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Surgical and oncological updates in the management of gastric cancer: The role of neoadjuvant therapy and minimally invasive surgery

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Optimal extent of lymph node dissection in gastric cancer

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Gastric cancer still remains a major cause of cancer-related deaths globally. Stage-adapted, individualized treatment is crucial to achieving optimal oncological outcomes. Postoperative morbidity and accurate nodal staging are heavily influenced by the extent of lymph node dissection. On one hand, insufficient lymphadenectomy may result in understaging and undertreatment of a patient, on the other hand, unnecessary lymph node dissection may result in a higher rate of postoperative complications. Approximately one-third of patients with gastric cancer undergoes an avoidable lymph node dissection. Many of the recent treatment updates in the management of gastric cancer have a major influence on both surgical and oncological approaches. Currently, a wide range of endoscopic, minimally invasive, and hybrid surgical techniques are available. The concept of sentinel node biopsy and utilization of the Maruyama Computer Program are significant components of stage-adapted gastric cancer surgery. Likewise, centralization and application of national guidelines, widespread use of neoadjuvant therapy, and the stage migration phenomenon are serious concerns to be discussed. Our goal is to review the available surgical strategies for gastric cancer, with a primary focus on lymphadenectomy.

KEYWORDS

gastric cancer, lymph node, lymphadenectomy, D1D2, gastrectomy, laparoscopy

Introduction

According to the recent GLOBOCAN 2020 estimation (1), gastric cancer is the fifth most common cancer worldwide. The number of new cases was estimated to be 1 089 103 with 768 793 deaths. The diagnosis of gastric cancer is frequently made at an advanced stage, resulting in a high mortality rate. Countries with the highest incidence and mortality are located in East Asia, Eastern Europe, and South America. The incidence rates in males are more than two-fold higher (15.8 and 7.0 per 100 000) than in females (1). Economic development has contributed to the global reduction in the prevalence of H. pylori, a major factor for gastric cancer, as well as eradication therapy. Additionally, gastroduodenoscopy screening programs in Asia have led to a significant decline in the mortality of this disease (2). There is a well-known positive association between gastroesophageal reflux disease (GERD) and proximal gastric cancer (3). Despite the current promising tendency, the dietary habits and aging of the population in developed countries might reverse these trends. Moreover, in Western societies, there has been a gradual decrease in the incidence of the distal, intestinal type of gastric cancer, and an increase in the proximal, diffuse type (4). In 2014 the Cancer Genome Atlas Research Network identified and

published four molecular subtypes of gastric cancer: Epstein-Barr virus positive, microsatellite unstable tumors, genomically stable, and chromosomally unstable tumors (5). In recent years, novel diagnostic tools utilizing algorithmic analysis in digital imaging (6), as well as liquid biopsy techniques, have evolved.

It has been more than 140 years since Theodor Billroth's (1829–1894) first successful gastric resection for cancer in 1881. Regardless of the scientific and technological advancement, the development of a multimodal treatment approach using resection (surgical or endoscopic) is still the foundation of curative management in gastric cancer (7). Stage-adapted, individualized treatment is crucial to achieving optimal oncological outcomes. The latest, 8th edition of the TNM Classification of Malignant Tumours (8) is most frequently used to stage patients. Diagnostic modalities including contrast-enhanced chest-abdomen-pelvis CT, esophagogastroduodenoscopy, endoscopic ultrasound, and explorative laparoscopy are all helpful in the staging process. The latter procedure, along with peritoneal lavage is recommended for stage IB–III patients before surgical resection (9). The clinical stage will determine the treatment approach, which is decided by a competent multidisciplinary tumor board. There is however a concerning amount of variation among treatment guidelines, depending on the region (7). Generally, clinically staged T1N + M0 and T2–T4aN(any)M0 gastric cancer requires surgical resection with adequate lymphadenectomy, together with perioperative or adjuvant chemotherapy. Surgery aims to achieve local control through free surgical resection margins and clearance of regional lymph nodes.

In 1973 the Japanese Research Society for Gastric Cancer established the blueprint that standardized lymph node dissection in gastric cancer (10). In this manual, they recognized 16 distinct lymph node stations based on their anatomical location, and created a system to measure the extent of lymphadenectomy, namely D1, D2 and D3. Since then, the guideline has been revised multiple times. The latest, 5th edition was published in 2018 (11) where D-levels are now defined by the location of the tumor and the surgery performed. As a simplification, D1 lymphadenectomy implicates the removal of the perigastric nodes plus those along the left gastric artery (station 1–7), while D2 implies the removal of D1 nodes, plus nodes along the common hepatic and splenic artery, and the coeliac trunk. D1 + lymphadenectomy is defined according to the type of gastrectomy. D3 lymphadenectomy includes dissection of all D2 lymph node stations, extended by well-defined abdominal paraaortic and hepatoduodenal lymph nodes.

Postoperative morbidity and accurate nodal staging are heavily influenced by the extent of lymph node dissection. Insufficient lymphadenectomy may result in understaging and undertreatment of a patient, however, unnecessary lymph node dissection may have higher rates of postoperative complications. The optimal extent of lymph node dissection has been debated over the last decades. The Eastern rationale focuses on more accurate staging and better locoregional control, whereas early Western data showed notable morbidity and mortality by this procedure. This review aims to summarize the current guidelines and evidence on this subject.

Lymph node metastases

Lymph node (LN) involvement is one of the most important prognostic factors for gastric cancer. Conventional preoperative imaging techniques provide an accurate T and M stage, but there is significant uncertainty regarding the N stage. The sensitivity, specificity, and accuracy of CT scans in the detection of LN involvement are 73.1%, 50.0%, and 84.2%, respectively. Endoscopic ultrasonography performance is relatively similar with an accuracy of 68.6% and sensitivity and specificity of 66.7% and 73.7% (12).

It has been previously reported that in early gastric cancer the rate of lymph node metastasis is 2%–20% (13). Consequently, lymphadenectomy for node-negative patients bears unnecessary risks for complications. The term „early gastric cancer" (EGC) was first described by the Japanese Society of Gastroenterology and Endoscopy in 1971 (14). They then defined it as being „limited to the gastric mucosa and/or submucosa", regardless of the lymph node status. These tumors should have a favorable prognosis, but lymph node positive patients are known to have much worse outcomes: the 99% 5-year overall survival (OS) rate for node-negative patients decreases to 73.2% in node-positive ones (15). The tumor size, depth of invasion, grade of differentiation, presence of ulceration and presence of lymphovascular invasion are known risk factors for lymph node metastases in gastric cancer (16). It is difficult to determine which patient could be spared from an unnecessarily extended lymphadenectomy, since gastric cancers can have multidirectional and complicated lymphatic flow.

Sentinel lymph node biopsy (SLNB)

The concept of sentinel lymph node (SLN) mapping has been suggested and later implemented to identify these patients during a surgical resection (17).

The SLN is defined as the first node to receive lymphatic flow from a tumor, theoretically representing the status of the other regional lymph nodes. Their use was first described in parotid tumors and mentioned later in penile cancer, melanoma, testicular cancer, and breast cancer (18). In gastric cancer surgery, various tracers have been used: blue dye, indocyanine green (ICG), radiocolloids, and their combinations (19).

Sentinel node navigation surgery (SNNS) is a type of surgical technique that is performed according to the status of the sentinel lymph node. If the sentinel lymph node is free of metastases, gastrectomy and D2 lymph node dissection may not be necessary. The promise of this approach is the lesser extent of resection and lymph node dissection, resulting in organ preservation, faster postoperative recovery, and better quality of life (QoL) without compromising oncological safety. But this concept has yet to be proven in a clinical setting.

The application of different agents is influenced by their technical demand, visibility, cost-effectiveness, and safety. A recent systematic review and meta-analysis has shown similar pooled sensitivity rates: 82% (95%CI: 77%–86%) for blue dye, 87% (95%CI: 81%–92%) for radiocolloid tracer, 90% (95%CI: 82%–95%) for ICG, 89% (95%CI: 84%–93%) for a combination of radiocolloid with blue dye, and 88% (95%CI: 79%–94%) for a combination of radiocolloid with ICG (20). Blue dye is the most convenient and cost-effective, but its use might be limited in obese patients. The use of radioactive substances is associated with biohazard production, high costs, and high demand for specific logistical arrangements. The use of ICG seemed promising, however, suitable applications of near-infrared or fluorescence imaging have yet to be determined. Factors requiring measurement include ICG concentration, used volume, injection site, timing after injection and patient selection.

Another obstacle for intraoperative SLNB is the reliability of the pathological assessment. The Japanese JCOG0302 study was terminated due to the high (46.4%) false negative rate. The main reason for this unreliability was the single-plane frozen section. The use of interval sections, immunohistochemistry, reverse transcription polymerase chain reaction and one-step nucleic acid amplification assay have all been described (21). In the study protocol of the Korean SENORITA trial, nodes that were thicker than 4 mm were sliced at 2-mm intervals parallel to the long axis, so as not to miss macrometastasis. This promising clinical trial assessed the feasibility of laparoscopic stomach-preserving surgery with sentinel basin dissection in early gastric cancer.

The concept of sentinel basin dissection was first introduced by Miwa et al. in 2003 (22). They divided the gastric lymphatic compartments into five regions. It improved the accuracy of the conventional pick-up biopsy to 98%, however, the histological evaluation of this larger number of lymph nodes takes more time. The frequency of skip metastases in a patient with early gastric cancer was 2,8% by Lee SE et al. (23).

Tumor control

Primary tumor control during SNNS is the key to a successful procedure. Several endoscopic and hybrid resection techniques have been published. Endoscopic submucosal dissection (ESD) has proven to be superior to endoscopic mucosal resection. The guideline of the European Society of Gastrointestinal Endoscopy (ESGE) was updated in 2022 and still recommends ESD as the treatment of choice for most gastric superficial neoplastic lesions to provide an en-bloc resection (24). Along with ESGE, the Japanese Gastric Cancer Association (JGCA) (11), European Society for Medical Oncology (ESMO) (9) and National Comprehensive Cancer Network (NCCN) (25) placed strict criteria for endoscopic resection. The NCCN and ESMO guidelines recommend endoscopic resection only in well-differentiated (G1-G2), ≤2 cm, non-ulcerated T1a lesions. There are several other cases when the JGCA guideline recommends endoscopic resection based on absolute, expanded, and relative indications. It also mentions the categories of endoscopic curability, which will determine whether the patient needs observation, additional ESD, or surgery.

There are numerous hybrid techniques published, mostly taken from the management of gastric subepithelial lesions. In 2012, Nunobe et al. published the application of laparoscopy endoscopy cooperative surgery (LECS) for lateral-spreading mucosal gastric cancer (26). Other advanced endoscopic techniques are laparoscopic-assisted endoscopic resection, endoscopically assisted wedge resection, endoscopic assisted transgastric and intragastric surgery, laparoscopic-assisted endoscopic full-thickness resection (LAEFR), the combination of laparoscopic and endoscopic approaches to neoplasia with a non-exposure technique (CLEAN-NET), and non-exposed endoscopic wall-inversion surgery (NEWS). There is profoundly limited clinical experience with these methods (27).

T1 tumors that do not meet the criteria for endoscopic resection, will require surgery, although less extensive than other gastric cancers (9). Complication rates are lower in pylorus-preserving gastrectomy, laparoscopic wedge resection, and proximal gastrectomy as compared to conventional distal or total gastrectomy. However, they can result in procedure-specific complications, eg. high rates of reflux esophagitis and anastomotic stenosis after conventional proximal gastrectomy (28). The use of jejunal interposition and double-tract reconstruction can improve nutritional parameters and anemia (29), but can be technically challenging. The short-term outcomes of the KLASS-05 trial (which randomized patients between proximal gastrectomy with double-track reconstruction and total gastrectomy with Roux-en-Y reconstruction) were comparable in the two groups (30). Another limitation of their spread is the relatively low number of patients diagnosed with early gastric cancer out of Asia. The ESMO guideline does not even mention these techniques as feasible alternatives.

In resectable, clinically staged T1N + M0 and T2–T4aN (any)M0 gastric cancer, gastrectomy with adequate lymphadenectomy is indicated to achieve local control. The JGCA recommends a resection margin of at least 2 cm for T1

tumors, and at least a 3 cm proximal margin in T2 or deeper tumors with Borrmann type I and II tumors. For Borrmann types III and IV it recommends a 5 cm proximal margin (11). The NCCN and ESMO suggest a distal gastrectomy (DG) for distal gastric cancers if safe margins can be achieved, otherwise, a total gastrectomy should be performed (TG) (9, 25). The ESMO recommends a proximal margin of 5 cm for stage IB–III gastric cancer and 8 cm for diffuse cancer when performing DG (9). When these rules cannot be satisfied, it is advisable to examine the entire thickness of the proximal resection margin by frozen section. While it seems an independent issue, the level of nodal dissection is strongly influenced by the extent of gastrectomy, and it has been extensively debated.

As for radiotherapy, there are no randomized trials were assessing the benefit of preoperative chemoradiotherapy (CRT) for non-cardia gastric cancers. The Dutch CRITICS (ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach) trial addressed the role of postoperative CRT (31). Patients involved with potentially resectable gastric cancer, who received induction chemotherapy followed by surgery then were randomized to postoperative chemotherapy (CT) vs. chemoradiotherapy (CRT). Postoperative compliance was poor: of the 788 patients, 478 started post-operative treatment according to protocol, 233 (59%) patients in the CT group, and 245 (62%) patients in the CRT group. Although the initial median survival after a median follow-up of 61.4 months was not significantly different between postoperative CT and CRT (43 months in the CT group and 37 months in the CRT, $p = 0.90$), per protocol analysis (32) of patients who started the allocated post-operative treatment in the trial showed that the CT group had a significantly better 5-year overall survival than the CRT group (57.9% in the CT group vs. 45.5% in the CRT group, $p = 0.0004$).

The CRITICS II trial (33) is about to evaluate the three preoperative strategies: neoadjuvant chemotherapy followed by surgery vs. neoadjuvant chemotherapy and subsequent chemoradiotherapy followed by surgery vs. neoadjuvant chemoradiotherapy followed by surgery in resectable gastric cancer.

D1 vs. D2 lymphadenectomy

Three early European, phase III studies conducted by the British or Medical Research Council (MRC) (34), the Dutch (35), and the Italian (36) randomized control trials found that there was no early survival benefit in D2 dissection compared to D1. Interestingly, the 15-year follow-up results of the Dutch D1D2 trial showed lower locoregional recurrence and gastric-cancer-related death rates in the D2 group (37). It was preceded by the subgroup analysis of the Italian study. Degiuli et al. found that in patients with T2–T4 node-positive gastric cancer the 5-year disease-specific survival (DSS) after D2 lymph node dissection was greater than that in the D1 group (59% vs. 38%, $p = 0.055$) (36). Similarly, after a 15-year follow-up of the Italian study, disease-specific survival of patients with advanced disease and lymph node metastases was improved by the D2 procedure (38). DSS was significantly higher after D2 in pT > 1N + patients (29.4% vs. 51.4%, $p = 0.035$).

The British and Dutch studies were rightly the subjects of major criticism. The lack of survival benefit after D2 dissection is explained by the extremely high postoperative mortality in this group (13% in the British and 10% in the Dutch trial for D2 patients). In contrast, the mortality rate in the JCOG9501 study was 0.8% for D2 patients. It was likely the result of inexperienced surgeons, low-volume centers, and high rates of splenectomies and pancreatic resections in these classic trials. The 15-year follow-up Dutch data resolved this problem, showing that D2 patients without pancreatosplenectomy had a significantly higher OS than those who had D1 surgery: 35% (95% CI: 29%–42%) vs. 22% (95% CI: 17%–26%) (37). Besides, the Dutch trial enrolled 40% of patients, who had early gastric cancer, a surprisingly high proportion. In America, the famous Intergroup Trial 0116 showed an alarming snapshot: 54.3% of patients received less than D1 lymphadenectomy, and only 9.8% received a D2 procedure (39).

Meanwhile in Asia, the role of more extensive lymphadenectomies was examined. The JCOG9501 randomized controlled trial compared Japanese standard D2 and D3 (D2 + para-aortic) dissections in T2b, T3, or T4 stage gastric cancer patients. It failed to demonstrate the superiority of the extended, D3 lymphadenectomy since the 5-year OS was similar (70.3% for D3 and 69.2% for D2). The rate of morbidity was higher in the D3 group (28.1% vs. 20.9%), and mortality was very low (0.8% in both groups) (40).

The goal of lymph node dissection is also to provide adequate staging and prevent the so-called stage migration (or Will-Rogers) phenomenon. Based on the UICC and NCCN guidelines, harvesting and examining a minimum of 15 lymph nodes is required (25).

There is growing international consensus supporting the performance of gastrectomies with D2 lymphadenectomy on non-early gastric patients, especially in high-volume centers, by experienced surgeons (9).

The emerging role of perioperative chemotherapy in patients with locally advanced gastric cancer in the Western hemisphere should be noted. There is a strong recommendation for the use of neoadjuvant therapy for a patient with resectable gastric cancer stage 1B or greater (9). The effect on the lymphatic drainage of the tumors and the usefulness of all these previous findings remains unknown.

In 2006, the results of the multicentric Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial were published and became a landmark in perioperative systemic treatment (41). The study involved 503 patients with gastric and distal esophageal adenocarcinoma, including

esophagogastric junction tumors. The recruitment lasted for 8 years. The patients on the control arm received surgery alone ($n = 253$), while patients on the experimental arm ($n = 250$) received surgery and 3 cycles of ECF (intravenous epirubicin, cisplatin, and fluorouracil) both in pre-and post-operative settings. Eventually, 104 of 250 patients (41.6%) assigned to perioperative chemotherapy completed all six cycles. The type of resection was left at the discretion of the participating surgeon, and likewise the extent of lymph node dissection. The study showed a significant improvement in oncological outcomes. The 5-year overall survival was 36.3% in the experimental group and 23% in the control group ($p = 0.009$).

The conclusions were heavily debated (42) of the long recruitment period, the inclusion of esophageal cancers, poor quality of surgery, and insufficient lymphadenectomy. Besides the low completion rate of the postoperative treatment, neither the clinical nor the pathological response to chemotherapy was not evaluated. One might presume that there is a bias towards chemotherapy, as it did no more than compensate to a certain extent for insufficient lymphadenectomy and inadequate surgery.

Another cornerstone study for perioperative oncological treatment in the West was published in 2019 (43). The FLOT4 randomized phase II/III trial has reported that the combination of docetaxel-based triplet FLOT (fluorouracil plus leucovorin, oxaliplatin, and docetaxel) was superior to standard ECF or ECX (capecitabine instead of 5-FU) regimens. The study population consisted of 716 patients with locally advanced resectable gastric (44%) or gastro-esophageal junctional (Siewert I-II-III, 56%) non-metastatic adenocarcinoma. After randomization 360 patients were assigned to the standard regimen and 356 to FLOT. Surgery was performed 4 weeks after the completion of preoperative chemotherapy. For gastric cancer, total or subtotal distal gastrectomy with D2 lymphadenectomy was performed. The 5-year overall survival was 45% in the FLOT group and 36% in ECF/ECX. It was shown that more pathologically node-negative patients were found in the FLOT group (49% vs. 41%, $p = 0.025$) and more patients had negative surgical margins in the FLOT group (85% vs. 78%, $p = 0.0162$). The superiority of FLOT therapy made ECF/ECX regimens fall out of favor for patients with excellent performance status.

D1 + lymphadenectomy is thoroughly discussed in Eastern guidelines. In the JGCA Guideline (11) that refers to a D1 lymphadenectomy plus stages 8a, 9, and 11p in total and proximal gastrectomy; D1 + No. 8a, 9 in distal gastrectomy and pylorus-preserving gastrectomy. It is noted, that for tumors invading the esophagus, No. 110 (lower thoracic para-esophageal nodes) should additionally be dissected in D1 + lymphadenectomy.

Both JGCA and ESMO Guideline recommend D1 + lymphadenectomy for cT1N0 tumors, which do not meet the criteria for endoscopic resection (hence these criteria are different in these two guidelines) (9, 11). NCCN guideline does not mention it as an option (25).

Splenectomy and splenic hilar lymph nodes

Approximately 7.3% to 18.3% of proximal gastric cancer metastasize to the lymph nodes in the splenic hilum (44). No studies have demonstrated the advantage of prophylactic splenectomy so far. In addition, the JCOG0110 trial showed higher morbidity for the splenectomy group (30.3% vs. 16.7%) without improving survival (5-year OS rates were 75.1% vs. 76%) (45). In this study they recruited patients with T2-4N0-2M0 proximal gastric adenocarcinoma that did not invade the greater curvature.

