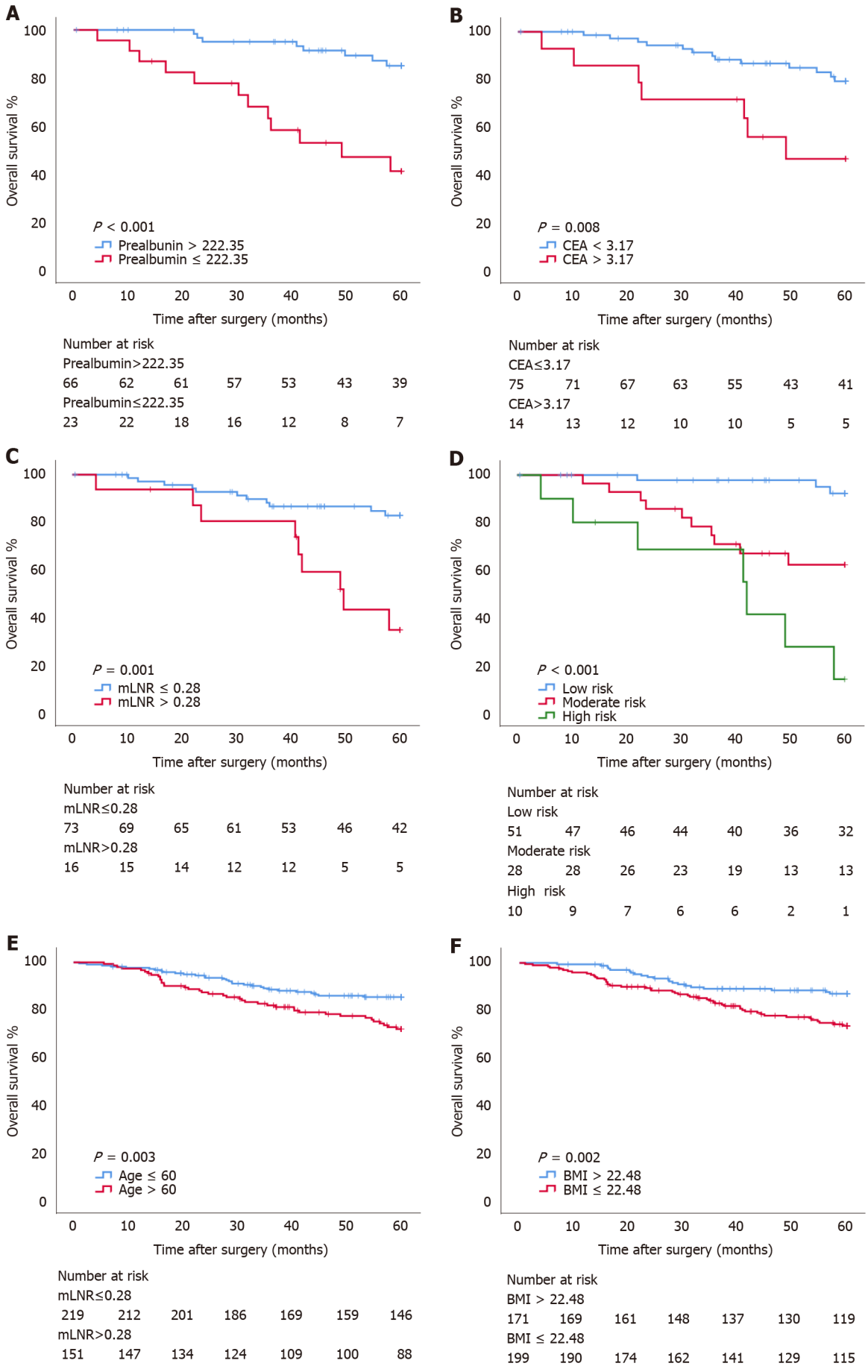
Figure 2 Receiver operating characteristic curves of clinicopathological factors of patients with pT1N2-3 and pT3N0 GC. A: Assessing the prognosis of patients with pT1N2-3 GC; B: Assessing the prognosis of patients with pT3N0 GC. CEA: Carcino-embryonic antigen; mLNR: Metastatic lymph node ratio; BMI: Body mass index.

predicting the 3-year OS of the pT1N2-3 group and the 3- and 5-year OS of the pT3N0 group but did not perform well for predicting the 5-year OS of the pT1N2-3 group (Figure 5).

DISCUSSION

To date, much evidence has been found indicating that appropriate postoperative adjuvant chemotherapy can improve the survival probability after radical resection[3,13-15]. According to the results of the ACTS-GC trial[3], the indications for postoperative chemotherapy excluded pT1N2-3 patients who were classified as stage II/III due to pT1 and pT3N0 patients who were classified as stage IB based on the 13th edition of the Japanese Classification of Gastric Carcinoma[16]. And in the current 14th edition, pT3N0 patients were classified as stage IIA[6]. However, there are still patients with pTIN2-3 and pT3N0 GC who have a poor prognosis, and identifying them through a clinical retrospective study is of substantial value.

Based on the Cox hazards regression model, our study identified prealbumin, CEA, and mLNR as independent prognostic factors for pT1N2-3 patients, while age, BMI, and gastrectomy were independent prognostic factors for pT3N0 patients. Some studies have shown that, as an important indicator of nutritional assessment, prealbumin plays a key role in the complicated link among systemic inflammation, malnutrition, and the tumor immune microenvironment[17,18]. Our study showed that low preoperative prealbumin levels may cause immunodeficiency in patients with stage T1 disease accompanied by extensive lymph node metastasis, leading to tumor progression[19]. Consistent with the results of Qiao *et al*[20], we found that high preoperative CEA level was associated with positive lymph node metastasis in patients with pT1 disease and predicted a poor prognosis. This is related to the function of CEA as an isotype of intercellular adhesion molecule that can promote the aggregation and distant metastasis of tumor cells[21]. In addition, we found that advanced age, low preoperative BMI, and total gastrectomy, as independent prognostic risk factors for pT3N0 patients, were closely related to postoperative malnutrition, which was consistent with the results of the previous studies[22,23]. Short- to medium-term postoperative malnutrition might weaken immune function throughout the body, resulting in an increased risk for cancer recurrence, infectious disease, and death[19]. The mechanism by which immune function is weakened in malnourished individuals involves cytoplasmic nutrient sensors affecting T lymphocyte metabolism and intestinal dysfunction changing the pathway of nutrient sensing[24,25]. Additionally, surgical stress compromises the activity of natural killer (NK) cells and causes immune dysfunction, which is associated with high cancer recurrence and mortality rates[26,27]. Therefore, immune dysfunction due to surgical stress and malnutrition may increase the risk for


A
Overall survival %
P < 0.001
Prealbunin > 222.35
Prealbumin ≤ 222.35
Time after surgery (months)
Number at risk
Prealbumin>222.35
66 62 61 57 53 43 39
Prealbumin≤222.35
23 22 18 16 12 8 7
B
Overall survival %
P = 0.008
CEA < 3.17
CEA > 3.17
Time after surgery (months)
Number at risk
CEA≤3.17
75 71 67 63 55 43 41
CEA>3.17
14 13 12 10 10 5 5
C
Overall survival %
P = 0.001
mLNR ≤ 0.28
mLNR > 0.28
Time after surgery (months)
Number at risk
mLNR≤0.28
73 69 65 61 53 46 42
mLNR>0.28
16 15 14 12 12 5 5
D
Overall survival %
P < 0.001
Low risk
Moderate risk
High risk
Time after surgery (months)
Number at risk
Low risk
51 47 46 44 40 36 32
Moderate risk
28 28 26 23 19 13 13
High risk
10 9 7 6 6 2 1
E
Overall survival %
P = 0.003
Age ≤ 60
Age > 60
Time after surgery (months)
Number at risk
mLNR≤0.28
219 212 201 186 169 159 146
mLNR>0.28
151 147 134 124 109 100 88
F
Overall survival %
P = 0.002
BMI > 22.48
BMI ≤ 22.48
Time after surgery (months)
Number at risk
BMI > 22.48
171 169 161 148 137 130 119
BMI ≤ 22.48
199 190 174 162 141 129 115

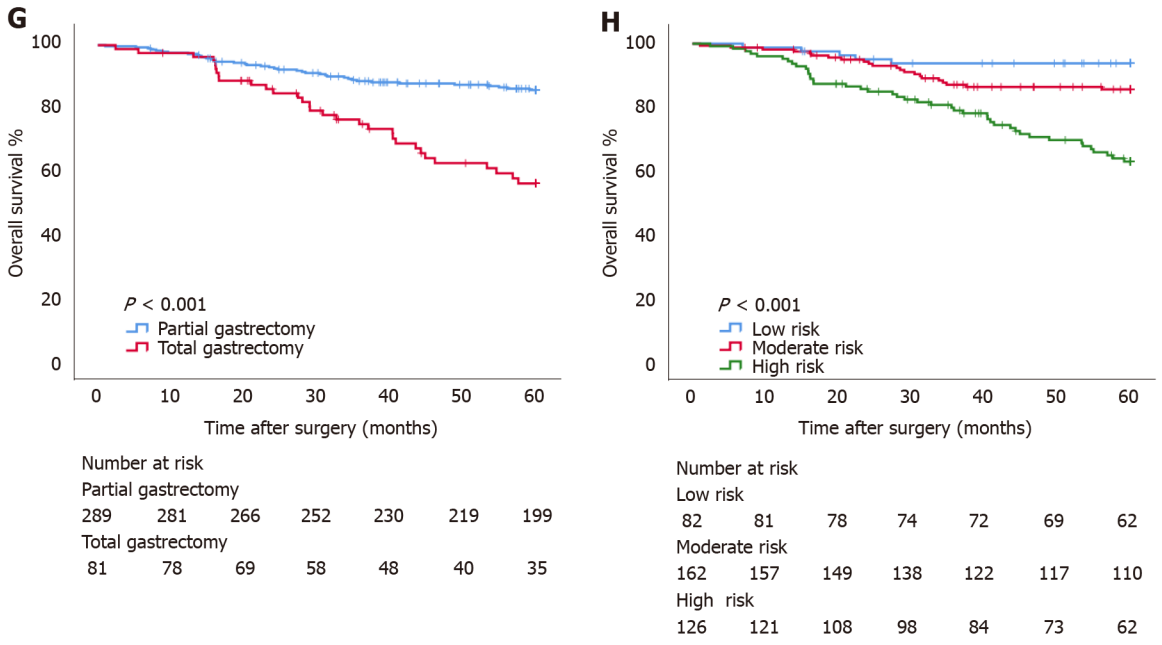
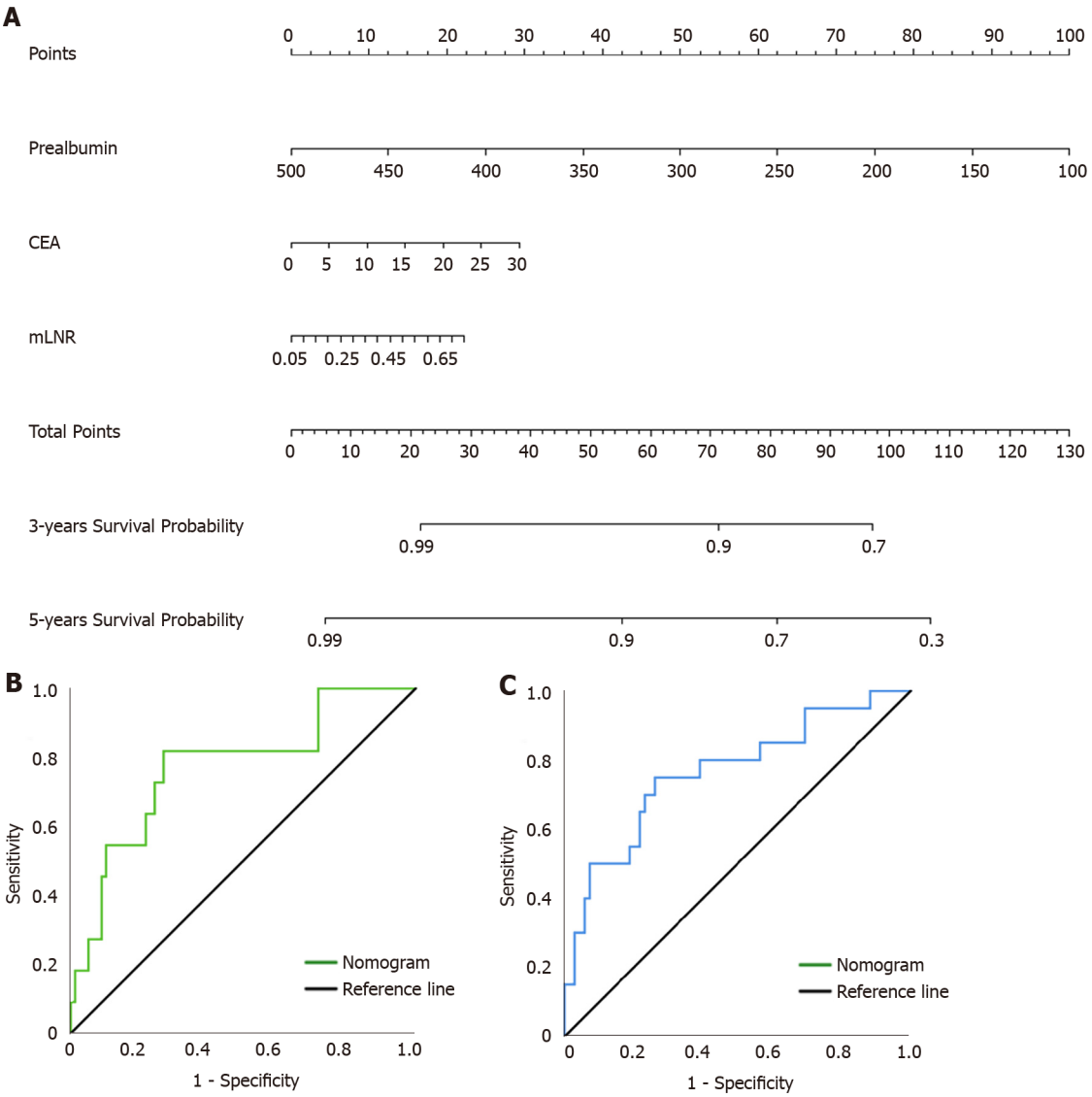


Figure 3 Survival curve subgroup analyses of patients. A: Overall survival curves for patients with prealbumin ≤ 222.35 mg/L and prealbumin > 222.35 mg/L in the pT1N2-3 group; B: Overall survival curves for patients with carcino-embryonic antigen (CEA) ≤ 3.17 ng/mL and CEA > 3.17 ng/mL in the pT1N2-3 group; C: Overall survival curves for patients with metastatic lymph node ratio (mLNR) ≤ 0.28 and mLNR > 0.28 in the pT1N2-3 group; D: Overall survival curves for patients with low risk, moderate risk, and high risk in the pT1N2-3 group; E: Overall survival curves for patients aged ≤ 60 years and aged > 60 years in the pT3N0 group; F: Overall survival curves for patients with body mass index (BMI) ≤ 22.48 kg/m^2 and BMI > 22.48 kg/m^2 in the pT3N0 group; G: Overall survival curves for patients with partial gastrectomy and total gastrectomy in the pT3N0 group; H: Overall survival curves for patients with low risk, moderate risk, and high risk in the pT3N0 group. CEA: Carcino-embryonic antigen; mLNR: Metastatic lymph node ratio; BMI: Body mass index.

early cancer recurrence after surgery.

However, contrary to the findings of Yura *et al*[5], our findings suggested that mLNR is an independent prognostic factor for patients with pT1N2-3, rather than N stage. Schwarz *et al*[28] found that the prediction of survival based on N stage depended on the total number of lymph nodes resected and the quantity of negative nodes. However, there is considerable heterogeneity in the number of recovered lymph nodes due to differences in the skill level of the surgeons and the experience of the pathologists. Some researchers suggested that variability due to the difference in the number of recovered lymph nodes might be eliminated by mLNR, and they also found that mLNR was an independent prognostic factor[29,30]. Therefore, we believe that for evaluating the prognosis of pT1N2-3 GC patients, mLNR is more suitable than N stage. Furthermore, we found that tumor diameter was not an independent prognostic factor for pT1N2-3 patients. Tumor diameter was included by Yura *et al*[5] as a categorical variable, and the *P* value became significant only when the optimal cutoff value of tumor diameter was 30 mm. We included the tumor diameter as a continuous variable, which improved the reliability of the results. Previous studies have revealed that pT3N0 GC patients with vascular infiltration have a higher risk of tumor recurrence[6-8], indicating a poor prognosis, which was not consistent with our findings. In fact, determination of the presence or absence of postoperative vascular infiltration may vary due to different staining methods and diagnostic criteria between single centers[31]. Therefore, in the future, a multicenter study that uses unified methods and standards is needed to more accurately determine the prognostic value of vascular infiltration in pT3N0 patients.

Our study showed that whether patients with pT1N2-3b and pT3N0 receive postoperative adjuvant chemotherapy has no significant effect on the OS, which was consistent with the results of previous studies[3,32]. The JCOG8801 phase III trial compared adjuvant chemotherapy with mitomycin and fluorouracil to surgery alone. They found that for patients with pT1N+ or pT2-3N0 GC, adjuvant chemotherapy did not provide additional survival benefits compared with surgery alone and excluded pT1N2-3 and pT3N0 from the indications for postoperative adjuvant chemotherapy. In that trial, the subgroups of pT1N2-3 and pT3N0 were not examined. It was not known whether all patients with pT1N2-3 and pT3N0 who receive surgical treatment alone have a good prognosis. In this study, we evaluated the independent risk factors that affected the prognosis of patients in both groups and attempted to identify patients who would potentially benefit from adjuvant chemotherapy based on peripheral blood biomarkers and clinicopathological features. Our study found that pT1N2-3 patients with high-risk factors, such as low preoperative prealbumin level, high preoperative CEA level, and high mLNR, would potentially benefit from postoperative adjuvant chemotherapy, while surgical treatment alone was not guaranteed to improve prognosis. Therefore, appropriate use of adjuvant chemotherapy after surgery, as well as regular reexamination and close follow-up, is recommended.


A
Points
0 10 20 30 40 50 60 70 80 90 100
Prealbumin
500 450 400 350 300 250 200 150 100
CEA
0 5 10 15 20 25 30
mLNR
0.05 0.25 0.45 0.65
Total Points
0 10 20 30 40 50 60 70 80 90 100 110 120 130
3-years Survival Probability
0.99 0.9 0.7
5-years Survival Probability
0.99 0.9 0.7 0.3
B
Sensitivity
1 - Specificity
Nomogram
Reference line
C
Sensitivity
1 - Specificity
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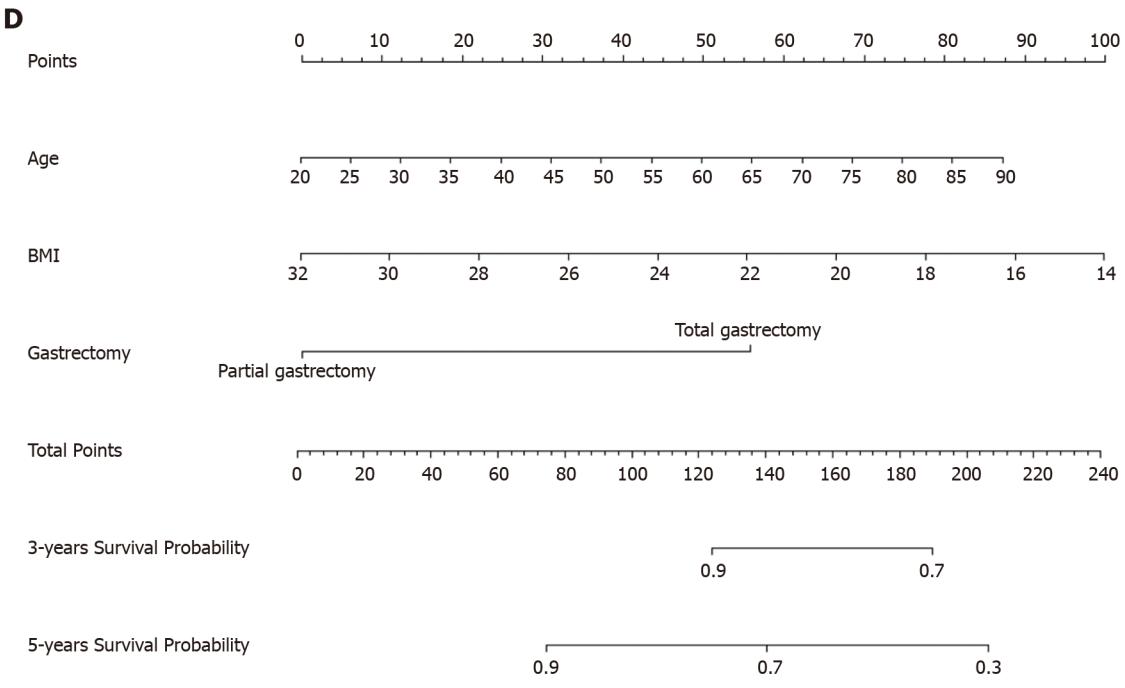
D
Points
0 10 20 30 40 50 60 70 80 90 100
Age
20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
BMI
32 30 28 26 24 22 20 18 16 14
Gastrectomy
Total gastrectomy
Partial gastrectomy
Total Points
0 20 40 60 80 100 120 140 160 180 200 220 240
3-years Survival Probability
0.9 0.7
5-years Survival Probability
0.9 0.7 0.3

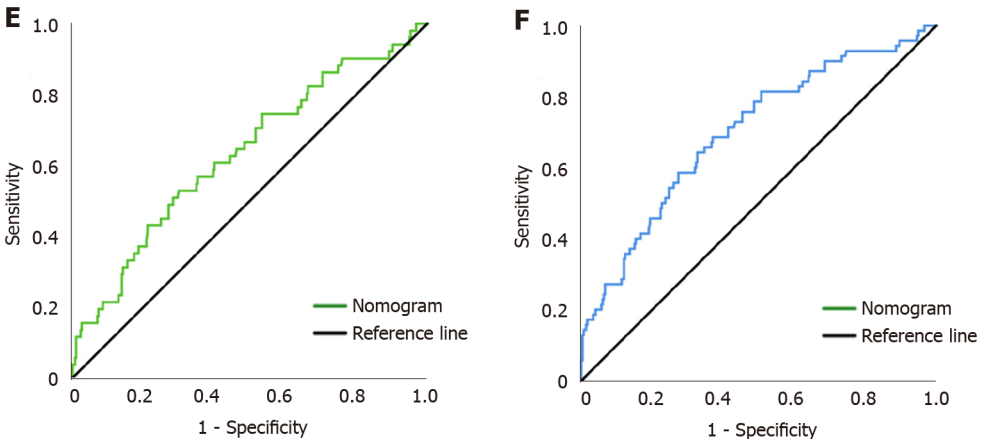

Figure 4 Nomogram models for predicting the survival of patients with pT1N2-3 and pT3N0 GC. A: Nomogram model predicting the 3- and 5-year survival of patients with pT1N2-3 GC; B: Receiver operating characteristic curve (ROC) of the nomogram model for predicting the 3-year survival of patients with pT1N2-3 GC; C: ROC of the nomogram model for predicting the 5-year survival of patients with pT1N2-3 GC; D: Nomogram model for predicting the 3- and 5-year survival of patients with pT3N0 GC; E: ROC of the nomogram model for predicting the 3-year survival of patients with pT3N0 GC; F: ROC of the nomogram model for predicting the 5-year survival of patients with pT3N0 GC. CEA: Carcino-embryonic antigen; mLNR: Metastatic lymph node ratio; BMI: Body mass index.

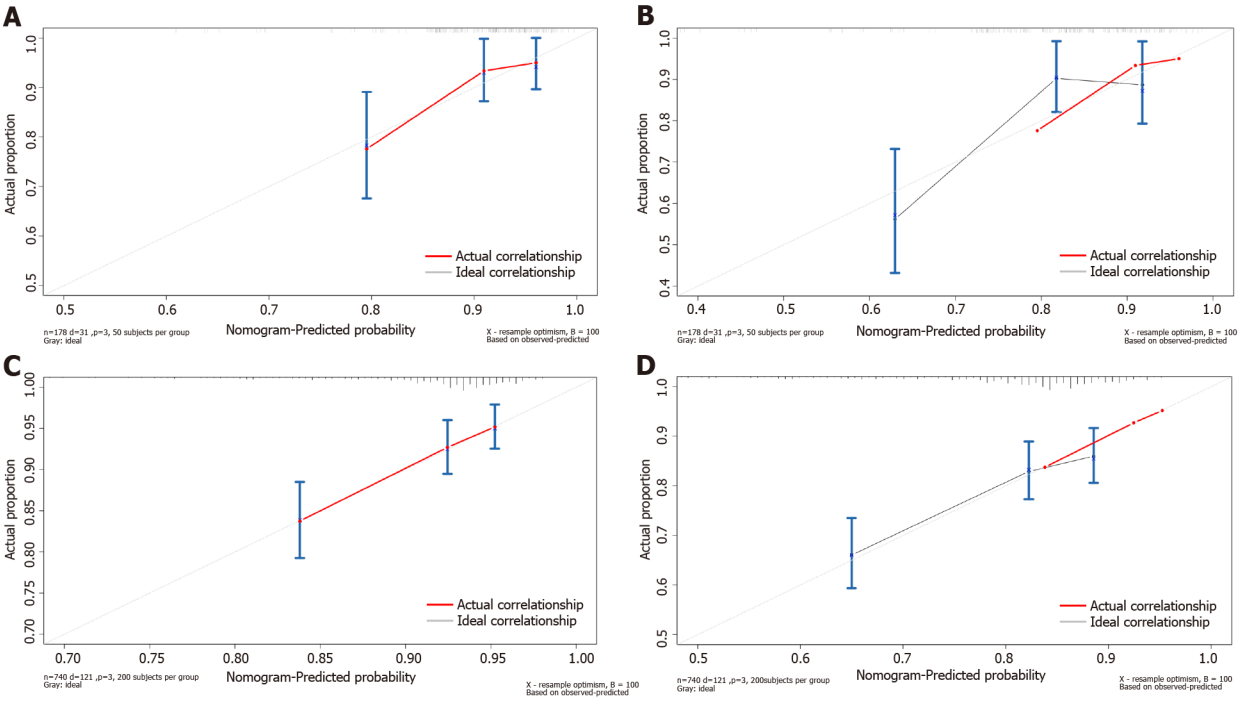

Figure 5 Calibration plots for the nomograms. Correlation between the predicted probabilities based on the nomograms and actual values is shown. A: 3-year survival of patients with pT1N2-3 GC; B: 5-year survival of patients with pT1N2-3 GC; C: 3-year survival of patients with pT3N0; D: 5-year survival of patients with pT3N0 GC.