The current JGCA guideline recommends splenic hilar lymph node (station No. 10) dissection with or without splenectomy for proximal gastric cancer invading the greater curvature (11). It suggests total gastrectomy with splenectomy for tumors located along the greater curvature and harbor metastasis to No. 4sb lymph nodes. The NCCN did not recommend routine splenectomy without direct splenic invasion or hilar lymphadenopathy (25). The ESMO guideline has no recommendations for splenectomy (9).

With the ongoing JCOG1809, the Japan Clinical Oncology Group has initiated a study to evaluate the safety of surgery involving laparoscopic and robotic dissection of the splenic hilar nodes without splenectomy.

Maruyama computer program

The Maruyama Computer Program (MCP) was developed by Keiichi Maruyama and published in 1989 (46). It uses a database of 4,302 primary gastric cancer patients, who were treated at the National Cancer Center Hospital in Tokyo between 1968 and 1989. The software can calculate the probability of lymph node involvement in stations No. 1–16., based on various prognostic factors. MCP was first validated in Japanese patients and the program was able to predict LN involvement in 94% (47). The accuracy was increased from 66% to 93% by using an artificial neural network (48).

Our previous study successfully demonstrated a similarly high level of reliability of MCP, reaching 90.2% of sensitivity, 63.3% of specificity, and 78.4% of accuracy (49). The prediction of LN metastases was shown to be superior to the standard pre-operative imaging techniques.

Traditionally the MCP was a great tool to determine the expected long-term oncological outcomes. Its usefulness was demonstrated by Hundahl (39) after the Intergroup 0116 Trial. He defined the term Maruyama Index (MI) first to measure the unresected regional nodal disease. Later, Hundahl made a blinded reanalysis of the Dutch D1-D2 trial by the autopsy findings. He demonstrated, that MI < 5 or a low MI surgery is associated with enhanced regional control and survival (50). Based on previous data, the Maruyama Index of

less than 5 had a better impact on survival than any D-level guided surgery.

Dikken et al. proved the prognostic significance of low MI in a 2-year survival rate (82% vs. 59%) (51), as did Sachdev, who represented the correlation between lower MI values and higher survival rates, as continuous ($P < 0.02$) and categorical ($P < 0.04$) variables (52).

In light of contemporary oncological treatment, these results are worth reassessing. By predicting the probability of lymph node involvement better than any conventional imaging modalities, it still has the potential to indicate the necessity for neoadjuvant oncological treatment and also helps the surgeon to focus on key lymph node stations during the subsequent lymphadenectomy.

Discussion

Gastric cancer is still a major cause of cancer-related deaths. Despite the advances in prevention, diagnostics, and therapy, it accounts for 768 793 deaths worldwide. A crucial challenge is to translate recent discoveries in molecular biology into oncological treatment for patients with gastric cancer.

Surgery is still the most important modality to properly stage and eradicate gastric cancer. For most patients, performed with curative intention, is the best chance for long-term survival. The type and extent of the operation are greatly influenced by the histological type, location, and stage of the tumor.

The concept of hybrid laparo-endoscopic techniques, sentinel node navigation surgery, and utilization of the Maruyama Computer Program are significant components of stage-adapted gastric cancer surgery. Centralization and application of national guidelines could improve both the surgical and the oncological outcomes.

The widespread use of neoadjuvant therapy and its effect on the lymphatic drainage of tumors is mostly unknown, as are the future benefits of information regarding the extent of lymph node dissection.

Author contributions

All authors contributed to the review's conception and design. DT and ZsV performed the literature search and data analysis. The first draft of the manuscript was written by ZsV, and DT critically revised the work first. All authors commented on previous versions of the manuscript. All authors contributed to the article and approved the submitted version.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Prognostic and clinicopathological value of the geriatric nutritional risk index in gastric cancer: A meta-analysis of 5,834 patients

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Background: Recent studies have explored the prognostic value of the geriatric nutritional risk index (GNRI) in patients with gastric cancer (GC), but the results are controversial. We aimed to systemically identify the association between the GNRI and prognosis in GC using a meta-analysis.

Methods: The databases of PubMed, Web of Science, Cochrane Library, and Embase were searched until September 25, 2022. Pooled hazard ratios and the corresponding 95% confidence intervals (CIs) were used to estimate the prognostic value of the GNRI in GC. Odds ratios (ORs) and 95% CIs were used to assess the correlation between the GNRI and clinicopathological characteristics of GC.

Results: Ten studies including 5,834 patients with GC were included in this meta-analysis. The merged results indicated that a low pretreatment GNRI was associated with inferior overall survival (hazard ratio = 1.21, 95% CI = 1.12–1.30, $P < 0.001$) and worse cancer-specific survival (hazard ratio = 2.21, 95% CI = 1.75–2.80, $P < 0.001$) for GC. Moreover, a low GNRI was significantly associated with an advanced pathological stage (OR = 2.27, 95% CI = 1.33–3.85, $P = 0.003$), presence of adjuvant chemotherapy (OR = 1.25, 95% CI = 1.01–1.55, $P = 0.040$), and tumor location in the lower stomach (OR = 1.33, 95% CI = 1.06–1.65, $P = 0.012$) in GC. However, there was no significant association between GNRI and sex, tumor differentiation, or lymph node metastasis in patients with GC.

Conclusion: Our meta-analysis identified that the pretreatment GNRI level was a significant prognostic factor for patients with GC. A low GNRI is associated with worse overall survival and inferior cancer-specific survival in patients with GC.

KEYWORDS

gastric cancer, prognosis, meta-analysis, risk factors, geriatric nutritional risk index

Introduction

Gastric cancer (GC) is the fifth most prevalent cancer and fourth leading cause of cancer-related death worldwide (1). GC accounts for 5.6% of new cancer cases and 7.7%

Abbreviations

GNRI, geriatric nutritional risk index; GC, gastric cancer; CI, confidence interval; OR, odds ratio; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PICO, population-intervention-control-outcome; HR, hazard ratio; OS, overall survival; CSS, cancer-specific survival; NOS, Newcastle-Ottawa Scale; ESD, endoscopic submucosal dissection

of cancer-related deaths in 2020 globally (1). Although its incidence and mortality have declined over the past several decades, more than one million cases of GC are diagnosed each year worldwide (2). Surgical resection is the mainstay of treatment for early GC, whose 5-year survival rate is approximately 80% (3). However, approximately 60% of patients with GC present with a late-stage diagnosis (4). The mortality rate of GC remains high, with 5-year survival rates ranging from 28% to 51% worldwide (5). Reliable prognostic markers could have important implications for the management of patients with GC. Therefore, identifying novel biomarkers is pivotal for the early prediction of prognosis so as to develop individualized treatment strategies for patients with GC.

Nutritional status is an important factor affecting the response and prognosis of patients with cancer, and approximately 30%–40% of patients have malnutrition (6). Previous studies have demonstrated the prognostic value of nutritional indexes in patients with GC, including the prognostic nutritional index (7), controlling nutritional status score (8), albumin-to-globulin ratio (9), and C-reactive protein to albumin ratio (10). The geriatric nutritional risk index (GNRI) is a novel nutrition-based parameter calculated as$1.489 \times$ albumin (g/dl) $+ 41.7 \times$ actual body weight/ideal body weight (kg). It is favored to assess nutritional status and disease prognosis in older patients (11, 12). Previous studies have explored the prognostic significance of the GNRI in patients with GC; however, the results were inconsistent (13–22). For example, some studies have confirmed the independent prognostic role of the GNRI for survival in GC (13, 14, 16). However, other researchers have reported that the association between the GNRI and prognosis in GC was not significant (15, 21). Therefore, in this study, we retrieved the most recent data and performed a comprehensive meta-analysis to quantitatively identify the prognostic value of the GNRI in GC. Moreover, the association between the GNRI and clinicopathological features of GC was also investigated.

Materials and methods

Data sources and search strategy

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (23); the checklist is provided in **Supplementary Material S1**. The databases of PubMed, Web of Science, Cochrane Library, and Embase were searched with the following search items: (geriatric nutritional risk index OR GNRI) AND (gastric cancer OR gastric carcinoma OR gastric adenocarcinoma OR stomach neoplasm OR stomach cancer). Data were collected from the inception of each database to September 25, 2022. The language of the studies was limited to English. Additionally, the reference lists of relevant studies were manually reviewed to identify additional studies.

Inclusion and exclusion criteria

The inclusion criteria for this study were formulated on the basis of the Population-Intervention-Control-Outcome (PICO) framework.

The inclusion criteria were as follows: (1) P (patients): patients who were pathologically diagnosed with primary GC; (2) I (intervention—exposure): patients with malnutrition risk as determined by a low pretreatment GNRI level; (3) C (control): patients with a normal nutritional status as determined by a high pretreatment GNRI level; and (4) O (outcomes): studies that reported the prognostic role of GNRI for any survival outcome, including overall survival (OS), progression-free survival, and cancer-specific survival (CSS). A cut-off value to divide patients into low and high GNRI groups was identified for (2) and (3). The hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for (4) were either directly reported by the studies or could be calculated using the data provided.

The exclusion criteria were as follows: (1) meeting abstracts, case reports, letters, reviews, and comments; (2) duplicate studies; and (3) animal experiments.

Data extraction and quality assessment

Two investigators (LH and YL) independently extracted the information from eligible studies, and all disagreements were resolved by consensus with a third investigator (FZ). The following data were extracted from each included study: name of the first author, year of publication, country, recruitment period, sample size, tumor stage, treatment, age, sex, follow-up, cut-off value of the GNRI, HR analysis type, survival endpoints, and HRs with 95% CIs for survival outcomes. The quality of all included studies was systematically evaluated using the Newcastle-Ottawa Scale (NOS) (24). The NOS scores ranged from 0 to 9. Studies with the NOS scores $\geq$6 were considered high-quality research.

Statistical analyses

All statistical analyses were performed using Stata version 12.0 (Stata Corporation, College Station, Texas, USA). The pooled HRs and 95% CIs were used to estimate the prognostic value of the GNRI in GC. Heterogeneity among all included studies was analyzed using the chi-squared test and quantitatively assessed using the I^2 value. $I^2 > 50\%$ or P for heterogeneity <0.10 indicates significant heterogeneity, and a random-effects model was applied for this event. Otherwise, a

fixed effects model was used. Subgroup analyses were performed to evaluate the prognostic effect of the GNRI in various subgroups. Odds ratios (ORs) and 95% CIs were used to assess the correlation between the GNRI and clinicopathological characteristics of GC. Begg's test and funnel plots were used to assess potential publication bias. Statistical significance was set at $P < 0.05$.

Ethics statement

Ethical review and approval were waived because this study summarized the published literature.

Results

Study retrieval

A flowchart of the study selection process is presented in Figure 1. During the initial literature retrieval, we identified 114 records, of which 74 remained after the removal of duplicate records. After screening titles and abstracts, 54 studies were further excluded, and the remaining 20 were evaluated by full-text examination. Subsequently, ten studies were excluded for the following reasons: four did not include the GNRI in the analyses, three did not provide survival data, and three recruited overlapping patients. Ultimately, 10

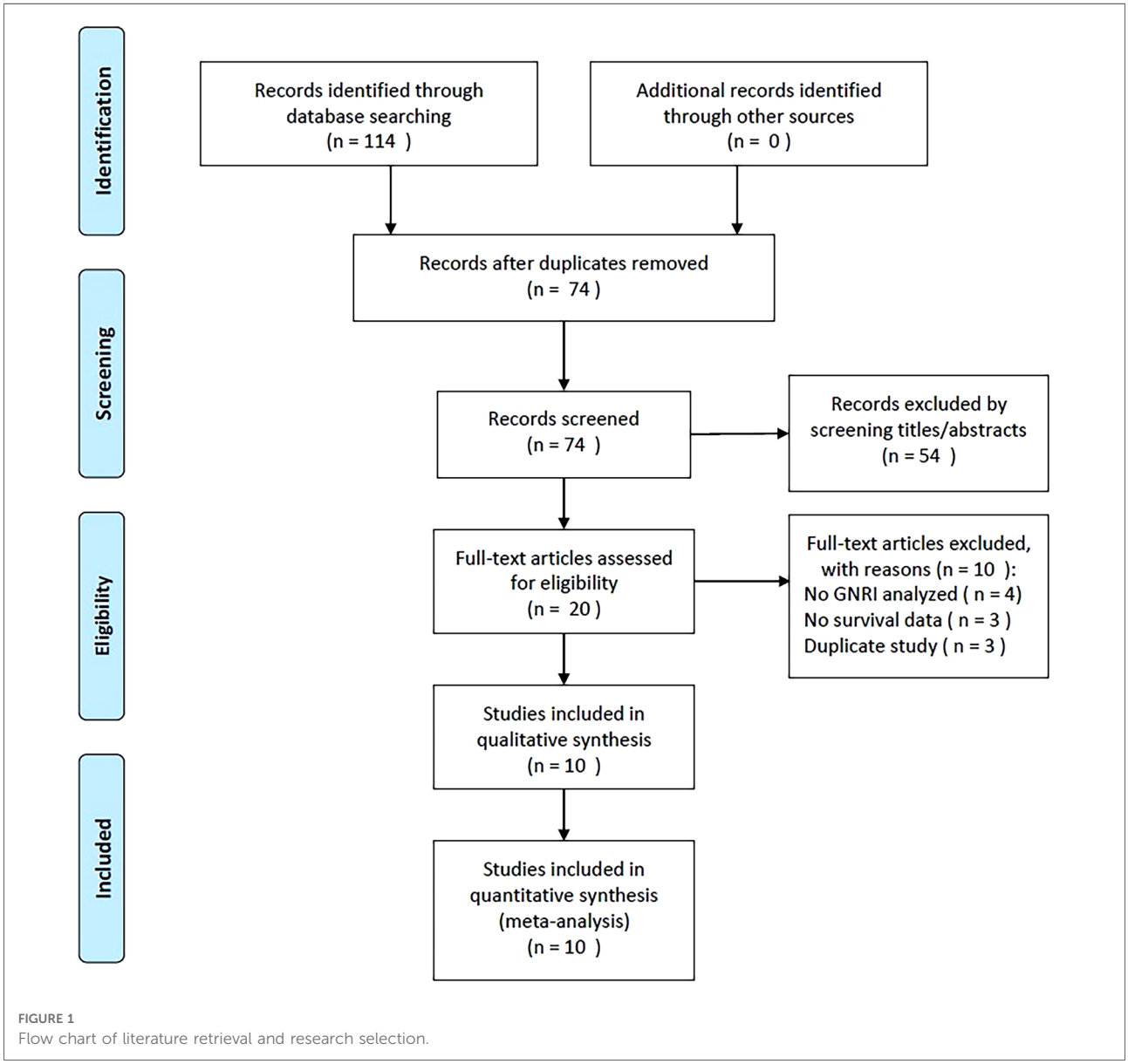

FIGURE 1
Flow chart of literature retrieval and research selection.

studies recruiting 5,834 patients (13–22) with GC were included in this meta-analysis (**Figure 1**, **Table 1**).

Characteristics of included studies

Basic characteristics of the included studies are summarized in **Table 1**. All 10 studies (13–22) were of a retrospective design. Nine studies were conducted in Japan (13–16, 18–22) and one in Korea (17). The total sample size was 5,834, ranging from 106 to 1,166. Six studies recruited patients with stages I-III GC (13, 14, 16, 17, 19, 21), and four studies enrolled patients with early GC (15, 18, 20, 22). Five studies selected 92 as the cut-off value of the GNRI (14, 15, 17, 18, 22), two selected 98 (16, 21), and three selected 94.8 (13), 96 (20), and 97 (19) as their respective GNRI cut-off values. Nine studies reported the prognostic value of the GNRI for OS (13, 14, 16–22), and five studies presented HRs and 95% CIs for CSS (13–16, 19). Seven studies provided HRs and 95% CIs using multivariate analysis (13–16, 18, 19, 22), whereas three studies used univariate analysis (17, 20, 21). The NOS scores of the included studies ranged from 6 to 8, with a median value of 7.5, suggesting that all the included studies were of high quality.

GNRI and OS

A total of nine studies with 5,728 patients (13, 14, 16–22) demonstrated the prognostic role of the GNRI for OS in GC. A random-effects model was applied because of the significant heterogeneity ($I^2 = 88.3\%$, Ph < 0.001). As shown in **Figure 2** and **Table 2**, pooled HR = 1.21, 95% CI = 1.12–1.30, and $P < 0.001$, which suggests that a lower GNRI is a significant prognostic biomarker for patients with GC. Subgroup analysis was conducted through stratification of diverse factors, including sample size, country, treatment, cut-off value, and HR type. As shown in **Table 2**, the combined results suggest that a decreased GNRI remains a significant prognostic indicator for worse OS, irrespective of sample size, country, cut-off value, and HR type (all $P < 0.05$).

GNRI and CSS

Five studies comprising 2,861 patients (13–16, 19) investigated the prognostic efficiency of the GNRI for CSS in GC. There was no significant heterogeneity ($I^2 = 0$, Ph = 0.526), and a fixed-effects model was used. As shown in **Table 2** and **Figure 3**, our results indicate that a lower GNRI is a significant prognostic marker for poor CSS in GC (HR = 2.21, 95% CI = 1.75–2.80, $P < 0.001$). Subgroup analysis demonstrated that the prognostic role of the GNRI for CSS was not affected by sample size or cut-off value (all $P < 0.05$) (**Table 2**).

Relationship between GNRI and clinicopathological factors

The correlation between the GNRI and multiple clinicopathological features was explored in four studies that included 2,755 patients (13–16, 19). As shown in **Figure 4** and **Table 3**, our pooled data illustrates that a low GNRI is significantly associated with advanced pathological stage (OR = 2.27, 95% CI = 1.33–3.85, $P = 0.003$), presence of adjuvant chemotherapy (OR = 1.25, 95% CI = 1.01–1.55, $P = 0.040$), and tumor location in the lower stomach (OR = 1.33, 95% CI = 1.06–1.65, $P = 0.012$). However, there was no significant association between the GNRI and sex (OR = 0.83, 95% CI = 0.67–1.03, $P = 0.087$), tumor differentiation (OR = 0.77, 95% CI = 0.55–1.10, $P = 0.148$), or lymph node metastasis (OR = 1.75, 95% CI = 0.72–4.26, $P = 0.214$; **Figure 4**, **Table 3**) in patients with GC.

Publication bias

Potential publication bias was detected using funnel plots and Begg's test. As shown in **Figure 5**, the shape of the funnel diagram was symmetrical. Moreover, the results of Begg's test ($P = 0.602$ for OS and $P = 0.806$ for CSS) also demonstrated no significant publication bias in this meta-analysis.

Discussion

Previous studies have explored the prognostic significance of the GNRI in patients (13–22), with inconsistent results. In the current meta-analysis, we retrieved data from 10 studies comprising 5,834 cases to systemically shed light on this issue. Our results demonstrated that a lower GNRI is a significant prognostic indicator of worse OS and CSS in patients with GC. The subgroup analysis confirmed the robustness of the results. Furthermore, we also found a significant association between the GNRI and advanced pathological stage, presence of adjuvant chemotherapy, and tumor location in the lower stomach in patients with GC. Taken together, our meta-analysis showed that the pretreatment GNRI is a reliable and readily available prognostic marker for survival outcomes in GC. In addition, patients with GC who have a lower GNRI may have an advanced pathological stage and should be treated with adjuvant chemotherapy following surgical resection.

TABLE 1 Baseline characteristics of included studies in the present meta-analysis.

Study	Year	Country	Study duration	Sample size	Tumor stage	Age (year) median (range)	Gender (M/F)	Treatment	Cut-off value	Follow-up (month) median (range)	Survival outcome	HR type	NOS score
Hirahara, N.	2020	Japan	2010–2017	297	I–III	74 (65–89)	205/92	Surgery	94.8	36.0 (2.8–96.5)	OS, CSS	Multivariate	8
Furuke, H.	2021	Japan	2008–2016	795	I–III	68 (29–89)	534/261	Surgery	92	1–60	OS, CSS	Multivariate	7
Shimada, T.	2021	Japan	2004–2017	106	EGC	76	83/23	ESD	92	89	CSS	Multivariate	7
Sugawara, K.	2021	Japan	2001–2014	1,166	I–III	63 (25–91)	816/350	Surgery	98	82.2	OS, CSS	Multivariate	8
An, S.	2022	Korea	2006–2017	450	I–III	60 (26–92)	301/149	Surgery	92	72	OS	Univariate	7
Hisada, H.	2022	Japan	2009–2019	767	EGC	75 (65–95)	559/208	ESD	92	56.1 (0.6–147.6)	OS	Multivariate	8
Matsunaga, T.	2022	Japan	2005–2015	497	I–III	80.6	325/164	Surgery	97	1–60	OS, CSS	Multivariate	8
Toya, Y.	2022	Japan	2002–2017	740	EGC	86	469/271	ESD	96	1–60	OS	Univariate	7
Tsuchiya, N.	2022	Japan	2002–2018	186	I–III	82 (80–93)	128/58	Surgery	98	1–60	OS	Univariate	6
Yoshikawa, T.	2022	Japan	2006–2020	830	EGC	35–96	615/215	ESD	92	1–166	OS	Multivariate	8

M, male; F, female; EGC, early gastric cancer; ESD, endoscopic submucosal dissection; OS, overall survival; CSS, cancer-specific survival; HR, hazard ratio; NOS, Newcastle-Ottawa Scale.

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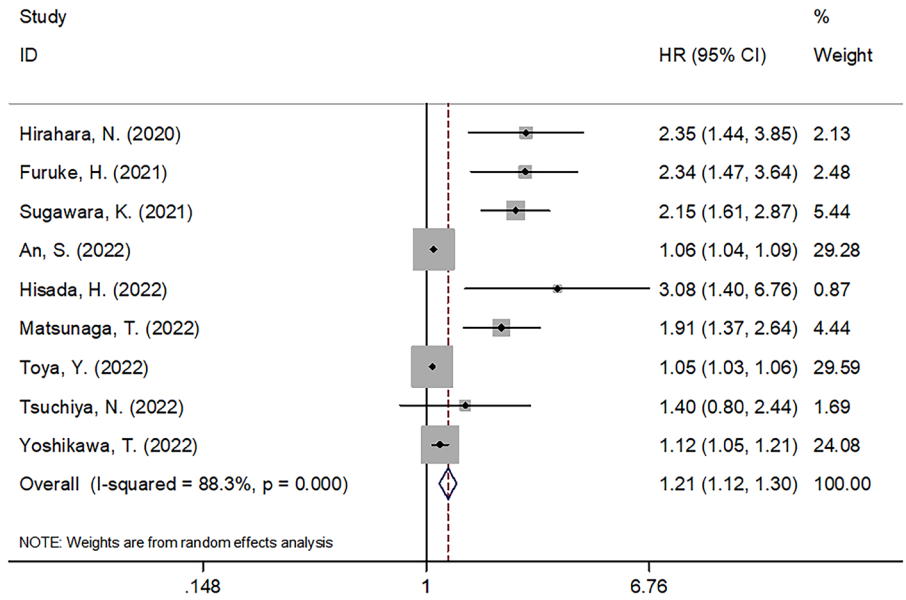

FIGURE 2
Forrest plots of the correlation between GNRI and OS in GC patients.

The GNRI is an objective and simple predictive tool for nutritional status. The underlying mechanism by which a low GNRI results in worse prognosis than a high GNRI among patients with GC is unclear. The GNRI is calculated from albumin, height, and body weight, which are generally measured on admission for most patients. Therefore, the acquisition of the GNRI is easy and cost-effective. A low GNRI can be the result of low serum albumin levels and being underweight. The association between the GNRI and poor prognosis in GC can be explained as follows. First, albumin is the most commonly used indicator in the clinical evaluation of patients' nutritional status (25). Malnutrition is closely associated with impaired immune function, which weakens host antitumor immunity. Hypoalbuminemia is regarded as an indicator of chronic malnutrition and has been proven to be associated with poor long-term prognosis in hospitalized patients, including those with GC (26, 27). Second, weight loss is expected with negative cell-regulating mechanisms of cancer or in patients with aggressive cancers. Lower body weight and body mass index are well-established prognostic factors in patients with various types of cancer (28, 29). Taken together, a low GNRI is a stable prognostic indicator for patients with GC.

The strengths of this meta-analysis are the following. First, the sample size in this meta-analysis was large. A total of 5,834 patients were included, representing a relatively comprehensive patient population. Second, the publication years of all the included studies were in the last 3 years (2020–2022), and more than half of the studies were published in 2022. Therefore, this meta-analysis considers the most recent and updated data on the association between the GNRI and survival in GC. Third, all the included studies were published in English, so their availability is good. Our meta-analysis showed some hematological parameters that are promising prognostic factors in patients with cancer. These indexes are simple and easily accessible, with no additional costs to or examination of patients. Additional research efforts should be devoted to hematological prognostic factors. Furthermore, this meta-analysis has implications for clinical practice. During treatment of patients with GC who have a low GNRI, attention should be paid to their nutritional status. Improved nutrition in patients with a low GNRI may prevent poor prognosis.

Subgroup analyses showed that a low GNRI remained a significant prognostic factor for worse OS in GC in subgroups of sample size, country, cut-off value, and HR type (all $P < 0.05$; **Table 2**). However, a decreased GNRI predicted OS in patients with GC undergoing surgery (HR = 1.77, 95% CI = 1.20–2.62, $P = 0.004$), but not in those undergoing endoscopic submucosal dissection (ESD) (HR = 1.10, 95% CI = 1.00–1.23, $P = 0.062$) (**Table 2**). Similar results were also found for CSS (**Table 2**). This result is interesting and can be explained as follows. First, patients with GC undergoing ESD must meet the gastric cancer treatment guidelines (30) and are usually diagnosed with early GC. In contrast, patients undergoing surgery are in the early and advanced stages and typically undergo adjuvant chemotherapy (30). Second, ESD is less invasive than surgery. Therefore, malnutrition is less prevalent in patients with GC undergoing ESD than in those undergoing surgery. Moreover, the GNRI is not a prognostic

TABLE 2 Subgroup analysis of prognostic value of GNRI for OS and CSS in patients with gastric cancer.

Subgroup	No. of studies	No. of patients	HR (95% CI)	P	Effects model	Heterogeneity I^2 (%)	Ph
OS							
Overall	9	5,728	1.21 (1.12–1.30)	<0.001	Random	88.3	<0.001
Sample size							
≤500	4	1,430	1.56 (1.02–2.41)	0.042	Random	86.9	<0.001
>500	5	4,298	1.40 (1.17–1.67)	<0.001	Random	91.1	<0.001
Country							
Japan	8	5,278	1.55 (1.31–1.84)	<0.001	Random	89.8	<0.001
Korea	1	450	1.06 (1.04–1.09)	<0.001	-	-	-
Treatment							
Surgery	6	3,391	1.77 (1.20–2.62)	0.004	Random	91.2	<0.001
ESD	3	2,337	1.10 (1.00–1.23)	0.062	Random	80.8	0.006
Cut-off value							
≤92	4	2,842	1.20 (1.04–1.38)	0.012	Random	85.6	<0.001
>92	5	2,886	1.68 (1.10–2.55)	0.016	Random	91.5	<0.001
HR type							
Multivariate	6	4,352	1.97 (1.34–2.90)	0.001	Random	89.5	<0.001
Univariate	3	1,376	1.06 (1.04–1.07)	<0.001	Fixed	0	0.481
CSS							
Overall	5	2,861	2.21 (1.75–2.80)	<0.001	Fixed	0	0.526
Sample size							
≤500	3	900	1.76 (1.15–2.70)	0.009	Fixed	0	0.996
>500	2	1,961	2.45 (1.84–3.25)	<0.001	Fixed	37.9	0.204
Treatment							
Surgery	4	2,755	2.22 (1.75–2.82)	<0.001	Fixed	3.6	0.375
ESD	1	106	1.60 (0.17–15.03)	0.681	-	-	-
Cut-off value							
≤92	2	901	1.99 (1.33–3.00)	0.001	Fixed	0	0.845
>92	3	1,960	2.33 (1.75–3.11)	<0.001	Fixed	28.0	0.250

GNRI, geriatric nutritional risk index; OS, overall survival; CSS, cancer-specific survival; HR, hazard ratio; ESD, endoscopic submucosal dissection.

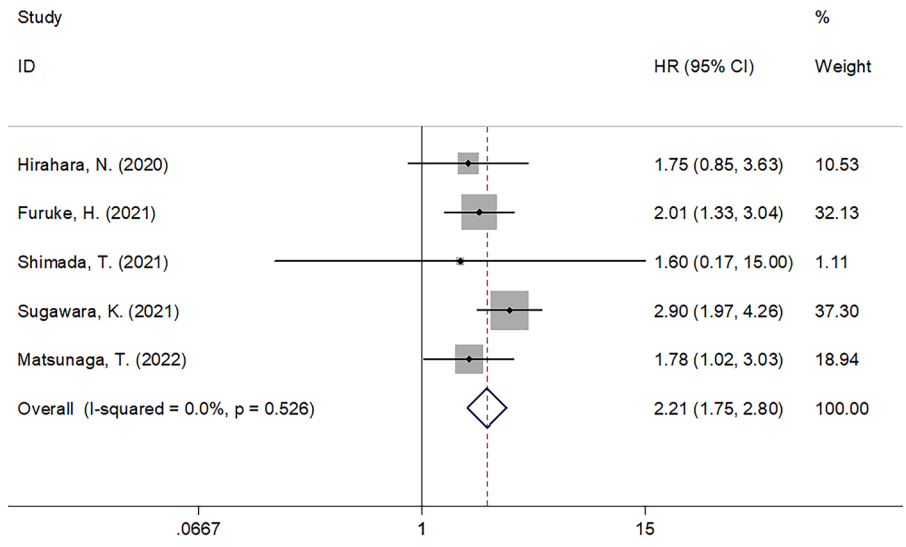

FIGURE 3
Forrest plots of the correlation between GNRI and CSS in GC patients.

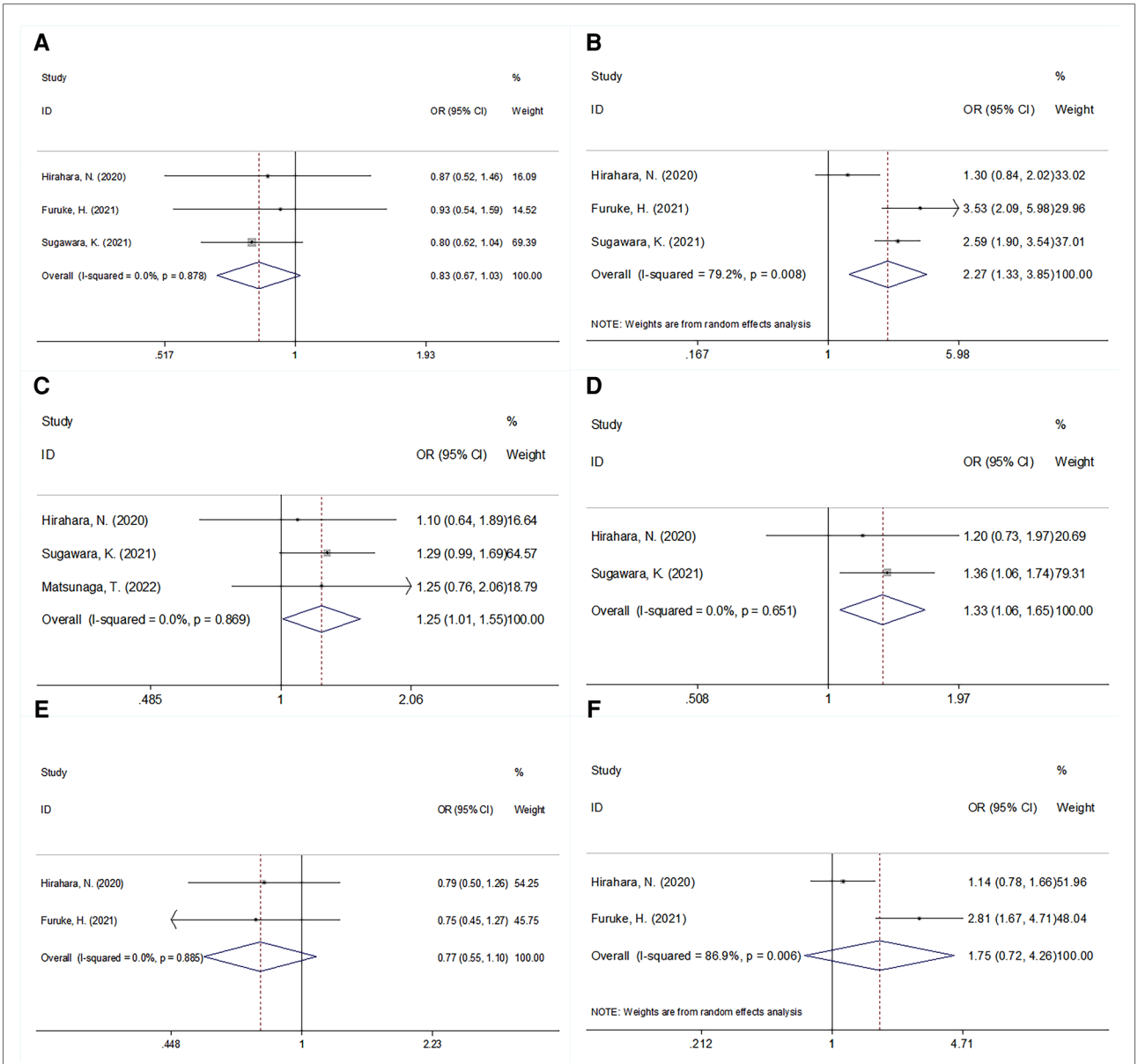

FIGURE 4
Forrest plots of the relationship between GNRI and clinicopathological features in patients with GC. (A) Gender (male vs. female); (B) pathological stage (III vs. I–II); (C) adjuvant chemotherapy (presence vs. absence); (D) tumor location (lower vs. upper + middle); (E) tumor differentiation (poor vs. well/moderate); and (F) lymph node metastasis (N+ vs. N0).

TABLE 3 The association between GNRI and clinicopathological features in patients with gastric cancer.

Factors	No. of studies	No. of patients	OR (95% CI)	*P*	Effects model	Heterogeneity	
						I^2 (%)	Ph
Gender (male vs. female)	3	2,258	0.83 (0.67–1.03)	0.087	Fixed	0	0.878
Pathological stage (III vs. I–II)	3	2,258	2.27 (1.33–3.85)	0.003	Random	79.2	0.008
Adjuvant chemotherapy (presence vs. absence)	3	1,960	1.25 (1.01–1.55)	0.040	Fixed	0	0.869
Tumor location (lower vs. upper + middle)	2	1,463	1.33 (1.06–1.65)	0.012	Fixed	0	0.651
Tumor differentiation (poor vs. well/moderate)	2	1,092	0.77 (0.55–1.10)	0.148	Fixed	0	0.885
LN metastasis (N+ vs. N0)	2	1,092	1.75 (0.72–4.26)	0.214	Random	86.9	0.006

GNRI, geriatric nutritional risk index; OR, odds ratio; LN, lymph node.

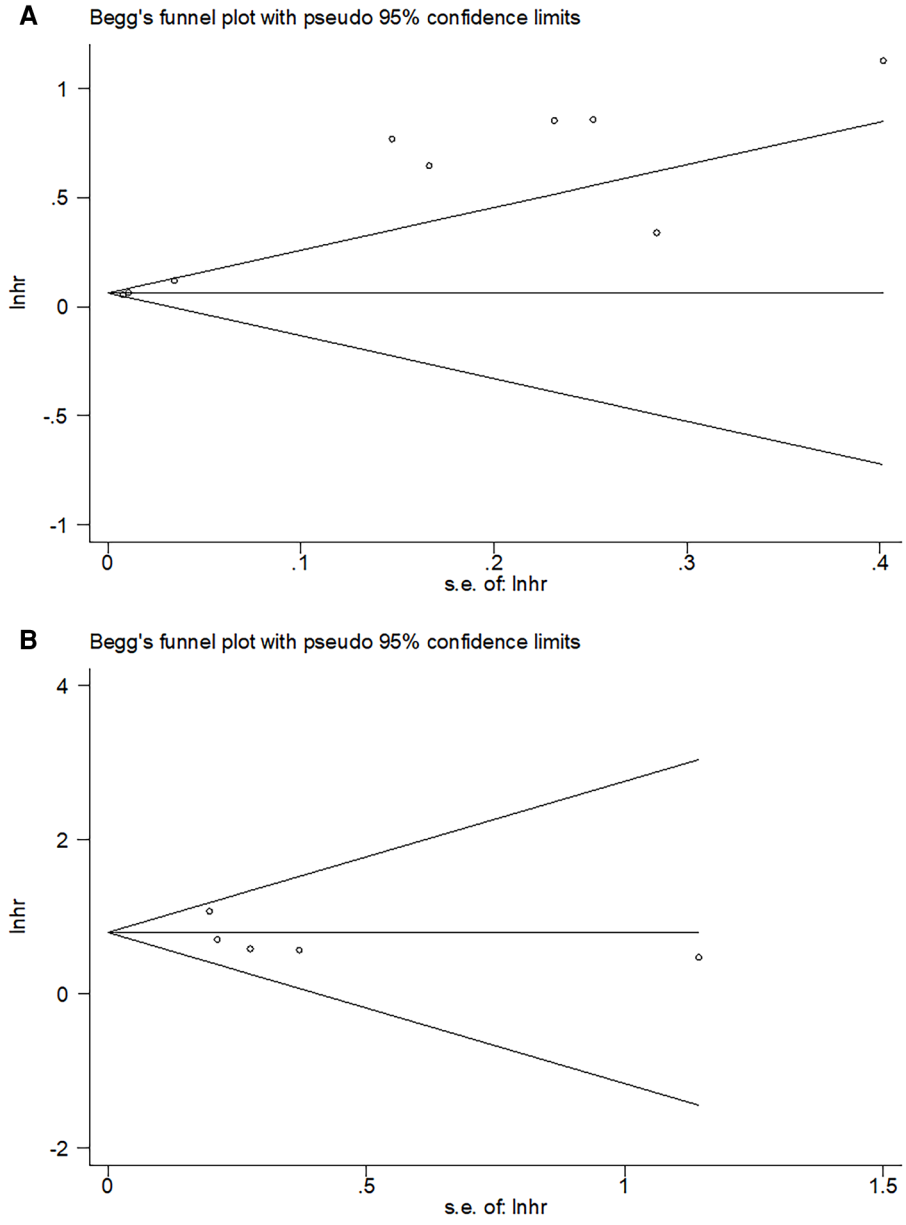

FIGURE 5
Begg's funnel plot. (**A**) OS, $P = 0.602$; (**B**) CSS, $P = 0.806$.

marker for patients with GC undergoing ESD. The GNRI can also be applied in combination with other nutritional indexes, including the prognostic nutritional index, controlling nutritional status score, albumin-to-globulin ratio, and C-reactive protein to albumin ratio, to improve the prognostic efficiency for GC. Nomograms based on these parameters can also be explored in future studies.

Many meta-analyses have recently reported the prognostic significance of the GNRI in a variety of solid tumors (31–35). A recent meta-analysis including 3,981 patients showed that the pretreatment GNRI was significantly associated with prognosis in patients with esophageal cancer, and a lower GNRI predicted a worse survival rate (32). Another meta-analysis indicated that patients with lung cancer with a lower pretreatment GNRI had inferior prognoses on the basis of data from 2,012 patients (36). Zhao et al. reported in their meta-analysis that the GNRI at baseline could be an independent predictor of poor survival outcomes in patients with colorectal cancer (31). In this meta-analysis, we observed a significant prognostic role of GNRI in GC, which was in line with the findings for other types of cancer, suggesting the general prognostic impact of GNRI on solid tumors.

This meta-analysis had some limitations. First, all the included studies had a retrospective design. Therefore, a selection bias may exist. Second, all the included studies were conducted in East Asia, although we did not restrict the geographical regions of the eligible studies. However, the publication language of all the studies was English. This may be due to Japan's efforts to prevent and treat gastric cancer (37–39). Third, the cutoff values of the GNRI ranged from 92 to 98, which may have introduced heterogeneity in this meta-analysis. Fourth, the heterogeneity exists and is significant in several analysis groups, including in OS, pathological stage, and lymph node metastasis (**Tables 2**, **3**). To address this, we used a random effects model in these groups. Thus, large multicenter prospective trials are needed to validate the prognostic role of the GNRI in patients with GC.

In summary, our meta-analysis identified that the pretreatment GNRI level was a significant prognostic factor for patients with GC. A low GNRI is associated with worse OS and inferior CSS in patients with GC.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

Author contributions

LH contributions, data collection, drafting, and critical revision of the manuscript. YL and LQ contributions, drafting and critical revision of the manuscript. LH, YL, and FZ contributions, study design and conception, drafting, and critical revision of the manuscript. All authors revised and checked the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.1087298/full#supplementary-material.