However, considering that independent risk factors for prognosis in pT3N0 patients, such as advanced age, preoperative low BMI, and total gastrectomy, are strongly associated with postoperative malnutrition, we recommend pT3N0 patients whose indicators mentioned above indicate a poor prognosis as candidates for active nutritional intervention. Furthermore, their tolerance to postoperative adjuvant chemotherapy is poor, and postoperative adjuvant chemotherapy may increase the risk for malnutrition among these patients[23]. Therefore, postoperative adjuvant chemotherapy is not a preferred treatment strategy. Clinicians should pay more attention to the postoperative nutritional condition, complications, and infections of these patients, and select the appropriate time for postoperative adjuvant chemotherapy based on these factors.

Clinically, some experts have found that pTNM stage based on postoperative pathology can provide effective but incomplete information for treatment. Patients at the same stage show significant individual differences in prognosis. Many studies have shown that peripheral blood biomarkers and clinicopathological features can play effective complementary roles and are widely used in the early

detection, clinical staging, treatment response monitoring, and prognosis prediction of GC. For example, Liu *et al*[33] constructed a nomogram based on inflammatory biomarkers and mLNR to predict the survival of patients with radical gastrectomy. Therefore, the predictive models constructed by combining peripheral blood biomarkers with clinicopathological features have the advantages of more accurate and individualized evaluation of patient prognosis and reducing the differences caused by heterogeneity. Based on the Cox hazards regression model, we found that prealbumin, CEA, and mLNR were independent risk factors associated with the prognosis of pT1N2-3 GC patients, and age, BMI, and gastrectomy were independent risk factors associated with the prognosis of pT3N0 GC patients. Then, we constructed nomogram models to predict the prognosis of patients with pT1N2-3 and pT3N0. ROC analysis showed that the AUC of the nomogram model in predicting the 3-year and 5-year prognosis of pT1N2-3 patients was 0.772 (95%CI: 0.617-0.926) and 0.765 (95%CI: 0.639-0.891), respectively; the sensitivity was 81.8% and 75.0%, respectively, and the specificity was 73.1% and 73.9%, respectively. The AUC of the nomogram model in predicting the 3-year and 5-year prognosis of pT3N0 patients was 0.632 (95%CI: 0.547-0.837) and 0.699 (95%CI: 0.629-0.768), respectively; the sensitivity was 52.9% and 64.3%, respectively, and the specificity was 69.9% and 67.3%, respectively. The lower AUC may be related to the fact that patients with pT3N0 tend to have a good prognosis and fewer significant clinicopathological factors. In addition, the calibration plots showed that the nomogram performed well for predicting the 3-year OS of the pT1N2-3 group and the 3- and 5-year OS of the pT3N0 group but did not perform well in predicting the 5-year OS of the pT1N2-3 group. This may be due to the small number of patients in the pT1N2-3 group included in our study. Our results showed that the predictive model constructed by peripheral blood biomarkers and clinicopathological features can evaluate the prognosis of patients with pT1N2-3 and pT3N0, which is worthy of further validation and promotion in clinical practice.

There were some limitations in this study. First, this was a retrospective study, and the sample size in the pT1N2-3 group was small. The results of this study need to be verified by more prospective studies. Second, this was a single-center study, focusing only on Asian populations. Whether these results are widely applicable to both White and Black populations needs to be further studied by enlarging the sample size. Third, because pT1N2-3 and pT3N0 GC patients are too rare, there is a lack of sufficient sample size for internal and external validation of nomogram model, which is also the direction of our further study in the future.

CONCLUSION

The nomogram model based on prealbumin, CEA, and mLNR can be used to predict the prognosis of pT1N2-3 GC patients. The nomogram model based on age, BMI, and gastrectomy can be used to predict the prognosis of pT3N0 GC patients.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer (GC) is an important public health burden worldwide. The TNM staging system based on tumor infiltration, regional lymph node metastasis, and distant metastasis is considered as the conventional criterion for evaluating prognosis and guiding treatment after surgery. Adjuvant chemotherapy can effectively reduce the disease recurrence. Based on the results of the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC), stage II/III disease as the standard target of adjuvant chemotherapy after surgery, with the exception of pathological stages T1N2-3 (pT1N2-3) and pT3N0. However, in these two groups, there is still a portion of high-risk patients with a poor prognosis.

Research motivation

Analyzing the independent risk factors for the prognosis of pT1N2-3 and pT3N0 GC patients will provide a basis for clinicians to treat and predict the prognosis of these patients in the future.

Research objectives

To identify the high-risk group among these patients after radical surgery by analyzing biomarkers and clinicopathological features and construct prognostic models for them.

Research methods

This retrospective study analyzed the clinicopathological characteristics and long-term survival data of 459 patients with pT1N2-3/pT3N0 GC, all of whom underwent radical gastrectomy at the Harbin Medical University Cancer Hospital between January 2000 and April 2016. The chi–square test was used to analyze the differences in the clinicopathological features between the pT1N2-3 and pT3N0 groups.

The Kaplan–Meier analysis and log-rank test were used to analyze overall survival (OS). The independent risk factors for patient prognosis were analyzed by univariate and multivariate analyses based on the Cox proportional hazards regression model. The cutoff values of continuous variables were analyzed by receiver operating characteristic curve. The nomogram models were constructed with R studio.

Research results

According to the postoperative pathology report, there were 89 and 370 patients in the pT1N2-3 group and pT3N0 group, respectively. There was no statistically significant difference in OS between the pT1N2-3 and pT3N0 groups (P = 0.374). Prealbumin (P = 0.040), carcino-embryonic antigen (CEA) (P = 0.021), and metastatic lymph node ratio (mLNR) (P = 0.035) were independent risk factors for prognosis in the pT1N2-3b group. Age (P = 0.039), body mass index (BMI) (P = 0.002), and gastrectomy (P < 0.001) were independent risk factors for prognosis in the pT3N0 group. The area under the curve values of the nomogram models predicting the 5-year prognosis of the pT1N2-3 group and pT3N0 group were 0.765 and 0.699, respectively.

Research conclusions

The nomogram model based on peripheral blood biomarkers and clinicopathological features, including prealbumin, CEA, and mLNR, can be used to predict the prognosis of pT1N2-3 GC patients. Age, BMI, and gastrectomy can be used to predict the prognosis of pT3N0 GC patients.

Research perspectives

Further multicentric studies are needed to expand the sample size and external validation of the nomogram models will be performed to determine their predictive ability.

FOOTNOTES

Author contributions: Wang YF and Yin X designed and conceived this study, and they contributed equally to this work; Wang YF, Yin X, Fang TY, and Wang YM interpreted and analyzed the data; Xue YW revised the manuscript for important intellectual content; Wang YF, Yin X, Fang TY, Wang YM, Zhang DX, Zhang Y, Wang XB, and Wang H participated in the patient information collection; all authors read and approved the final manuscript.

Supported by Nn10 Program of Harbin Medical University Cancer Hospital, China, No. Nn10 PY 2017-03.

Institutional review board statement: The study was approved by the Ethics Committee of the Affiliated Tumor Hospital of Harbin Medical University.

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

Conflict-of-interest statement: All the authors have no conflict of interest related to the manuscript.

Data sharing statement: Patients' data were saved in the Gastric Cancer Information Management System v1.2 of Harbin Medical University Cancer Hospital (Copyright No. 2013SR087424, http//:www.sgihmu.com).

Country/Territory of origin: China

ORCID number: Yu-Fei Wang 0000-0002-1410-2716; Xin Yin 0000-0003-3587-371X; Tian-Yi Fang 0000-0002-5015-4898; Yi-Min Wang 0000-0002-9824-4097; Dao-Xu Zhang 0000-0002-2202-7437; Yao Zhang 0000-0002-3405-570X; Xi-Bo Wang 0000-0002-4141-8134; Hao Wang 0000-0003-4909-8937; Ying-Wei Xue 0000-0003-4525-8163.

S-Editor: Gong ZM
L-Editor: Wang TQ
P-Editor: Wu RR

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2022 February 27; 14(2): 161-173

DOI: 10.4240/wjgs.v14.i2.161

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Laparoscopic *vs* open total gastrectomy for advanced gastric cancer following neoadjuvant therapy: A propensity score matching analysis

Hai-Tao Hu, Fu-Hai Ma, Jian-Ping Xiong, Yang Li, Peng Jin, Hao Liu, Shuai Ma, Wen-Zhe Kang, Yan-Tao Tian

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Kawabata H, Masaki S, Taira K

Received: July 15, 2021
Peer-review started: July 15, 2021
First decision: November 8, 2021
Revised: December 13, 2021
Accepted: February 10, 2022
Article in press: February 10, 2022
Published online: February 27, 2022

Hai-Tao Hu, Fu-Hai Ma, Jian-Ping Xiong, Yang Li, Peng Jin, Hao Liu, Shuai Ma, Wen-Zhe Kang, Yan-Tao Tian, Department of Pancreatic and Gastric Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, Beijing Province, China

Corresponding author: Yan-Tao Tian, MD, Chief Doctor, Department of Pancreatic and Gastric Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17, Panjiayuan Nanli, Chaoyang District, Beijing 100021, Beijing Province, China.
tianyantao@cicams.ac.cn

Abstract

BACKGROUND

Laparoscopic total gastrectomy (LTG) has drawn increasing attention over the years. Although LTG has shown surgical benefits compared to open TG (OTG) in early stage gastric cancer (GC), little is known about the surgical and oncological outcomes of LTG for advanced GC following neoadjuvant therapy (NAT).

AIM

To compare the long- and short-term outcomes of advanced GC patients who underwent LTG *vs* OTG following NAT.

METHODS

Advanced GC patients who underwent TG following NAT between April 2011 and May 2018 at the Cancer Hospital of the Chinese Academy of Medical Sciences were enrolled and stratified into two groups: LTG and OTG. Propensity score matching analysis was performed at a 1:1 ratio to overcome possible bias.

RESULTS

In total, 185 patients were enrolled (LTG: 78; OTG: 109). Of these, 138 were paired after propensity score matching. After adjustment for propensity score matching, baseline parameters were similar between the two groups. Compared to OTG, LTG was associated with a significantly shorter length of hospital stay (P = 0.012). The rates of R0 resection, lymph node harvest, and postoperative morbidity did not significantly differ between the two groups. Overall survival (OS) outcomes were comparable between the two groups. Pathological T and N stages were

found to be independent risk factors for OS.

CONCLUSION
LTG can be a feasible method for advanced GC patients following NAT, as it appears to be associated with better short- and comparable long-term outcomes compared to OTG.

Key Words: Gastric cancer; Laparoscopic total gastrectomy; Open total gastrectomy; Neoadjuvant therapy; Propensity score matching

Core Tip: Laparoscopic total gastrectomy (LTG) is known to have better short-term outcomes and prognosis than open TG (OTG) in early gastric cancer (GC). However, its application in advanced GC remains controversial. In this study, we evaluated both long- and short-term outcomes of LTG compared to those of OTG in 185 patients with advanced GC who had received neoadjuvant therapy (NAT). Our results indicate that LTG is associated with better short-term and comparable long-term outcomes compared to the traditional OTG surgery. Therefore, it can be a feasible surgical treatment for advanced GC patients following NAT.

Citation: Hu HT, Ma FH, Xiong JP, Li Y, Jin P, Liu H, Ma S, Kang WZ, Tian YT. Laparoscopic *vs* open total gastrectomy for advanced gastric cancer following neoadjuvant therapy: A propensity score matching analysis. *World J Gastrointest Surg* 2022; 14(2): 161-173
URL: https://www.wjgnet.com/1948-9366/full/v14/i2/161.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i2.161

INTRODUCTION

According to the latest data from the Global Cancer Statistics 2020 report, gastric cancer (GC) is the fifth most common cancer and the fifth leading cause of cancer-related deaths worldwide[1]. Despite a slight drop in mortality rates, a considerable number of patients with GC have locally advanced disease at first diagnosis. Since the MAGIC trial[2], neoadjuvant therapy (NAT) has played a significant role in the comprehensive treatment of advanced GC (AGC). Numerous prospective studies have been carried out in Western and Eastern Asian countries, and although the efficacy of NAT has been validated, chemotherapy regimens are quite different between Western and Eastern Asian countries.

After NAT, patients generally undergo D2 gastrectomy with curative intent. Laparoscopic gastrectomy (LG) has gained popularity in the management of early GC (EGC) because of its minimal invasiveness and similar long-term outcomes compared to those of conventional open gastrectomy (OG)[3]. Although its use is still under debate, the application of LG in AGC has drawn increasing attention over the years. The available evidence from the CLASS-01 and KLASS-02 trials suggests that laparoscopy-assisted distal gastrectomy is safe and provides faster postoperative recovery than open distal gastrectomy (ODG) does for patients with AGC[4]. Moreover, the CLASS-01 trial demonstrated that laparoscopic distal gastrectomy (LDG) did not lead to inferior disease-free survival at 3 years compared to ODG for patients with AGC[5].

Since there has been a recent increase in the prevalence of adenocarcinoma of the esophagogastric junction (AEG), total gastrectomy (TG) constitutes an increasing proportion of all gastric operations[6]. Laparoscopic TG (LTG) has been confirmed to have better short-term outcomes and prognosis than those of open TG (OTG) in EGC; however, its application in AGC remains controversial[7,8]. Some retrospective studies and meta-analyses have shown that LTG has lower rates of complications and amount of blood loss; however, there is still a need for high-volume research to validate its efficacy and safety compared to those of OTG[9,10].

Chemotherapy-induced tissue fibrotic changes and edema provide new technical challenges for LG, and the effect of NAT on LG compared to that on OG remains unclear. A randomized controlled trial conducted by Li *et al*[11] (2019) reported the safety and efficacy of LDG with D2 lymphadenectomy following neoadjuvant chemotherapy (NAC) for AGC. The STOMACH trial also published preliminary results for LTG after NAC, showing that LTG is not inferior to OTG in short-term outcomes[12]. However, the rate of D2 lymphadenectomy was quite low in both groups-49% for OTG and 36.2% for LTG-and it is still doubtful whether LTG is safe in clinical oncology practice. To the best of our knowledge, only two studies with small sample sizes have investigated the long-term survival of LG following NAC, and no previous study has examined the long-term survival of patients who received LTG[13,14].

Therefore, we conducted this study to evaluate the long- and short-term outcomes of LTG for AGC following NAT and to determine the surgical and oncological safety of LTG as an acceptable alternative to OTG.

MATERIALS AND METHODS

Patients

We retrospectively screened our database of patients with GC and identified those with preoperative and pathological diagnoses of AGC who received LTG or OTG with lymphadenectomy after NAT from April 2011 to May 2018 at the Cancer Hospital of the Chinese Academy of Medical Sciences. The inclusion criteria were as follows: (1) Gastric adenocarcinoma; (2) Clinical stages cT2-4a, N-/+, and M0; and (3) Received chemotherapy or chemoradiotherapy before surgery. The exclusion criteria were as follows: (1) Remnant GC; (2) Siewert type I AEG; (3) Emergent gastrectomy; (4) Other simultaneous malignant diseases; and (5) Missing clinical data. In total, 185 patients were included, of whom 107 had undergone LTG, and 78 had undergone OTG. This study was approved by the Ethics Committee of the Cancer Hospital of the Chinese Academy of Medical Sciences and the requirement was waived.

Administration of NAT

NAC regimens were divided into three categories: (1) Platinum-based doublets (SOX, XELOX, CS, FOLFOX, and TP); (2) Epirubicin-based triplets (ECF); or (3) Taxane-based triplets (DCF, DCX). As neoadjuvant chemoradiotherapy (NCRT), patients received concurrent chemoradiotherapy with tegafur/gimeracil/oteracil (S-1). The planned dose of total radiotherapy was 45 Gy with a daily fraction of 1.8 Gy for 5 wk. S-1 was administered orally twice daily when receiving radiotherapy. After evaluation by experienced oncologists and surgeons, surgery was performed approximately 4-6 wk after the completion of NAT.

Surgical procedure

Approximately 2-4 wk after the end of NAT, patients underwent TG with standard D2 lymphadenectomy following the Japanese Gastric Cancer Treatment Guidelines[15]. A total of 5 trocars were used in the LTG surgery. The resection margins were examined intraoperatively in the frozen sections. Reconstruction of the gastrointestinal passage is typically accomplished using the Roux-en-Y gastric bypass. All operations were performed by a lead surgeon who had performed at least 60 OG or LG operations and two or three assistants. Intraoperative and postoperative complications and corresponding outcomes were documented.

Definitions

Clinical and pathological data were collected from medical records. Clinical staging was assessed using the 8th American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) classification through biopsy, endoscopic ultrasonography, and computed tomography (CT) data. Enlarged lymph nodes > 8 mm along their longest axis or those with necrosis were classified as cN+. Postoperative complications included pancreatic fistula, abdominal bleeding, anastomotic leakage, wound infection, lymphorrhagia, intestinal obstruction, abdominal infection, duodenal fistula, and gastroparesis. These were considered surgical and other medical complications and graded according to the Clavien-Dindo system[16]. The response to NAT was evaluated using the Mandard tumor regression grading (TRG) system[17]. Pathological T status, N status, and ypTNM stage were also determined using the 8th AJCC/UICC staging system. Overall survival (OS) was measured from the day of surgery.

Follow-up

In the first 2 years, patients were followed-up every 3 mo, then every 6 mo for the next 3 years, and yearly thereafter. Any loss to follow-up was censored. The final follow-up was completed in October 2020.

Propensity score matching and statistical analysis

We performed propensity score matching (PSM) to minimize bias between the baseline of the two groups. Propensity scores were calculated using a logistic regression model and the following variables: Sex, age, American Society of Anesthesiologists physical status classification (ASA), body mass index (BMI), tumor size, histological differentiation, ypT, ypN, and ypTNM status. Patients were then individually matched using the 1:1 nearest neighbor matching method with a caliper width of 0.05. This method randomly ordered the case (LTG) and control (OTG) subjects based on the propensity score and matched the control subject with the closest comparison from the first case subject[18].

Categorical values are presented as percentages and continuous values are presented as mean ± SEM. Clinical and pathological variables were analyzed using the chi-squared test, Fisher's exact test and

Table 1 Patients and tumors' clinical and pathological characteristics before and after propensity score matching

Variable	All patients		*P* value	Matched patients		*P* value
	LTG (*n* = 78)	OTG (*n* = 107)		LTG (*n* = 69)	OTG (*n* = 69)	
Age (yr)	52.7 ± 16.1	56.0 ± 12.0	0.120	53.42 ± 13.4	53.9 ± 12.7	0.828
Gender *n* (%)						
Male	61 (78.2)	78 (72.9)	0.409	53 (76.8)	52 (75.4)	0.842
Female	17 (21.8)	29 (27.1)		16 (23.2)	17 (24.6)	
BMI (kg/m^2)	22.6 ± 3.1	23.7 ± 3.7	0.028	22.6 ± 3.1	22.8 ± 3.3	0.750
ASA *n* (%)						
1-2	74 (94.9)	99 (92.5)	0.522	65 (94.2)	64 (92.8)	1.000
3	4 (5.1)	8 (7.5)		4 (5.8)	5 (7.2)	
The history of abdominalsurgery *n* (%)						
Yes	10 (12.8)	19 (17.8)	0.362	8 (11.6)	13 (18.8)	0.236
No	68 (87.2)	88 (82.2)		61 (88.4)	56 (81.2)	
Tumor location *n* (%)			0.775			0.698
Upper	30 (38.5)	35 (37.6)		28 (25.0)	22 (25.0)	
Middle	25 (32.1)	42 (39.3)		23 (33.3)	26 (37.7)	
Lower	9 (11.5)	12 (11.2)		7 (10.1)	10 (14.5)	
More than two position or total	14 (17.9)	18 (16.8)		11 (15.9)	11 (15.9)	
Clinical T stage *n* (%)			0.402			0.784
2	3 (3.8)	1 (0.9)		3 (4.3)	1 (1.4)	
3	19 (24.4)	26 (24.3)		17 (24.6)	18 (26.1)	
4	56 (71.8)	80 (74.8)		49 (71.0)	50 (72.5)	
Clinical N stage *n* (%)			0.404			0.619
0	1 (1.3)	5 (4.7)		1 (1.4)	3 (4.3)	
1-3	77 (98.7)	102 (95.3)		68 (98.6)	66 (95.7)	
Clinical TNM stage *n* (%)			0.966			1.000
II	4 (5.1)	6 (5.6)		4 (5.8)	4 (5.8)	
III	73 (93.6)	100 (93.5)		64 (92.8)	65 (94.2)	
IVA	1 (1.3)	1 (0.9)		1 (1.4)	0 (0)	
Tumor size (cm)	5.2 ± 3.1	6.0 ± 3.4	0.126	5.4 ± 3.3	5.4 ± 3.1	0.953
Nerve invasion *n* (%)			1.000			0.394
Yes	43 (55.1)	59 (55.1)		38 (55.1)	33 (47.8)	
No	35 (44.9)	48 (44.9)		31 (44.9)	36 (52.2)	
Lymph-vascular invasion *n* (%)			0.410			1.000
Yes	43 (55.1)	59 (55.1)		23 (33.3)	23 (33.3)	
No	35 (44.9)	48 (44.9)		46 (66.7)	46 (66.7)	
Differentiation *n* (%)			0.360			0.780
Well	4 (5.1)	3 (2.8)		1 (1.4)	2 (2.9)	
Moderate	24 (30.8)	25 (23.4)		22 (31.9)	19 (27.5)	
Poor	50 (64.1)	79 (73.8)		46 (66.7)	48 (69.6)	
Pathological T stage *n* (%)			0.254			0.282
ypT0-1	8 (10.3)	8 (7.5)		6 (8.7)	7 (10.1)	

ypT2	11 (14.1)	7 (6.5)		11 (15.9)	4 (5.8)	
ypT3	23 (29.5)	31 (29.0)		17 (24.6)	21 (30.4)	
ypT4a/4b	36 (46.2)	61 (57.0)		35 (50.7)	37 (53.6)	
Pathological N stage *n* (%)			0.168			0.443
ypN0	26 (33.3)	26 (24.3)		23 (33.3)	18 (26.1)	
ypN1	12 (15.4)	23 (21.5)		11 (15.9)	18 (26.1)	
ypN2	16 (20.5)	14 (13.1)		14 (20.3)	11 (15.9)	
ypN3	24 (30.8)	44 (41.1)		21 (30.4)	22 (31.9)	
Distant metastasis *n* (%)			0.531			1.000
Yes	6 (7.7)	5 (4.7)		4 (5.8)	3 (4.3)	
No	72 (92.3)	102 (95.3)		65 (94.2)	66 (95.7)	
Pathological TNM stage *n* (%)			0.576			0.781
IIA	12 (15.4)	13 (12.1)		10 (14.5)	9 (13.0)	
IIB	17 (55.1)	20 (64.5)		17 (24.6)	13 (18.8)	
III	43 (55.1)	69 (64.5)		38 (55.1)	44 (63.8)	
IV	6 (7.7)	5 (4.7)		4 (5.8)	3 (4.3)	
Adjuvant chemotherapy *n* (%)			0.824			0.848
Yes	58 (74.4)	78 (72.9)		50 (72.5)	51 (73.9)	
No	20 (25.6)	29 (27.1)		19 (27.5)	18 (26.1)	

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; BMI: Body mass index; ASA: Anesthesiologists physical status classification.

Student's *t*-test, depending on the distribution of the parameters. We used the Kaplan-Meier survival analysis and the log-rank test to estimate OS and compare the survival distributions. Multivariate Cox regression analysis was used to adjust for confounding factors and non-balanced between-group variables in univariate analysis. Statistical significance was set at $P < 0.05$. All analyses were performed using SPSS statistical software (version 26.0; IBM Corp., Armonk, New York, United States).

RESULTS

Clinicopathologic characteristics of patients

Table 1 shows the clinical data, clinical staging, tumor status, and pathological staging of the patients before PSM ($n = 185$) and after PSM ($n = 138$). Before PSM, there was a significant difference between the two groups in terms of BMI ($P = 0.028$). Compared to the OTG group, the average age was younger ($P = 0.120$), tumor size was smaller ($P = 0.126$), and occurrence of yN stage ($P = 0.168$) was lower in the LTG group; however, the differences were not statistically significant. Distant metastasis was confirmed by operative pathological examination in all 11 patients (LTG: 6, OTG: 5). In the LTG and OTG groups, distant metastasis occurred in the peritoneum of five and four patients and in the liver of one and one patients, respectively. After PSM, all clinicopathological characteristics were comparable between the LTG and OTG groups.

NAT and response

There was no significant difference in the type of NAT between the two groups neither before nor after PSM. A total of 17 patients received NCRT, and the remaining received NAC. For NAC regimens, there was no significant difference between the groups with respect to the use of platinum-based doublets or epirubicin/taxane-based triplets, although the former was more common. The mean cycles of the groups after PSM were not statistically significantly different (3.3 *vs* 3.6, $P = 0.300$). There was no significant difference between the two groups in terms of clinical response and TRG scores before and after PSM (Table 2).

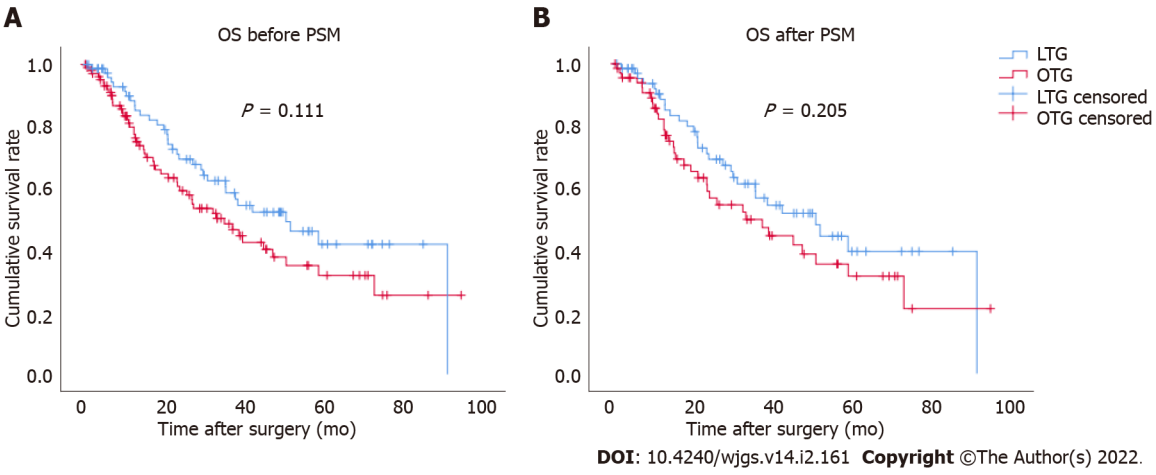
Intraoperative and recovery outcomes

In total, 4 patients in the OTG group and none in the LTG group underwent combined resection. Before and after PSM, the LTG group showed significant differences in the following characteristics:

Table 2 Neoadjuvant therapy and response before and after propensity score matching

Variable	All patients		*P* value	Matched patients		*P* value
	LTG (*n* = 78)	OTG (*n* = 107)		LTG (*n* = 69)	OTG (*n* = 69)	
Type *n* (%)			0.345			0.784
NAC	69 (88.5)	99 (92.5)		61 (88.4)	62 (89.9)	
NCRT	9 (11.5)	8 (7.5)		8 (11.6)	7 (10.1)	
NAC regimens *n* (%)			0.491			0.659
Platinum-based doublets	41 (59.4)	64 (64.6)		36 (59.0)	39 (62.9)	
Epirubicin/taxane-based triplets	28 (40.6)	35 (35.4)		25 (41.0)	23 (37.1)	
Cycles	3.3 ± 1.3	3.8 ± 1.8	0.086	3.3 ± 1.3	3.6 ± 1.6	0.300
Clinical response *n* (%)			0.939			0.859
PR	50 (64.1)	68 (63.6)		44 (63.8)	45 (65.2)	
SD	28 (35.9)	39 (36.4)		25 (36.2)	24 (34.8)	
Mandard TRG score *n* (%)			0.316			0.654
1	26 (33.3)	52 (48.6)		22 (31.9)	29 (42.0)	
2	4 (5.1)	4 (3.7)		4 (5.8)	2 (2.9)	
3	30 (38.5)	34 (31.8)		26 (37.7)	25 (36.2)	
4	5 (6.4)	5 (4.7)		5 (7.2)	5 (7.2)	
5	13 (16.7)	12 (11.2)		12 (17.4)	8 (11.6)	

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; NAC: Neoadjuvant chemotherapy; NCRT: Neoadjuvant chemoradiotherapy; PR: Partial response; SD: Stable disease; TRG: Tumor regression grading.



DOI: 10.4240/wjgs.v14.i2.161

Figure 1 Comparison of cumulative survival rates between laparoscopic total gastrectomy and open total gastrectomy. A: Before propensity score matching (PSM); B: After PSM. There was no statistically significant difference in overall survival between the two groups before (*P* = 0.111) and after PSM (*P* = 0.205). LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; OS: Overall survival; PSM: Propensity score matching.

Postoperative hospital days (11.5 ± 7.1 *vs* 16.0 ± 12.8 d, *P* = 0.012), time to removal of gastric tube (5.1 ± 2.0 *vs* 6.8 ± 5.2, *P* = 0.013), and length of incision (10.4 ± 4.6 *vs* 21.9 ± 3.8, *P* < 0.001). Although the difference was not statistically significant, we found that blood loss during surgery in the LTG group was less than that in the OTG group (200.6 ± 162.0 *vs* 237.1 ± 194.9, *P* = 0.116). The R0 resection rates of the LTG and OTG groups were 95.7% and 97.1%, respectively, and the numbers of dissected lymph nodes were 37.3 ± 14.2 and 35.5 ± 15.9, respectively, which were not significantly different (Table 3).

Postoperative complications

The overall postoperative complication rates of the LTG and OTG groups were 19.2% and 29.9%,

Table 3 Description of intraoperative and recovery features before and after propensity score matching

Variable	All patients		*P* value	Matched patients		*P* value
	LTG (*n* = 78)	OTG (*n* = 107)		LTG (*n* = 69)	OTG (*n* = 69)	
Operation time (min)	207.6 ± 49.3	205.2 ± 52.1	0.744	204.0 ± 45.8	207.1 ± 53.1	0.713
Blood loss (mL)	197.2 ± 162.4	228.1 ± 193.4	0.252	200.6 ± 162.0	237.1 ± 194.9	0.116
Combined resection *n* (%)			0.139			0.245
Yes	0 (0)	4 (3.7)		0 (0)	3 (4.3)	
No	78 (100)	107 (96.3)		69 (100)	66 (95.7)	
Resection *n* (%)			0.651			1.000
R0	75 (96.2)	105 (98.1)		66 (95.7)	67 (97.1)	
R1/R2	3 (3.8)	2 (1.9)		3 (4.3)	2 (2.9)	
Blood transfusion *n* (%)			0.608			0.507
Yes	13 (16.7)	21 (80.4)		11 (15.9)	14 (20.3)	
No	65 (83.3)	86 (19.6)		58 (84.1)	55 (79.7)	
Length of incision (cm)	10.29 ± 4.4	21.6 ± 3.8	< 0.001	10.4 ± 4.6	21.9 ± 3.8	< 0.001
Postoperative hospital stay (d)	11.6 ± 7.0	15.1 ± 10.9	0.015	11.5 ± 7.1	16.0 ± 12.8	0.012
Dissected lymph nodes	37.7 ± 14.5	37.8 ± 17.6	0.950	37.3 ± 14.2	35.5 ± 15.9	0.465
Time to ambulation (d)	3.0 ± 1.2	3.4 ± 2.4	0.130	3.0 ± 1.3	3.4 ± 2.3	0.229
Time to first flatus (d)	4.8 ± 1.7	5.2 ± 2.3	0.235	4.9 ± 1.7	5.1 ± 1.8	0.381
Time to first liquid intake (d)	9.2 ± 5.6	10.1 ± 7.8	0.404	9.1 ± 5.6	10.7 ± 8.7	0.201
Time to removal of gastric tube (d)	5.0 ± 2.0	6.5 ± 5.0	0.008	5.1 ± 2.0	6.8 ± 5.2	0.013
Time to removal of all drainage tubes	9.7 ± 10.1	11.1 ± 11.1	0.391	9.7 ± 10.5	10.9 ± 10.3	0.488

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy.

respectively, before PSM, and 20.3% and 29.0%, respectively, after PSM. The overall postoperative complications had no significant difference between the two groups before and after PSM. The most common surgical complications after LTG include abdominal infection, anastomotic leakage and wound infection. For OTG, the most common surgical complications include wound infection, anastomotic leakage, abdominal infection, and gastroparesis. Notably, 8 patients in the OTG group developed medical complications, including pulmonary infection, arterial catheter-related infection, and renal failure, whereas none in the LTG group did. There were no significant differences in terms of minor complications (Grades I-II according to the Clavien-Dindo classification) and severe complications (Grade III-V) between the two groups before and after PSM (Table 4). None of the patients in either group died within the first 30 d after surgery.

Long-term oncological outcomes

The Kaplan-Meier survival curve for OS between the LTG and OTG groups was plotted (Figure 1). The median follow-up period was 45 mo (range, 3-94 mo). There were no significant differences between the two groups before (P = 0.111) and after PSM (P = 0.205). After PSM, the calculated 5-year cumulative survival rates of the LTG and OTG groups were 39.4% and 31.4%, respectively.

To identify prognostic factors, univariate and multivariate Cox regression analyses were performed after PSM (Table 5). In the univariate analysis, ypT (P = 0.002), ypN (P = 0.004), metastasis (P = 0.103), nerve invasion (P = 0.064), lymph-vascular invasion (P = 0.005), Mandard TRG scores (P = 0.007), type of NAT (P = 0.083), and R0 (P = 0.109) were closely associated with OS. These variables were entered into the multivariate analysis and revealed that ypT0–3 (P = 0.014) and ypN0 (P = 0.010) were independently associated with OS (Figure 2).

DISCUSSION

Recently, LTG has been widely performed in many high-volume hospitals and has gradually expanded

Table 4 Postoperative complications before and after propensity score matching

Variable	All patients		*P* value	Matched patients		*P* value
	LTG (*n* = 78)	OTG (*n* = 107)		LTG (*n* = 69)	OTG (*n* = 69)	
Complications, *n* (%)						
Overall			0.100			0.236
Yes	15 (19.2)	32 (29.9)		14 (20.3)	20 (29.0)	
No	63 (80.8)	75 (70.1)		55 (79.7)	49 (71.0)	
Surgical complications						
Pancreatic fistula	0 (0)	1 (0.9)	1.000	0 (0)	1 (1.4)	1.000
Abdominal bleeding	1 (1.3)	0 (0)	0.422	1 (1.4)	0 (0)	1.000
Anastomotic leakage	5 (6.4)	6 (5.6)	1.000	4 (5.8)	3 (4.3)	1.000
Wound infection	4 (5.1)	5 (4.7)	1.000	4 (5.8)	4 (5.8)	1.000
Lymphorrhagia	1 (1.3)	0 (0)	0.422	1 (1.4)	0 (0)	1.000
Intestinal obstruction	0 (0)	2 (1.9)	0.510	0 (0)	1 (1.4)	1.000
Abdominal infection	5 (6.4)	9 (8.4)	0.611	5 (7.2)	2 (2.9)	0.441
Duodenal fistula	0 (0)	1 (0.9)	1.000	0 (0)	0 (0)	NA
Gastroparesis	0 (0)	3 (2.8)	0.264	0 (0)	3 (4.3)	0.245
Medical complications						
Pulmonary infection	0 (0)	6 (5.6%)	0.04	0	5 (7.2)	0.058
Arterial catheter-related infection	0 (0)	1 (0.9)	1.000	0 (0)	1 (1.4)	1.000
Renal failure	0 (0)	1 (0.9)	1.000	0 (0)	1 (1.4)	1.000
Clavien-Dindo classification *n* (%)			0.331			1.000
Grade I-II	12 (80.0)	20 (64.5)		11 (78.6)	14 (73.7)	
Grade III-V	3 (20.0)	11 (35.5)		3 (21.4)	5 (26.3)	

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy.

the indications for surgery from EGC to AGC[19,20]. However, only one study to date has confirmed the non-inferiority of LTG compared to OTG after NAC in short-term outcomes[12]. To the best of our knowledge, our study is the first to report the long- and short-term outcomes of LTG. Moreover, we found that LTG offered significant advantages in terms of shorter postoperative hospital days and earlier gastric tube removal and had similar postoperative complication rates and OS to those of OTG for patients with GC treated with NAT.

Although NAT is regarded as a key step in the comprehensive treatment of GC, the difference in NAC regimens between Western and Eastern Asian countries should be considered. Three or four-drug NAC regimens have been proved effective in AGC[2,21-24]; however, NAC clinical trials based on two-drug regimens have been exten-sively undertaken in Eastern Asian countries, including JCOG 0210[25], JCOG 0405[26], JCOG 0501[27] in Japan, the NEO-CLASSIC study[28] and the RESOLVE trial (NCT01534546) in China. The optimal NAC regimen for treating AGC remains controversial worldwide, and the differences between Eastern and Western treatment regimens in GC cannot be neglected[29]. In our study, over 60% of all patients received platinum-based doublets, and the overall response rate was more than 60%. Over 80% of all cases were TRG 1-3, which was proved to be an independent prognostic factor[30].

Previous studies have confirmed the oncological and surgical safety of LDG after NAC. Studies by Li *et al*[11] demonstrated that compared to open surgery, LDG has an advantage in postoperative rehabilitation and complications. A number of meta-analyses and retrospective studies have shown that although there is no significant difference between LTG and OTG in the number of lymph node dissections and the rate of radical surgery, LTG has a lower amount of intraoperative bleeding, lower rate of postoperative complications, and faster postoperative rehabilitation[9,10,31-33]. However, none of these studies specifically focused on the influence of NAT on TG. In our study, we found that in addition to the advantage in incision length, the LTG group had a faster postoperative recovery than that of the OTG group after NAT, which was mainly reflected in the postoperative hospital stay.

Table 5 Univariate and multivariate analysis of overall survival after propensity score matching

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	95%CI	*P* value	Hazard ratio	95%CI	*P* value
Age (yr): < 60 *vs* ≥ 60	0.806	0.491-1.323	0.393			
Sex: Female *vs* Male	1.244	0.711-2.177	0.444			
ASA: 1-2 *vs* 3	0.978	0.355-2.696	0.965			
Surgery: LTG *vs* OTG	0.729	0.446-1.192	0.207			
BMI: < 28 *vs* ≥ 28	1.608	0.504-5.133	0.422			
Differentiation: Well/moderate *vs* Poor	0.713	0.416-1.224	0.220			
ypT stage: T0-3 *vs* T4	0.446	0.267-0.746	0.002	0.520	0.308-0.877	0.014
ypN stage: N0 *vs* N1-3	0.401	0.217-0.741	0.004	0.431	0.227-0.821	0.010
Metastasis: M0 *vs* M1	0.425	0.152-1.188	0.103	0.529	0.185-1.510	0.234
Nerve invasion: Yes *vs* No	1.601	0.973-2.635	0.064	0.930	0.531-1.628	0.799
Lymph-vascular invasion: Yes *vs* No	2.046	1.236-3.388	0.005	1.155	0.623-2.140	0.647
Mandard TRG: ≤ 3 *vs* > 3	0.510	0.312-0.833	0.007	0.666	0.390-1.136	0.136
Postoperative complication: Yes *vs* No	0.635	0.338-1.193	0.158			
Type of NAT: NAC *vs* NCRT	2.248	0.900-5.619	0.083	1.647	0.619-4.382	0.317
Resection: R0 *vs* R1/R2	0.385	0.120-1.237	0.109	0.357	0.110-1.154	0.085

LTG: Laparoscopic total gastrectomy; OTG: Open total gastrectomy; CI: Confidence interval; ASA: American Society of Anesthesiologist; BMI: Body mass index; TRG: Tumor regression grading; NAT: Neoadjuvant therapy; NAC: Neoadjuvant chemotherapy; NCRT: Neoadjuvant chemoradiotherapy.

Compared to a previous study[19], the mean postoperative hospital stay in the LTG group (11.5 d) was slightly longer, which was possibly attributed to the NAT. The number of dissected lymph nodes can be considered an indicator to evaluate the quality of gastrectomy, and is positively correlated with the prognosis of GC[34-36]. The number of dissected lymph nodes between the LTG and OTG groups was not significantly different, and the mean number in LTG (37.3 ± 14.2) was similar to that observed in a previous study[37].

Whether NAT will negatively influence the incidence of postoperative morbidities is of great concern to oncologists and surgeons. A few prospective studies have indicated that NAT does not significantly increase postoperative morbidity in patients with GC[2,22,38]. In the present study, morbidity rates were in accordance with those observed in previous studies, which ranged from 9.6% to 23.8% in LTG, and from 15.6% to 68% in OTG[10,39-41]. To fully elucidate the influence of NAT, large-sample multicenter studies are needed. As for the specific complications, we noticed that both groups had comparable numbers of cases of anastomotic leakage. Moreover, pulmonary infection occurred in 6 patients in the OTG group and none in the LTG group, which was in accordance with a previous study [10]. This rather intriguing finding might be a result of minimally invasive techniques which avoid unnecessary trauma while detaching the cardia region[42].

Whether LTG can achieve the same oncologic outcomes as those of OTG is still debatable. Although LTG is minimally invasive and offers quicker rehabilitation, it also allows a limited visual field and poses challenges to prognosis. Current guidelines only recommend attempting LTG with caution[15, 43]. Several retrospective studies showed that there is no significant difference between LTG and OTG in oncological results[44]; however, none of these studies focused on the prognosis of patients treated with NAT. In our study, we found a comparable OS between the LTG and OTG groups, which showed that LTG is non-inferior to OTG after NAT in long-term oncologic outcomes. By using a univariate and multivariate Cox regression analysis, we further found that pathological T stage and N stage were independent risk factors for OS and that the type of TG did not influence the prognosis. With the development of the concept of comprehensive treatment for GC, patients are expected to have a better prognosis.

The major limitation of our study is that it was a single retrospective study. To reduce sample bias and balance the baseline, PSM was performed, which decreased the sample size. In our study, we excluded the missing data instead of multiple imputation, which may bring less statistical power and bias. Therefore, further high-volume, prospective, and multi-center clinical trials are required to

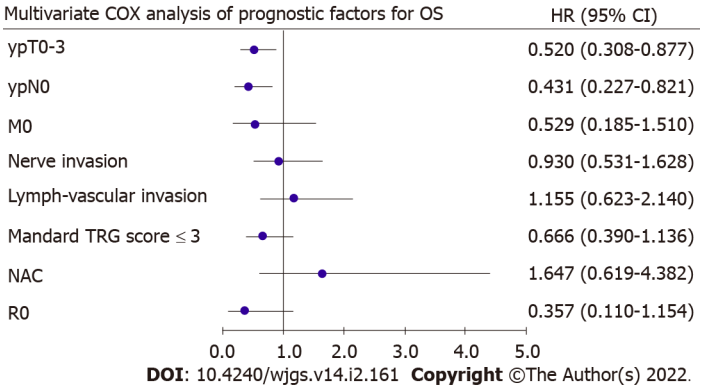


Figure 2 Forest graph of multivariate COX analysis of prognostic factors for overall survival. Pathological T stage and N stage were found as independent risk factors for overall survival. OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; TRG: Tumor regression grading; NAC: Neoadjuvant chemotherapy.

evaluate the surgical and oncological outcomes of LTG after NAT.

CONCLUSION

In conclusion, LTG is considered advantageous in the postoperative rehabilitation of AGC patients treated with NAT and can achieve similar long-term outcomes compared to those of OTG.

ARTICLE HIGHLIGHTS

Research background

Laparoscopic total gastrectomy (LTG) has been widely used these days. Its surgical and oncological outcomes following neoadjuvant therapy (NAT) is still unkown.

Research motivation

To compare the long- and short-term outcomes between LTG and open TG (OTG) following NAT.

Research objectives

Advanced gastric cancer (GC) patients who underwent TG following NAT.

Research methods

Patients were divided into two groups: LTG and OTG. Propensity score matching analysis was performed to minimize possible bias.

Research results

LTG had advantages in short-term outcomes, such as shorter length of hospital stay (P = 0.012), and the oncological outcomes were close to OTG. Overall survival (OS) outcomes were comparable between the two groups. Pathological T and N stages were independent risk factors for OS.

Research conclusions

LTG can be a safe and effective method for advanced GC patients following NAT.

Research perspectives

Further high-volume, prospective, and multi-center clinical trials are required to evaluate the surgical and oncological outcomes of LTG.

FOOTNOTES

Author contributions: Hu HT contributed to the design of the study, collected data and drafted the manuscript; Ma FH and Xiong JP performed the data analyses and revised the manuscript; Li Y, Jin P and Liu H helped perform the analysis with constructive discussions; Ma S and Kang WZ contributed to manuscript preparation data for the work;

Tian YT conceived the work that led to the submission and approved the final version; and all authors issued final approval for the version to be submitted.

Supported by National Natural Science Foundation of China, No. 81772642.

Institutional review board statement: This study was approved by the Ethics Committee of the Cancer Hospital of the Chinese Academy of Medical Sciences (No.14-067/857).

Informed consent statement: This study obtained informed consent exemptions approved by the Ethics Committee of the Cancer Hospital of the Chinese Academy of Medical Sciences.

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

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Hai-Tao Hu 0000-0003-0585-6070; Fu-Hai Ma 0000-0003-2437-6881; Jian-Ping Xiong 0000-0001-6593-6377; Yang Li 0000-0002-4549-1087; Peng Jin 0000-0001-8179-6191; Hao Liu 0000-0001-5809-6824; Shuai Ma 0000-0003-1738-6651; Wen-Zhe Kang 0000-0001-9965-8109; Yan-Tao Tian 0000-0001-6479-7547.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2022 February 27; 14(2): 174-184

DOI: 10.4240/wjgs.v14.i2.174

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Impact of parenchyma-preserving surgical methods on treating patients with solid pseudopapillary neoplasms: A retrospective study with a large sample size

Yu-Qiong Li, Shu-Bo Pan, Shu-Shu Yan, Zhen-Dong Jin, Hao-Jie Huang, Li-Qi Sun

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

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

P-Reviewer: Ashihara N, Isaji S

Received: October 7, 2021
Peer-review started: October 7, 2021
First decision: December 4, 2021
Revised: December 9, 2021
Accepted: January 25, 2022
Article in press: January 25, 2022
Published online: February 27, 2022

Yu-Qiong Li, Shu-Bo Pan, Zhen-Dong Jin, Hao-Jie Huang, Li-Qi Sun, Department of Gastroenterology, Changhai Hospital, Shanghai 200433, China

Shu-Bo Pan, Department of Gastroenterology, Suzhou Science and Technology Town Hospital, Suzhou 215000, Jiangsu Province, China

Shu-Shu Yan, Department of Anesthesiology, Changhai Hospital, Shanghai 200433, China

Li-Qi Sun, Department of Gastroenterology, 72nd Group Army Hospital, Huzhou University, Huzhou 313000, Zhejiang Province, China

Corresponding author: Li-Qi Sun, MD, Assistant Professor, Department of Gastroenterology, Changhai Hospital, No. 168 Changhai Road, Yangpu District, Shanghai 200433, China. zjhzslqsmmu@qq.com

Abstract

BACKGROUND

Solid pseudopapillary neoplasm of the pancreas (SPN) is a rare neoplasm that mainly affects young women.

AIM

To evaluate the impact of parenchyma-preserving surgical methods (PPMs, including enucleation and central pancreatectomy) in the treatment of SPN patients.

METHODS

From 2013 to 2019, patients who underwent pancreatectomy for SPNs were retrospectively reviewed. The baseline characteristics, intraoperative index, pathological outcomes, short-term complications and long-term follow-up data were compared between the PPM group and the conventional method (CM) group.

RESULTS

In total, 166 patients were included in this study. Of them, 33 patients (19.9%) underwent PPM. Most of the tumors (104/166, 62.7%) were found accidentally. Comparing the parameters between groups, the hospital stay d (12.35 *vs* 13.5 d, *P*

= 0.49), total expense (44213 *vs* 54084 yuan, P = 0.21), operation duration (135 *vs* 120 min, P = 0.71), and intraoperative bleeding volume (200 *vs* 100 mL, P = 0.49) did not differ between groups. Regarding pathological outcomes, tumor size (45 *vs* 32 mm, P = 0.07), Ki67 index (P = 0.53), peripheral tissue invasion (11.3% *vs* 9.1%, P = 0.43) and positive margin status (7.5% *vs* 6%, P = 0.28) also did not differ between groups. Moreover, PPM did not increase the risk of severe postoperative pancreatic fistula (3.8% *vs* 3.0%, P = 0.85) or tumor recurrence (3.0% *vs* 6.0%, P = 0.39). However, the number of patients who had exocrine insufficiency during follow-up was significantly lower in the PPM group (21.8% *vs* 3%, P = 0.024). CM was identified as an independent risk factor for pancreatic exocrine insufficiency (odds ratio = 8.195, 95% confident interval: 1.067-62.93).

CONCLUSION

PPM for SPN appears to be feasible and safe for preserving the exocrine function of the pancreas.

Key Words: Solid pseudopapillary neoplasm; Surgical resection; Parenchyma-preserving method; Pancreatic exocrine insufficiency

Core Tip: Solid pseudopapillary neoplasm of the pancreas (SPN) is a rare neoplasm that mainly affects young women. The prognosis of SPN is excellent following complete surgical resection. However, the conventional surgical method is associated with a high rate of morbidity and a high rate of long-term endocrine/exocrine insufficiency due to the loss of pancreatic parenchyma. Our study identified a parenchyma-preserving surgical method (PPM) for SPN that appears to be feasible and safe for preserving the exocrine function of the pancreas. The risk of PPM did not increase the risk of severe postoperative pancreatic fistula or tumor recurrence. PPM should be taken into consideration in SPN patients with a long life expectancy.