SUPPLEMENTARY TABLE S1
The PRISMA

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Feasibility and preliminary experience of single-incision plus one-port laparoscopic total gastrectomy with Overlap esophagojejunostomy for gastric cancer: A study of 10 cases

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Background: This study aimed to explore the feasibility and safety of single-incision plus one-port laparoscopic total gastrectomy (SITG + 1) with Overlap esophagojejunostomy (SITG + 1-Overlap) and to share preliminary experiences.
Methods: This retrospective study included 10 patients with gastric cancer located in the cardia or body who underwent SITG + 1-Overlap between August 2020 and October 2021.The demographics, tumor characteristics, postoperative outcomes, and short-term complications of all the enrolled patients were summarized and statistically analyzed. Data were expressed as mean ± standard deviation (SD) if they were normally distributed. Otherwise, Median (Quartile1, Quartile3) was used.
Results: In the collective perioperative data of these 10 patients who underwent radical gastrectomy, the median of the length of transumbilical incision and blood loss were 3.0 cm and 100.0 ml respectively, and the mean operation time and 385.5 ± 51.6 min. Postoperative data indicated that the gastric tube was removed on 2.0 (2.0, 3.0) days, and the timing of first feeding, activity, flatus, and defecation was 1.5 (1.0, 2.0) days, 2.0 (2.0, 2.0) days, 3.0 (2.0, 3.0) days, and 3.8 ± 0.6 days, respectively. The timing of drainage tube removal was 4.6 ± 1.0 days after operation. The duration of hospital stay was 7.5 ± 1.2 days and the VAS pain scores for the 3 days following surgery were 3.0 (2.0, 3.3), 2.0 (2.0, 3.0), and 1.5 (1.0, 2.0) respectively. The mean number of retrieved lymph nodes was 30.7 ± 13.2. Most biochemical indicators gradually normalized with the recovery of the patients after surgery. No 30-day postoperative complications were noted.
Conclusions: For the first time, our preliminary data indicate the feasibility and safety of Overlap esophagojejunostomy in SITG + 1 surgery. This modified Overlap procedure has the potential to simplify the reconstruction procedure and lower the technical challenge of SITG + 1 radical gastrectomy for cardia or upper gastric cancer in the early and advanced stages.

KEYWORDS
gastric cancer, single-incision plus one-port laparoscopic total gastrectomy (SITG + 1), Overlap esophagojejunostomy, total gastrectomy, minimally invasive technique

1. Introduction

As a novel, minimally invasive technique, laparoscopic surgery has become the primary treatment for gastric cancer (1). Furthermore, new emerging techniques have been developed to reduce the invasiveness of laparoscopic surgery (2). In recent years, single-incision laparoscopic surgery (SILS) has emerged as a popular research topic (3). The SILS technique takes full advantage of the innate fold of the umbilicus. The vertical endoscope operation channel significantly improved the postoperative cosmetic appearance of the abdominal wall and reduced the surgical trauma. The SILS technique has been used in gastric cancer surgery, and the number of case reports in this field is increasing. However, most studies on SILS have focused on distal gastric cancer, and the application of total gastrectomy has only been sporadically reported, mainly because of the difficulty of performing radical total gastrectomy and subsequent esophagojejunostomy under a single incision (4).

As an alternative method to increase the feasibility and reduce the technical challenges of pure single-incision laparoscopic gastrectomy, the single-incision plus one-port laparoscopic gastrectomy (SILG + 1) technique has been gradually adopted by an increasing number of surgical teams in recent years (5, 6). We have already demonstrated the great potential of SILG + 1 procedures in radical surgery for gastric cancer in both early and advanced stages (7). The shorter incision length, improved postoperative pain, and similar postoperative complication rates fully demonstrate the advantages of the SILG + 1 procedure over the conventional 5-port laparoscopic procedure. The better cosmetic score and similar cosmetic effect after month postoperatively display the unique advantage of a single incision procedure. Moreover, for the first time, a π-shaped anastomosis, named SILT-π, was introduced to overcome the technical challenges and simplify the esophagojejunal reconstruction procedure after single-incision plus one-port laparoscopic total gastrectomy (SITG + 1).

It is noteworthy that the unique characteristics of "pre-pulling and latter transection" in π-shaped anastomosis have its own limitations as compared with other reconstruction methods: once the upper esophageal resection margin of the intraoperative frozen section is positive after π-shaped esophagojejunostomy, it will be more challenging for the surgeon to re-perform the esophagojejunostomy in the higher position after the extended resection of the adjacent esophagus, especially in SITG + 1 conditions. Therefore, new reconstruction methods are needed for esophagojejunostomy, especially for cardia cancer with a relatively higher location and poorly defined upper margin on endoscopic examination. The Overlap method for esophagojejunostomy was introduced by Inaba et al. in 2010 (8). This Overlap anastomosis renders the positions of the esophagus and jejunum consistent with the direction of the intestinal peristalsis, which was already well documented, with the lowed incidence of anastomotic-related complications, such as mesenteric tension, anastomotic stricture and leakage (9–11). Moreover, the "pre-transection and latter anastomosis" design of the Overlap method avoids the obvious limitation of the π-shaped anastomosis, considering the possibility of a positive upper resection margin. We retrospectively analyzed the short-term outcomes of 10 patients who underwent SITG + 1 with Overlap esophagojejunostomy (SITG + 1-Overlap), evaluated its feasibility and safety, and summarized the preliminary experience.

2. Materials and methods

2.1. Patients

Ten male patients with gastric cancer who underwent SITG + 1-Overlap surgery between August 2020 and October 2021 at the Xinqiao Hospital of the Army Medical University were included in our study. The criteria for eligibility included age within 18–80 years old, a preoperative pathological diagnosis of gastric cancer, a clinical tumor stage of T1-4N1-3M0, BMI within 18–27 kg/m^2. Exclusion criteria included pathological stage IV gastric cancer, neoadjuvant chemotherapy history, and history of severe heart, liver, lung, or kidney dysfunction. All procedures were performed in accordance with the ethical standards of the Committee on Human Experimentation (China Registered Clinical Trial Ethics Review Committee No. chiECRCT-201701109). Informed consent was obtained from all patients. The tumor-node-metastasis (TNM) stage was determined based on the eighth edition of the American Joint Committee on Cancer (AJCC) staging manual.

2.2. Surgical technique

2.2.1. SITG + 1 with D1+ or D2 lymph node dissection

Here, we describe the SITG + 1-Overlap with the D1+ or D2 lymph node dissection procedure. Briefly, the patient was placed in a supine reverse Trendelenburg position. The surgeon and assistant stood on the left and right sides of the patient, respectively, while the scopist stood between the patient's legs (**Figures 1A,B**). A commercial four-hole wound-protecting device was then inserted into a transumbilical incision measuring 2.5–5.0 cm (**Figure 1C**). The abdominal cavity was insufflated with carbon dioxide and a 10-mm three-dimensional high-definition scope was inserted *via* a 12-mm hole in the wound-protecting device. Separately, an 12-mm additional assistant trocar was placed as an auxiliary operating

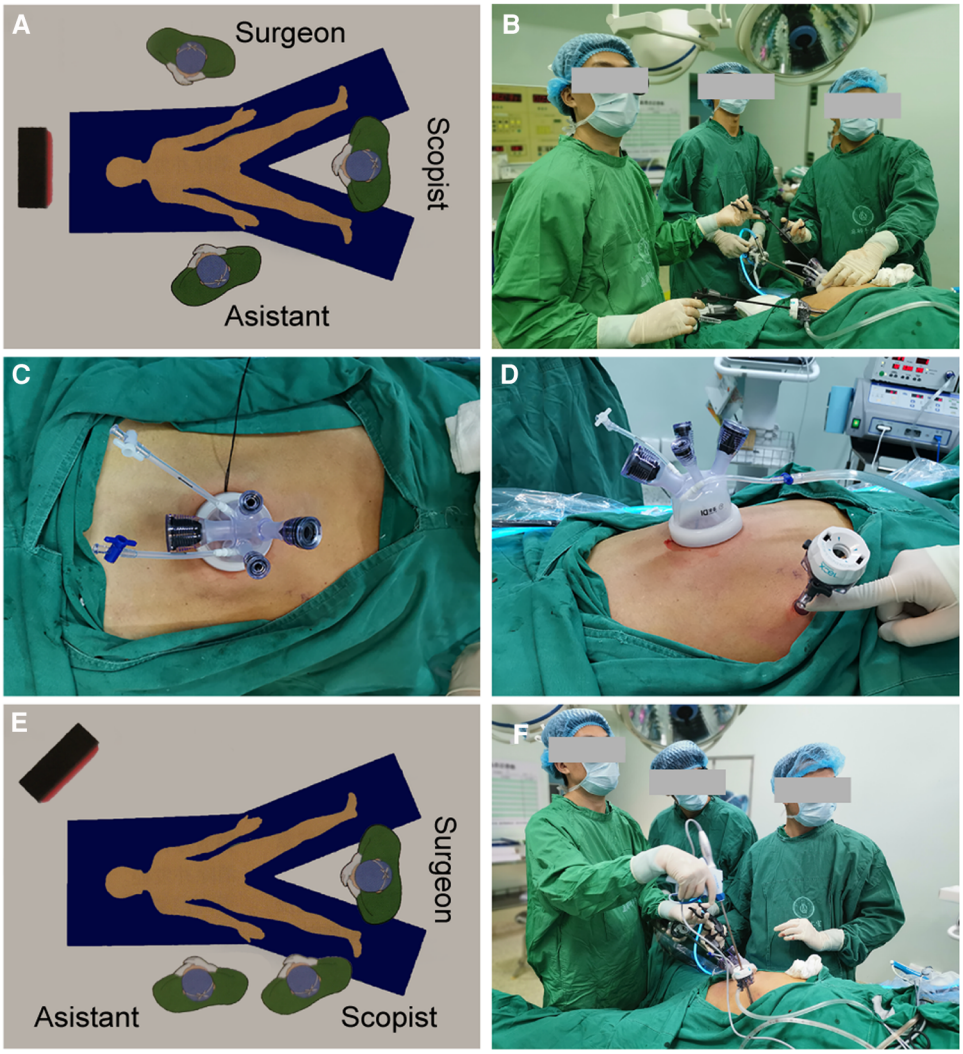

FIGURE 1
(A,B) Diagram illustrating the surgical field setup at the beginning of the surgery. (C,D) A commercial four-hole wound-protecting device was inserted into a transumbilical incision, and an 12-mm additional assistant trocar was placed as an auxiliary operating hole 2 cm below the costal margin of the anterior axillary line in the upper left abdomen. (E,F) When the surgeon cleaned the lymph nodes on the left side of the greater curvature of the stomach, the surgeon moved from the patient's left side to between the patient's legs, with the first assistant and the other assistant holding the lens while standing on the right side of the patient.

hole, 2 cm below the costal margin of the anterior axillary line in the upper left abdomen (Figure 1D). After the left lobe of the liver was overhung using a percutaneous 2-0 nylon purse-string suture (one end of suture was secured to the abdomen; the another was secured to the dissected gastrohepatic ligament with a 2–3 hemolok ligation clip) (Figure 2A), we performed routine total gastrectomy with D1 + or D2 lymph node dissection, including partial omentectomy. When the surgeon cleaned the lymph nodes on the left side of the greater curvature of the stomach, the surgeon moved from the patient's left side to between the patient's legs, with the first assistant and the other assistant holding the lens while standing on the patient's right side (Figures 1E,F).

2.2.2. Intracorporeal Overlap esophagojejunostomy

The specific steps of this procedure are illustrated in Figure 2. Briefly, the lower esophagus was fully dissociated along its periphery. The Overlap anastomosis technique was used to create side-to-side esophageal and jejunal anastomoses. In this technique, the pre-separation plane of the lower esophagus is first determined according to the upper margin of the tumor. Suturing was performed *via* a stitch with a 4-0 barbed line on the left and right sides of the pre-separation esophagus. The assistant pulled the barbed suture and the surgeon pulled the stomach downward with the left hand. The esophagus and stomach were transected

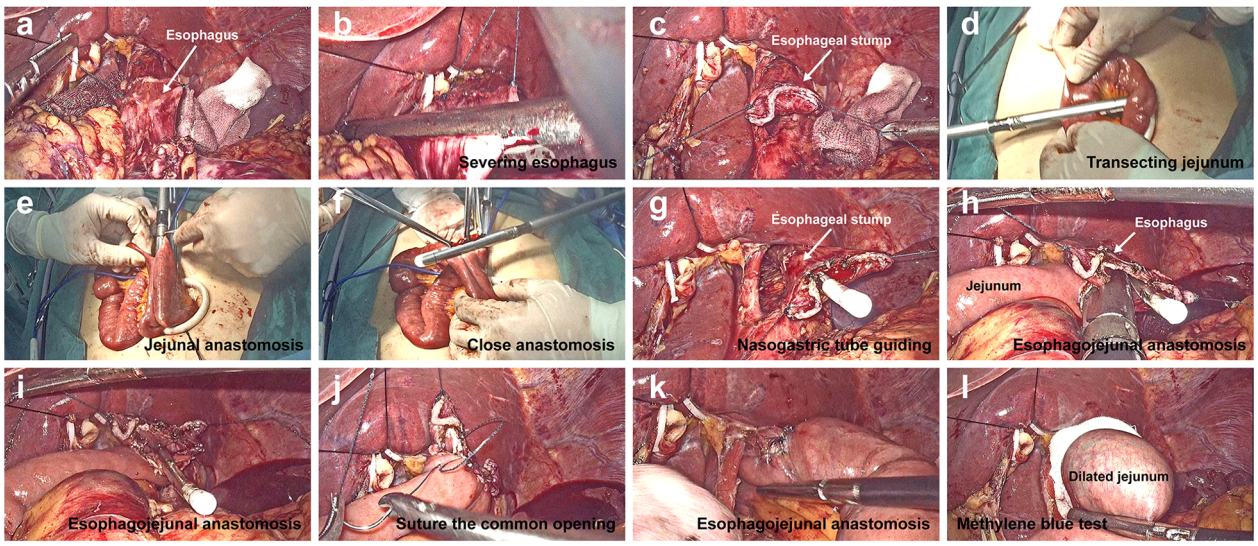

FIGURE 2
Digestive tract reconstruction in single-incision plus one-port laparoscopic gastrectomy (SILG + 1). (A–C) The left lobe of the liver was overhung using a percutaneous 2-0 nylon purse-string suture and hemolok ligation clip. Suturing was performed *via* a stitch with a 4-0 barbed line on the left and right sides of the pre-separation esophagus. The esophagus and stomach were transected using a linear stapler. (D–F) a side-to-side jejunal anastomosis was created using the stapler between the afferent jejunum and a point 40 cm below the efferent jejunum. (G) After opening a hole in the middle of the esophageal stump, the gastric tube was pulled out from the hole to guide the correct lumen. (H,I) a side-to-side esophagojejunal anastomosis (Overlap) was performed. (J,K) A 4-0 barbed line was used to close the common opening, and another 4-0 barbed line was used to reinforce the anastomotic stoma by suturing the seromuscular layer. (L) Methylthionine chloride was injected through the gastric tube to detect the integrity of the anastomosis.

using a linear stapler through an additional auxiliary hole (Figures 2B,C). The surgeon closed the pneumoperitoneum, removed the umbilical wound-protecting device, and removed the entire stomach specimen.

After a jejunal loop located approximately 30 cm distal to the Treitz ligament was taken out and transected using a linear stapler outside the abdominal cavity (Figure 2D), a side-to-side jejunal anastomosis was created using a stapler between the afferent jejunum and a point 40 cm below the efferent jejunum (esophagojejunal anastomosis) and common opening was closed using a stapler (Figures 2E,F). After the mesenteric hiatus was closed, the bowel was inserted into the abdominal cavity, and pneumoperitoneum was re-established. To facilitate esophagojejunal anastomosis, the diaphragmatic angles on both sides were cut appropriately to provide space for the anastomosis. After opening a hole in the middle of the esophageal stump, the gastric tube was pulled out to guide the correct lumen (Figure 2G). One fork of linear stapler was inserted through a hole 7 cm from the efferent jejunum stump, and another fork was inserted into the hole in the esophageal stump along the gastric tube, in the process of which the 4-0 barbed line was used to help pull the esophagus. A side-to-side esophagojejunal anastomosis was created (Figures 2H,I). A 4-0 barbed suture reserved in the stump of the esophagus was used to close the common opening, and another 4-0 barbed suture reinforced the anastomosis by suturing the seromuscular layer (Figures 2J,K). The gastric tube was placed at the anasomotic site and the distal jejunum was clipped using laparoscopic forceps. Methylthionine chloride was injected into the gastric tube to determine the integrity of the anastomosis (Figure 2L).

2.3. Data collection and statistical analysis

We recorded basic data on age, sex, body mass index (BMI), ASA score, clinical stage, and tumor location. Surgical data included incision length, operative time, intraoperative blood loss, and intraoperative blood transfusion. Postoperative data were also recorded, including VAS pain score, timing of gastric tube removal, first feeding, activity, flatus, defecation, duration of hospital stay, and any complications. Postoperative pathology included tumor size and differentiation, proximal and distal resection margin distances, number of dissected lymph nodes, and TNM stage. Perioperative biochemical indices were recorded separately. Data were analyzed using SPSS software (version 20.0; SPSS, Chicago, IL, United States). Data were expressed as mean ± standard deviation (SD) if they were normally distributed. Otherwise, median (Quartile1, Quartile3) was used.

3. Results

3.1. Patients' information and clinical characteristics of tumors

The basic information of the enrolled patients and the clinical characteristics of the tumors are summarized in Table 1. All patients were male, and their ages and BMI were 61.8 ± 8.2 years and 19.9 (18.0, 27.0) kg/m^2 respectively. Tumor locations included six in the gastric body and four in the cardia of the stomach. The preoperative clinical stage ranged from cT1N0M0 to cT4N3M0.

3.2. Perioperative situations and postoperative pathological examination

The intraoperative and postoperative data are presented in Table 2. The length of the surgical incision was 3.0 (2.5, 3.3) cm, and the total operation time was 385.5 ± 51.6 min. The intraoperative blood loss was 100.0 (50.0, 162.5) ml during their operations. A small incision around the umbilicus seems to be more aesthetic (on the day of surgery vs. day 21 after surgery) (Figures 3A,B). There were no any intraoperative adverse events.

Regarding the recovery process, the timing of the first feeding, activity, flatus, defecation, and duration of postoperative hospital stay are recorded in Table 2. The gastric tube was removed 2–3 days after surgery, and the abdominal drainage tube was removed 3–6 days after surgery. The timing of first exhaust was 3.0 (2.0, 3.0) days, and the timing of first defecation were 3.8 ± 0.6 days. The VAS pain scores were 3.0 (2.0, 3.3), 2.0 (2.0, 3.0), and 1.5 (1.0, 2.0) on POD1, 2 and 3 respectively. The postoperative hospital stay was 7.5 ± 1.2 days. Noteworthily, Patient 7 already met the discharge criteria on day 6 after surgery, but the outbreak of COVID-19 infection led to a prolonged hospital stay. The patency of the anastomosis was determined by barium meal examination (Figure 3C). No 30-day postoperative complications were noted.

Postoperative pathological results analysis recorded in Table 2 and showed that the proximal surgical margin was 3.1 ± 2.0 cm and the distal margin was 8.4 ± 3.0 cm. The number of dissected lymph nodes was 30.7 ± 13.2. Postoperative pathological stages ranged from pT1N0M0 to pT4N3M0.

3.3. Perioperative biochemical indicators

Perioperative biochemical indicators, including White Blood Cells (WBC), hemoglobin (Hb), procalcitonin (PCT), aspartate transaminase (AST), Creatinine, Prealbumin and Albumin, are shown in Table 3. These indicators were collected preoperatively and on POD 1, 3, and 5 days after surgery. Most biochemical indicators gradually normalized with the recovery of the patients after surgery. However, the prealbumin level was relatively low on POD 1, 3, and 5. Two patients had significantly abnormal liver function on postoperative first day, which may be related to intraoperative liver overhung.

4. Discussion

Reduced-port laparoscopic surgery (RPS) and single-incision laparoscopic surgery (SILS) have become increasingly popular (12). As an alternative method to increase the feasibility and reduce the technical challenges of pure SILS, the single-incision plus one-port laparoscopic surgery (SILS + 1) technique has been gradually applied by an increasing number of surgical teams in recent years (13, 14). Regarding the application of SITG + 1, most studies have only observed the short-term efficacy of SITG + 1 in distal early gastric

TABLE 1 Patients' basic information and clinical characteristics of tumor.

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Mean ± SD/ Median (Q1, Q3)
Gender (Male/ Female)	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	–
Age (years)	65	50	61	48	62	67	58	65	66	76	61.8 ± 8.2
BMI (kg/m^2)	26.4	18.7	18.0	25.7	20.7	19.0	18.9	27.0	23.4	18.6	19.9 (18.7, 25.9)
ASA Score	II	II	II	II	III	II	II	II	II	III	–
Clinical stage (M0)	cT4N1	cT4Nx	cT1N0	cT4N0	cT4N3	cT1N0	cT4N0	cT1N0	cT3N3	cT3N3	–
Tumor location	cardia	body	body	cardia	body	body	body	body	cardia	cardia	–

BMI, body mass index; ASA Score, american society of anesthesiologists score; Clinical stage is according to AJCC 8th edition; Q1, Quartile1; Q3, Quartile3.

TABLE 2 Perioperative situations and postoperative pathological examination.

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Mean ± SD/ Median (Q1, Q3)
Operation duration (min)	315.0	295.0	425.0	460.0	425.0	385.0	415.0	405.0	360.0	370.0	385.5 ± 51.6
Incision length (cm)	3.0	2.5	2.5	3.0	3.0	4.0	3.0	5.0	2.5	3.0	3.0 (2.5, 3.3)
Blood lose (ml)	100.0	100.0	50.0	150.0	50.0	200.0	150.0	100.0	50.0	200.0	100.0 (50.0, 162.5)
Intraoperative complications	no	no	no	no	no	no	no	no	no	no	–
Nasogastric Tube Removal (days)	2.0	2.0	2.0	3.0	3.0	3.0	3.0	2.0	2.0	2.0	2.0 (2.0, 3.0)
First feeding (days)	1.0	2.0	2.0	1.0	2.0	2.0	3.0	1.0	1.0	1.0	1.5 (1.0, 2.0)
First activity (days)	2.0	3.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0 (2.0, 2.0)
First Flatus (days)	3.0	3.0	2.0	2.0	3.0	3.0	3.0	3.0	2.0	2.0	3.0 (2.0, 3.0)
First Defecation (days)	4.0	5.0	4.0	5.0	5.0	6.0	5.0	4.0	3.0	4.0	3.8 ± 0.6
Drainage Tube Removal (days)	4.0	6.0	4.0	5.0	5.0	6.0	5.0	4.0	3.0	4.0	4.6 ± 1.0
Hospital Stay (days)	6.0	7.0	8.0	7.0	8.0	8.0	10.0	6.0	8.0	7.0	7.5 ± 1.2
VAS score											
POD 1	3.0	4.0	2.0	4.0	3.0	2.0	2.0	3.0	2.0	3.0	3.0 (2.0, 3.3)
POD 2	2.0	3.0	2.0	2.0	3.0	2.0	2.0	3.0	3.0	2.0	2.0 (2.0, 3.0)
POD 3	2.0	2.0	1.0	2.0	2.0	1.0	1.0	1.0	2.0	1.0	1.5 (1.0, 2.0)
Complications	no	no	no	no	no	no	no	no	no	no	–
Tumor cell differentiation	P	P	P	P	P	M	M	M	M	H	–
Proximal edge (cm)	0.5	5.0	3.0	2.0	4.5	3.0	5.0	6.0	1.0	1.0	3.1 ± 2.0
Distal edge (cm)	10.0	7.0	10.0	12.0	7.0	9.5	9.5	1.2	8.0	10.0	8.4 ± 3.0
Positive LNs	0	7	0	0	12	13	0	0	0	8	–
Retrieved LNs	17	24	18	14	30	40	54	47	41	22	30.7 ± 4.4
Tumor size (maximum diameter, cm)	4.2	3.5	3.0	1.5	4.0	3.5	1.0	4.3	3.0	3.5	3.2 ± 0.3
Pathological stage (M0)	pT4N0	pT4N3	pT1N0	pT4N0	pT4N3	pT4N3	pT1N0	pT4N0	pT1N0	pT4N3	–

POD, days postoperation; P, poorly differentiated; M, moderately differentiated; H, high differentiated; Q1, Quartile1, Q3, Quartile3.

cancer (5, 15, 16). Based on our clinical experience and on improvements in our technique, single-incision plus one-port laparoscopic total gastrectomy (SITG + 1) has been proven to be feasible and safe for radical resection of early and advanced gastric cancer (7). However, SITG + 1 is difficult to create a good surgical field because surgical instruments interfere with each other through a single incision. Owing to the narrow field of view, the doctor's operating space can be affected, leading to difficulties in constructing the digestive tract (17, 18). Additionally, the surgical procedure is complex and requires experienced surgeons. Unexpected adverse events can be difficult to manage intraoperatively.

In 2022, our study extended the indication of the SITG + 1 technique to advanced gastric cancer, particularly total gastrectomy (7). SITG + 1 combined with esophagojejunal π-shaped anastomosis (SITG-π) has been introduced to overcome technical challenges and simplify esophagojejunal anastomosis after total gastrectomy. Moreover, a good long-term outcome will be published recently, according to a 3-year follow-up study (unpublished data). However, we noticed

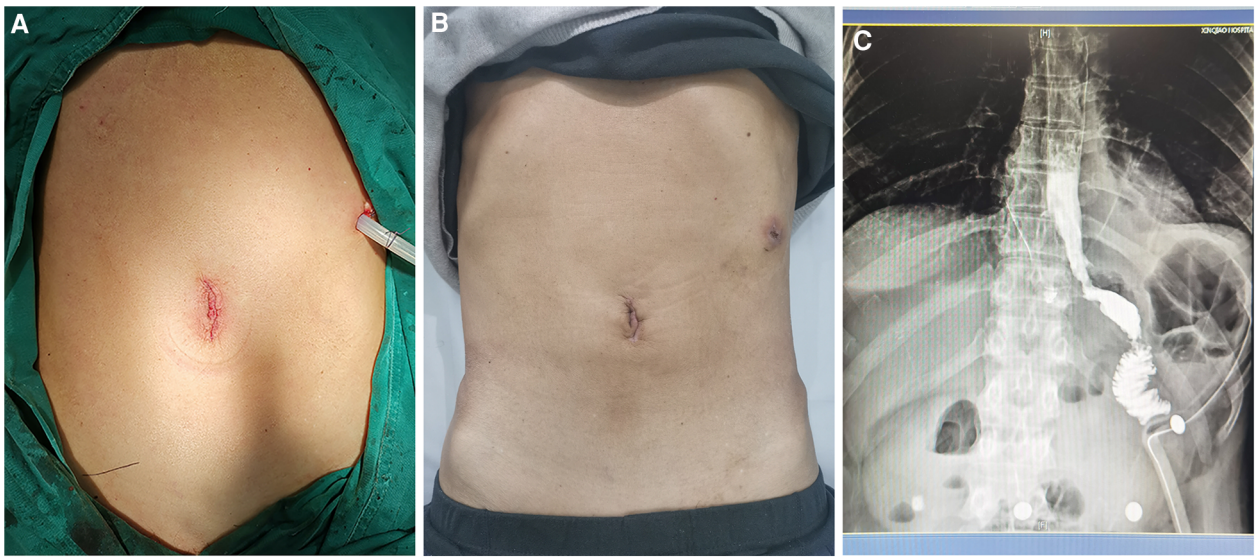

FIGURE 3
(A,B) Small incision around the umbilicus is shown on the day of surgery vs. day 21 after surgery. (C) Patency of the anastomosis was detected using barium meal examination.

some drawbacks of the SITG-π anastomosis. A fatal disadvantage of this method is that the tumor margin can only be checked after anastomosis, leading to a hidden danger of a positive margin. Once intraoperative freezing results in a positive esophageal margin, the surgeon needs to enlarge the resection of the esophagus under SITG + 1 and re-perform esophagojejunal anastomosis at a higher position, which can be challenging. Additionally, an esophagojejunal π-shaped anastomosis may lead to an antiperistalsis at the junction of the esophagus and jejunum, which is not conducive to esophageal emptying (19).

It is worth noting that a new esophagojejunal anastomosis (Overlap) can avoid the drawbacks of SITG-π. However, it is not clear whether SITG + 1 combined with esophagojejunal Overlap anastomosis (SITG + 1-Overlap) is feasible and safe for surgical treatment of early and advanced gastric cancer. In this study, 10 patients with early or advanced gastric cancer underwent SITG + 1-Overlap surgery. All procedures were performed successfully without any intra- or postoperative anastomosis-related complications. All esophageal resection margins were negative, and conversion to open surgery was not required. None of the patients showed any obvious postoperative choking. The feasibility and safety of SITG + 1-Overlap in the treatment of early and advanced gastric cancers were preliminarily confirmed. To the best of our knowledge, the present study is the first to report the introduction of the Overlap esophagojejunostomy in SITG + 1 procedures.

Esophagojejunal anastomosis is a key step in SITG + 1 for gastric cancer, which is difficult to perform using staplers or sutures under the limited laparoscopic view available. The Overlap anastomosis of the esophagus and jejunum is in the isoperistaltic direction, which is more in line with the normal physiological structure and is conducive to esophageal emptying. Wang et al. believed that reverse peristaltic anastomosis might lead to a physiological barrier in gastrointestinal continuity (20). In addition, the common opening was closed securely with hand sutures after creating an access opening hole using a linear stapler. This technique rarely results in anastomotic narrowing because of large triangular anastomosis and hand sutures (21). Finally, π-shaped anastomosis is difficult for gastric cardia cancer at a high position, especially in patients with fat bodies and a short mesentery. A higher esophagojejunal Overlap anastomosis can be performed due to the distal tension-free jejunum.

However, esophagojejunal Overlap anastomosis has some shortcomings. The complex closure with hand sutures during SITG + 1 requires a higher degree of surgical skill and takes longer time to perform, which is not suitable for beginners. To overcome these issues, we modified the procedure. First, for easier suturing of the common hole, the addition of an auxiliary port can effectively prevent instrument collisions and reduce the difficulty in stapling and suturing. Secondly, before the esophagus was cut off, the pre-separation plane was marked in advance, above which two knotless unidirectional barbed sutures were stitched on the left and right sides of the esophagus. Sutures enabled the surgeon to pull the separated esophagus to avoid effectively esophageal slippage, even within the deep area. The assistant lifted the two barb sutures

TABLE 3 Perioperative biochemical indicators.

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Mean ± SD/ Median (Q1, Q3)
WBC (10^9)											
pre-operation	5.9	4.2	4.9	4.1	4.4	3.6	4.5	4.3	6.3	4.0	4.6 ± 0.3
POD1	13.0	11.4	9.6	12.4	8.2	7.1	9.8	13.2	11.6	6.2	10.3 ± 0.8
POD3	6.4	7.9	5.9	5.2	6.4	7.0	9.9	15.0	7.7	7.6	7.3 (6.3, 8.4)
POD5	7.4	5.2	4.9	12.7	4.2	6.1	7.3	9.8	6.2	6.0	7.0 ± 0.8
Hb (g/L)											
pre-operation	140.0	110.0	132.0	120.0	90.0	92.0	168.0	137.0	143.0	100.0	123.2 ± 8.0
POD1	144.0	101.0	144.0	126.0	82.0	97.0	130.0	113.0	142.0	111.0	119.0 ± 6.8
POD3	128.0	88.0	117.0	122.0	88.0	94.0	117.0	110.0	121.0	92.0	107.7 ± 4.9
POD5	139.0	94.0	119.0	119.0	96.0	94.0	118.0	118.0	116.0	95.0	110.4 ± 5.0
PCT (ng/L)											
POD1	0.1	1.2	0.2	0.4	0.4	0.7	0.4	0.8	1.8	1.0	0.7 ± 0.2
POD3	0.1	1.0	0.7	0.9	0.2	0.5	1.6	0.4	1.7	0.6	0.8 ± 0.2
POD5	0.1	0.2	0.3	0.4	0.1	0.1	0.6	0.1	0.7	0.4	0.3 ± 0.1
AST (U/L)											
pre-operation	18.0	28.3	16.7	29.7	17.1	20.4	43.9	19.5	24.1	11.4	22.9 ± 2.9
POD1	161.8	207.9	281.7	93.8	85.6	146.7	268.5	157.3	108.6	448.4	196.0 ± 35.2
POD3	20.3	42.0	95.3	18.2	82.6	25.3	77.7	39.7	37.8	63.9	50.3 ± 8.8
POD5	28.6	30.2	33.0	15.9	35.7	15.7	36.6	80.2	33.9	23.9	31.6 (21.9, 35.9)
Creatinine (umol/L)											
pre-operation	64.4	60.7	56.9	93.7	69.8	68.7	68.2	66.4	77.2	50.8	67.7 ± 3.7
POD1	60.0	72.2	48.3	77.0	64.7	62.5	80.6	68.4	81.3	43.1	65.8 ± 4.1
POD3	63.7	65.8	47.0	111.8	58.9	62.1	65.7	51.9	80.5	42.4	62.9 (50.7, 69.5)
POD5	68.7	76.9	41.7	86.5	72.6	63.7	57.6	53.2	73.9	37.9	63.3 ± 4.9
Prealbumin (mg/L)											
pre-operation	256.0	145.0	234.0	200.0	195.0	174.0	432.0	223.0	255.0	115.0	222.9 ± 27.4
POD1	208.0	168.0	167.0	172.0	127.0	172.0	234.0	198.0	186.0	107.0	173.9 ± 11.7
POD3	114.0	118.0	71.0	75.0	106.0	95.0	158.0	124.0	83.0	34.0	97.8 ± 10.8
POD5	183.0	161.0	94.0	51.0	131.0	112.0	145.0	146.0	101.0	56.0	121.5 (94.0, 161.0)
Albumin (mg/L)											
pre-operation	42.3	29.9	44.7	33.8	41.1	41.2	44.5	40.4	45.9	35.8	40.0 ± 5.2
POD1	37.8	31	37.2	32.9	31.3	33.9	30.1	31.6	38.9	29.4	33.4 ± 3.4
POD3	30.5	31.6	31.2	29.7	34.3	31.1	31.8	32.4	35.0	30.2	31.8 ± 1.7
POD5	42.8	40.7	31.9	31.3	37.2	30.7	33.8	32.8	34.7	37.2	35.3 ± 4.1

POD, days postoperation; WBC, white blood cell; Hb, hemoglobin; PCT, procalcitonin; AST, aspartate transaminase; Q1, Quartile1, Q3, Quartile3.

upward, and the surgeon pulled the esophagus downward with his left hand and entered a linear stapler from the auxiliary hole to cut the esophagus with his right hand. After anastomosis was created, barbed sutures were directly used to suture the common opening. Third, a nasogastric tube was pulled out of the stump as a guide to identify the true lumen of the esophagus. A stay suture was then placed to avoid a false gap between the esophageal mucosa and wall.

5. Conclusions

The feasibility and safety of the SITG + 1-Overlap in early and advanced gastric cancers were confirmed in our study. SITG + 1-Overlap can be performed by experienced surgeons because of isperistalsis and less anastomotic stenosis despite its long operative time. Despite the very small number of cases without a control group, the present study shares the preliminary technical experience of SITG + 1-Overlap. The long-term outcomes were not evaluated in the present study. Therefore, large-scale RCT should be conducted to obtain a higher grade of evidence. Taken together, this study provides new options for surgeons who perform total gastrectomy under total laparoscopy.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by China Registered Clinical Trial Ethics Review Committee, no. chiECRCT-201701109. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Study conception and design: W-DX and G-SD; Data acquisition: RW, TW, Y-BR, SS, E-LJ, and Y-BL; Analysis and data interpretation: J-HY and Y-HC; Drafting of the manuscript: J-HY and Y-HC; Critical revision: W-DX and G-SD. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Indications and technical aspects of proximal gastrectomy

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According to the World Health Organization, gastric cancer is the fifth most common type of tumor, and is the third most common cause of tumor-associated death. Although gastric cancer incidence rates have decreased in the past few decades, the prevalence of proximal gastric cancer has been steadily rising in developed countries. Techniques regarding the improvement of treatment options must thus be developed. This can be achieved through incorporating both a wider use of endoscopic surgery (endoscopic mucosal resection—EMR, endoscopic submucosal dissection—ESD) and a review of applied surgical interventions. Even though there is no single international consensus available, the Japanese Gastric Cancer Association (JGCA) recommends proximal gastrectomy with D1+ lymphadenectomy in early gastric tumors. Despite recommendations from Asian guidelines and the short term outcomes of the KLASS 05 trial, surgical treatments in Western countries still rely on total gastrectomy. This is mostly due to technical and oncological challenges regarding surgical interventions in a proximal gastrectomy. However, the residual stomach after a proximal gastrectomy has been shown to diminish the incidence of dumping syndrome and anemia, and even improve postoperative quality of life (QoL). Therefore, it is necessary to define the place of proximal gastrectomy in the treatment of gastric cancers.

KEYWORDS

gastric cancer, proximal gastrectomy, minimally invasive surgeries, laparoscopic gastrectomy, upper third gastric cancer, early gastric cancer

Introduction

Incidence rates of gastric cancer have changed significantly in the past decades: in 2008, gastric carcinoma was considered the fourth most common malignancy, and the second most common cause of cancer-associated death; its incidence significantly declined by 2020 (1). According to WHO data, gastric carcinoma is currently the fifth most common type of tumor. It is also the third most common cause of tumor-associated mortality following lung and colorectal cancer (2). This decline in mortality may be due to systematic exploration of various risk factors, such as the leading role of Helicobacter pylori, an eradicable pathogen (3), as well as lifestyle factors promoting the incidence of gastric cancer, including high salt intake, smoking, or alcohol abuse (4, 5). Early endoscopic diagnosis, perioperative oncological treatment and surgical care must therefore be incorporated. Nevertheless, the overall five-year survival rate of gastric cancer in Western societies is still as low as 20% due to frequently late diagnosis. In comparison, Asian countries (South Korea, Japan) run complex screening programs for upper gastrointestinal cancer, and tend to diagnose gastric carcinomas at an early stage; their five-year survival rate there is nearly 70% for stage I and II (6).

Furthermore, even though the overall incidence of gastric cancer is decreasing, proximal gastric carcinoma cases are still on the rise (7). This increased incidence and subsequent decline in quality-of-life indices applied after a "gold standard" total gastrectomy (TG) has called for a paradigm shift in therapy. This can be reflected by the increasing application of endoscopic resection methods (endoscopic mucosal resection [EMR] and endoscopic submucosal dissection [ESD]). As a result of ESD allowing wider *en bloc* resection (presented

first by Gotoda et al. in 1999), these techniques cover more than 60% of all procedures in Japan for the treatment of early gastric cancers (EGC) (8–10). In cases where endoscopic methods are not feasible, proximal gastrectomy (PG) may be a reasonable alternative for TG. This is due to its shorter operation time, lower intraoperative blood loss and the better nutritional status in the postoperative period of patients who underwent PG. Even though there is an increasing amount of data on the oncological safety and technical feasibility of proximal gastrectomy, there is no international consensus providing a standardized guideline for the operative therapy in upper third gastric tumors. This is well shown by that their number is rather low regarding the Eastern countries most supporting PG, contrary to the changes in the incidence indices of gastric tumors. In South Korea, in 2009, these types of surgeries represented only 1% of all gastric tumor related surgical interventions, including open and laparoscopic surgeries (11). While in 2013 in Japan the number of proximal laparoscopic resections was as high as 4.6%, which was at the time, higher than the number of the open PG (12). Their increasing trend in the previous decade was constant mostly due to the Asian countries. The purpose of this review is to summarize the current status of PG in gastric surgery. Our aim is review PG's oncological radicality and discuss the important aspects of indication and technical applicability. Furthermore, the reconstructive procedures following PG that greatly influence postoperative short- and long-term results, will be presented in detail.

Technical aspects of PG

Oncological safety of PG

The use of oncological radicality in distal laparoscopic gastrectomy for distal gastric carcinomas is currently standard practice (11–13). The first line treatment for advanced upper third proximal gastric cancer, however, is still TG with D2 lymphadenectomy (14). The treatment method of early proximal gastric cancer underwent significant changes in the past decades. In early gastric carcinoma cases where endoscopic methods are unnecessary, a proximal gastrectomy may be performed as a suitable alternative to TG. Regardless, the basic surgical treatment of early upper third gastric tumors in Western countries is identical to that of advanced tumors. In Asian countries, developed complex care includes screening programs ensuring early diagnostics, gastroenterological interventions, such as the ones detailed above, and cutting-edge minimally invasive surgical techniques. This has resulted in improvement of the well-registered survival indices which brought both oncological results and postoperative quality of life into focus. Owing to the above, certain subtypes of PG presumably providing functional benefits in terms of nutrition, emerged.