Citation: Li YQ, Pan SB, Yan SS, Jin ZD, Huang HJ, Sun LQ. Impact of parenchyma-preserving surgical methods on treating patients with solid pseudopapillary neoplasms: A retrospective study with a large sample size. *World J Gastrointest Surg* 2022; 14(2): 174-184

URL: https://www.wjgnet.com/1948-9366/full/v14/i2/174.htm

DOI: https://dx.doi.org/10.4240/wjgs.v14.i2.174

INTRODUCTION

Solid pseudopapillary neoplasms (SPNs) are exceptionally rare. These tumors account for approximately 0.9%-2.7% of all exocrine pancreatic neoplasms[1,2] and approximately 3%-5% of pancreatic cystic neoplasms[3,4]. Although these tumors occur among a wide age range from children to elderly individuals, the mean age at presentation is 28.5 years[5]. SPNs occur predominantly in young women with a female-male ratio of 9.8:1[1]. Moreover, SPN is reported to be the most common pancreatic neoplasm among young females under the age of 40 years[6]. However, the tumor is an epithelial-originated low-grade malignant neoplasm with the possibility of locally advanced, recurrent, and metastatic disease[7]. Complete surgical resection is recommended as the main treatment for SPN[6].

Conventional pancreatic resection (pancreatoduodenectomy (PD), total pancreatectomy (TP) and distal pancreatectomy (DP)) is associated with a high rate of morbidity (40%-50%)[8] and a high rate of long-term endocrine/exocrine insufficiency (8-20% and 20-50%, respectively)[9] due to the loss of pancreatic parenchyma. However, the prognosis of SPN is excellent with a cure rate of approximately 98% following surgical resection[10]. Thus, approximately half of young SPN patients will suffer from lifelong complications.

In addition to drug therapies, improved surgical approaches are one way to address the issue.

The parenchyma preserving surgical methods (*i.e.*, enucleation or central pancreatectomy (CP)) have been explicitly advocated to be used for some benign or low-grade pancreatic neoplasms[11-13]. Parenchyma-sparing surgical approaches decrease the risk of developing endocrine and exocrine dysfunction postoperatively[14], and the subsequent quality of life is significantly higher than that of patients who underwent conventional resection. Recently, a parenchyma-sparing surgical approach was reported to be used for SPN in some retrospective studies with small-sized samples. The increased rate of postoperative pancreatic fistula (POPF) may hinder the utilization of this approach[15,16]. Moreover, although rare, SPN is associated with local recurrence or metastasis after surgery. The long-term

outcomes after the parenchyma-sparing surgical approach for SPN remain unclear.

Due to the unsolved issues noted above, we conducted this retrospective study with a large sample size. Our study aimed to compare the intraoperative, short-term, and long-term outcomes in SPN patients who underwent a parenchyma-sparing surgical approach *vs* conventional pancreatic resection with detailed surgical-related parameters included.

MATERIALS AND METHODS

Study population

We conducted a retrospective study at Changhai Hospital affiliated with Navy/Second Medical University and Suzhou Science and Technology Town Hospital, Suzhou. The Institutional Review Board of both hospitals approved the study. Patients who underwent surgical resection from January 2013 to December 2018 for pathologically identified SPN were included in our study. The following inclusion criteria were applied: (1) Patients pathologically diagnosed with SPN; (2) Patients whose full electronic medical records could be obtained; and (3) Patients whose follow-up data could be obtained. Exclusion criteria included: (1) Specimens obtained from reresections; (2) Concomitant other neoplasms on final pathology (*e.g.*, neuroendocrine tumor, cholangiocarcinoma); and (3) Patients with unavailable pathological and follow-up data. The selection procedure of the study participants is presented in Figure 1.

The decision on surgical treatment was made by our multidisciplinary hepatopancreatobiliary team. If the lesion was diagnosed as a pancreatic cystic lesion by imaging modality, the surgery indications would follow the International Consensus Guideline[17]. If diagnosed as invasive cancer, the surgery indications would follow the European Society for Medical Oncology guidelines[18]. The choices of surgical procedures depended on the location, degree, extent of diseases and experiences of the surgeons. The surgeons who were qualified to perform pancreatic surgery in our centers had at least 15 years of operation experience with an average of 100 operations per year.

Perioperative management

The operations for SPN were performed by experienced surgeons in our center. We performed

Roux-Y loop in patients with a suspicious injury of the main pancreatic duct or a wide wounded area (diameter > 3 cm) of the pancreatic parenchyma.

After surgery, amylase analysis from drainage fluid was performed to determine whether POPF existed. Routine blood examinations were performed to determine whether infection existed and whether antibiotics were used. Plain CT was performed to determine whether pancreatic fluid collection existed and to detect the causes of infection. If any clinically significant complications occurred, further treatments were needed.

The definition of included parameters

The parameters included in our study were composed of five parts: baseline characteristics, intraoperative index, pathological outcomes, short-term complications and long-term follow-up data.

The baseline characteristics included age, gender, symptoms, hospital stay d and total expense.

The intraoperative indices included surgical method, surgical approaches, operation duration, and intraoperative bleeding volume. The surgical methods included conventional methods (PD, TP and DP) and parenchyma-preserving methods (enucleation and CP). Surgical approaches include opening, laparoscopy and robotics. Intraoperative bleeding was noted as dark red liquid aspirated during the operation.

The pathological outcomes were tumor location, tumor size, Ki-67 index, margin status, and peripheral tissue invasion status. The tumor might be located in multiple head/body/tail sites of the pancreas. If multiple tumors occurred, only the size of the largest tumor was measured. The Ki-67 index of the tumor was divided into 3 grades: < 3%, 3%-20% and > 20%[19]. Positive margin status was defined as a tumor component ≤ 5 mm from the incisal margin. Peripheral tissue invasion status consisted of perineural invasion, vascular invasion, cancerization of ducts, lymphatic metastasis, common bile duct invasion, peripancreatic fat invasion, spleen invasion and duodenum invasion.

Short-term complications were adverse events that occurred within 30 d, including POPF, delayed gastric emptying, postoperative hemorrhage, postoperative infection and bile leakage. The grade of complications was based on the Claviene-Dindo score. Complications that scored Claviene Dindo grade III or greater were considered severe complications.

The long-term follow-up data included exocrine insufficiency, endocrine insufficiency, alimentary stricture due to the surgery and whether recurrence occurred. Follow-up data were obtained from telephone interviews and/or outpatient interviews in this study. Endocrine insufficiency was defined as a fasting plasma glucose level > 7.0 mmol/L and/or the need for diet modification, oral medication, or insulin use to control blood. Exocrine insufficiency was defined as symptoms (steatorrhea or weight loss) resolving after pancreatic enzyme supplementation[15]. Recurrence was defined as a local or a metastatic tumor confirmed by radiology or histology during postoperative follow-up.

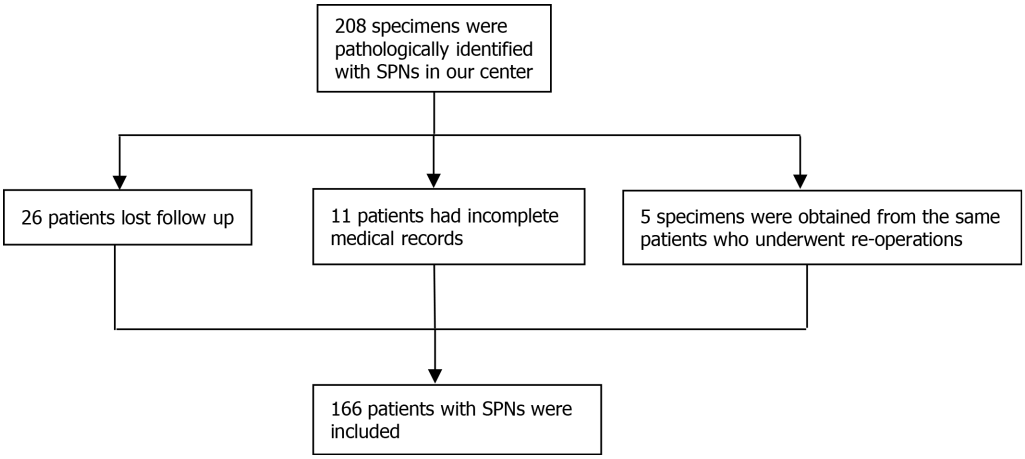

Figure 1 Patient selection flowchart. SPN: Solid pseudopapillary neoplasm.

Statistical analysis

The patients were divided into 2 groups according to their surgical methods: conventional method (CM) group and parenchyma preserving method (PPM) group. The parameters were compared between the 2 groups. Quantitative parameters were expressed as the medians and range. Continuous data are reported as the mean ± standard deviation (SD) or as the median and range. Categorical parameters were compared between the CM group and the PPM group using χ^2 or Fisher's exact test. The nonparametric Mann–Whitney U test was used to compare differences between groups for quantitative parameters. A Kaplan–Meier survival curve was established to estimate the recurrence-free survival (RFS) rate. Statistical analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, United States). All tests were two-sided, and a P value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

From January 2013 to June 2019, 166 patients who underwent pancreatic surgery were included in our study. All tumors were confirmed as SPNs according to the final histology examination. Among them, 33 patients (19.9%) underwent PPM, and 133 patients (80.1%) underwent CM. In the PPM group, 13 patients underwent enucleation and 20 patients underwent CP. The median age of the overall study cohort was 32.5 years (range, 10-68 years), and most of the participants were females (129/166, 77.7%). The majority of the tumors were incidentally found (104/166,62.7%). In the patients who were symptomatic, abdominal pain was the most common symptom (53/62.85.5%) followed by abdominal distension (6/62, 9.7%), nausea and vomiting (2/62, 3.2%) and jaundice (1/62, 1.6%). The mean hospital stay was 12.53 d (SD ± 6.87 d), and no difference was noted between the CM group and the PPM group (t = 0.692, P = 0.49). The mean total expense during hospitalization was 46248 Chinese yuan (SD ± 25414 yuan), and no difference was noted between the 2 groups (t = 1.284, P = 0.21). The baseline characteristics of the study cohort are shown in Table 1.

Intraoperative index

In the CM group, 44 patients (33.1%) underwent PD, 81 patients (60.9%) underwent DP, and 8 patients (6.0%) underwent TP. Moreover, 108 (81.2%) patients underwent laparotomy, 11 (8.3%) underwent laparoscopic surgery, and 14 (10.5%) underwent robot surgery. The average operation experiences for surgeons were 19 years. The median operation duration was 135 min (27-381 min), and the median intraoperative bleeding volume was 200 mL (0-2000 mL).

In the PPM group, 11 patients (33.3%) underwent enucleation, and 22 patients (66.6%) underwent CP. Moreover, 31 (93.3%) patients underwent laparotomy, 2 (6.7%) underwent laparoscopic surgery, and no patient underwent robot surgery. The average operation experiences for surgeons were 19.5 years. The median operation duration was 120 min (50-301 min), and the median intraoperative bleeding volume was 100 mL (50-600 mL).

Comparing the intraoperative index between the 2 groups, the surgical approach was not different between the 2 groups (χ^2 = 4.15, P = 0.126), and the surgeon experiences, operation duration and intraoperative bleeding volume were also not different between the 2 groups (t = 0.85, 0.385 and 0.695, P = 0.71 and 0.488) (Table 2).

Table 1 Characteristics of the study cohort stratified by surgical method

	Total (*n* = 166)	CM (*n* = 133)	PPM (*n* = 33)	*P* value
Female, *n* (%)	129 (77.7)	106 (77.4)	23 (69.7)	0.16
Age (yr), median (range)	32.5 (10-68)	32.0 (10-68)	33 (13-51)	0.85
Symptoms, *n* (%)				
Accidentally found	104 (62.7)	83 (62.4)	21 (63.6)	0.84
Abdominal pain	53 (31.9)	43 (32.3)	10 (30.3)	0.75
Abdominal distension	6 (3.6)	5 (3.8)	1 (3.0)	0.8
Nausea and vomiting	2 (1.2)	1 (0.8)	1 (3.0)	0.49
Jaundice	1 (0.6)	1 (0.8)	0 (0)	0.32
Hospital stay (d) ± SD	12.53 ± 6.87	12.35 ± 6.21	13.3 ± 9.14	0.49
Total expense (yuan) ± SD	46248 ± 25414	44213 ± 20487	54084 ± 38551	0.21

SD: Standard deviation; CM: Conventional method; PPM: Parenchyma preserving method.

Pathological outcomes

Regarding the pathological specimens, the median size of tumors in the CM group was 45 mm (3.5-140 mm), with 46 tumors (34.6%) located in the pancreatic head, 15 tumors (11.3%) located in the pancreatic body, 17 tumors (12.8%) located in the pancreatic tail and 55 tumors (41.4%) involving multiple sites. Grade I Ki67 was identified in 115 tumors (86.5%), Grade II Ki67 was identified in 16 tumors (12.0%) and Grade III Ki67 was identified in 2 tumors (1.5%). Positive margin status was observed in 10 patients (7.5%), and peripheral tissue invasion was observed in 15 patients (11.3%).

The median size of tumors in the PPM group was 32 mm (17-140 mm) with 23 tumors (69.7%) located in pancreatic head, 4 tumors (12.1%) located in pancreatic body, no tumors (0%) located in pancreatic tail and 6 tumors (18.2%) involving multiple sites. Grade I Ki67 was identified in 26 tumors (78.8%), Grade II Ki67 was identified in 6 tumors (18.2%), and Grade III Ki67 was identified in 1 tumor (3%). Positive margin status was observed in 2 patients (6%), and peripheral tissue invasion was observed in 3 patients (9.1%).

Comparing the pathological outcomes between the 2 groups, the tumor size was not significantly larger in the CM group compared with the PMM group with a borderline *P* value (t = 1.832, P = 0.069). Tumors involved in multiple sites were more common in the CM group (χ^2 = 15.9, P = 0.001). The Ki67 grade was not different between the 2 groups (χ^2 = 1.182, P = 0.53), indicating that the degree of malignancy was not different between the groups. The positive margin status and peripheral tissue invasion were also not different between the 2 groups (χ^2 = 1.155 and 0.832, P = 0.283 and 0.425) (Table 2).

Short-term complications

In the CM group, perioperative complications occurred in 27 patients (20.3%). POPF grade II or greater developed in 5 patients (5/27, 18.5%), delayed gastric emptying developed in 4 patients (4/27, 14.8%), abdominal infection developed in 12 patients (12/27, 44.4%), bleeding developed in 3 patients (3/27, 11.1%), pancreatitis developed in 2 patients (2/27, 7.4%), and 1 patient (1/27, 3.7%) developed both delayed gastric emptying and abdominal infection. Seven complications (7/27, 25.9%) scored Claviene Dindo grade III or above and were considered severe complications (Table 3).

In the PPM group, perioperative complications occurred in 6 patients (18.2%). One patient (1/6, 16.7%) developed severe POPF, 1 patient developed abdominal infection (1/6, 16.7%), 2 patients developed bleeding (2/6, 33.3%) and 2 patients (2/6, 33.3%) developed severe POPF, abdominal infection and bleeding. Two complications (2/6, 33.3%) scored Claviene Dindo grade III or greater and were considered severe complications.

The overall perioperative complication rate and severe complication rate were comparable between the groups (χ^2 = 0.075 and 0.00, P = 0.79 and 1.0). For each complications, the difference of incidences were not observed, either.

Long-term follow-up data

The final follow-up date was June 30, 2021. The median follow-up period was 49 mo (24-102 mo). Only 1 patient died due to perioperative complications, and the 3-, 5-, and 10-year overall survival (OS) rates were estimated to be 99.4%, 99.4%, and 99.4%, respectively. In total, 6 patients (3.6%) developed recurrence in the overall study cohort with 4 patients (3 Local recurrence and 1 Liver metastasis) in the CM group and 2 patients (1 Local recurrence and 1 Liver metastasis) in the PPM group. The median

Table 2 Intraoperative index and pathological outcomes of the study cohort stratified by surgical method

	Total (*n* = 166)	CM (*n* = 133)	PPM (*n* = 33)	*P* value
Intraoperative index				
Surgical approach, *n* (%)				0.126
laparotomy	139 (80.1)	108 (81.2)	31 (93.9)	
laparoscopic	13 (7.8)	11 (8.3)	2 (6.1)	
Robot	14 (8.4)	14 (10.5)	0 (0)	
Surgeon experiences, mean (yr)	19.3	19.0	19.5	0.85
Operation duration, median (range)	135 (27-381)	135 (27-381)	120 (50-301)	0.71
Intraoperative bleeding volume, median (± SD)	200 (0-2000)	200 (0-2000)	100 (50-600)	0.488
Pathological outcomes				
Median size (mm), median (range)	40 (3.5-140)	45 (3.5-140)	32 (17-140)	0.069
Tumor location, *n* (%)				0.001[a]
Head	69 (41.6)	46 (34.6)	23 (69.7)	
Body	19 (11.4)	15 (11.3)	4 (12.1)	
Tail	17 (10.2)	17 (12.8)	0 (0)	
Multiple sites	64 (38.6)	55 (41.4)	6 (18.2)	
Ki67 index, *n* (%)				0.53[a]
I	141 (84.9)	115 (86.5)	26 (78.8)	
II	22 (13.3)	16 (12.0)	6 (18.2)	
III	3 (1.8)	2 (1.5)	1 (3.0)	
Peripheral tissue invasion, *n* (%)	18 (10.8)	15 (11.3)	3 (9.1)	0.426
Positive margin status, *n* (%)	12 (7.2)	10 (7.5)	2 (6.0)	0.283

[a]The *P* value was based on overall comparison between 2 groups. SD: Standard deviation; CM: Conventional method; PPM: Parenchyma preserving method.

time to recurrence was 48 mo (range 6–84 mo). The 3-, 5-, and 10-year RFS rates were estimated at 98.8%, 97.0%, and 96.4% for the study cohort, respectively. The 3-, 5-, and 10-year RFS rates for the CM group were 99.2%, 97.7%, and 96.9%, respectively. The 3-, 5-, and 10-year RFS rates for the PPM group were 97.0%, 93.9%, and 93.9%, respectively. Kaplan–Meier analysis and the log-rank test showed that the recurrence rate was not significantly different between the groups ($P = 0.39$) (Figure 2).

The long-term complications were also evaluated. In the CM group, alimentary strictures were observed in 5 patients (3.0%), 3 of whom were treated by digestive tract bypass operations, and the other two were treated by duodenal stents. Six patients (4.5%) experienced pancreatic endocrine insufficiency, and 29 patients (21.8%) experienced exocrine insufficiency. In the PPM group, alimentary strictures were observed in 1 patient (3.0%) and treated by bypass operation. One patient (3.0%) experienced both pancreatic exocrine insufficiency and endocrine insufficiency. No other pancreatic exocrine insufficiency or endocrine insufficiency was observed in the PPM group. The incidence rates of alimentary stricture and pancreatic endocrine insufficiency were comparable between groups (both $\chi^2 = 0.00$ and both $P = 1.0$). However, the incidence of pancreatic exocrine insufficiency was significantly higher in the CM group compared with the PPM group ($\chi^2 = 5.09$, $P = 0.024$). Based on multivariate analysis, CM was identified as an independent risk factor for pancreatic exocrine insufficiency (odds ratio = 8.195, 95% confidence interval (CI): 1.067-62.93) after adjusting for age and sex.

DISCUSSION

Since it was first described in 1959, SPN has been widely acknowledged as a low-grade malignant neoplasm with a favorable prognosis after complete resection. If completely resected, the OS rate reached greater than 95% in previous studies[1,5]. Even in aggressive SPNs, the 5- and 10-year OS rates reached 71.1% and 65.5%, respectively[20]. In our study, only 1 patient died due to perioperative

Table 3 Short-term and long-term outcomes of the study cohort stratified by surgical method

	Total (*n* = 166)	CM (*n* = 133)	PPM (*n* = 33)	*P* value
Short-term complications				
Overall perioperative complication, *n* (%)	33 (19.9)	27 (20.3)	6 (18.2)	0.79
Severe POPF	6 (3.6)	5 (3.8)	1 (3.0)	0.85
delayed gastric emptying	3 (1.8)	3 (2.3)	0 (0)	0.56
abdominal infection	13 (7.8)	12 (9.0)	1 (3.0)	0.43
Bleeding	5 (3.0)	3 (2.3)	2 (6.0)	0.26
Pancreatitis	2 (1.2)	2 (1.5)	0 (0)	0.49
Multiple complications	4 (2.4)	2 (1.5)	2 (6.0)	0.18
Severe perioperative complication, *n* (%)	9 (5.4)	7 (5.3)	2 (6.0)	1.0
Long-term follow-up data				
Recurrence, *n* (%)	6 (3.6)	4 (3.0)	2 (6.0)	0.39
Local	4 (2.4)	3 (2.3)	1 (3.0)	
Distant	2 (1.2)	1 (0.8)	1 (3.0)	
Alimentary stricture, *n* (%)	6 (3.6)	5 (3.7)	1 (3.0)	1.0
Endocrine insufficiency, *n* (%)	7 (4.2)	6 (4.5)	1 (3.0)	1.0
Exocrine insufficiency, *n* (%)	30 (18.1)	29 (21.8)	1 (3.0)	0.024

CM: Conventional method; PPM: Parenchyma preserving method; POPF: Postoperative pancreatic fistula.

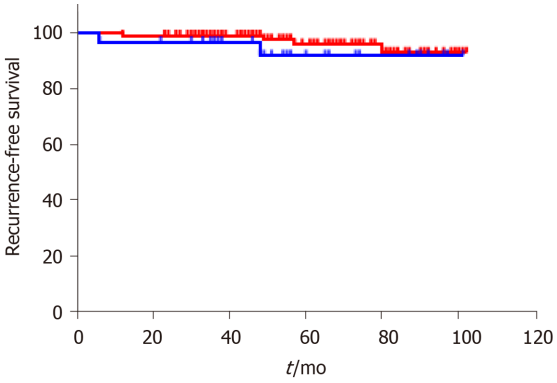

Figure 2 Kaplan–Meier curves of recurrence-free survival. The red line represents the conventional method group, and the blue line represents the parenchyma-preserving method.

complications, and the 10-year OS rate reached greater than 99%, indicating that SPNs have very low malignant potential. However, the tumor often occurs in young females whose life expectancy is very long. In our study, the median age of the included patients was 32.5 years. These consistent data highlight the crucial importance of standardizing treatment procedures to guarantee improved quality of life for this small but challenging subset of patients.

According to the current guidelines, complete resection with a negative surgical margin is suggested to be curative for SPN[21,22]. However, the CM (including PD, TP and DP) might bring a negative surgical margin but be accompanied by wide resection of the pancreatic parenchyma. The loss of pancreatic parenchyma may affect the quality of life of young SPN patients. The proper treatment for SPN should balance curative resection and adverse events related to surgery. PPM is increasingly used for low-grade or benign pancreatic neoplasms[23,24]. However, research regarding PPM of SPN is limited and mainly based on case reports and retrospective studies with small sample sizes[25-27] due to the rarity of the disease. However, the results were inconsistent. Christine *et al*[26] concluded that PPM harbors a significant risk for tumor recurrence. However, only 8 patients who underwent PPM were included in this study. Wang *et al*[26] found that enucleation for SPNs is feasible and safe for preserving exocrine and endocrine function of the gland, and they concluded that enucleation with a

negative surgical margin is adequate with no increased risk of tumor recurrence. In their study, 31 patients who underwent enucleation were included. Yao *et al*[27] concluded that CP was associated with a lower RFS rate than enucleation. However, only 11 patients were included in this case series, and only 5 of them were diagnosed with SPNs.

Due to the inconsistent data, we conducted a large series retrospective study to evaluate the efficacy of PPM in SPNs with various parameters included. Our results identified that PPM for SPNs had comparable intraoperative indices, pathological outcomes, and short-term complications to CM. The OS and RFS rates were also not different between groups. Long-term exocrine insufficiency was significantly lower (P = 0.024) in the PPM group, and CM was an independent risk factor for exocrine insufficiency. The OR was 8.2 (95%CI: 1.067-62.93). To avoid bias, the baseline characteristics were also compared between groups, and no difference was observed. The baseline characteristics of the patients included in our study were similar to those of resected SPNs previously reported[28], which included young age at diagnosis (mean 32.5 years), female predominance (129/166, 77.7%) and relatively large tumors (median 40 mm). Moreover, SPNs were mostly detected by accident (62.7%). However, the pancreatic head appeared to be the most common site of SPNs in our study. Actually, the body and tail were still the most common location sites because almost all of the SPNs located in multiple sites involved the body and tail of the pancreas (62/64, 96.9%).

The main complication after PPM was POPF, especially after enucleation. The POPF rates after enucleation in previously reported studies were 36-67%[29]. However, the POPF rates in our study were low (3%) because only clinically significant POPF was included in our study. Moreover, we tended to perform pancreaticojejunostomy if the main duct was injured during the operation. Therefore, we deemed PPM to be performed with no significantly increased risk of POPF in specialized centers, which was consistent with the results of Hüttner *et al*[16]. Moreover, the overall rate of severe complications (Claviene Dindo grade III and above, 6.0%) after PPM of SPN was consistent with other recent studies involving a large series of PPMs (6-18%)[15,16,29].