The oncological radicality of proximal gastrectomy in the treatment of early gastric cancers has been questioned by surgeons. The extension of surgical procedures—in addition to defining the place of PG—is also a controversial, for example indication for complete omentectomy vs. partial omentectomy, given the fact that the incidence of omental metastases in T3–T4 gastric cancer is only 3.8%–5% (15). Other doubts regarding oncological radicality have now been resolved, including the use of laparoscopy in early and advanced gastric cancer (CLAAS – 01 trial) (16), the estimation of probability of lymph node metastasis using the Maruyama computer program (17) and the extension of lymph node dissection performed in advanced gastric cancer.

The indication of PG is currently for early upper-third gastric cancers, but the latest studies are increasingly pointing beyond this, even for locally advanced cases. A study by Yura et al. reported that advanced (T2–T3) gastric tumors located in the upper third of the stomach had relatively low metastasis rates in the infra- or suprapyloric lymph nodes. In quantitative terms: their data analysis for both T2 and T3 gastric tumors showed a 0% rate for lymph node metastatic potential in stations 5 and 6 (18). A study by Ri et al. showed that locally advanced T2–T4 gastric tumors at the level of the cardia and fornix did not show metastatic potential in the lymph node stations 4, 5, 6, and 12a. In these cases, a PG is permissible. At the same time, tumors that infiltrated the gastric body showed an increased possibility of metastasis in the distal lymph nodes. Accordingly, the role of PG in the treatment of these tumors is highly questionable (19). Similar to Yura's and Ri's data, Takeuchi et al. did not find metastasis in the lymph nodes 5, 6, 10 or 11d in early upper third (T1N0) gastric tumors either (20). A similar conclusion was also reached i.e., lymph node station 5 and 6 had a metastatic potential of 0.5% and 1.6%, respectively. With the notion of PG oncological radicality in mind, Haruta's study group found that all tumors in the upper third of the stomach that measured less than 4 cm, whose distal border also ended in the upper third, had low (2.2%, $p < 0.001$) rates of 3b lymph node metastasis (3b lymph nodes: distal lymph nodes of the lesser curvature, located along the right gastric artery), thus 3b lymphadenectomy was not necessary (21). This conclusion was further supported by sentinel lymph node (SLN) mapping of tumors in the upper third of the stomach, which were identified using double-guided (radio- and dye-guided) methods. According to Niihara, the incidence rate of parapyloric presentation of SLN from these tumors is around 0%–3%, and zero at station 8. Therefore, PG excluding the dissection of these lymph node stations can be performed with oncological safety (22).

As defined by the JGCA, upper gastric tumors are located in the upper third of the stomach, with or without the involvement of the esophagogastric junction (EGJ). EGJ tumors, however, should be mentioned as a specific indication for PG. Yamashita et al. found that the metastatic potential of EGJ tumors below 4 cm in lymph node stations No. 1, 2, 3, and 7 was particularly high, even in esophageal-predominant tumors. The susceptibility for metastasis in lymph node stations No. 4, 5, and 6 was almost zero, regardless of the esophageal or gastric predominance of the EGJ tumor or the T stage. Thus, for EGJ tumors less than 4 cm, removal of distal lymph nodes around the stomach is not indicated (23). This was also supported by a meta-analysis by Li et al., who concluded that PG may be the most appropriate procedure for Siewert II-III. tumors, considering both the oncological radicality and postoperative functional benefits (24). Kurokawa et al. conducted a prospective nationwide study in collaboration with the JGCA and the Japanese Esophageal Society (JES). They reported that performing a distal esophagectomy combined with PG is sufficient

for Siewert II. EGJ tumors, regardless of the presence of adenocarcinoma or squamous cell carcinoma. A total gastrectomy and paraaortic lymph node dissection (LND) is not necessary; however, mediastinal lymphadenectomy should be considered for esophageal involvement (EI) above 2 cm. (EI > 2 cm – 110 LND; EI > 4 cm – 106 right recurrent laryngeal nerve LND) (25).

With regards to long-term oncological outcomes, it is worth analyzing the rate of local recurrence. The 2004 study by Yoo et al. introduced findings of a former period of proximal gastric tumor surgeries. By processing data from 74 patients who had undergone a PG, and 185 patients who had undergone a TG, they experienced that out of 66 patients to PG (8 patients had R1 resection) local recurrence appeared for 17 (25.7%). The authors explained this high rate by the more extended or so to say less-defined circle of indication, including the selected malignancies with serosal infiltration (T4 tumors), the diffuse tumor type or the tumor size over 5 cm (26). Similar recurrence rates were also found for proximal and total gastrectomy's performed in patients with stage IA and IB gastric tumors (below 4 cm in size, located in the upper third). The same was found by Chen et al. in their meta-analysis where the five-year overall survival rate [odds ratio (OR): 0.95, 95% CI, 0.64–1.40; $p = 0.790$] and recurrence ratio (OR: 3.79, 95% CI, 0.37–38.46; $p = 0.260$) of proximal and total gastrectomy's were similar (27). The systematic review and meta-analysis performed by Xu et al. concluded the same upon comparing the two types of surgery (OR: 0.841, 95% CI, 0.549–1.287 $p = 0.430$) (28), which was seen in the level of significance as well owing to Li's analysis having processed the data of 1,734 patients in 12 studies (OR: 1.35, 95% CI, 0.99–1.85, $p = 0.06$) (24).

Feasibility of PG

Regarding technical feasibility, several aspects must be considered. First, whether laparoscopy used in distal gastrectomy (13) provides advantage in proximal surgeries as well. The first laparoscopically assisted PG was described more than 20 years ago (Kitano et al., 1999) (29). Several retrospective studies were dealing with the benefits of laparoscopic PG, including the well-known: less pain due to minimal invasiveness, faster recovery and easier mobilization of the patient.

After PG, there are three standard reconstruction procedures: esophagogastric anastomosis (EG), double—tract reconstruction (DTR) and the jejunal—interposition (JI) technique (**Figure 1**). However, considering the difficulty of these reconstruction techniques following PG and the subsequent outcomes, laparoscopy was not clearly defined as standard surgical procedure for proximal surgeries. The retrospective analysis performed by Kinoshita et al. compared PGs reconstructed by open and laparoscopic JI. There was no reported difference in lymph node resection, esophagojejunal anastomotic insufficiency or occurrence of postoperative complications. Although the duration of the surgery was significantly longer in the laparoscopic group (233 vs. 201 min., $p = 0.0002$), decreased blood loss (20 vs. 242 grams, $p = 0.0001$) and the reduced need for painkillers after surgery (the number of times of additional analgesia, 2 vs. 4, $p = 0.0001$) were also significant (30). The aim of the JCOG 1,401 single-arm confirmatory trial published in 2019 was to revolutionize retrospective processing and prove the safety of laparoscopically assisted total and proximal gastrectomies with double—tract reconstruction or jejunal—interposition in case of stage I (T1N0, T1N1, T2N0) upper third early-stage gastric tumors. Even though the total esophagojejunal anastomotic insufficiency rate was predicted to be 8% (one-sided $p = 0.0002$), the research showed that patients had a rate of only 2.5%. This insufficiency did not show any difference between the two surgical types (6 cases out of 244 surgeries, 95% CI, 0.9–5.3). Major complications and conversions occurred at a similarly low ratio, and postoperative mortality was found to be zero. Accordingly, the standard surgical intervention recommended by the authors in case of early, stage I proximal gastric malignancies is laparoscopic surgery. However, it should be noted that the authors mentioned these surgeries must be performed only in high-volume centers by accredited upper GI surgeons (31). Similar intraoperative and postoperative aspects can be considered when comparing the findings of laparoscopic total gastrectomy (LTG) with laparoscopic proximal gastrectomy (LPG), According to the findings of the meta-analysis performed by Chen et al. mentioned above, proximal surgeries involve less lymph node removal [weighted mean difference (WMD): −12.86, 95% CI, −17.44 to −8.28; $p = 0.000$] and lower blood loss in the case of LPG (WMD: −102.18, 95% CI, −180.41 to −23.94; $p = 0.010$). However, they require more time (WMD: −65.47, 95% CI, −103.39 to −27.55, $p = 0.001$) and are accompanied by higher rates of anastomotic stenosis (OR: 3.18; 95% CI, 1.46–6.92; $p = 0.004$), the latter of which shows high variability among reconstruction types. The most frequent is in direct EG anastomoses. and the probability of postoperative ileus is also lower than in LTG (OR: 0.27; 95% CI, 0.10–0.72; $p = 0.010$) (27). The meta-analysis performed by Li found a similar relationship regarding intraoperative blood loss and the duration of surgery, and also mentions the better postoperative nutrition level in PG (24).

Functional benefit of PG

The partial preservation of the reserve function of stomach plays an unambiguous role in the above, which is positively reflected by the postoperative nutrition, the formation and severity of the incidental dumping syndrome and the abundance of postoperative diarrhea episodes. To quantify the above, Ahn et al. found that 6 months after a PG surgery, the loss of body weight was 5.9% compared to a weight loss of 16% found after TG (32). Takiguchi et al. found similar outcomes in their study, with patients experiencing significantly higher weight loss after TG (TG 13.8% vs. PG 10.9%, $p = 0.003$) (33). Weight loss alone is not sufficient enough to assess postoperative status, so analysis of qualitative indices must be performed as well. This is achieved through the monitoring of serum hemoglobin, serum albumin, total protein and Vitamin B12 level. Some studies did not find any significant difference between the two types of surgery in terms of nutritive findings. In their multicentric, prospective and non-randomized study, Yamasaki et al. saw no significant difference in serum albumin and hemoglobin levels in the short term postoperative period. There was also no significant difference in Vitamin B12 levels one year after surgery (4.2% vs. 7.2%, $p = 0.07$), however there was a

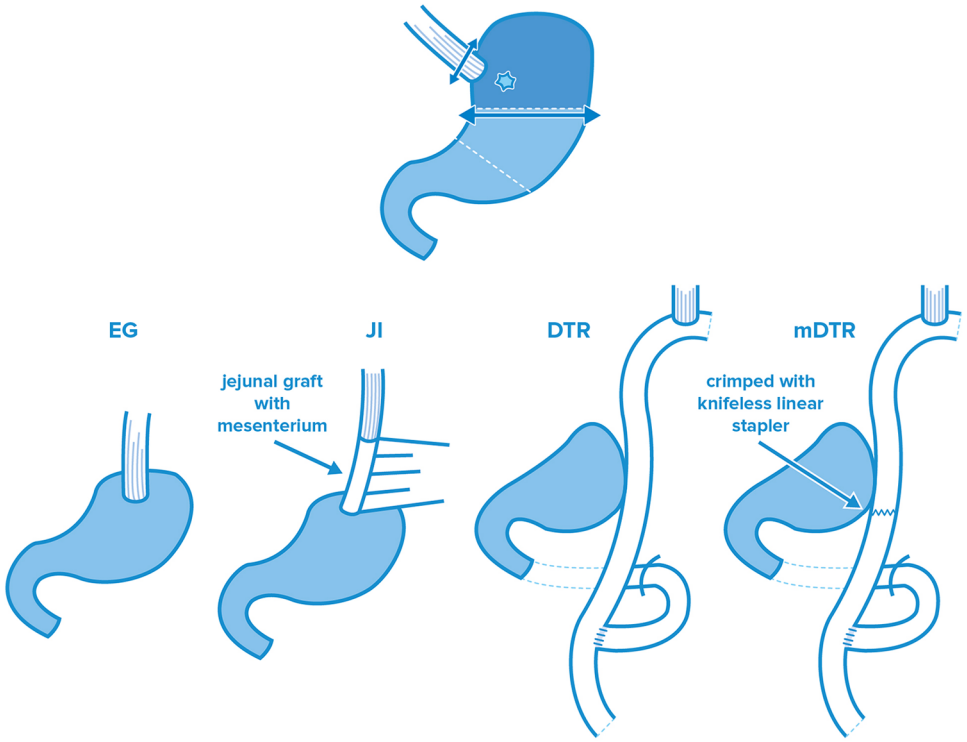

FIGURE 1
Standard reconstruction procedures after PG: esophagogastric anastomosis (EG), jejunal-interposition technique (JI), double—tract (DTR) and modified double—tract (mDTR) reconstruction.

significant difference after the two year mark (2.2% vs. 7.7%, $p = 0.003$) (34). Masuzawa experienced similar results regarding the postoperative monitoring of patients, by comparing PGs reconstructed by EG JI to those operated on using the Roux-en-Y TG technique. 3 years after the surgery, the patients subject to TG had lower serum levels of both albumin and hemoglobin (albumin $p = 0.012$, hemoglobin $p = 0.046$) (35), showing the advantage of PG's in long-term nutritive status. However, functional advantages after PG occur only if at least half of the stomach remains after PG resection. Accordingly, based on the most recent Japanese Gastric Cancer Treatment Guideline, 2021, PG is only recommended if at least 50% of the whole volume of the stomach is retained (36).

We currently have high-quality randomized prospective research on retrospective processing, owing to the KLASS – 05 trial. The KLASS – 05 trial is the first randomized multicentric study comparing proximal PG for upper third T1 stage early gastric tumors (by double-tract reconstruction) with TG. The research conducted between October 2016 and September 2018 selected 68 undergoing a PG and 69 TG patients, in order to compare the short-term and long-term effects of these two types of surgery. By analyzing the perioperative stage (by registering the preoperative data and the postoperative data on days two and five) it was concluded that no significant difference was found between proximal and total gastrectomy in terms of certain serum parameters (hemoglobin, albumin, white blood cells, C reactive protein) and other short-term mortality and morbidity indices. However, the authors wrote that PG can still be an alternative to TG for these patients, by considering that the long-term findings are still to come (37).

Reconstruction types after PG

As mentioned above, the JGCS guideline 6th edition differentiates 3 basic reconstruction procedures after proximal gastrectomy (36): (a) esophagogastric (EG) anastomosis, (b) double—tract technique (DTR) and (c) jejunal—interposition (JI) reconstruction. Although several modified procedures (e.g., gastric tube EG, modified DTR) were elaborated on in the previous decades, no clear recommendation was given for any of these surgeries. Within the framework of this review article, in addition to the governing techniques, we intend to introduce other procedures besides the default which have the potential to even become the new "gold standard" surgery. Accordingly, in addition to the 3 standard surgical reconstruction techniques, the surgeries based on the flap technique aiming at the formation of a new EG sphincter (double—flap technique [DFT], side—overlap fundoplication [SOFY], modified side—overlap funduplication [mSOFY]) are introduced as separate techniques. Both DFT and SOFY are considered a subtype of EG, which try to combine the simplicity of EG anastomosis with the outstanding functional results of the other reconstruction procedures.

Esophagogastrostomy

In EG, after the removal of the proximal part of the stomach, the restoration between the esophagus and the gastric stump is performed by a circular stapler, predominantly with transorally-

inserted anvil (Orvil™). Due to the application of JI or DTR, the EG anastomosis type widely applied earlier has somewhat declined. This decline is due to controversy surrounding the high reflux esophagitis to anastomosis stenosis ratio in the postoperative stage (33, 38). However, there is significant variability in terms of the applied surgical technique. Compared to the traditional circular stapler technique, the first promising EG modification linked to Adachi who, in 1999, elaborated the gastric tube EG technique to terminate reflux complaints (39). The basis of this surgery is to provide a significantly longer piper gastric stump to create a greater distance for the bile to travel for reflux.The modification provided by Adachi had outstanding results in terms of reflux esophagitis, however, multiple studies reported higher rate of anastomotic stenosis compared even to the traditional EG surgeries. This surgical technique has thus not been widely accepted. In their retrospective data processing, Ahn et al. found that there is a significant difference between the findings of end-to-end esophagogastrostomy (EEEG) performed by a circular stapler, as compared to side-to-side esophagogastrostomy (SSEG) performed by a linear stapler. After EEEG, stenosis appeared with a rate of 46.2%, a significant difference when compared with the 0% found after SSEG ($p < 0.001$). No significant difference was found in terms of reflux esophagitis during the primary processing (15.4% vs. 37.8%, $p = 0.135$) until the five years of the research was divided into three separate phases (early, middle and late phases) In the late phase, every patient was subject to supplementary esophagopexy by hiatus reconstruction, demonstrating no significant change in reflux symptoms. The late phase results showed no patients with Visick grade IV reflux esophagitis proving that SSEG anastomosis by linear stapler, with supplementary anti-reflux treatment, is a suitable alternative for optimal reconstruction surgery (40).

Esophagogastrostomy flap techniques: DFT, SOFY

To eliminate reflux complications resulting from traditional EG surgeries, in 2001, Kamikawa et al. devised an anti-reflux technique (41) (**Figure 2**). The technique involved a hand-sewn laparoscopic EG after the removal of the proximal part of the stomach, which is covered by a sero-muscular flap from two sides. Due to the difficulty of the handmade sutures, this surgical technique was subject to heavy criticism, however the comparative study conducted by Hayami et al. showed outstanding results. They compared the findings of DFT with laparoscopic TG and found that even though DFT requires longer surgery time, it is more favorable in terms of hospitalization time ($p = 0.002$) and the nutritive status of the patients (weight $p = 0.003$, total protein $p < 0.001$, albumin $p = 0.06$, hemoglobin $p = 0.003$) (42). Saze et al. found better outcomes not only compared to the total removal of the stomach by analyzing the change of postoperative weight loss but also after comparing it with certain PG subtypes (traditional EG, JI, DTR, $p = 0.001$–0.013) (43). On the contrary, several studies pointed out that in addition to the technical difficulty and high skill required to perform a DFT, there was also increased risk for stenosis or incidental ischemia following formation of the flap with consequential necrosis (44). To exclude the above, the modified laparoscopic Kamikawa anastomosis was elaborated by Mo et al.; during this, the esophagogastric anastomosis is made by a traditional circular stapler, however, the suture line was covered by a unilateral seromuscular flap. The theoretical basis of this technique is the higher speed of the standardized machine-made anastomosis, the lower stenosis rate compared to the manual suture line and the valve function of the seromuscular flap forming (45).

In side overlap funduplication surgery, the linear stapler EG technique originally performed by Ahn is combined with the sphincter function of the flap. This surgery type was described by Yamashita et al. in 2017, who further modified it in 2022 [modified SOFY (mSOFY)]. In the original technique, a 5 cm overlap between the distal part of the esophagus and the gastric stump is created and anastomosis is formed by turning the linear stapler device counterclockwise and sewing the residual stomach to the left side of the esophagus. In the 2022 modification, anastomosis is formed according to the same method on the right side of the esophagus, which is followed by the formation of a "plica" from the gastric stump, which covers the last part of the esophagus. Owing to this surgical modification (whether it is the original or the modified SOFY procedure), the distal part of the esophagus serves as a neosphincter with a "flat" form. Yamashita et al. found no suture insufficiency for the SOFY nor mSOFY. Anastomosis stricture appeared only once, and outstanding results were obtained in terms of reflux symptoms as well (46, 47). The judgement of the flap-type EG surgeries is complicated by the lack of detailed and prospective data covering a wide period of time both for the modified Kamikawa anastomosis and the SOFY technique. Accordingly, even though their application as standard reconstruction procedure is currently out of question, the monitoring of these surgery types is by all means recommended due to their "simplicity" and efficiency compared to the laparoscopic hand-sewn EG anastomosis.

Reconstruction with small intestine: double-tract reconstruction (DTR and mDTR), jejunal pouch (JP) and jejunal interposition (JI)

During jejunal reconstruction surgeries, PG is performed by a jejunum loop to restore gastrointestinal continuity. In case of the jejunal pouch technique, a reservoir is formed from an isolated jejunum limb, which is followed by the PG reconstruction stage (**Figure 3**). In the comparative pilot study performed by Takagawa in 2010, better results were experienced than in case of JI in several aspects. The most striking aspect was the worse short-term morbidity data of JI, including anastomosis insufficiency and postoperative bleeding, surgical site infection (SSI) and postoperative pneumonia ($p = 0.036$) (48). Similarly, better results were experienced after JP in terms of postoperative body weight ($p = 0.095$) and food intake ($p = 0.002$). Although the formation of JP provides a clear advantage in terms of food intake right after surgery, this technique was recently dismissed due to challenges in pouch formation and the abundance of residual food, which was experienced in an extreme extent, for more than 90% of the patients (49).