The intraoperative index was not different in our study, which was inconsistent with previous studies [26,30]. The reason may be due to the high pancreatic surgery volume in our center. The operation duration (median, 135 min) and intraoperative bleeding volume (median, 200 mL) had already reached a very low level. In the meta-analysis by Chua *et al*[30], the mean operation duration for CM was 325 min, and the mean blood loss was 300 mL. In the study by Wang *et al* [25], the median operation duration was 245 min, and the median blood loss was 380 mL for CM. Therefore, the benefit of PPM during operations was not identified by our study.

Avoiding tumor recurrence is another important endpoint for the management of SPNs. In addition to the efficacy and safety of PPM for SPNs identified in our study, our results also indicated that PPM did not result in an increased rate of tumor recurrence or metastasis compared with CM (P = 0.39). The risk factors associated with recurrence were not analyzed in our study due to the adequate evidence reported before. The main risk factors were large tumor size, lymphovascular invasion, positive margin status, Ki-67 index and synchronous metastasis[31,32]. However, the influence of these factors on the OS rate was not concluded[28,33]. As the overall prognosis is favorable for SPNs, the factors that worsen the OS rate should be clarified in future studies.

Our study had several limitations worth discussing. First, its retrospective nature prevented us from making stronger conclusions. The second limitation was the small sample size. Due to the rarity of SPNs, SPN cases were not common in our center. Moreover, the patients were often transferred from other referral institutions. Their initial medical records and follow-up data were not fully presented in our medical system.

The 2 factors greatly limited the size of the single institution series. More multicenter prospective studies with large sample sizes are necessary to better understand SPNs.

CONCLUSION

This retrospective study identified SPN as a rare pancreatic tumor with excellent prognosis after surgical resection. PPM for SPN appears to be feasible and safe for preserving exocrine function of the gland. The risk of recurrence or metastasis did not increase in patients who underwent PPM. PPM can be taken into consideration in SPN patients whose life expectancy is long.

ARTICLE HIGHLIGHTS

Research background

Conventional surgical methods (CM) including pancreatoduodenectomy (PD), total pancreatectomy (TP) and distal pancreatectomy are standard surgical methods in the treatment of patients with Solid pseudopapillary neoplasm (SPN). CM is associated with a high rate of morbidity. However, the tumor mainly affects young women and the prognosis of the tumor is excellent.

Research motivation
The parenchyma-preserving surgical methods (PPM, including enucleation and central pancreatectomy) are more and more often applied in clinical practice. The role of PPM in treating SPN remains clarified.

Research objectives
To evaluate the impact of PPM in the treatment of SPN patients.

Research methods
Patients who underwent surgical resection for a pathological identified SPN were included in this study. Patients were divided into 2 groups: PPM group and CM group. The baseline characteristics, intraoperative index, pathological outcomes, short-term complications and long-term follow-up data were compared between the 2 groups.

Research results
Patients with SPN had an excellent prognosis. PPM did not increase the surgical risks. After long-term follow-up, we identified PPM did not worsen the prognosis of patients with SPN. However, PPM is suitable for preserving the exocrine function of pancreas in young patients.

Research conclusions
PPM can be taken into consideration in SPN patients whose life expectancy is long.

Research perspectives
More multicenter prospective studies with large sample sizes are necessary to better understand the best surgical method for patients with SPN.

FOOTNOTES

Author contributions: Li YQ, Pan SB and Yan SS contributed equally to this study and are co-first authors, were responsible for study design/planning, study conduct, data analysis and writing and revising the paper; Huang HJ and Sun LQ designed the study and they shared senior authorship; all authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Shanghai Changhai Hospital Ethics Committee (CHEC No. 2019-091).

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

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Yu-Qiong Li 0000-0002-4227-2923; Shu-Bo Pan 0000-0003-1863-5146; Shu-Shu Yan 0000-0002-0846-3718; Zhen-Dong Jin 0000-0002-9358-7351; Hao-Jie Huang 0000-0002-3100-5301; Li-Qi Sun 0000-0002-1151-3931.

S-Editor: Wang LL
L-Editor: A
P-Editor: Wang LL

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World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2022 February 27; 14(2): 185-199

DOI: 10.4240/wjgs.v14.i2.185

ISSN 1948-9366 (online)

SYSTEMATIC REVIEWS

Status of bariatric endoscopy–what does the surgeon need to know? A review

Diogo Turiani Hourneaux de Moura, Anna Carolina Batista Dantas, Igor Braga Ribeiro, Thomas R McCarty, Flávio Roberto Takeda, Marco Aurelio Santo, Sergio Carlos Nahas, Eduardo Guimarães Hourneaux de Moura

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Cabezuelo AS, Zhang H

Received: July 29, 2021
Peer-review started: July 29, 2021
First decision: October 3, 2021
Revised: October 14, 2021
Accepted: February 12, 2022
Article in press: February 12, 2022
Published online: February 27, 2022

Diogo Turiani Hourneaux de Moura, Igor Braga Ribeiro, Eduardo Guimarães Hourneaux de Moura, Departamento de Gastroenterologia, Faculdade de Medicina, Universidade de Sao Paulo, Serviço de Endoscopia Gastrointestinal do Hospital das Clínicas HCFMUSP, Sao Paulo 05403-010, Brazil

Anna Carolina Batista Dantas, Flávio Roberto Takeda, Marco Aurelio Santo, Sergio Carlos Nahas, Departamento de Gastroenterologia, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Unidade de Cirurgia Bariátrica e Metabólica, Disciplina de Cirurgia do Aparelho Digestivo e Coloproctologia, Sao Paulo 05403-010, Brazil

Thomas R McCarty, Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, Boston, MA 021115, United States

Corresponding author: Igor Braga Ribeiro, MD, Doctor, Research Assistant, Research Scientist, Surgeon, Departamento de Gastroenterologia, Faculdade de Medicina, Universidade de Sao Paulo, Serviço de Endoscopia Gastrointestinal do Hospital das Clínicas HCFMUSP, Av. Dr En éas de Carvalho Aguiar, 225, 6o andar, bloco 3, Cerqueira Cesar, Sao Paulo 05403-010, Brazil. igorbraga1@gmail.com

Abstract

BACKGROUND

Obesity is a chronic and multifactorial disease with a variety of potential treatment options available. Currently, there are several multidisciplinary therapeutic options for its management, including conservative, endoscopic, and surgical treatment.

AIM

To clarify indications, technical aspects, and outcomes of bariatric endoscopy.

METHODS

Narrative review of current literature based on electronic databases including MEDLINE (PubMed), Cochrane Library, and SciELO.

RESULTS

Bariatric endoscopy is in constant development and comprises primary and revisional treatment options as well as management of surgical complications. Various devices act upon different mechanisms of action, which may be individualized to each patient. Despite favorable results for the endoscopic treatment of

obesity, prospective randomized studies with long-term follow-up are required to fully validate primary and revisional endoscopic therapies. Regarding the management of bariatric surgery complications, endoscopic therapy may be considered the procedure of choice in a variety of situations. Still, as there is no standardized algorithm, local experience should be considered in decision-making.

CONCLUSION
The treatment of patients with obesity is complex, and a multidisciplinary approach is essential. Bariatric endoscopy has shown impressive results both in the treatment of obesity and its surgical complications, and therefore, must be part of the armamentarium in the fight against this disease.

Key Words: Endoscopy; Gastrointestinal; Surgery; Obesity; Bariatric; Weight regain

Core Tip: Obesity is a chronic and recurrent disease with multiple treatment options available. Currently, there are several multidisciplinary therapeutic options for its management, including conservative, endoscopic, and surgical treatment. This study aims to clarify indications, technical aspects, and results of bariatric endoscopy based upon a detailed literature review and individual authors' experience.

Citation: de Moura DTH, Dantas ACB, Ribeiro IB, McCarty TR, Takeda FR, Santo MA, Nahas SC, de Moura EGH. Status of bariatric endoscopy–what does the surgeon need to know? A review. *World J Gastrointest Surg* 2022; 14(2): 185-199
URL: https://www.wjgnet.com/1948-9366/full/v14/i2/185.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i2.185

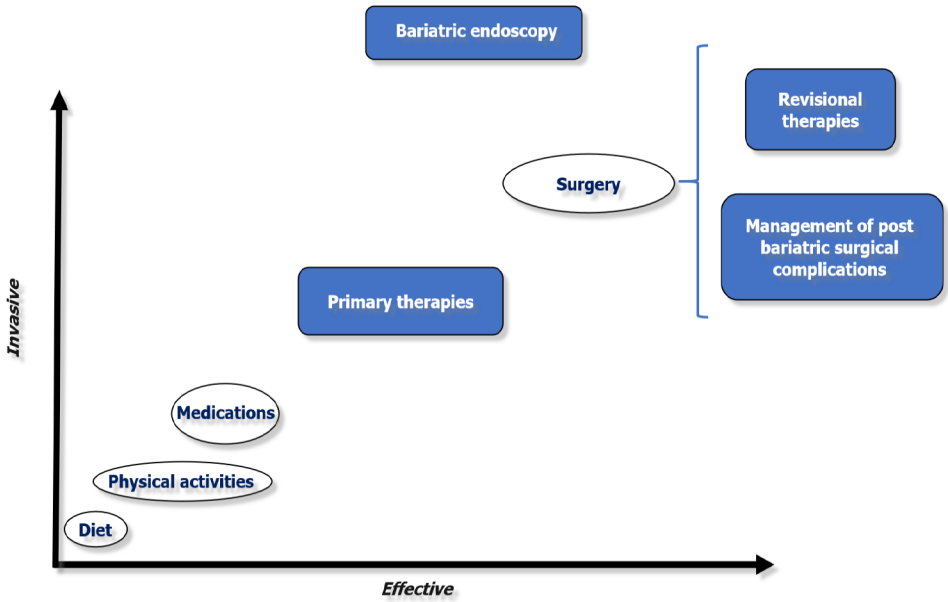
INTRODUCTION

Obesity is defined as a body weight disorder resulting from a long-term positive energy balance and is characterized by excess adiposity. This disorder significantly increases the risk for developing many obesity-associated co-morbidities. It is a chronic, multifactorial disease resulting in a global pandemic associated with several comorbidities–most notably type 2 diabetes and hypertension–and an increase in all-cause mortality. Data from the Centers for Disease Control and Prevention (CDC) illustrates that the prevalence of obesity in the United States is 42.4%[1]. In Latin America, more specifically in Brazil, recent data from the National Health Survey (PNS) released by the Brazilian Institute of Geography and Statistics (IBGE) demonstrates that six out of 10 Brazilian adults are overweight, representing approximately 96 million individuals. If we exclusively consider those with body mass index (BMI) greater than 30 kg/m^2, one in every four Brazilians has obesity[2].

Treatment for obesity includes lifelong lifestyle modifications including behavioral, dietary, and exercise changes, pharmacotherapy, endoscopic therapies, and surgery. The treatment of obesity should be individualized and tailored to specific patients, taking into account several factors such as the degree of obesity (*i.e.*, class of obesity), individual associated comorbid conditions (*i.e.*, health risks), psychobehavioral and metabolic characteristics, as well as proper assessment of previous weight loss strategies. As obesity is a multifactorial disease, treatment must also be multidisciplinary[3].

Although diet, exercise, and pharmacotherapy are the least invasive and most widely utilized methods, it is clear that long-term results are unsatisfactory. Surgery, on the other hand, is proven to be the most effective and durable method for sustained weight loss and control of obesity-associated comorbidities[4]. However, while surgery is highly effective, this strategy is the most invasive option and may be associated with perioperative complications in about 0.5% to 9.6% of patients[5,6]. Additionally, approximately 50% of patients will develop some degree of long-term weight regain, requiring complex clinical management[7].

In this sense, the treatment for obesity and its associated comorbidities have recently expanded into the field of bariatric endoscopy: (1) *via* primary therapies, bridging a gap between less invasive therapies (lifestyle modification and/or pharmacological therapy) and bariatric surgery; (2) By optimizing the treatment of weight regain after bariatric surgery through revision therapies; and (3) Or in the management of postoperative bariatric surgery complications (Figure 1). In this review, we discuss the current state of bariatric endoscopy and highlight currently available treatments, including primary and revisional therapies



DOI: 10.4240/wjgs.v14.i2.185

Figure 1 The role of bariatric endoscopy.

MATERIALS AND METHODS

This is a narrative review including all available literature data obtained through electronic databases including MEDLINE (*via* PUBMED), Cochrane Library, and SciELO. This study was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The search study time period was from inception until January 15, 2022, using the search "bariatric endoscopy" AND "obesity".

RESULTS

Primary therapies

Primary therapies include intragastric balloons (IGBs), endoscopic suturing, and botulinum toxin injection.

IGBs: IGBs are indicated for patients with a BMI > 27 kg/m^2 who have not achieved or maintained weight loss with conservative measures. Other qualifying patients include those with a BMI > 35 kg/m^2 with comorbidities or > 40 kg/m^2 in patients who have contraindications or do not wish to undergo bariatric surgery. Additional indications include patients with BMI > 50 kg/m^2 as a bridge therapy for surgery. Absolute contraindications include active peptic ulcer disease, previous gastric surgery, large hiatal hernia, and patients with underlying eating disorders.

IGB models approved for use in most countries include "traditional" fluid filled (6 mo and one year), adjustable fluid filled (one year), and air filled (6 mo). The mechanism of action of IGBs is not yet fully established; however, it is believed that it is related to three factors: (1) Mechanical restriction, decreasing gastric capacity and leading to an increase in gastric emptying time, resulting in early satiety; (2) Hormonal changes due to direct contact with the gastric fundus, leading to a decrease in ghrelin and an increase in cholecystokinin, altering appetite and gastric emptying; and (3) Neurogenic, *via* central stimulation of the paraventricular nucleus of the solitary tract through vagal stimulation[8].

The IGB is the most widely adopted endoscopic method with proven efficacy and safety[9,10]. In a meta-analysis including only randomized studies evaluating fluid filled IGBs, the average difference in BMI loss was 1.41 kg/m^2 with an absolute weight loss of 3.55 kg between the IGB group *vs* the control group[10]. However, most studies do not support the effectiveness of IGBs in long-term follow-up[11]. Despite being considered a safe method, close monitoring of the patient is essential to avoid serious adverse events (AEs), such as gastrointestinal obstruction, digestive hemorrhage, pancreatitis, gastric necrosis, and perforation[9-12].

Fluid filled IGB ("Traditional"): The "traditional" IGB should be filled with 400 to 750 mL of saline and methylene blue (to alert the patient when their urine appears greenish in case of leak or rupture of the IGB). In addition to the efficacy known in the short-term follow-up, this type of IGB has the advantage of a low rate of AEs. It should be noted; however, that fluid filled IGBs possess a higher rate of early withdrawal since the initial volume cannot be changed and patients may be unable to tolerate the

balloon due to nausea and vomiting, especially within three days after placement[9-11].

Fluid filled adjustable balloon: The adjustable IGB (aIGB) may be filled up to 900 mL of fluid, having the advantage of adjusting the volume of liquid contained in the balloon. This may result in a lower rate of early withdrawal due to patient intolerance and supposedly greater weight loss after adjustment with increasing volume after initial implantation. However, due to the presence of the catheter used for the adjustment, this IGB is associated with a higher rate of ulcerations and abdominal discomfort. In a randomized study comparing the aIGB with lifestyle intervention *vs* lifestyle intervention alone, the aIGB group presented a mean total weight loss (TWL) at 32 wk of 15% compared to 3.3% of the control group. Adjustments to the aIGB occurred among 80% of patients for weight loss plateau or intolerance. Upward volume adjustment facilitated an additional mean of 5.2% TWL. Downward volume adjustment allowed 75% of patients in the aIGB group to complete the full duration of therapy. Intolerance caused early removal of the device in 17% of patients. Severe AEs were observed in 4% of patients[12].

Air balloon: The air IGB is traditionally known for being well tolerated and associated with fewer AEs including nausea and vomiting. However, air IGBs are also associated with less %TWL compared to the fluid filled IGBs, and air filled IGB removal is often challenging as these balloons may more rigid than the other types of IGBs[13,14].

Endoscopic suturing (endoscopic sleeve gastroplasty): Endoscopic sleeve gastroplasty (ESG) aims to restrict gastric volume by performing full-thickness sutures in the gastric body. At this time, there are several suture patterns which have been performed; however, the most commonly utilized pattern is the "U" stitch pattern. This pattern is characterized by suturing initially along the anterior wall towards the greater curvature and the posterior wall, with the turn through the posterior wall along the greater curvature and ending at the anterior wall. Often 6 to 8 sutures are performed in the "U" pattern. With this endoscopic technique, the gastric fundus is not sutured, maintaining a reservoir that contributes to the promotion of early satiety. Although the mechanism of action of ESG is not fully understood, circumferential and longitudinal reduction in the size of the stomach as well as delayed gastric emptying time are believed to promote early satiety[15-18].

ESG has been shown to be highly effective and safe in the management of patients with a BMI classified > 25 kg/m^2 (overweight) and > 30 kg/m^2 (obesity). A recent meta-analysis demonstrated a %TWL of 16.1% and 16.8% and an %EWL of 60% and 73% at 1-year and 18 mo follow-up, respectively [16]. Currently, there are still many unknowns regarding the long-term efficacy of primary endoscopic therapies, especially ESG[15-17]; however, a recent study showed satisfactory results during 5-year follow-up after ESG[18]. ESG has also been shown to be superior to IGB in terms of weight loss and side effect profile, solidifying this treatment strategy as an effective and safe option for individuals who do not quality for surgery or among patients who wish to avoid a traditional surgical approach. In a recent systematic review comparing ESG and IGB strategies, %TWL was superior in the ESG group (%TWL: 15.34% at 6 mo; 17.51% at 12 mo, and 17.85% at 24 mo) compared to the IGB group (%TWL: 12.16% at 6 mo; 10.35% at 12 mo; and 6.89% at 24 mo)[19]. This suggests improved initial weight loss as well as an improved ability to maintain that weight loss. While additional long-term data is needed, these results suggest a promising role for ESG in the management of obesity.

Unlike IGB, which is associated with nausea and vomiting in immediate post-procedure setting, post-ESG patients may experience abdominal pain as a primary symptom. However, like the initial symptoms of IGB, symptoms associated with ESG rapidly improve within three to five days post-procedure[19]. The safety of ESG has also been confirmed in a meta-analysis, demonstrating the rate of severe AEs to be 0.8%, and the rate of total AEs to be 2.3%[16]. Although safe, care during the procedure is essential to minimize complication. Therefore, we recommend use of CO2 for insufflation, general anesthesia with endotracheal intubation, proper patient positioning in the left lateral position, and specialized training to ensure adequate provider knowledge of the device, technique, and understanding of anatomy[15].

Botulinum toxin injection: Botulinum toxin injection of the gastric wall works *via* the inhibition of acetylcholine in the cholinergic neuromuscular endings, promoting delay in gastric emptying, thereby leading to early satiety. However, most randomized studies and meta-analyses have not demonstrated the effectiveness of the method in the treatment of obesity[20].

Revisional therapies

Weight recidivism (more commonly described as weight regain) does not have a standardized definition. The most widely accepted definition is considered regain of 50% of the weight loss with initial bariatric surgery (*i.e.*, increase from the nadir weight) or regain of 20% of the nadir weight associated with the recurrence or development of an obesity-associated comorbidity. Weight regain is a multifactorial condition, including hormonal factors, the balance between expenditure and caloric intake, as well as behavioral, genetic, and anatomical factors[21,22]. While all of these factors are essential to providing complete care and ensuring success after bariatric surgery, bariatric endoscopy seeks to primarily alleviate or treat factors related to anatomical changes after bariatric surgery[21-23].

Among the currently available revisional therapies, endoscopic bariatric treatments include use of argon plasma coagulation (APC) and endoscopic suturing[24,25]. These two treatment modalities are typically used in the management of those who have undergone prior Roux-en-Y Gastric Bypass (RYGB) and aim to achieve reduction of the gastric pouch, gastrojejunal anastomosis (GJA), and in some cases, successful closure of gastrogastric fistulas (GGFs) when present. Furthermore, endoscopic suturing has recently been used to treat patients with weight regain after sleeve gastrectomy (sometimes referred to as a sleeve-in-sleeve procedure).

Reduction of the gastric pouch and gastrojejunal anastomosis after RYGB: APC: APC is performed circumferentially around the edge of the GJA (gastric face-about 1 to 1.5 cm). As a result, scarring and fibrosis of this area occurs, resulting in a reduction in the diameter of the GJA. In some cases, more than one session may be necessary to achieve the goal of reducing the diameter of the GJA to approximately 10 to 12 mm. A recent randomized study demonstrated no superiority of the group that underwent APC + suturing compared APC alone in terms of weight loss or complications between the techniques at one-year follow-up[25].

Endoscopic suturing (transoral outlet reduction): Endoscopic suturing for patients with a history of RYGB is typically undertaken using a transoral outlet reduction (TORe) technique. The reduction in the diameter of the GJA may also be performed using an endoscopic suturing technique–often performed after APC of the GJA since the combination of methods may result in better weight loss results compared to a suturing alone[24]. The APC technique alone is more widely used due to shorter procedure times, decreased need for deep sedation or endotracheal intubation, and cost-savings. However, endoscopic suturing also allows for the possibility of reducing the gastric pouch, which in selected cases may help to promote better weight loss results. Additionally, pursestring suturing of the GJA is likely a superior strategy to APC alone. Despite limited data at this time, TORe appears to be a highly effective and safe procedure[24].

Modified endoscopic submucosal dissection + APC + endoscopic suturing: Another strategy, based upon TORe as described above, is a modified endoscopic submucosal dissection (ESD)-TORe procedure. This treatment involves making a modified submucosal dissection around the circumference of the GJA, to expose the muscular propria. Once this accomplished, traditional APC is performed around the GJA and a pursestring, endoscopic suture pattern is made around the outlet with bites taken through the exposed muscle layer (minimizing the drawbacks of a non-full thickness or superficial bite that may occur with a traditional TORe technique). This technique was recently described and demonstrated encouraging results in a retrospective study, where the association of a modified ESD technique with APC and endoscopic suturing was superior to APC and suturing alone. In this study, both in the 6-mo follow-up (13.4% *vs* 8.5%; $P = 0.045$) and 1 year follow-up (12.1% *vs* 7.5%; $P = 0.036$) demonstrated greater %TWL in the modified ESD-TORe cohort[26]. However, the increase in costs and procedure time, as well as the need of previous experience in submucosal dissection may limit more widespread adoption of this technique. As such, this technique is likely to continue to only be available at highly specialized centers.

Treatment of gastrogastric fistula: Common endoscopic therapies such as APC, clips, and endoscopic suturing are associated with a low clinical success rate in the treatment of GGF. In a study including 29 patients with GGF, despite 100% technical success, clinical success after 1 year was only 17.1%[27]. The use of the cardiac septal defect occluder (CSDO) for the treatment of GGF has also been described. However, more studies are needed to prove the effectiveness and safety profile of this novel approach. In our experience, endoscopic management of GGF may be effective only in GGF smaller than 10 mm.

Reduction of gastric volume after sleeve gastrectomy: After sleeve gastrectomy, the ability to perform endoscopic suturing *via* a modified ESG technique is a promising method in the management of patients with postoperative weight regain. In a multicenter study, this technique demonstrated results similar to primary ESG, with %TWL in one year of 14.2%, 19.3%, 17.5%, and 20.4%, for overweight and patients with obesity class I, II, and III, respectively. Perhaps most importantly, in this study, no AEs were reported[28]. The use of a plication device *via* a USGI platform has also been described with promising results[29].

Complications of revisional therapies: Adverse effects after revisional endoscopic therapies are uncommon, occurring in approximately 3% to 7% of cases. The most common events reported include nausea and vomiting, abdominal discomfort, post-procedure bleeding, and the development of intraluminal strictures[22]. Additionally, a reverse Barrett´s esophagus, characterized as receding of the squamous columnar junction into the gastric pouch among patients with RYGB has also been described [30]. While the mechanism of action is not fully understood, management of these patients is typically conservative and a vast majority of other complications are managed endoscopically[22,24,31].

Management of complications after bariatric surgery

Endoscopic treatment of bariatric surgery complications is considered by many as the gold standard due to its high efficacy and minimally invasive nature with a low rate of AEs. Endoscopic treatment can be used for treating intraluminal bleeding, leaks, fistulas, and stenoses. Despite the fear of anastomotic

and staple line dehiscence during an endoscopic exam in the very early post-operative period, endoscopic techniques are safe and have been well-documented to be effective in the literature[32-35].

Hemorrhage: In patients with early bleeding after bariatric surgery, initial supportive measures such as volume resuscitation, temporary cessation of anticoagulation, and blood transfusion when necessary, should be performed. While highly effective, it should be noted that endoscopic management is only plausible in cases of intraluminal bleeding, especially along gastric suture lines. The main signs of intraluminal hemorrhage include hematemesis, enterorrhagia, or melena. In addition to assistance with diagnosis, endoscopy may provide therapy through a variety of mechanisms–*via* injection, mechanical, thermal, and topical therapies. If endoscopic treatment fails, angiography therapy or emergency surgery may be indicated[34,35]. The proposed algorithm for the management of early bleeding after bariatric surgery is described in Figure 2.

Treatment of postoperative leaks and fistulas: The endoscopic treatment of postoperative leaks and fistulas includes a wide variety of techniques and devices, with therapeutic options that aim to close (glues, clips, and sutures), cover (stents and CSDO), and drain [double-pigtails stents (DPS)], septotomy, and endoscopic vacuum therapy (EVT)[32,35] (Tables 1 and 2). It is imperative to understand that early treatment is the key to success. Additionally, basic surgical principles such as drainage of associated collections (by endoscopic, radiologic, or surgical approaches) and treatment of related factors such as distal strictures as well as removal of foreign bodies (preferably by endoscopic techniques), are essential for the successful treatment of postoperative leaks and fistulas[32,35]. These therapies are described individually below, and a proposed algorithm for the management of leaks and fistulas after bariatric surgery is highlighted in Figure 3.