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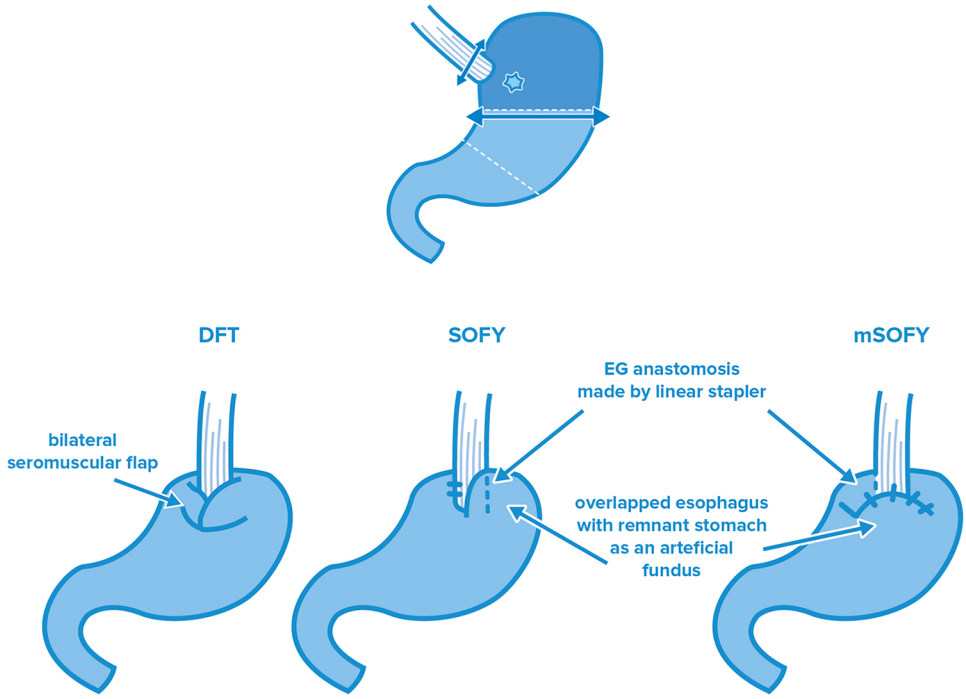

FIGURE 2
Esophagogastrostomy flap techniques after PG: double—flap technique (DFT), side overlap funduplication (SOFY), and modified side overlap funduplication (mSOFY).

In case of both DTR and JI surgeries, the dissection plane of the jejunum is set approximately 20 cm from the ligament of Treitz. After the dissection of the jejunum, esophagojejunal (EJ) and gastrojejunal (GJ) anastomoses are formed with the aboral gut section. In order to ensure bile discharge, a jejunal junction (JJ) is formed. To prevent reflux esophagitis, most the authors recommend a distance of 10–15 cm between EJ and GJ anastomoses. In case of DTR, the consumed food is passed on towards the stomach and the jejunum as well; according to the passage study of Ahn, the passage of food is distributed between the residual stomach and the jejunal loop in a ratio of 3 : 2 (32). In case of the modified DTR (mDTR) also known as single-tract jejunal interposition (STJI), the jejunum is closed below the GJ anastomosis by a knifeless linear stapler, which facilitates the passage of the consumed food towards the stomach. The DTR and the STJI techniques have clear advantages when compared to traditional EG anastomoses in terms of reflux esophagitis and anastomotic stenosis (34). Compared to gastrectomy, both techniques are more effective in terms of postoperative nutritive status (35). In the prospective study by Nomura et al. comparing the findings of DTR and STJI, even though no substantial difference was found in the meal intake ratio (postoperative—preoperative meal intake ratio: the mean of the whole postoperative meal intake per day compared to the preoperative meal intake), STJI had significantly better results in terms of postoperative body weight and postprandial serum insulin levels ($p < 0.05$) (50). Lu et al. obtained similar findings: although STJI had significantly longer duration ($p = 0.04$), it proved to be significantly better in terms of postoperative body weight ($p = 0.002$) (51). Accordingly, these work-groups recommended STJI regarding reconstruction following PG surgeries. In the meta-analysis by Wang et al., it was found that early complications, stenosis, reflux esophagitis and residual food appeared at a ratio of 18.1%, 9.6%, 4.5% and 19.0% for JI, and at a ratio of 11.6%, 4.7%, 4.7% and 48.9% for DTR, respectively (52). Most of the authors agree that the higher incidence ratio of early complications may be due to the complexity of DTR and mDTR surgeries, as well as the presence of multiple anastomoses. Being the first prospective, randomized and controlled study, the KLASS – 05 trial can be a guide for the

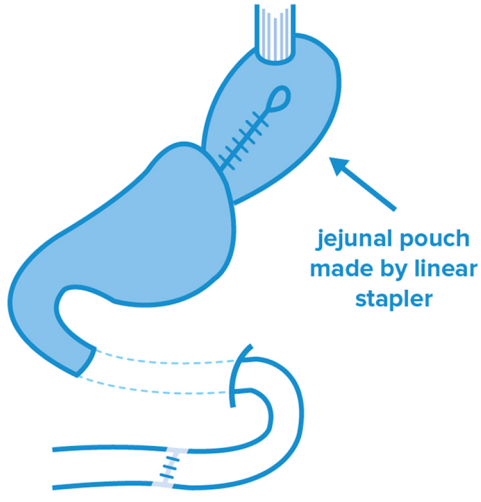

FIGURE 3
Jejunal pouch technique after PG.

applicability of DTR. Compared with the LTG – as mentioned above—no significant difference was obtained between the two groups in terms of postoperative complications and laboratory values. DTR does not exhibit a significant difference with LTG in terms of reflux complaints either. We are looking forward to the long-term findings of the study (37).

Discussion

Although the global consideration of PGs is constantly changing, the increasing incidence of upper third gastric tumors makes it necessary to rethink conventional surgical approaches and to fit PGs into the prevailing therapeutic algorithm. By observing the appropriate indication criteria in terms of oncological radicality, PGs seem to be appropriate in terms of the analysis of both local recurrence and lymph node dissection. By comparing certain subtypes of PG with TG, better results were found after PG if sufficient reconstruction procedures were applied. In this regard it must be emphasized that PG reconstruction procedures accompanying lower postoperative anastomosis stenosis rates provide good results in terms of the formed reflux esophagitis, and can be accepted in terms of performance and surgical difficulty. Instead of the DTR/mDTR procedure thought to be applied most frequently nowadays, the recently appeared EG modifications combining the simplicity of stapler anastomoses with antireflux mechanism (mDFT, SOFY, mSOFY) may offer a good alternative. The selection of the ideal reconstruction procedure is limited by the lack of prospective analyses, therefore, further RCTs for a wide range of patients are needed for the most optimal decision. Although the ideal reconstruction procedure after PG has still not been found, the gradual expansion of PGs is out of question. This tendency is typical mostly in Asian countries, however, the results of the studies proving the safety of PGs cannot be disregarded by surgeons in Western societies either. Our article has many limiting factors which should be noted. The majority of the presented data was provided after retrospective analysis. At the moment, no critical conclusion can be drawn without the long-term findings of high-volume prospective studies, such as the KLASS-05 trial. Nevertheless, similar to Asian countries, a paradigm shift in the care of early upper-third gastric cancer is necessary for Western countries. In this regard, the technical feasibility and oncological radicality of PG may become less of an issue with the correct indication. In terms of reconstructive procedures, the combination of stapler anastomoses with the flap technique can provide both technical and functional advantages, and may become the standard of PG surgery in the future.

Author contributions

All authors contributed to the review's conception and design. DT and PK performed the literature search and data analysis. The first draft of the manuscript was written by PK and DT critically revised the work first. All authors commented on previous versions of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Clinical significance of the largest histopathological metastatic lymph node size for postoperative course of patients undergoing surgery for gastric cancer

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Aim: The aim of this study was to investigate the effect of the largest metastatic lymph node (MLN) size on postoperative outcomes of patients with stage II-III gastric cancer (GC).

Methods: A total of 163 patients with stage II/III GC who underwent curative surgery were included in this single-center retrospective study. The lymph nodes were counted, each lymph node was analyzed for metastatic involvement by histopathological examination, and the diameter of the largest metastatic lymph node was recorded. The severity of postoperative complications was assessed by Clavien–Dindo classification system. Two groups of 163 patients were defined according to ROC analysis with cut-off value of histopathologically maximum MLN diameter. A comparative analysis of demographic and clinicopathological characteristics of the patients and their postoperative outcomes were performed.

Results: The median hospital stay was significantly longer in patients with major complications compared to patients without major complications [18 days (IQR: 13–24) vs. 8 days (IQR: 7–11); ($p < 0.001$)]. The median MLN size was significantly larger in deceased patients compared to survived [1.3 cm (IQR: 0.8–1.6) vs. 0.9 cm (IQR: 0.6–1.2), respectively; ($p < 0.001$)]. The cut-off value of MLN size predicting mortality was found as 1.05 cm. MLN size ≥1.05 cm had nearly 3.5 times more negative impact on survival.

Conclusions: The largest metastatic lymph node size had a significant association with survival outcomes. Particularly, MLN size over 1.05 cm was associated with worse survival outcomes. However, the largest MLN was not shown to have any effect on major complications. Further prospective and large-scale studies are required to draw more precise conclusions.

KEYWORDS

gastric cancer, lymph node metastasis, lymph node size, survival, postoperative complication

Introduction

Gastric cancer (GC) is the third most common cause of cancer-related deaths worldwide. Surgery is the gold standard for curative treatment of GC (1). Following surgical resection, examination of lymph nodes (LNs) are important for accurate staging, postoperative treatment approach, clinical follow-up and prognosis. LN metastasis plays a key role in the recurrence and long-term survival of the gastric cancer patients undergoing surgery (2, 3). D2 LN dissection and the number of metastatic LNs are well-known prognostic factors. In addition, the number of harvested LN and MLN ratio are important prognostic factors (3, 4). Eighth Edition of The American Joint Committee on Cancer (AJCC) Staging Manual is currently used for pathological examination (5). In this TNM classification, N staging is done by the number of metastatic lymph nodes (MLNs), neither MLN size nor MLN ratio is considered. Similar to the LN rate, the effect of the size of the positive LN on the pathological stage, clinical follow-up, postoperative treatment approach, and prognosis are not taken into account in this staging system.

Chen et al. reported that tumor size can be included in AJCC staging, considering that it may have different prognostic roles in gastric cancer at different stages (6). In some series, it has been shown that MLN size is effective in the determination of the prognosis and it provides valuable support to the classification systems in patients with gastrointestinal malignancies, including colon and esophageal cancer (7, 8). However, there are limited number of reports investigating the relationship between the largest MLN size, prognosis and survival in gastric cancer (9, 10). The role of MLN size in the postoperative period of the gastric cancer patients remained a serious gap in the literature. Furthermore, to our knowledge, there is no research in the literature evaluating the relationship between metastatic largest LN size and postoperative complications in patients with GC. We aimed to investigate the effect of histopathologically determined metastatic largest LN size on postoperative outcomes in patients with Stage II-III GC.

Materials and methods

This single-center, retrospective study was conducted at the Department of Gastroenterological Surgery, University of Health Sciences Kosuyolu High Specialization Education and Research Hospital, Istanbul, Turkey. The study was carried out in accordance with the Helsinki Declaration and local laws and regulations. This study was approved by the ethical committee of Kosuyolu High Specialization Education and Research Hospital with an IRB number: 2020/14/404.

Between December 2006 and December 2019, medical records of 324 patients who underwent gastric cancer surgery were retrospectively reviewed and data of 163 eligible patients were enrolled in the study (**Figure 1**). Patients aged over 18 who underwent a curative surgery for TNM stage II or III GC were considered eligible for this study. All patients underwent open total or subtotal gastrectomy with D2 lymphadenectomy. Patients who underwent emergency surgery, had immunodeficiency or lymphoproliferative disease and had taken immunomodulatory drugs were excluded. Also, patients whose adjuvant chemotherapy was not completed were not included into the study.

Data regarding the patients' age, gender, comorbidity status, presence/absence of lymphovascular and perineural invasions (LVI and PNI), tumor histological grade, tumor size and location, total number of harvested LNs and metastatic LNs, size of the largest MLN, length of hospital stay, postoperative complications, overall survival (OS), neoadjuvant treatment status were recorded. The Clavien-Dindo classification was used to analyze postoperative complications, and grade III or higher complications were defined as major complications (11).

Adjuvant chemotherapy was given to all patients with a pathological stage II and III gastric cancer with LN metastases. DCF (Docetaxel, cisplatin, 5-fluorouracil) or FLOT (5-fluorouracil, leucovorin, oxaliplatin, docetaxel) regimens were given as both neoadjuvant and adjuvant chemotherapy.

The software IBM® SPSS® (Statistical Package for the Social Sciences) version 23 (IBM Corp. Armonk, NY, USA) was used for statistical analysis. Qualitative data were presented as frequency and percentage. The distribution of numerical data was performed using the Kolmogorov–Smirnov test with the non-normal distribution results. Quantitative data were given as median with Interquartile Range (IQR). The association of major complications and survival with categorical variables was analyzed using Chi-square, Fisher's exact tests, and Likelihood ratio. The Mann–Whitney-*U* test was used to examine whether major complications and survival were related to age, metastatic lymph node size, and length of hospital stay. The Kaplan–Meier method and the log-rank test were used to conduct the survival analyses of the metastatic lymph node size. Further, multivariate Cox regression analyses were performed to examine role of the metastatic lymph node size in predicting mortality. A *p*-value of less than 0.05 was defined as statistically significant.

Results

Patients' demographic and clinicopathologic characteristics considering the major complications and survival status were presented in **Table 1**. The median hospital stay was 18 (IQR: 13–24) days in patients with major complications, while it was 8 (IQR: 7–11) days in patients without major complications ($p < 0.001$). The median age of deceased patients was significantly higher than those who survived (63 [IQR: 57–69] vs. 57 [IQR: 50–65], respectively, $p = 0.005$). Both pT stage and pN stage were significantly higher in the deceased patient group ($p = 0.012$ and $p = 0.026$, respectively). The median MLN size was significantly larger among the deceased patients compared with the survived [1.3 cm (IQR: 0.8–1.6) vs. 0.9 cm (IQR: 0.6–1.2); ($p < 0.001$)]. The frequency of lymphovascular invasion and perineural invasion was also significantly higher in deceased patients ($p = 0.043$ vs. $p = 0.017$, respectively).

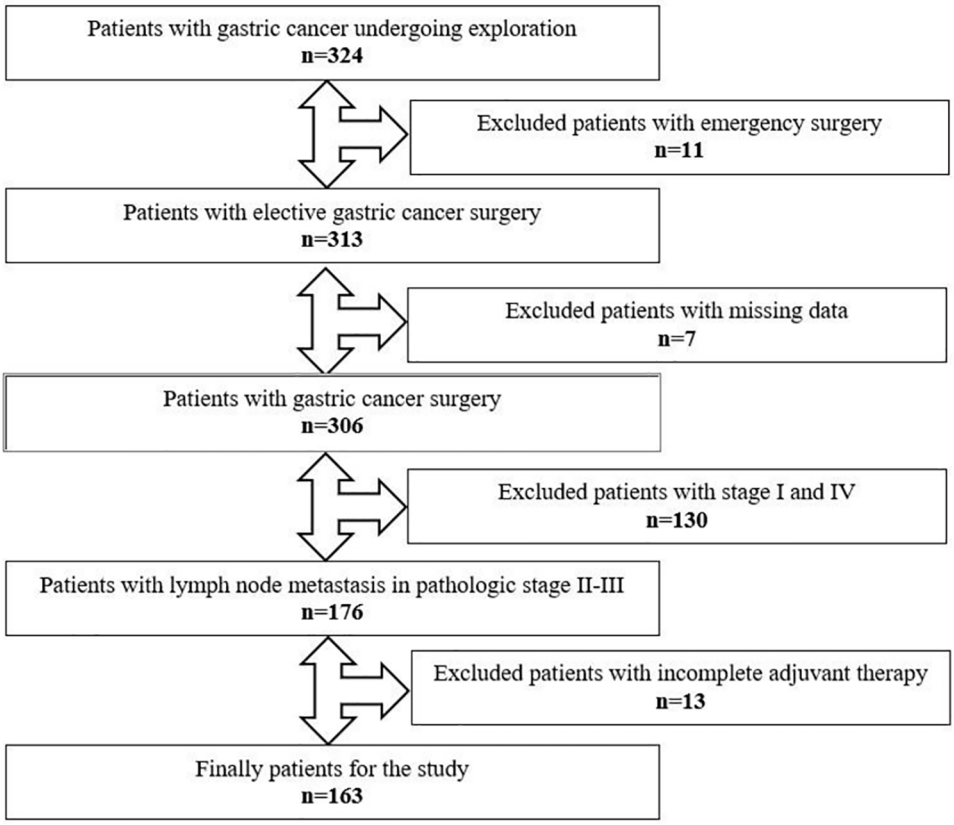

FIGURE 1
Flowchart of the inclusion.

The rate of surviving patients was 20.9% for those who received neoadjuvant treatment, and 39.6% for those who did not ($p = 0.012$). It was observed that patients who did not receive neoadjuvant therapy had a higher rate of 5-year OS than those who received neoadjuvant therapy (44.5% vs. 15.3%). The rate of advanced-stage patients was higher in the population who received neoadjuvant therapy (Table 2). No significant impact on survival was observed considering gender, Charlson Comorbidity Index (CCI), body mass index (BMI), type of surgical procedure or stage of differentiation.

Assessment of the reliability of MLN size in predicting mortality and major complications with ROC curves was presented in Table 3. The cut-off value of MLN size predicting mortality was determined as 1.05 cm. The area under the curve (AUC) was 0.699, the sensitivity was 65.8%, and the specificity was 67.3% for this cut-off value ($p < 0.001$). On the other hand, the sensitivity and specificity of the MLN size cut-off value (1.05 cm), which predicts major complications, was quite low and was not statistically significant ($p = 0.164$) (Figure 2).

The relationship between cut-off value of metastatic lymph node size and clinicopathological features was presented in Table 4. Most of the patients (68.7%) who received neoadjuvant treatment had MLN size ≥1.05 cm ($p = 0.004$). Among the patients with MLN size ≥1.05 cm, 90.4% were in the pN3 group, and only 5.9% were in the pN1 group ($p < 0.001$). In addition, LVI positivity rate was 59.5% ($p = 0.025$) and PNI positivity rate was 62.5% ($p < 0.001$) in patients with MLN size ≥1.05 cm.

The Kaplan–Meier method was used to analyze the role of MLN size on OS (Figure 3). Survival rate was significantly decreased in patients with MLN size ≥1.05 cm compared to those with MLN size <1.05 cm [17.2% vs. 42%; ($p < 0.001$)].

Results of multivariate logistic regression analysis of factors associated with mortality were given in Table 5. Age, receiving neoadjuvant therapy, pN stage, and MLN size ≥1.05 cm were found as independent risk factors for mortality. Among these, the most prominent risk factor was the diameter of MLN size (≥1.05 cm), and had nearly 3.5 times more negative impact on survival.

Discussion

Our study results showed that evaluation of the largest MLN size *via* the histopathological examination may provide valuable information predicting mortality in patients with stage II-III GC. MLN size may be considered a reliable prognostic factor in GC.

The importance of LN size in gastric cancer has been investigated decades ago. LNs with and without metastases in GC patients were examined and it was reported that LN size was not an important factor in the determination of metastasis (12).

TABLE 1 Patients' demographic and clinicopathologic characteristics and the effect of variables on major complications and survival status.