Endoscopic glue: The use of "glue" such as cyanoacrylate, tissue adhesive, or sealants and the acellular fibrogenic matrix is unpopular in Brazil due to its high associated cost and heterogeneous results in the literature. Additionally, multiple sessions are typically required, further making this a less than ideal strategy for many patients. The best results for endoscopic glue use are described in chronic fistulas, typically smaller than 10 mm, with low drain output (traditionally < 200 mL in 24 h), and when used in conjunction with other therapeutic options (*i.e.*, use with endoscopic suturing for oversewing marginal ulcerations). In a national study, the clinical success of the acellular fibrogenic matrix was 80%; however, this was a combined percentage accounting for a 30% success with the initial session, 55% success with the second treatment, and 15% success for patients requiring a third session[36].

Clips: The use of conventional clips are not indicated for the treatment of surgical leaks or fistulas, as this material does not have adequate tension to approximate tissue in these conditions[32]. However, cap-mounted clips can be effective as these devices approximate transmural defects with more tension than the conventional clips and have been proven to adequate close mucosal defects in longer term studies. In a recent systematic review, the effectiveness of the cap-mounted clip was 72.6% for anastomotic leaks and 55.8% for fistulas. It is important to understand that this device can only be used in fistulous orifices up to 20 mm due to its size, being best situated and utilized for small transmural defects not associated with intracavitary collections[37].

Endoscopic suturing: Endoscopic suturing is another strategy that allows for closure of leaks or fistulas *via* the use of transmural sutures, typically using a running mattress pattern to provide successful closure and reduce the risk or recurrent leak. However, despite the high technical success and safety, the clinical success is less than ideal, especially when adapted to fistula close. In a study including 56 patients with fistula, clinical success after one year was 17.1% for GGFs and 31.4% for other types of fistulas. Thus, due to the high cost of the device and unsatisfactory results, its use has been limited for this indication at this time in most countries[27,32,38].

Stents: Esophageal stents are traditionally used with satisfactory closure rates. However, these conventional (esophageal) stents have been associated with some AEs, ranging from symptoms such as pain, reflux, and nausea, to more severe complications such as perforation and migration[32,39]. In a meta-analysis including only post-bariatric surgery leaks and fistulas, clinical success was 72.8% and migration rate was 28.2%[40]. Due to the high rate of AEs, stents specifically designed for leaks and fistulas after bariatric surgery (*i.e.*, sleeve gastrectomy) have been developed. In a multicenter study, including 37 patients, the clinical success rate with these novel stents was 78.27% (similar to the conventional stents), but the rate of the complications including migrations and perforations remained high. Therefore, based upon the literature and our own experience, these novel stents do not appear to be superior to conventional (esophageal) stents and should be utilized with caution–utilized mostly in centers with expertise in the management of this condition[41]. A recent meta-analysis also did not show any advantage of these customized stents when compared to conventional stents for the treatment of sleeve leaks and fistulas[42].

Cardiac septal defect occluder: The CSDO is a shape-memory, self-expanding double-disc closure device composed of nitinol and polyester, with impressive expansion force[43]. Traditionally used to provide closure for atrial or ventricular septal cardiac defects, off-label use has expanded to the realm of gastroenterology. In a multicenter study evaluating its off-label use in fistulas after bariatric surgery, the rate of clinical success in late and chronic fistulas was 97.1%[44]. At present, the use of CSDO devices is recommended for chronic fistulas due to the presence of an epithelialized tract; however, it is important

Table 1 Endoscopic closure and occlusion techniques for the treatment of leaks and fistulas after bariatric surgery

Endoscopic technique	Indications/advantages	Not indicated/disadvantages	Our experience
Glues (Closure)	(1) Acute/early/late/chronic; (2) Low-debit (< 200 mL/24 h); (3) Diameter < 10 mm; and (4) Safe	(1) Multiple sessions are usually required; (2) High costs; (3) Need for external drainage; and (4) Variable efficacy	(1) Low efficacy; (2) Multiple sessions; (3) High costs; (4) Late/chronic; (5) Combined approach; and (6) Can be used in select cases
Cap-mounted clips (Closure)	(1) Acute/early/late/chronic; (2) Small orifices (< 2 cm); and (3) Safe	(1) > 2 cm orifice; (2) Need for external drainage; and (3) Variable efficacy	(1) Low efficacy; (2) Late/chronic; and (3) Can be used in select cases
Suturing (Closure)	(1) Acute/early/late/chronic; and (2) Safe	(1) Need for external drainage; (2) Challenging-need previous experience with the device; (3) Low efficacy; and (4) High cost	(1) High cost; (2) Very poor long-term clinical success; and (3) We do not recommend it!
Stents (conventional esophageal or specific design for LSG) (over)	(1) Acute and early; (2) Very popular; (3) Efficacy > 70%; (4) Conventional = bariatric stent; (5) Early oral intake; and (6) Lower number of repeat procedures	(1) High rates of migration (up to 30%); (2) Need for external drainage; (3) Symptoms related to the stent; (4) Late and Chronic; and (5) You may have a "surprise" when remove it	(1) High rates of migration; (2) Partially covered > fully-covered (challenging to remove-do not keep it for more than 3 wk!); and (3) Bariatric stents: Similar efficacy, more SAE; Symptoms related to the stent (pre pyloric); More migration (post pyloric); We´re avoiding stents, specially Bariatric Stents
Cardiac septal defect occlude (Cover)	(1) Late and chronic; (2) Efficacy > 95%; and (3) Safe	(1) Off-label use; (2) Acute and Early; (3) High cost; and (4) Need for external drainage	(1) High efficacy in late/chronic fistulas with epithelialized tract without associated collection; (2) Safe; and (3) Good option after failure of conventional techniques

Table 2 Endoscopic drainage techniques for the treatment of leaks and fistulas after bariatric surgery

Endoscopic technique	Indications/advantages	Not indicated/disadvantages	Our experience
Septotomy	(1) You must do it when a septum is identified; (2) Early, late and chronic; (3) High efficacy: 80%-100%; and (4) Safe	It is just performed when a septum is identified!	(1) Very high clinical success rates; and (2) Septum is the cause of most late and chronic leaks/fistulas treated in a center without experience
EVT	(1) Acute, early, late and chronic; (2) High efficacy (> 90%) in leaks with or without associated collection; (3) No need of external drainage; and (4) Superior to stent in upper GI tract	(1) Patient discomfort related to NGT; (2) Usually repeat procedures are needed (sponge); (3) Respiratory/Cutaneous fistula; (4) Longer hospital stay (?); and (5) High costs (?)	(1) Very high clinical success rates; (2) Modified EVT: Easy placement, reduction in procedure time and need for repeat procedures, lower costs and Aes; and (3) Modified trelumina EVT: Drainage and nutrition with one tube through the nares
DPS	(1) Acute, early, late and chronic; (2) High efficacy (> 85%) in leaks/fistulas with associated collection; (3) Easy placement (7fr-gastroscope); (4) No need of external drainage; and (5) Short hospital stay	(1) Longer period for complete healing; (2) Risk of migration and bleeding; (3) No place to accommodate the stent in small collections; and (4) Usually fluoroscopy is needed	(1) Very high clinical success rates; (2) Shorter hospital stay; (3) Faster oral intake (clear liquids); and (4) Better patient acceptance–no symptoms

EVT: Endoscopic vacuum therapy; DPS: Double-pigtails stents; SAE: Severe adverse events; Aes: Adverse events.

to understand that CSDO device should not be used in acute and early leaks or fistulas as these can increase the size of the orifice due to the significant expansion force[43,44].

Endoscopic internal drainage with double pigtail plastic stents: Endoscopic internal drainage with DPS of perigastric collections after bariatric surgery has also been widely employed. This technique has demonstrated satisfactory results associated with less need for prolonged hospital stay and few AEs. The principles of the DPS method are similar to that of transgastric drainage of pancreatic pseudocysts,

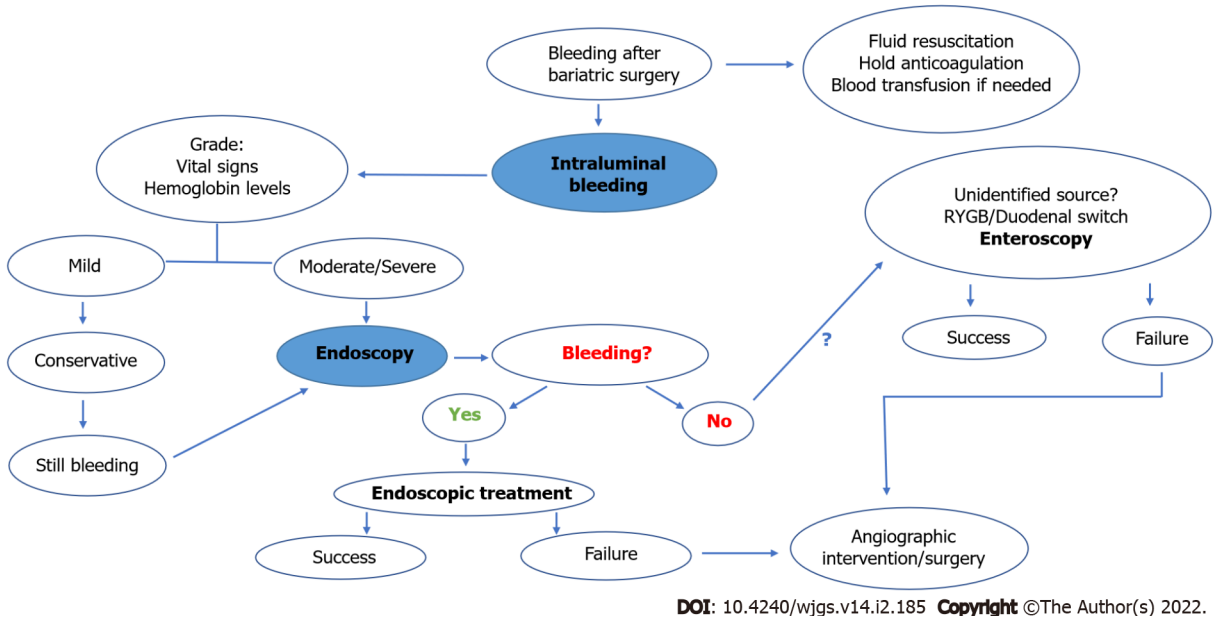


Figure 2 Proposed algorithm for the endoscopic management of bleeding after bariatric surgery.

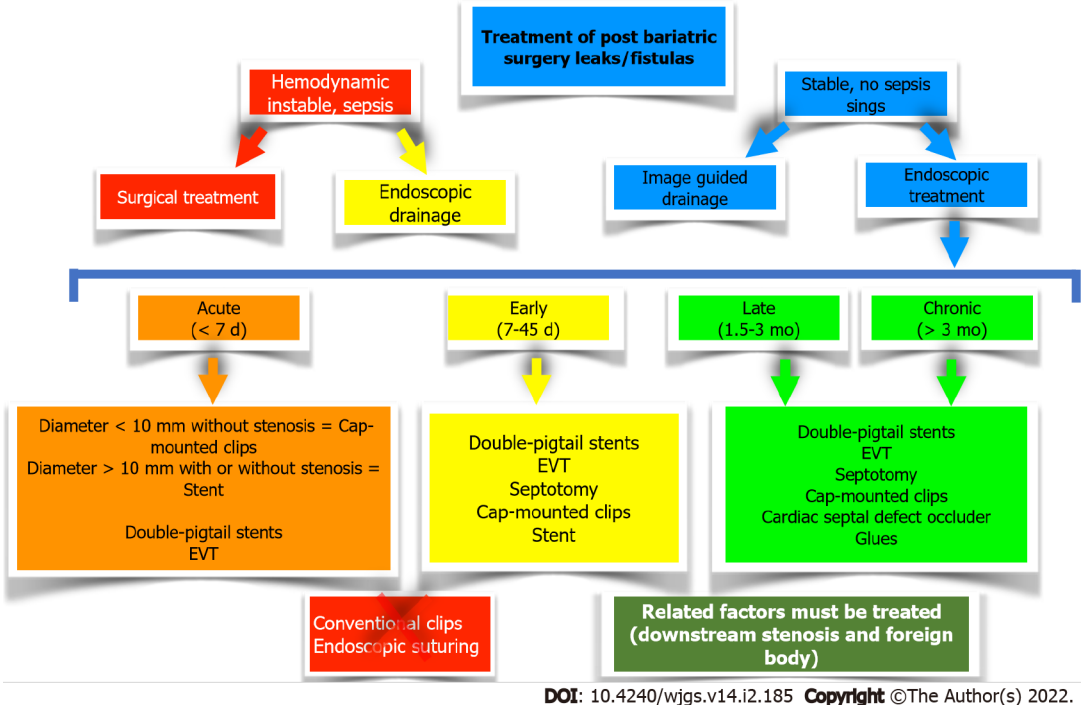


Figure 3 Proposed algorithm for the treatment of leaks and fistulas after bariatric surgery. EVT: Endoscopic vacuum therapy.

providing adequate internal drainage and closure of the tract around the pigtail catheter[45]. The vast majority of current studies have shown an efficacy greater than 85% and endoscopic drainage with DPSs have been associated with a low rate of AEs, including stent migration, bleeding, and perforation[46,47].

Septotomy: Endoscopic septotomy is another technique that is currently used worldwide and has a similar principle to the treatment of Zenker's diverticulum. When most helpful, the septotomy technique is beneficial where the septum must be sectioned to match the pressure of the leak or fistula site within the gastric chamber[48]. The septotomy must be performed up to the depth of the suture line, but not exceed this limit to avoid perforation. In a study involving 27 patients after bariatric surgery, including patients with RYGB, sleeve gastrectomy, and duodenal switch, the clinical success rate after septotomy was 100%, with an average treatment time of 18.11 days and the need for one to six procedures[48]. As such, this septotomy strategy can be highly effective when individual patient factors warrant this technique.

Endoscopic vacuum therapy: EVT is traditional strategy used in Europe, though its use and adoption has more recently spread across the world. The technique is performed by placing a sponge (or gauze covered by surgical adhesive when using a modified technique) on the distal end of a nasogastric tube, which is positioned in the perigastric collection (intracavitary) or in the lumen (intraluminal). Next, this nasogastric tube is connected to a vacuum machine or wall suction with continuous negative pressure (between-125 and -175 mmHg). The EVT system positioning is based on endoscopic findings, and the intracavitary position should be used whenever there is an associated collection. Mechanisms of action include microdeformation and macrodeformation, improvement of perfusion (angiogenesis), control of local edema, and bacterial clearance[49-51].

Several studies have reported high efficacy and low AE rates associated with EVT. Nonetheless, the need for repeated procedures, every seven days for traditional (polyurethane) EVT sponge, and patient discomfort due to continuous and prolonged use of a nasogastric tube are considered limiting factors by some centers. The advantages of the recently described low-cost modified EVT system includes easy placement (through nares), decreased procedure time, longer interval between EVT system exchanges, and decreased AEs[49,50]. In a meta-analysis comparing EVT *vs* stent placement for the treatment of upper gastrointestinal transmural defects, EVT was superior in closing transmural defects, associated with decreased treatment time, and found to have a lower associated mortality rate[52].

Treatment of stenoses: Stenosis after RYGB: Dilation with a hydrostatic balloon for stenoses after RYGB is a well-established method, with clinical success rates up to 100% after one to five treatment sessions. In addition to its effectiveness, balloon dilation is considered safe with low rates of AEs–perforation (4.9% of cases) is the most common[53]. It is important to acknowledge that the presence of an ischemic segment is associated with therapeutic failure and an increased risk of complications[53,54]. In recent years, metallic stents with lumen apposition (lumen apposing metal stents) have been used for cases refractory to dilation–with technical success rates of 100%, high clinical success rates in the short follow-up, and infrequent AEs compared to esophageal stent placement, including decreased migration, pain, recurrent stenosis, and bleeding. However, the need for re-intervention in long-term follow-up continues to be considered high[54]. In addition to the use of self-expandable metallic stents for refractory cases, incisional therapy and corticosteroid injection are less expensive options and may be performed in specialized centers.

Ring slippage after RYGB: Slipping of the ring may cause stenosis of the gastric pouch or even in the jejunal limb, leading to food intolerance. The endoscopic treatment of this condition can be carried out through pneumatic balloon dilation (using an achalasia balloon) or self-expandable stent (plastic or metal) placement. Patients who underwent pneumatic balloon dilation, aiming to stretch or rupture the ring, achieved high rates of clinical success after one to four sessions, usually with no recurrence of symptoms or perioperative complications[55]. Likewise, in a study evaluating the use of self-expandable stents in 41 patients, removal of the ring was possible in all cases. However, it should be noted that 22% of patients developed post-procedure stenosis due to local fibrosis, requiring endoscopic balloon dilation[56]. Despite these complications, reoperation or deaths are extremely rare after these approaches[55,56]. Due to the higher rate of stenosis after using self-expandable stents, we recommend treatment with pneumatic dilation as a first-line strategy whenever possible.

Erosion of the ring after RYGB: Ring erosion after RYGB is traditionally treated by endoscopy due to its ease and minimally invasive nature. Endoscopic removal of the ring is indicated with minimal intraluminal extrusion of 30%. This can be performed through the ring section, either with endoscopic scissors (silastic ring) or with APC [polypropylene (marlex) ring], followed by ring removal using a foreign body forceps or a polypectomy snare[56].

Erosion of the gastric band: Erosion of the gastric band has been noted to less frequently occur due to the more recent shift away from this surgical technique in clinical practice. Endoscopic band cutting is performed by passing a guidewire through the intragastric fragment of the band, followed by cutting using a lithotripter device. Then, with a polypectomy snare, the device is removed. The subcutaneous port must be removed before the endoscopic removal. Technical and clinical success rates are extremely high, with a low rate of AEs, mainly pneumoperitoneum. Most of these cases may be treated conservatively through decompression with an abdominal puncture[57,58]. While less individuals are undergoing the laparoscopic adjustable gastric band procedure, provider knowledge of potential complications and appropriate understanding of endoscopic treatment remain critically important.

Treatment of stenosis after sleeve gastrectomy: Several algorithms for the management of stenosis after sleeve gastrectomy have been described. Our experience is similar to the results of a recent meta-analysis, where conservative management in the first two to three weeks is recommended, with improvement in obstructive symptoms in 68.8% of cases. If patients remain symptomatic and are refractory to conservative management, endoscopic treatment is therefore recommended, with success rates approaching 82%, *via* dilation with a pneumatic balloon (one to three sessions), starting with dilation up to 30 mm, followed by dilation up to 35 mm. Dilatation up to 40 mm can be performed; however, this is not usually recommended due to the high risk of complications. Some groups report success using hydrostatic balloons (up to 20 mm) in selected cases, but it is rarely used in our practice due to limited long-term relief and symptom and stenosis recurrence.

Another endoscopic option is the use of self-expanding metal stents; however, these are indicated mainly for patients that remain refractory to pneumatic dilation. Primary surgical treatment may also be performed, but it is more invasive and results are not superior to endoscopy. In cases refractory to endoscopic therapy, surgical treatment is traditionally indicated, with a 98% success rate[59]. Recently, the endoscopic tunneled stricturotomy technique has been described with promising results in refractory cases, becoming another minimally invasive alternative to surgery[60]. The algorithm proposed by our group is shown in Figure 4.

DISCUSSION

The exponential growth of bariatric surgery in the last decades has evolved inseparably from the advances in the field of endoscopy. In this article, we have reviewed the main therapeutic options of bariatric endoscopy that should be known by general, digestive, and bariatric surgeons. These have been summarized above and divided into three main areas: Primary treatments for obesity, revisional therapies, as well as the management of complications after bariatric surgery.

Among the primary treatments, the IGB is the most widely used, with satisfactory results in the short-term when appropriately indicated. Endoscopic suturing has been utilized with promising results and considerable weight loss; however, the evidence with long-term follow-up remains scarce. When a patient seeks a surgeon in demand for these techniques, we must emphasize that these procedures are not a substitute for bariatric surgery, and we should highlight three aspects: Adequate indication; expectation of realistic results within the BMI profile and associated comorbidities; and safety and quality of the procedure when performed by a specialized endoscopist in an appropriate medical facility. Furthermore, like other treatments for obesity, the support of a specialized multidisciplinary team and regular adherence to follow-up is necessary to ensure an optimal long-term result.

Weight regain has become a challenge due to the cumulative increase in the number of patients undergoing bariatric surgery. Mechanisms for weight regain are complex and again require a multidisciplinary approach–taking into account factors outside of just anatomic changes. In most cases mechanism of weight regain are multifactorial. Therefore, the initial step in treating these patients is a comprehensive assessment of the patient by a multidisciplinary team. For individuals with appropriate indications, endoluminal therapies are safe, reproducible and effective in treating patients with weight regain and as a less invasive therapy then revisional surgery. Therefore, endoscopic bariatric treatment should be utilized as a first line intervention to manage this condition.

When considering surgical complications, the management of postoperative bariatric surgery patients is challenging and, to achieve a positive outcome, again requires a multidisciplinary approach. Didactic knowledge, technical mastery, and good communication between the surgery, endoscopy, and interventional radiology teams remains essential. In this manner, it is also key to have a collaborative hospital structure and environment since minimally invasive treatment by endoscopic therapy may be used as first-line therapy to avoid more invasive procedures in the treatment of acute postoperative complications.

When diagnosing a leak or fistula, endoscopic treatment may be considered an early therapeutic option. As shown in Figure 3 and Table 2, the surgeon may rely upon endoscopic treatment even for severe cases. Endoscopic adjuncts to traditional surgical cases, such as peritonitis and sepsis, may include placement of an enteral feeding tube or, more recently, endoscopic internal drainage therapies such as EVT intraoperatively. Regarding late complications, bariatric endoscopy should be considered a first-line strategy for diagnosis and treatment along with an upper gastrointestinal series. This is essential for assessing patients with recurrent nausea, vomiting, reflux, or regurgitation. Additionally, endoscopy may often be used as an option for the treatment of stenosis and ring/band erosions, avoiding reoperations which include greater complexity and risk, since these are patients with long-standing surgeries, many by open access, and presenting with malnutrition due to recurrent vomiting.

As obesity treatment algorithms evolve, bariatric endoscopy procedures and their devices have been gradually adopted. However, it is important to note that there are still significant limitations due to its high associated costs and even restrictions for authorization and/or importation of these devices.

Despite being a comprehensive review of the literature, this article is not without limitations. As this is a recent topic, most studies are small or uncontrolled series, and more prospective and randomized studies are needed to establish the best therapeutic options for each situation. Also, many of these studies were carried out in large referral centers, with a team and structure dedicated to this patient profile. In this manner, not all the therapeutic options reviewed here can be applied to the reality of all services and hospitals.

CONCLUSION

Obesity and weight regain are multifactorial disorders, and, therefore, multidisciplinary treatment is essential. Bariatric and metabolic endoscopic therapies are in constant development, including devices

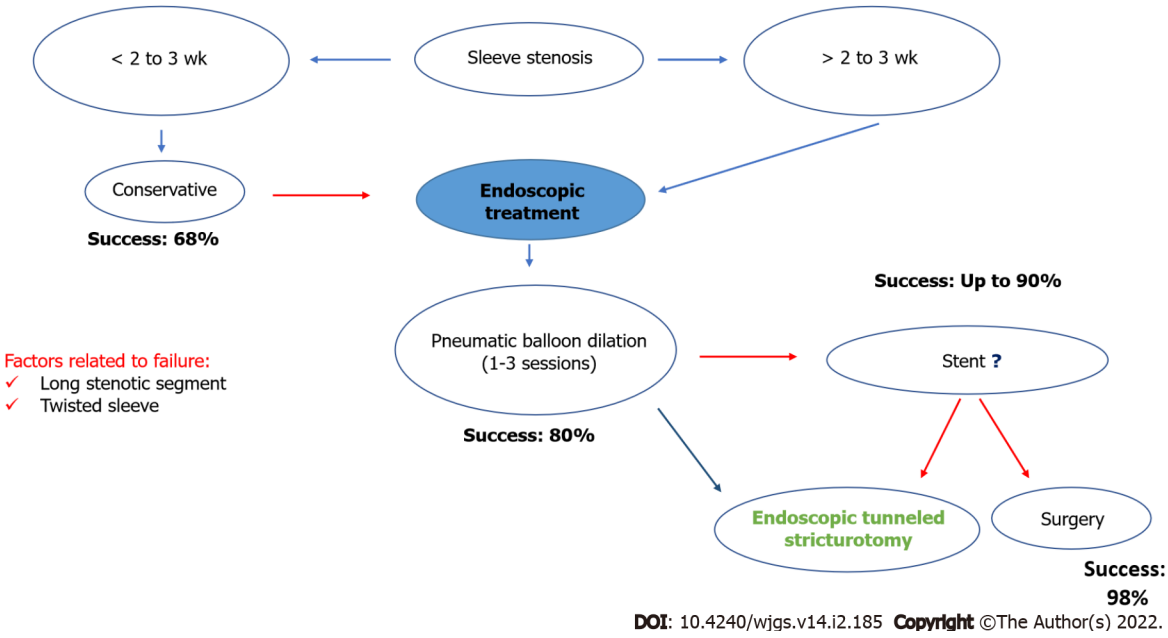


Figure 4 Proposed algorithm for the endoscopic management of stenosis after sleeve gastrectomy.

with a wide variety of mechanisms of action. Available endoscopic approaches have been shown to be effective and safe in the management of obesity and in patients with weight regain. However, as there is no gold standard method for managing these patients, the assessment must be individualized. Despite the favorable results, randomized studies with long-term follow-up are still required for complete validation of primary and revisional endoscopic bariatric therapies.

Regarding the management of complications after bariatric surgery, it is essential to underscore the complexity of patient care, where follow-up with a multidisciplinary team is critical. Endoscopic therapies are associated with high rates of clinical success in the management of intraluminal bleeding conditions, stenoses, leaks and fistulas, especially when performed early in the post-operative period. To date, there is no precise algorithm for the management of these patients, and therefore, local experience and device availability should be considered when choosing a therapy. Institutions without specialized staff should consider referring these patients to a center of excellence.

ARTICLE HIGHLIGHTS

Research background

Obesity is a chronic and recurrent disease resulting in a global pandemic associated with several associated comorbidities. Current treatments include lifestyle modifications including behavioral, dietary, exercise changes, and medications which are associated with less than ideal long-term outcomes. Bridging the gap between these therapies and traditional bariatric surgery is the field of bariatric endoscopy, which seeks to provide less invasive therapies to treat primary obesity, treat weight regain after bariatric surgery, and manage complications of bariatric surgery.

Research motivation

To review the current literature of bariatric endoscopy and highlight the field of to colleagues from other disciplines such as surgeons, endocrinologists, and primary care physicians.

Research objectives

Discuss the current state of bariatric endoscopy, including primary therapies, endoscopic management of weight regain, and the management of complications after bariatric surgery including hemorrhage, stenoses, and leaks and fistulas.

Research methods

Narrative review including available literature data obtained through electronic databases and authors' experience.

Research results

Bariatric endoscopy is in constantly evolving field which comprises primary and revisional treatment as well as the management of surgical complications. While longer-term, randomized studies are still warranted to fully validate primary and revisional endoscopic therapies, the field provides a high effective and safe means to treat patients with obesity and associated comorbid conditions. Regarding endoscopic treatment of post bariatric surgery complications, endoscopic management remains a first-line strategy to avoid the morbidity and mortality associated with repeat surgical operations.

Research conclusions

Bariatric and metabolic endoscopic therapies are in constant development, including devices with a wide variety of mechanisms of action. Available endoscopic approaches have proved to be effective and safe for a variety of obesity associated treatments. In this manuscript, we have highlighted these indications, provided a detailed review of the literature, and summarized our own experience to improve the management and care of patients with obesity.

Research perspectives

The advances in the bariatric endoscopy field have the unique opportunity to improve the quality of life and health outcomes for patients with obesity and associated comorbid conditions. The field as a whole as the ability to bridge the gap between lifestyle modifications and conventional surgery to provide treatment to a wide range of individuals, offering a minimally invasive approach for conditions and complications that previously required surgery.

FOOTNOTES

Author contributions: All authors performed the conception and design of the work; de Moura DTH, Dantas ACB and Ribeiro IB drafted the manuscript; all authors contributed to the critical review of the manuscript for important intellectual contents; McCarty TR, Santo MA, Nahas SC, and de Moura EGH contributed to the manuscript supervision; all authors contributed to the approval of the version to be published, have participated in conceptualizing the research or content of the manuscript, in writing or critically editing the manuscript, and/or in analysis of data presented in the manuscript; Consent to submit has been received from all co-authors.

Conflict-of-interest statement: Dr. Eduardo Guimarães Hourneaux de Moura reports personal fees from Boston Scientific, personal fees from Olympus, outside the submitted work; Dr. Diogo Turiani Hourneaux de Moura reports personal fees from Bariatek, outside the submitted work; The others authors reported no potential conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: Brazil

ORCID number: Diogo Turiani Hourneaux de Moura 0000-0002-7446-0355; Anna Carolina Batista Dantas 0000-0001-9505-6784; Igor Braga Ribeiro 0000-0003-1844-8973; Thomas R McCarty 0000-0003-4517-5261; Flávio Roberto Takeda 0000-0001-7338-922X; Marco Aurelio Santo 0000-0002-7813-6210; Sergio Carlos Nahas 0000-0002-2268-4146; Eduardo Guimarães Hourneaux de Moura 0000-0003-1215-5731.

S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Fan JR

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World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2022 February 27; 14(2): 200-210

DOI: 10.4240/wjgs.v14.i2.200

ISSN 1948-9366 (online)

CASE REPORT

Surgery for Cronkhite-Canada syndrome complicated with intussusception: A case report and review of literature

Jie Dong, Tian-Shi Ma, Jiang-Feng Tu, You-Wei Chen

Specialty type: Gastroenterology and hepatology

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

Peer-review model: Single blind

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

P-Reviewer: Elghali MA

Received: August 18, 2021
Peer-review started: August 18, 2021
First decision: October 2, 2021
Revised: October 15, 2021
Accepted: January 20, 2022
Article in press: January 20, 2022
Published online: February 27, 2022

Jie Dong, Jiang-Feng Tu, You-Wei Chen, Cancer Center, Department of Gastroenterology, Zhejiang Provincial People's Hospital (Affiliated People's Hospital, Hangzhou Medical College), Hangzhou 310014, Zhejiang Province, China

Tian-Shi Ma, Cancer Center, Department of Pathology, Zhejiang Provincial People's Hospital (Affiliated People's Hospital, Hangzhou Medical College), Hangzhou 310014, Zhejiang Province, China

Corresponding author: You-Wei Chen, MSc, Associate Chief Physician, Cancer Center, Department of Gastroenterology, Zhejiang Provincial People's Hospital (Affiliated People's Hospital, Hangzhou Medical College), No. 158 Shangtang Road, Hangzhou 310014, Zhejiang Province, China. cyw@zju.edu.cn

Abstract

BACKGROUND

Cronkhite-Canada syndrome (CCS) is a rare nonhereditary disease with a syndrome of multiple gastrointestinal polyps, skin pigmentation, hair loss, and fingernail/toenail dystrophy. Intussusception is a serious condition with an occurrence rate of 5% in adults, which is mainly caused by intestinal tumors or other intestinal occupations.

CASE SUMMARY

A 57-year-old woman was admitted to our hospital due to abdominal distension and pain for the past year. Her nausea and vomiting symptoms had been aggravated for the past month. Previous transoral enteroscopy results one year prior showed chronic erosive gastritis protuberans, duodenitis, and jejunitis. She had sparse body hair and brown pigmentation on the skin of her hands and bilateral anterior tibias. The nails of both hands were pale and lacked luster, and the fingernail of her ring finger was longitudinally cracked. Gastroscopy showed extensive diffuse polypoid lump changes in the gastric body and antrum, of 0.5-3 cm in size. Colonoscopy showed multiple polypoid mucosal bulges in the terminal ileum and multiple polyps (0.3-5 cm) throughout the colon. The patient was diagnosed with CCS and underwent partial excision of the polyps, but she refused hormone therapy. One month later, the patient complained of nausea and vomiting, accompanied by abdominal pain and inability to pass gas or stool. Contrast-enhanced computed tomography of the abdomen showed gastrointestinal polyposis and ileocecal intussusception. She underwent stomach and bowel surgery.

CONCLUSION
CCS, as a rare disease with poor prognosis, should be treated aggressively. Systematic steroids, immunosuppressive agents, and biological agents were not applied; thus, the patient's symptoms quickly progressed, and intussusception occurred. She had to undergo surgery. Improved compliance may lead to a better prognosis.

Key Words: Cronkhite-Canada syndrome; Intussusception; Treatment; Prognosis; Surgery; Case report

Core Tip: Cronkhite-Canada syndrome (CCS), a syndrome of multiple gastrointestinal polyps, skin pigmentation, hair loss, and fingernail/toenail dystrophy, is a rare nonhereditary disease. We report a case of CCS that quickly progressed, and intussusception occurred, which eventually led to surgery because systematic steroids, immunosuppressive agents, and biological agents were not applied. As a rare disease with poor prognosis, CCS should be treated aggressively. Meanwhile, improved compliance may lead to a better prognosis.

Citation: Dong J, Ma TS, Tu JF, Chen YW. Surgery for Cronkhite-Canada syndrome complicated with intussusception: A case report and review of literature. *World J Gastrointest Surg* 2022; 14(2): 200-210
URL: https://www.wjgnet.com/1948-9366/full/v14/i2/200.htm
DOI: https://dx.doi.org/10.4240/wjgs.v14.i2.200

INTRODUCTION

Cronkhite-Canada syndrome (CCS) is a rare nonhereditary disease with multiple gastrointestinal polyps, skin pigmentation, hair loss, and fingernail/toenail dystrophy. The disease was first reported in 1955[1]. More than 500 confirmed cases have been reported worldwide to date, resulting in an incidence of approximately 1 *per* million[2,3]. Approximately 75% of the existing reports are from Japan, where the incidence is approximately 3.7 *per* million[4].

Intussusception is a common complication in children, while in adults, the incidence of intussusception is only approximately 5% and is mainly caused by occupations, such as tumors[5].

CASE PRESENTATION

Chief complaints

A 57-year-old woman was admitted to our hospital due to abdominal distension and pain for 1 year, which had been aggravated with nausea and vomiting for 1 mo.

History of present illness

The patient experienced abdominal distension and pain accompanied by the absence of exhaust defecation without obvious inducement 1 year prior. She was evaluated in a local hospital before admission to our hospital. Abdominal computed tomography (CT) (July 14, 2019) showed edema and thickening of the duodenal wall, with mild dilation of some parts of the small intestine with effusion. Transoral enteroscopy showed chronic erosive gastritis protuberans, duodenitis, and jejunitis. She was treated by fasting, gastrointestinal decompression, antibiotics, a proton pump inhibitor (PPI), and fluid supplementation, and then she was discharged after relief of abdominal distension and pain and restoration of anal gas evacuation. The patient had cracked fingernails, accompanied by hair loss, weakened sense of taste, and repeated abdominal distension and abdominal pain starting 10 mo prior. One month prior, the patient had nausea and vomiting with aggravated abdominal distension, and diarrhea consisting of yellow-green loose stools. She experienced anorexia and fatigue. In the previous month, her weight loss was approximately 5-6 kg.

History of past illness

The patient was healthy overall except for a 5-year history of hypertension. She had brown pigmentation on the anterior tibia skin of her lower limbs for more than 10 years, and the pigmentation size varied from a coin-sized area when the condition was relieved to an area extending from above the ankle to below the knee when the condition was more severe. The lesion produced itching and

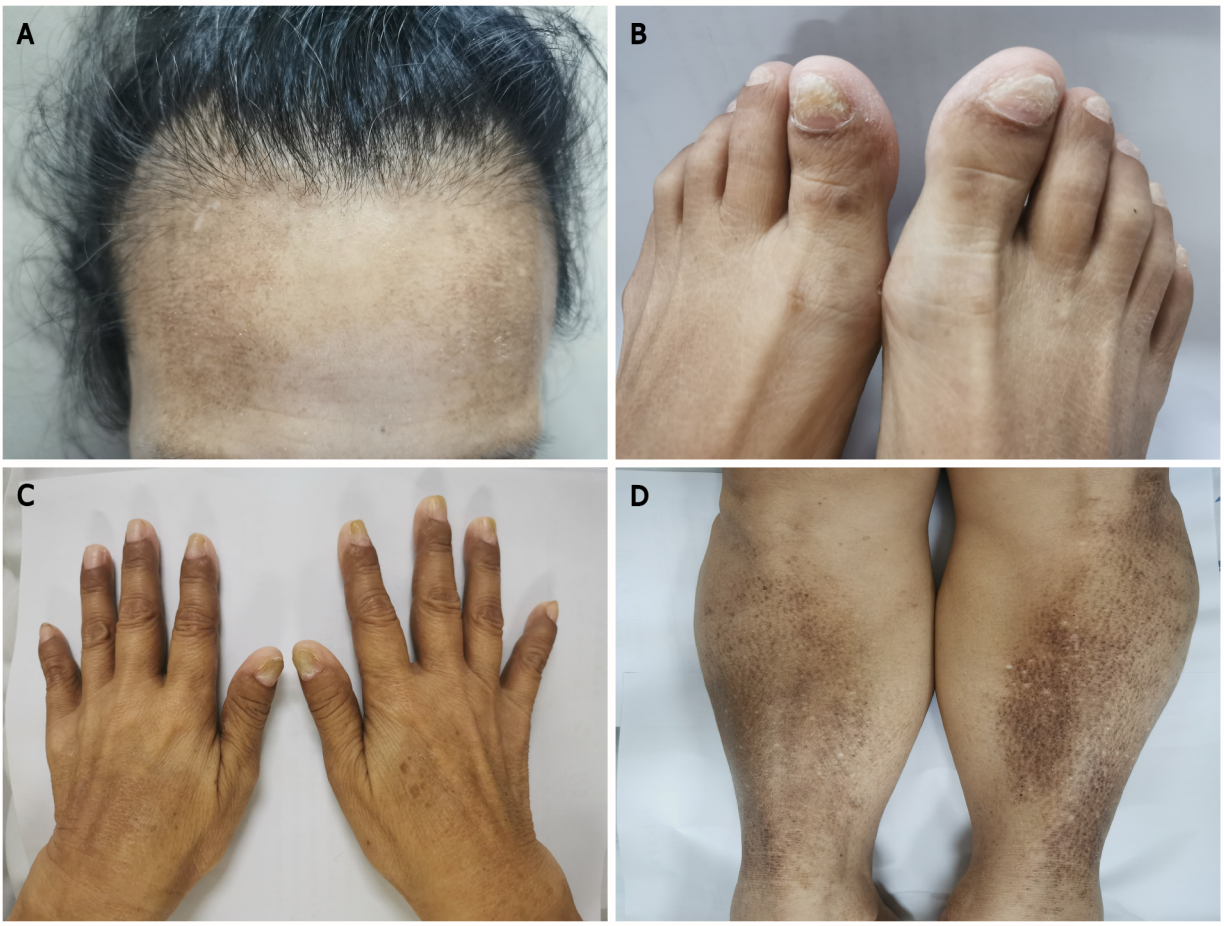

Figure 1 Physical examination. A: Sparse hair; B: Nail dystrophy; C: Skin pigmentation of the hands; D: Skin pigmentation of the legs.

discomfort but did not exhibit redness, swelling, or ulceration. The patient had sparse body hair since childhood and had no history of oral steroids or long-term medication use.

Personal and family history

She had no infectious disease, drug or food allergy, surgery, or blood transfusion. She also had no family history of gastrointestinal polyposis or other genetic diseases.

Physical examination

Height: 157 cm; weight: 36 kg; body mass index: 14.6 kg/m^2; ear temperature: 36.2 °C; breaths: 18/min; pulse: 118 beats/min; blood pressure: 110/78 mmHg. The patient was conscious and alert but less vigorous than usual. Her conjunctivas appeared pale. Brown pigments were visible, particularly on the skin of her hands and bilateral anterior tibia. She had sparse body hair. The nails of both hands were pale and lacked luster, and the fingernail of her ring finger was longitudinally cracked (Figure 1). Small nodules (the size of a red bean) in the right supraclavicular lymph node could be palpated, with clear borders and no adhesions. No edema was noted in either lower limb.

Laboratory examinations

The blood test results were as follows: White blood cell count (11.63 × 10^9/L↑), neutrophil count (8.4 × 10^9/L↑), hemoglobin 119 g/L (115-150), and platelet count (545 × 10^9/L↑). The C-reactive protein level was 1.9 mg/L. The biochemical test results were: Albumin 23.2 g/L (40-55) and blood calcium 1.85 mmol/L (2.11-2.52). The tumor marker test results were as follows: CA19-9 41.1 U/mL (0-37), immunoglobulin E (IgE) 193/mL (0-87), and gastrin 129 ng/L (13-115). Serum *Helicobacter pylori* (*H. pylori*) antibodies were positive. The occult blood test in stool was positive (++), and the fat globule test was positive.

No abnormalities were found in the following test results: Liver and kidney function, coagulation function, troponin level, thyroid function, routine urine, erythrocyte sedimentation rate, immunoglobulin (G, A, M) levels, immunoglobulin G (IgG) 4 level, complement levels, rheumatoid factor level, hepatitis (A, B, C, D, E) antibodies, TORCH (*Toxoplasma gondii*, Rubella virus, Cytomegalovirus, Herpes simplex virus type 1 and 2) antibodies, Epstein-Barr virus antibodies, anemia test (ferritin, folic acid,

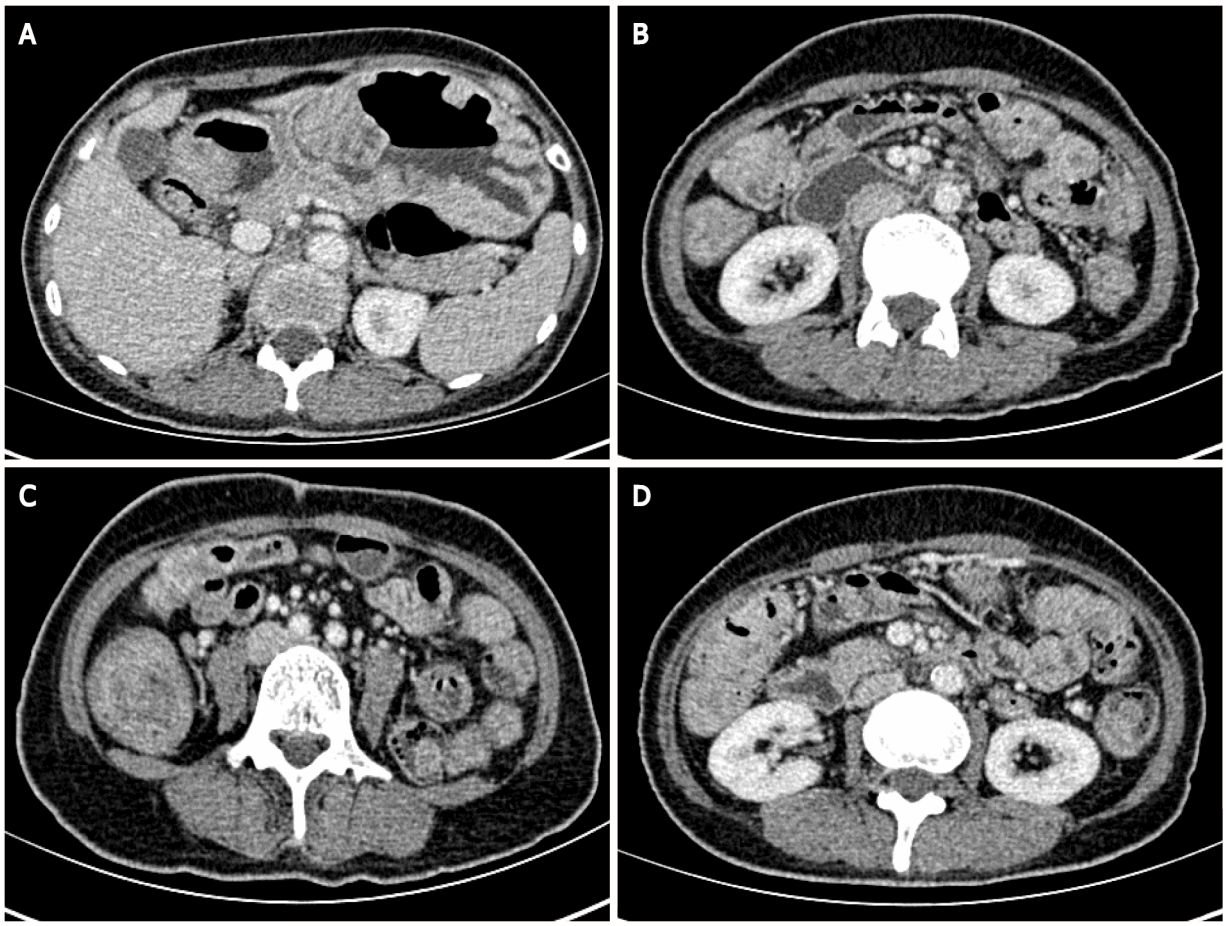

Figure 2 Abdominal enhanced computed tomography. Thickening of the gastrointestinal tract with multiple cauliflower-like and nodular protrusions. A: The stomach wall; B: Part of the small intestinal wall; C and D: Part of the colon wall.

vitamin B12), *Mycobacterium tuberculosis* antibodies, tuberculosis infection T cells, anti-neutrophil cytoplasmic antibodies, antinuclear antibodies, and blood lead level.

During the entire treatment, we recommended that the patient undergo further genetic examination, but she refused because of the expense.

Imaging examinations

Contrast-enhanced CT of the abdomen suggested that the gastric wall and part of the small intestine and colon were thickened with multiple cauliflower-like and nodular protrusions and showed obvious heterogeneous enhancement. A diagnosis of multiple polyps (malignant changes were not ruled out) was considered (Figure 2).

Positron-emission tomography (PET)/CT showed multiple nodules with increased ^{18}F-fluorodeoxyglucose (FDG) intake in the gastric wall (SUVmax 3.4), descending duodenum and bulb, small intestine, and colon (SUVmax 7.3). Multiple areas of nodular thickening with increased FDG intake were noted in the proximal rectum. Based on her medical history, a diagnosis of multiple polyps throughout the gastrointestinal tract (the possibility of malignant changes in individual polyps could not be excluded) was considered (Figure 3).

Endoscopic examinations

Gastroscopy showed extensive diffuse polypoid lumps of 0.5-3.0 cm in the gastric body, gastric fundus and antrum (Figure 4).

Colonoscopy showed multiple polypoid mucosal bulges in the terminal ileum and multiple polyps (0.3-5 cm) throughout the colon. Some were villus-like changes. Severe hyperemia was found on the surface. Larger polyps appeared in the ascending colon and the hepatic flexure (Figure 5).

Gastroscopic pathology showed juvenile polyps in the gastric antrum (*H. pylori*$^{+}$) (Figure 6). Colonoscopic pathology showed juvenile polyps in the ascending colon (Figure 7).

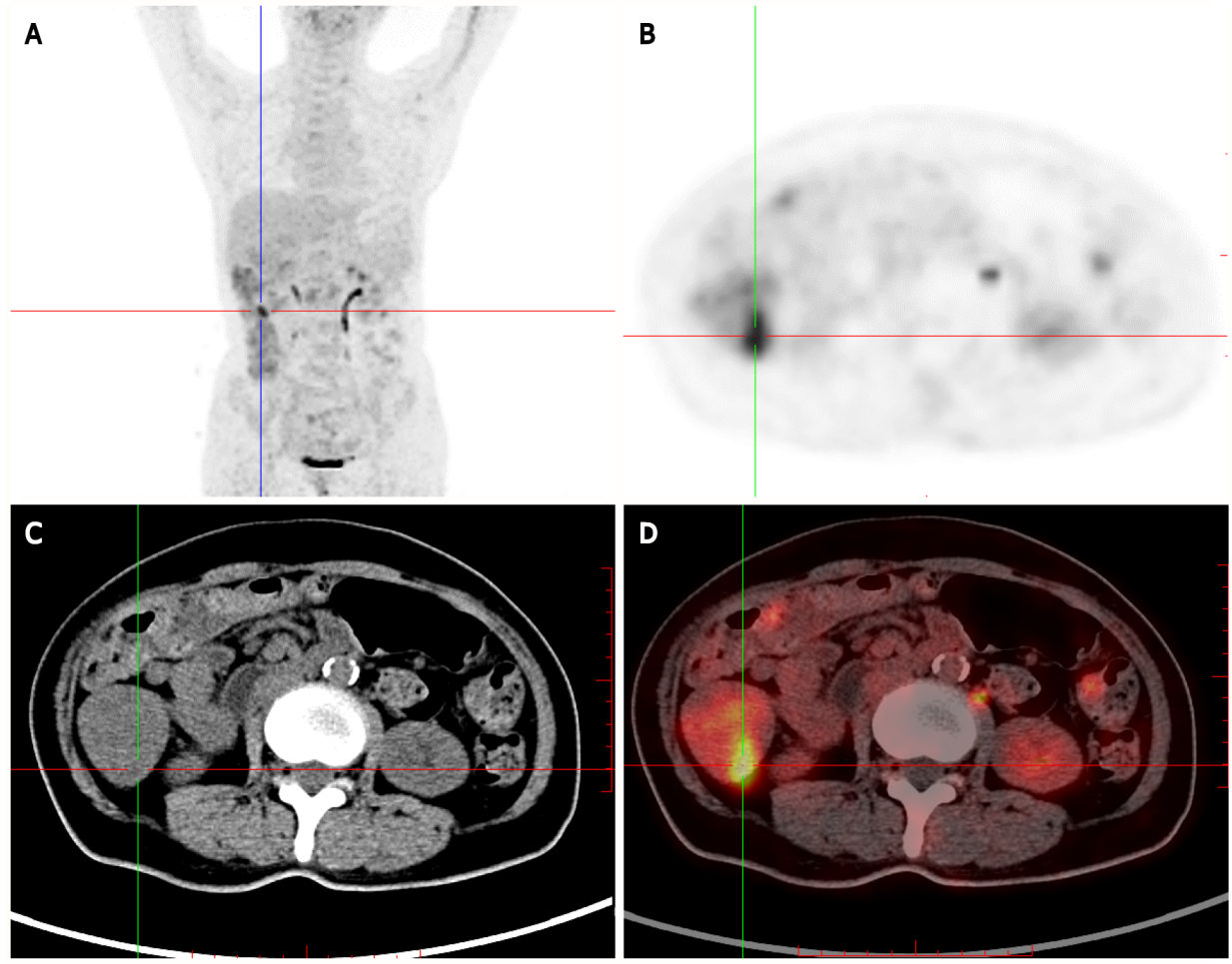

Figure 3 Positron-emission tomography/computed tomography showing multiple nodules with increased fluorodeoxyglucose uptake in the stomach wall, descending duodenum, and bulb, in the small intestine (obvious increase in the ileum), and the colon (obvious increase in the ascending colon). Multiple nodular thickening with increased fluorodeoxyglucose (FDG) uptake was observed in the proximal rectum. A: Whole-body maximum intensity projection 18F-FDG and positron-emission tomography (PET) image; B: PET; C: Computed tomography (CT); D: PET/CT.

FINAL DIAGNOSIS

Cronkhite-Canada syndrome.

TREATMENT

The patient was admitted to the hospital and treated with nutritional agents, digestive enzymes, a PPI, and anti-*H. pylori* agents (rabeprazole 10 mg bid + bismuth potassium citrate 0.6 g bid + amoxicillin 1 g bid + clarithromycin 0.5 g bid, 14 d). The nail dystrophy and skin pigmentation improved after treatment.

One month after treatment, the patient complained of nausea and vomiting, accompanied by abdominal pain and inability to pass gas or stool. Contrast-enhanced CT of the abdomen showed gastrointestinal polyposis and ileocecal intussusception (Figure 8).

After fasting, gastrointestinal decompression, somatostatin administration, PPI treatment, and total parenteral nutrition, her symptoms were not significantly improved. The patient and family members refused surgical treatment followed by glucocorticoids. Her symptoms worsened 1 mo later, and she underwent right hemicolon + partial transverse colon + partial ilium resection at another hospital. Postoperative pathology showed inflammatory changes.

OUTCOME AND FOLLOW-UP

After the operation, vomiting and decreased bowel movements recurred. CT showed intestinal

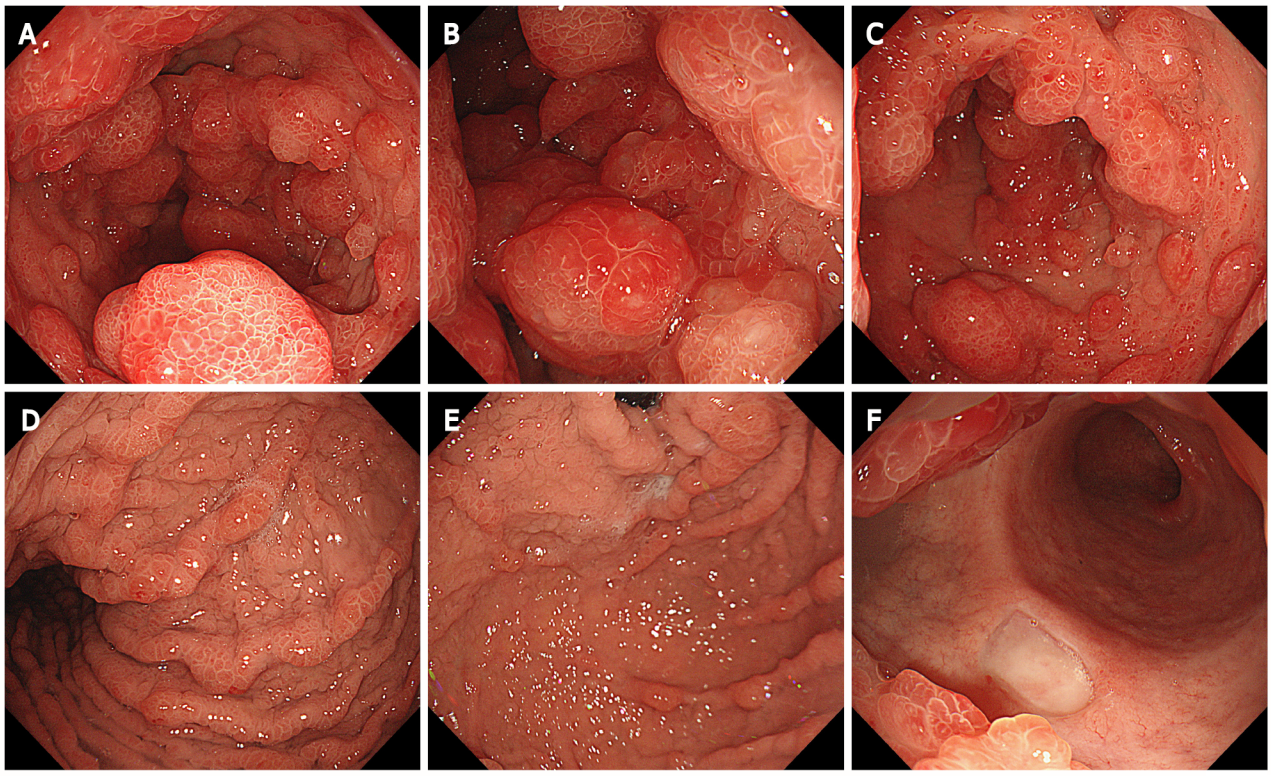

Figure 4 Endoscopic findings in the stomach. Extensive and diffuse polypoid eminences in the stomach. A: Antrum; B: Lower part of the gastric body; C: Middle part of the gastric body; D: Upper part of the gastric body; E: Gastric fundus; F: Duodenal bulb.

obstruction. She underwent subtotal gastrectomy 3 mo after the surgery.

DISCUSSION

Diarrhea and the triad of abnormal ectodermal lesions (hair loss, skin pigmentation, fingernail/toenail atrophy and loss) are the most common clinical manifestations of CCS. Other manifestations include weight loss, hypoalbuminemia, edema of both lower limbs, dysgeusia, abdominal pain, bloating, nausea, vomiting, anorexia, and itching[3]. Some patients also have electrolyte disturbances (most common types: Hypokalemia and hypocalcemia), and fractures have been reported occasionally. Almost all of the clinical features of CCS were present in this patient.

CCS is a rare hereditary or familial disorder with multiple intestinal polyps distributed throughout the digestive tract. Most are in the stomach and colon (90%), followed by 80% in the small intestine and 67% in the rectum. They are rare in the esophagus[6]. Approximately 12.3% (26/211) of CCS patients have esophageal involvement[7]. Endoscopy has demonstrated that most polyps are sessile or broad-based and diffusely distributed, vary in size, and are granular, nodular, or irregular in shape. The polyp mucosa is congested with obvious edema, and intestinal folds are thickened[2,8].

Hyperplastic polyps and hamartoma-like polyps are common in CCS histopathology examinations. In addition, 31%-71% of patients may have digestive tract adenomas or adenomatous changes during the course of this disease[9]. The pathological features of typical CCS polyps include propria edema, mild to moderate inflammatory cell infiltration, eosinophil and lymphocyte infiltration (even IgG4 plasma cell infiltration), tortuous hyperplasia of glands, and some cystic expansion filled with protein-rich liquid or concentrated mucus[2].

The histopathology of non-polyp tissue includes edema, mucus-like expansion of the propria, damage to the crypt structure (dilation or branching)[10], and mixed inflammatory infiltration composed of lymphocytes, plasma cells, and neutrophils[11].

Due to the extremely low incidence of CCS and the small number of studies available, controversies remain regarding the causes, mechanisms, and effective treatments of CCS.

The mainstream view is that the pathogenesis of CCS is related to autoimmune disorders[12,13]. Patients may have abnormal expression of antinuclear antibodies[14], abnormal IgG4 expression[6,12] (elevated serum IgG4 or infiltration of IgG4 plasma cells in the tissue), other autoimmune diseases (such as systemic lupus erythematosus, rheumatoid arthritis and scleroderma)[8,13], and impaired T cell regulatory function[11]. Case studies have shown that steroids and anti-tumor necrosis factor (TNF)-α

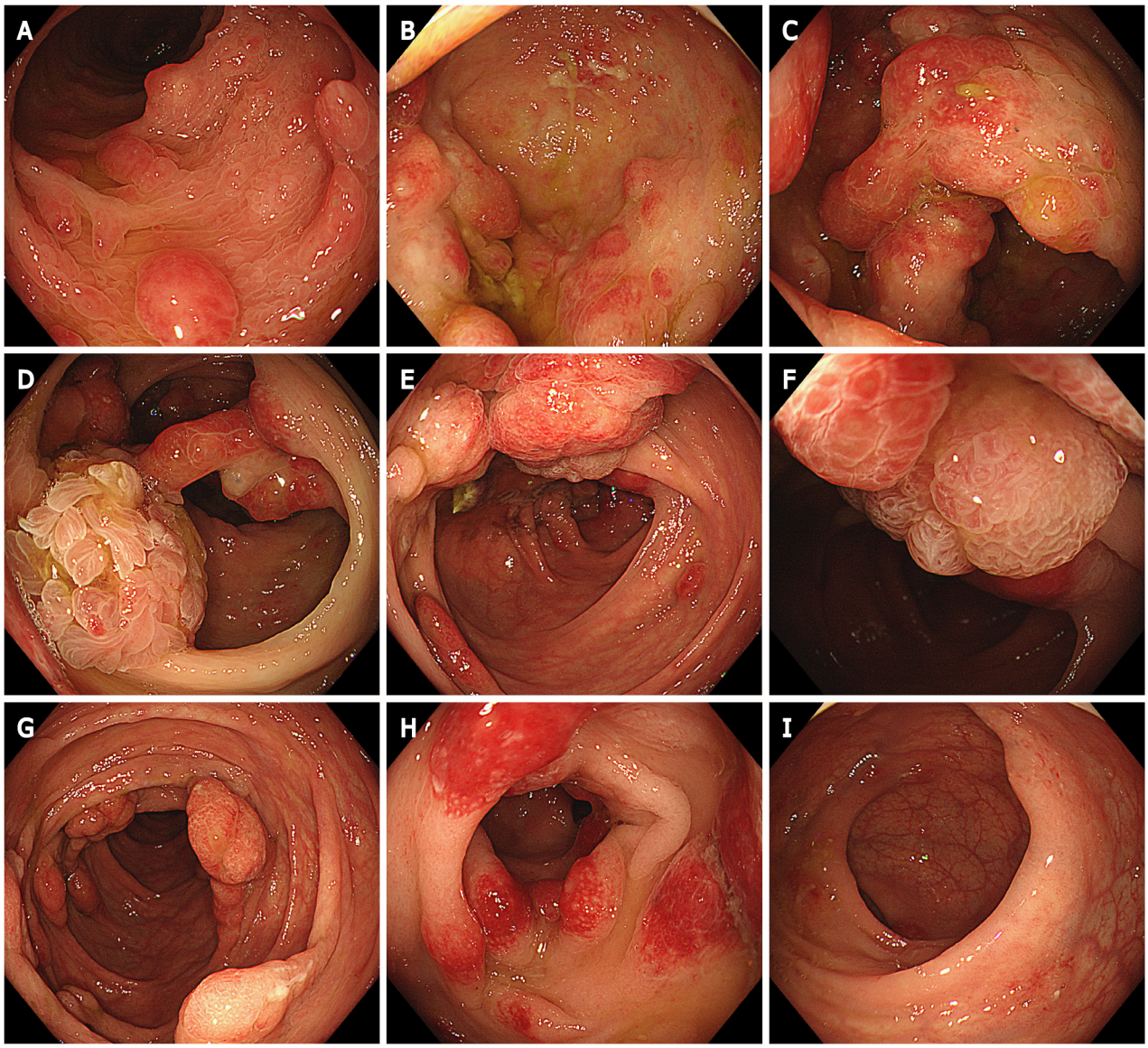

Figure 5 Endoscopic findings in the colon. Multiple polypoid mucosal bulges in the distal small intestine and multiple polyps throughout the colon. Some were villus-like changes, and severe hyperemia was observed on the surface. A: Terminal ileum; B: Cecum; C and D: Ascending colon; E and F: Transverse colon; G: Descending colon; H: Sigmoid colon; I: Rectum.

antibody therapy are not effective against CCS in some cases, suggesting that the relationship between CCS and immunity is complicated[15]. The histopathology of the nail matrix of some patients with CCS shows stromal granuloma. Because stromal hypergranulation is common in a variety of inflammatory nail diseases, the inflammatory process may be an important pathogenic factors of CCS[16]. *H. pylori* infection is also believed to play an important role in the pathogenesis of CCS. Watanabe *et al*[7] found that approximately 54% of CCS patients had *H. pylori* infection, and the symptoms of CCS disappeared after anti-*H. pylori* treatment[17,18].

The diagnosis of CCS should be based on comprehensive consideration of the medical history, physical examination, endoscopic examination and histopathological results. CCS needs to be differentiated from juvenile polyposis, Peutz-Jeghers syndrome, Cowden syndrome, Turcot syndrome, and familial adenomatous polyposis[7,19].

The common complications of CCS include gastrointestinal bleeding with anemia, intussusception, gastrointestinal tumors, hypoproteinemia, rectal prolapse, malabsorption, electrolyte imbalance, and vitamin deficiency[20]. Rare complications include recurrent severe acute pancreatitis[21], portal vein thrombosis, membranous glomerulonephritis[14], and recurrent arteriovenous embolism[22]. The probability of a CCS patient with a malignant tumor is 13%[23]. Three histological structures, including polyps[24], adenomas, and adenocarcinomas, may be present concurrently in the gastrointestinal tract in CCS patients. Histological evidence has shown transformation of CCS from polyps to adenomas and then to adenocarcinomas. In 15%-25% of CCS patients, gastric or intestinal carcinoma is diagnosed at the onset of CCS. The total adenoma detection rate over the course of CCS is 31%-71%[7,9]. Therefore, long-

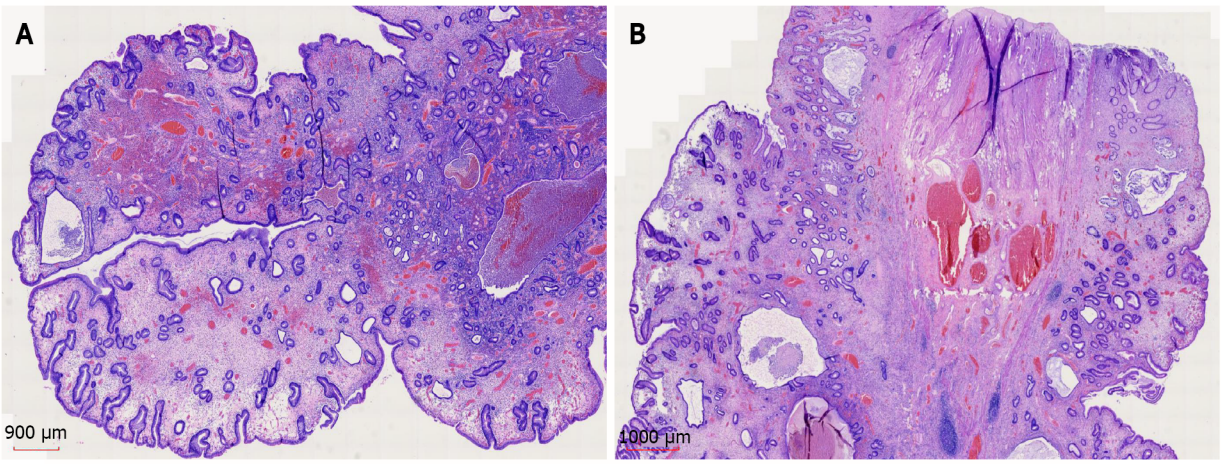

Figure 6 Histopathology and hematoxylin and eosin staining of gastroscopic pathology samples suggested a diagnosis of juvenile polyps. A: × 11; B: × 12.5.

term endoscopic monitoring of patients with confirmed or suspected CCS is needed[7].

Due to the low incidence of CCS and the small number of reported cases, no unified or standardized CCS treatment guidelines have been issued in China or abroad. To date, empirical treatment is mainly applied, including steroids, immunosuppressants, biological agents, antibiotics, nonsteroidal anti-inflammatory agents, acid blockers, nutritional support, and endoscopic surgical treatment. Steroids are currently well accepted for the treatment of CCS[12,25]. No consensus has been reached about the steroid dosage or duration. Watanabe *et al*[7] reported that the most significant effective dose of prednisolone for active CCS was 30-49 mg *per* day. Early tapering of steroids may be related to early recurrence, which suggests that the prednisolone dose should be slowly reduced after endoscopic confirmation of polyp regression. Approximately 61.1%[7] to 61.3%[3] of patients achieve clinical relief after steroid treatment. Osteoporosis is a major side effect of steroids. After steroid-induced remission, immunosuppressive maintenance therapy should be continued[26]. If the abovementioned drug treatments are ineffective, biological agents can be an option[27]. However, it has been suggested that steroids and anti-TNF-α antibodies are not effective for some CCS patients. Whether steroids or biological agents have better efficacy in IgG4-positive patients remains to be proven[15]. Early proactive drug treatment may reduce the incidences of intussusception and surgical intervention. Because most adult intussusceptions are accompanied by tumor changes, surgical treatment is the first choice once intussusception is confirmed. Endoscopic reduction is also an option, but with a high risk; in theory, reduction may lead to abdominal perforation and tumor spread[5,28]. Partial endoscopic mucosal resection plus corticosteroids and anti-plasmin treatment can be used to avoid surgery.

The prognosis of CCS is poor. Lesion size, age, and complications are factors for a poor prognosis[3]. Serious complications can be life-threatening. The 5-year survival rate is less than 45%[29]. The main causes of death are gastrointestinal bleeding, infection, malnutrition, electrolyte imbalance, and heart failure[8]. Because CCS is a rare disease, clinicians may misdiagnose it because they are not familiar with it. Meanwhile, CCS has a risk of malignancy[30]. More than 10% of CCS patients relapse after the disease is relieved *via* standardized steroid and endoscopic treatments. Therefore, standardized follow-up and endoscopic monitoring are essential during the whole treatment process to reduce the mortality rate of CCS. Evaluation should be performed at an interval of 6-12 mo after treatment or confirmed diagnosis[7]. During the first year after onset of the illness, the patient and her family members refused glucocorticoids, immunosuppressants, or biological agents for treatment. The disease progressed rapidly even after she received symptomatic treatment, nutritional support, and surgical treatment. An in-depth understanding of CCS and advanced diagnosis and treatment may improve its prognosis; therefore, the prognosis needs to be reassessed after treatment.

CONCLUSION

In this case, endoscopy did not show large or multiple polyps at the onset of the symptoms one year prior, and no specific treatment was applied during that year. Large polyps appeared quickly in the gastrointestinal tract. After routine nutritional support and anti-*H. pylori* treatment, the polyps did not significantly subside. Because systematic steroids, immunosuppressive agents, and biological agents were not applied, the patient's symptoms quickly progressed, and intussusception occurred. She had to eventually undergo surgery. Thus, CCS, a rare disease with poor prognosis, should be treated aggressively. Learning more about the disease and improved compliance may lead to a better prognosis.

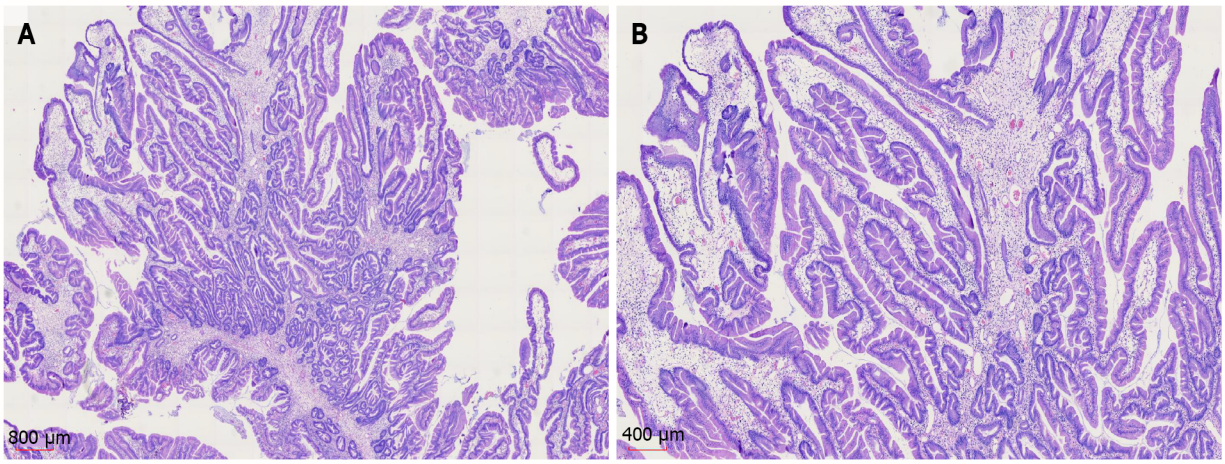

Figure 7 Histopathology and hematoxylin and eosin staining of colonoscopic pathology samples suggested a diagnosis of juvenile polyps. A: × 12.5; B: × 25.

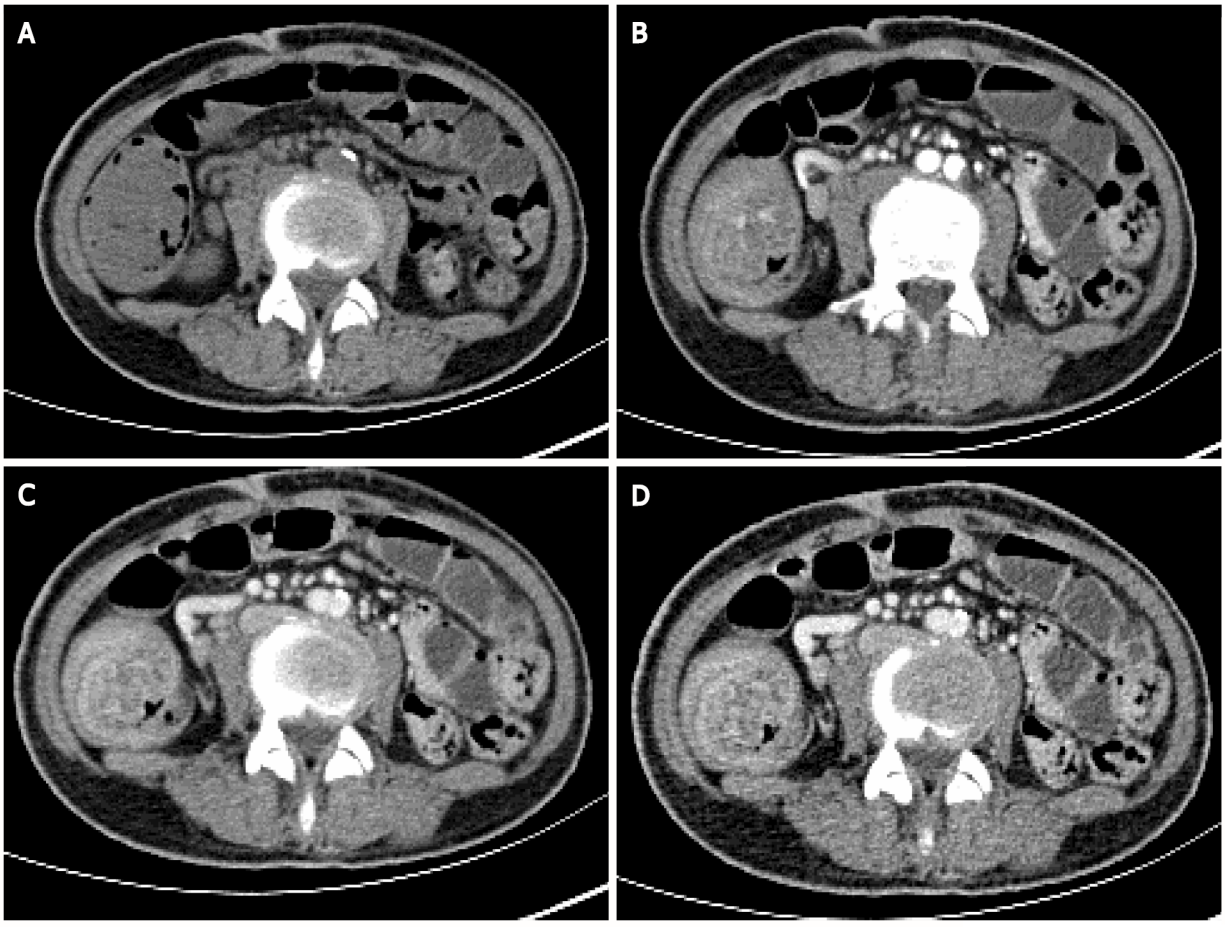

Figure 8 Abdominal enhanced computed tomography. Multiple concentric ring signs in the ileocecal area indicating ileocecal intussusception. A: Plain computed tomography scan; B: Arterial phase; C and D: Venous phase.

ACKNOWLEDGEMENTS

We would like to show our deepest gratitude to our friend, Dr. Yi Chen, a respectable, responsible and resourceful scholar, who has provided us with valuable guidance in every stage of the writing of this manuscript.

FOOTNOTES

Author contributions: Dong J was the patient's doctor in charge, who was responsible for collecting medical history, reviewed the literature and drafting the paper; Tu JF did the literature review; Ma TS was a pathologist who gave the pathological results; Chen YW designed the study with Dong J and made contribution to revise the manuscript; All authors have read and approved the final manuscript.

Supported by The Medical Health Science and Technology Project of Zhejiang Provincial Health Commission, No. 2021436506; and General Scientific Research Project of Zhejiang Science and Technology Department, No. Y202044280.

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

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: China

ORCID number: Jie Dong 0000-0002-2338-8955; Tian-Shi Ma 0000-0001-7606-6397; Jiang-Feng Tu 0000-0002-1893-9994; You-Wei Chen 0000-0002-5663-6118.

S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

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