Variables *n* (%)		Major Complication		*p-value*	Survival		*p-value*	5-year OS[e]
		No *n* = 139 (85.3%)	Yes *n* = 24 (14.7%)		Exitus *n* = 111 (68.1%)	Alive *n* = 52 (31.9%)		
Age, years, median (IQR)		62 (52–68)	64 (59–70)	0.148[a]	63 (57–69)	57 (50–65)	0.005[a]	–
Gender	Male	105 (86.1%)	17 (13.9%)	0.624[b]	80 (65.6%)	42 (34.4%)	0.233[b]	34.8%
	Female	34 (82.9%)	7 (17.1%)		31 (75.6%)	10 (24.4%)		28.5%
CCI	0–2	107 (86.3%)	17 (13.7%)	0.515[b]	87 (70.2%)	37 (29.8%)	0.314[b]	31.1%
	≥3	32 (82.1%)	7 (17.9%)		24 (61.5%)	15 (38.5%)		40.1%
BMI, kg/m^2	<30	112 (84.8%)	20 (15.2%)	0.503[c]	93 (70.5%)	39 (29.5%)	0.183[b]	31.1%
	≥30	27 (87.1%)	4 (12.9%)		18 (58.1%)	13 (41.9%)		43.1%
Neoadjuvant	No	79 (82.3%)	17 (17.7%)	0.198[b]	58 (60.4%)	38 (39.6%)	0.012[b]	44.5%
	Yes	60 (89.6%)	7 (10.4%)		53 (79.1%)	14 (20.9%)		15.3%
Surgery	Total	71 (84.5%)	13 (15.5%)	0.780[b]	55 (65.5%)	29 (34.5%)	0.459[b]	36.8%
	Subtotal	68 (86.1%)	11 (13.9%)		56 (70.9%)	23 (29.1%)		29.9%
pT stage	T1/T2	13 (76.5%)	4 (23.5%)	0.225[c]	7 (41.2%)	10 (58.8%)	0.012[b]	58.8%
	T3/T4	126 (86.3%)	20 (13.7%)		104 (71.2%)	42 (28.8%)		30.2%
pN stage	N1	41 (80.4%)	10 (19.6%)	0.405[b]	33 (53.8%)	18 (46.2%)	0.026[b]	44.2%
	N2	33 (84.6%)	6 (15.4%)		21 (64.7%)	18 (35.3%)		37.7%
	N3	65 (89.0%)	8 (11.0%)		57 (78.1%)	16 (21.9%)		25.1%
MLN size, cm, median (IQR)		1.2 (0.7–1.5)	1.0 (0.6–1.4)	0.163[a]	1.3 (0.8–1.6)	0.9 (0.6–1.2)	<0.001[a]	–
LVI	No	27 (84.4%)	5 (15.6%)	0.531[c]	17 (53.1%)	15 (46.9%)	0.043[b]	44.5%
	Yes	112 (85.5%)	19 (14.5%)		94 (71.8%)	37 (28.2%)		30.4%
PNI	No	29 (82.9%)	6 (17.1%)	0.649[b]	18 (51.4%)	17 (48.6%)	0.017[b]	46.1%
	Yes	110 (85.9%)	18 (14.1%)		93 (72.7%)	35 (27.3%)		29.5%
Differentiation	Well	2 (50.0%)	2 (50.0%)	0.159[d]	3 (75.0%)	1 (25.0%)	0.673[d]	–
	Moderately	44 (89.8%)	5 (10.2%)		31 (63.3%)	18 (36.7%)		39.6%
	Poorly	93 (84.5%)	17 (15.5%)		77 (70.0%)	33 (30.0%)		31.2%
LOS, days, median (IQR)		8 (7–11)	18 (13–24)	<0.001[a]	9 (7–12)	8 (7–17)	0.717[a]	–

[a]Mann–Whitney *U* test.
[b]Pearson's Chi-Square test.
[c]Fisher's exact test.
[d]Likelihood ratio.
[e]Kaplan–Meier test.
OS, Overall survival; CCI, Charlson Comorbidity Index; BMI, Body Mass Index; MLN, Metastatic lymph node; LVI, Lymphovascular invasion; PNI, Perineural invasion; LOS, Length of hospital stay.

TABLE 2 Disease staging of the patients considering neoadjuvant therapy status.

			pT stage		pN stage			pTNM stage	
			T1/T2	T3/T4	N1	N2	N3	IIA	III
Neoadjuvant therapy	No	*n*	12	84	34	27	35	36	60
		%	12.5%	87.5%	35.4%	28.1%	36.5%	37.5%	62.5%
	Yes	*n*	5	62	17	12	38	9	58
		%	7.5%	92.5%	25.4%	17.9%	56.7%	13.4%	86.6%

TABLE 3 Assessment of the metastatic lymph node size in predicting mortality and major complications with ROC curves .

	AUC	95% CI	Cutoff	Sensitivity	Specificity	Youden Index	*p-value*
MLN size (cm)[a]	0.699	0.615–0.782	1.05	65.8%	67.3%	0.331	**<0.001**
MLN size (cm)[b]	0.411	0.287–0.585	1.05	37.5%	41.7%	−0.208	0.164

[a]for mortality status.
[b]for major complications.
ROC, Receiver operating characteristic; AUC, Area Under Curve; CI, Confidence interval; MLN, Metastatic lymph node.

Later, studies conducted with MLNs showed that MLN size significantly affected prognosis of the patients with esophageal and colorectal cancers. Dhar et al. (7) reported the size of the largest MLN as the strongest independent predictor in a study of 187 patients with squamous cell carcinoma of the esophagus. Similarly, in a study in which a survival analysis of 311 colorectal cancer patients was performed, MLN size was found to be a strong prognostic variable in colorectal carcinoma (8). There was also a study in which the LN size was examined radiologically before surgery in GC. The size of the largest LN visualized on computed tomography (CT) was useful for predicting the MLN status of gastric cancer (13).

The first study in the literature investigating the largest MLN size in gastric cancer histopathologically and evaluating its effect on prognosis was conducted by Dhar et al. in 2003 (9). In that study, a total of 237 patients who had undergone surgery due to GC were included in the survival analysis. The largest MLN size was ranging from 0.3 to 3.0 cm and they determined a cut-off value of 7 mm for survival comparison. All tumors were classified using the 1997 The Union for International Cancer Control (UICC) pTNM categories; only patients with visceral metastases and distant lymph node metastases were excluded, all T and N stages were included. Results from this Japanese study demonstrated that MLN size was an independent risk factor in determination of OS and disease-free survival (DFS). Furthermore, it was also revealed that MLN size may supplement the UICC nodal classification system by stratifying node positive patients (9). Another similar study which was conducted in Korea evaluated the effect of the largest MLN size on prognosis in GC (10). Using a categoric cut-off value of 2 cm, they found that OS and DFS were significantly better in patients with smaller (<2 cm) MLN size. A large MLN (≥2 cm) had been reported to be an independent predictor of poor prognosis in patients with node-positive gastric carcinoma (10). A cut-off value of MLN size for survival comparison was 1.05 cm and largest MLN size was ranging from 0.3 to 2.3 cm in our study. Even though with different cut-off values, we found similar results to previously reported studies that the largest MLN size may be an important prognostic factor for OS in GC with lymph node metastasis.

Nodal involvement (*N* stage) was one of the prognostic factors for patients eligible for surgery in GC and used in the most commonly applied staging systems (2). It was reported as an independent prognostic factor since there's a close relationship between lymph nodes, tumor stage, and prognosis (14). In our MLN size <1.05 cm group, 48 patients were in the pN1 stage and 7 patients were in the pN3 stage. The MLN size ≥1.05 cm group included 3 patients at pN1 stage and 66 patients at pN3 stage. In the patient population included in our study, as pN stage

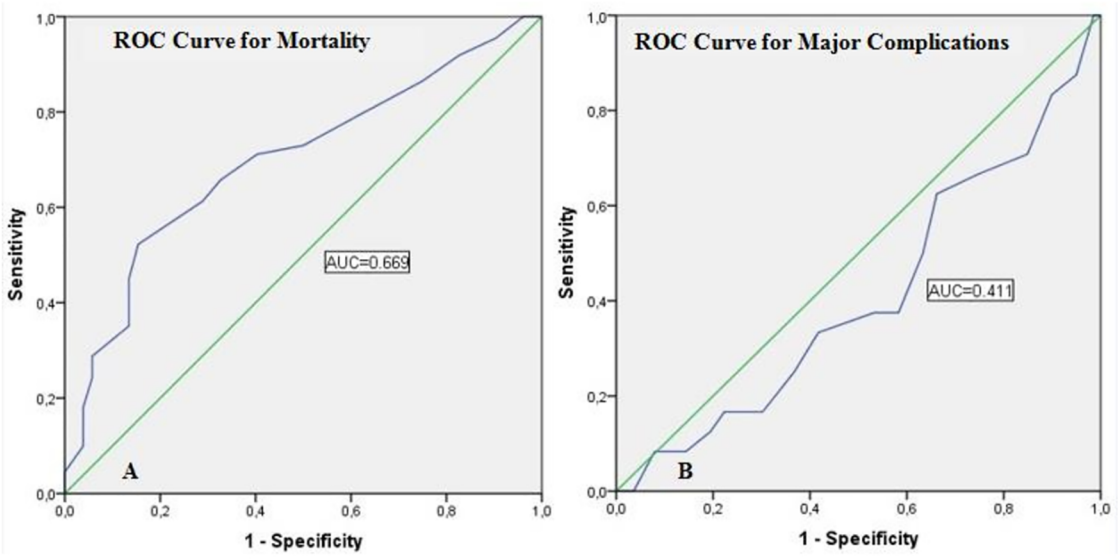

FIGURE 2
ROC analysis of MLN size in predicting mortality and major complications.

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TABLE 4 Relationship between cut-off value of metastatic lymph node size and clinicopathological features.

Variables, *n* (%)		Metastatic lymph node size				*p*-value
		<1.05 cm (*n* = 73)		≥1.05 cm (*n* = 90)		
		n	%	*n*	%	
Age, years, median (IQR)		63 (56–71)		62 (51–66)		0.105[a]
Gender	Male	57	46.7%	65	53.3%	0.391[b]
	Female	16	39.0%	25	61.0%	
CCI	0–2	53	42.7%	71	57.3%	0.350[b]
	≥3	20	51.3%	19	48.7%	
BMI, kg/m^2	<30	56	42.4%	76	57.6%	0.211[b]
	≥30	17	54.8%	14	45.2%	
Neoadjuvant	No	52	54.2%	44	45.8%	0.004[b]
	Yes	21	31.3%	46	68.7%	
Surgery	Total	41	48.8%	43	51.2%	0.287[b]
	Subtotal	32	40.5%	47	59.5%	
pT stage	T1/T2	10	58.8%	7	41.2%	0.219[b]
	T3/T4	63	43.2%	83	56.8%	
pN stage	N1	48	94.1%	3	5.9%	<0.001[b]
	N2	18	46.2%	21	53.8%	
	N3	7	9.6%	66	90.4%	
LVI	No	20	62.5%	12	37.5%	0.025[b]
	Yes	53	40.5%	78	59.5%	
PNI	No	25	71.4%	10	28.6%	<0.001[b]
	Yes	48	37.5%	80	62.5%	
Differention	Well	3	75.0%	1	25.0%	0.054[c]
	Moderately	28	57.1%	21	42.9%	
	Poorly	42	38.2%	68	61.8%	
Major Complications	No	58	41.7%	81	58.3%	0.059[b]
	Yes	15	62.5%	9	37.5%	
LOS, days, median (IQR)		8 (7–14)		9 (7–12)		0.717[a]
OS, estimated months		42.0% (87.9)		17.2% (71.8)		<0.001[d]

[a]Mann–Whitney *U* test.
[b]Pearson's Chi-Square test.
[c]Likelihood ratio.
[d]Kaplan–Meier analysis.
CCI, Charlson Comorbidity Index; BMI, Body Mass Index; LVI, Lymphovascular invasion; PNI, Perineural invasion; LOS, Length of hospital stay; OS, Overall survival.

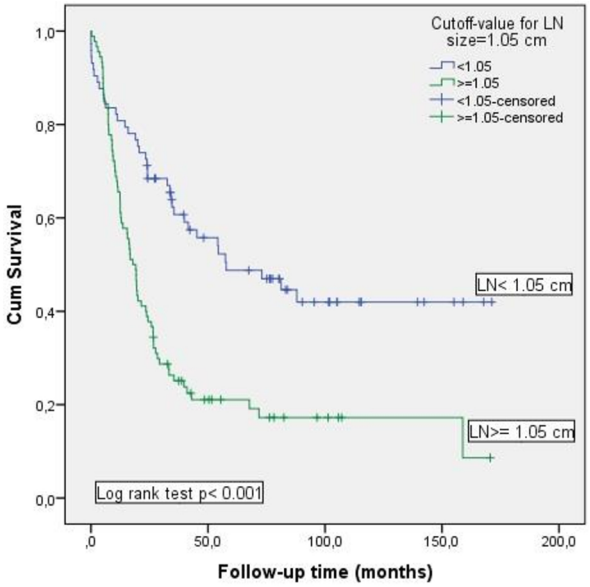

FIGURE 3
Kaplan–Meier analysis of the impact of metastatic lymph node size on overall survival.

increased, we observed a significant increase in MLN size and a significant decrease in survival. This result is in line with the published literature.

It was reported that patients with major complications required longer hospital stays and these complications had a negative effect on survival outcomes (15). As expected, the length of hospital stay was longer in patients with major complications in the present study. In addition, patients with larger MLN size had longer hospital stays in our study. We evaluated the post-operative complications that were not investigated in the previous studies. However, we did not detect a relationship between the largest MLN size and the presence of major complications.

The absence or presence of LVI and PNI was important indicators of invasive tumors and they provide valuable information regarding survival outcomes in GC. They were associated with a higher number of positive LNs, pathologically more advanced tumors, and shorter OS and DFS (16). In our study, LVI and PNI positivity were prominent in patients with MLN size ≥1.05 cm and the positivity rate of LVI and PNI was significantly higher in the deceased patient group. Therefore, we consider that our results are in line with the literature.

Limitations of the study are its retrospective design and relatively small sample size. Another limitation relates to our analysis is disease free survival. Since recurrence data was not set as one of the

TABLE 5 Multivariate logistic regression analysis predicting mortality.

Variables	OR	95.0% CI	*p-value*
Age, years	1.029	1.012–1.046	0.001
Neoadjuvant, yes	2.167	1.450–3.240	<0.001
pT stage, T3/T4	1.758	0.794–3.889	0.164
pN stage, N2/N3	2.256	1.274–3.994	0.005
MLN size, ≥ 1.05 cm	3.584	2.030–6.328	<0.001
LVI, yes	1.311	0.751–2.290	0.340
PNI, yes	1.104	0.629–1.937	0.730

OR, Odds ratio; CI, confidence interval; LVI, Lymphovascular invasion; PNI, Perineural invasion; MLN, Metastatic lymph node.

endpoints, these data had not been assessed systematically and were incomplete. However, there were a limited number of previous studies in this area. In contrast to Dhars' and Cheongs' studies, not using categorical cut-off and preventing stage bias by including a limited pathological stage group are the strengths of our study. This paper expresses a different perspective on the relationship between postoperative complications and the largest MLN size.

Conclusion

Our study results indicated that the largest MLN size was an independent risk factor for survival and a cut-off value of 1.05 cm in MLN size had prognostic value in surgically treated stage II-III GC patients. However, we did not find a relationship between the largest MLN size and the presence of major complications. In the light of these results, a review of N-stage subgroups of TNM staging may be considered. Further multicenter studies with large sample size are required to confirm our study results.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

This study was approved by the ethical committee of Koşuyolu High Specialization Education and Research Hospital with an IRB number: 2020/14/404. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

SO, SG contributed to conception and design of the study. SO, SG, ASS, OU, OG organized the database. SO, SG, EC, UD performed the statistical analysis. SO, SG, PY wrote the first draft of the manuscript. SO, SG, EP and MD wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The reviewer EB declared a past co-authorship with the author SO to the handling editor.

Publisher's note

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Effects of different radical distal gastrectomy on postoperative inflammatory response and nutritional status in patients with gastric cancer

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Objectives: The inflammatory response caused by gastric cancer surgery and the low nutritional status of patients with gastric cancer can cause growth of tumour cells, reduce immunity, and increase tumour burden. We investigated the effects of different surgical methods on postoperative inflammatory response and nutritional status in patients with distal gastric cancer.

Methods: Clinical data of 249 patients who underwent radical distal gastrectomy for distal gastric cancer from February 2014 to April 2017 were retrospectively analysed. Patients were divided according to the surgical method (open distal gastrectomy [ODG], laparoscopic-assisted distal gastrectomy [LADG] and total laparoscopic distal gastrectomy [TLDG]). Characteristics of different surgical procedures, including inflammation parameters and nutritional indicators, and different time points (preoperatively, 1 day postoperatively, and 1 week postoperatively) were compared using non-parametric test analysis.

Results: At postoperative day 1, white blood cell count [WBC], neutrophil count [N], neutrophil/lymphocyte ratio [NLR], and platelet/lymphocyte ratio [PLR] increased in the three groups, and ΔN and ΔNLR were significant; the smallest change was observed in TLDG ($P < 0.05$). Albumin [A]and prognostic nutrition index [PNI] significantly decreased; the smallest ΔA and ΔPNI, which were statistically significant, were noted in TLDG. One week postoperatively, WBC, N, NLR, and PLR decreased, and WBC, N, and NLR showed significant difference. A and PNI of the three groups increased after 1 week, and A and PNI showed significant differences.

Conclusion: Postoperative inflammatory response and nutritional status of patients with distal gastric cancer are associated with the surgical technique. TLDG has little influence on the inflammatory response and nutritional level compared with LADG and ODG.

KEYWORDS

gastric cancer, total laparoscopic surgery, inflammation, nutritional status, neutrophil/Lymphocyte ratio, prognostic nutrition index

Introduction

With the development of minimally invasive techniques, total laparoscopic radical distal gastrectomy is currently one of the surgical techniques for distal gastric cancer. Although its application is increasing, its clinical value remains controversial. Several studies showed that the size of the surgical incision is related to local inflammatory response. Both open and minimally invasive surgeries have certain influence on the overall inflammatory response of the body (1), but the specific mechanism is unclear. Some scholars reported that mononuclear cell and cytokine levels after laparoscopic surgery are lower than those after open surgery (2–7) Additionally, postoperative patients with gastric cancer are prone to malnutrition. Patients with gastric cancer who had different radical surgeries have different postoperative levels of nutritional indicators (albumin, prognostic nutrition index, etc.). Low nutritional status among postoperative patients with gastric cancer may inhibit the body's humoral immunity and cellular immune function, thereby reducing the body's immunity to tumours and thus leading to tumour recurrence.

Hence, this study aimed to assess the relationship between different surgical techniques (open distal gastrectomy [ODG], laparoscopic-assisted distal gastrectomy [LADG] and total laparoscopic distal gastrectomy [TLDG]) and the body's inflammatory response and nutritional status based on the inflammatory markers (white blood cell count [WBC], neutrophil count [N], neutrophil/lymphocyte ratio [NLR] and platelet/lymphocyte ratio [PLR]) and the nutritional indicators (albumin [A]and prognostic nutrition index [PNI]).

Material and methods

Study design

In this retrospective study, standard demographic and clinicopathological data of 503 patients with distal gastric cancer who underwent radical distal gastrectomy from February 2014 to December 2017 in Fujian Provincial Hospital were obtained. All patients were diagnosed by gastroscopy and pathological examination before operation. Inclusion criteria were pathologically confirmed gastric cancer with TNM stages I, II and III; radical resection through distal gastrectomy; no liver, lung or other distant organ metastasis and no abdominal implant transfer; no major heart or lung dysfunctions. Exclusion criteria included perioperative complications (Clavien-Dindo grade II or higher), such as anastomotic leakage, arterial embolization, postoperative bleeding and gastric motility complications; palliative or emergency surgery; perioperative infection; history of blood transfusion, active bleeding or bleeding disorders in the past 2 months; and immunosuppressive therapy. After applying the exclusion criteria, the clinical data of 249 patients were retrospectively analysed. Patients were divided according to the different surgical techniques (ODG, LADG and TLDG). The effects of the different surgical methods on the body were evaluated and compared using inflammatory and nutritional indicators preoperatively, 1 day postoperatively and 1 week postoperatively. This study was reviewed and approved by the Ethics Committee of Fujian Provincial Hospital. Data were anonymized, and the requirement for informed consent from the patients was waived. All study procedures were performed in accordance with the Helsinki Declaration of 1964 and later versions.

Surgical procedure

General anaesthesia was induced *via* tracheal intubation. The most distal part of the stomach was resected according to the classic method (8), and the D2 lymphadenectomy was performed according to the 14th edition of the Japanese Gastric Cancer Treatment Protocol. The gastrointestinal reconstruction performed in the three groups differed, with the ODG and LADG groups undergoing proximal residual stomach-jejunum Roux-en-Y anastomosis and the TLDG group undergoing proximal residual stomach-jejunum uncut Roux-en-Y anastomosis (**Figure 1**).

Indicators

Routine blood and biochemical examinations were performed at 8 am preoperatively, 1 day postoperatively and 1 week postoperatively. WBC, N, L, PLT and A were recorded. The NLR and PLR were determined. The WBC, N, NLR and PLR were evaluated as the inflammatory parameters. Changes in the NLR (ΔNLR), PLR (ΔPLR), WBC (ΔWBC) and N (ΔN) during the perioperative period were evaluated to assess the body's inflammatory response. Moreover, PNI was calculated as follows: $PNI = A\ [g/L] + 5 \times L\ [\times 10^9/L]$ (9). ΔPNI and ΔA were calculated at different time points to determine the level of nutrition. The inflammatory response and nutritional status of the patients were evaluated based on the aforementioned indicators preoperatively, 1 day postoperatively and 1 week postoperatively.

Statistical analysis

Data were analysed using chi-squared test tests or Fisher's exact test to compare proportions. Non-parametric analysis of variance (Kruskal-Wallis method) was employed in the intra- and inter-group evaluations. Differences with P values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Pictures were drawn with GraphPad Prism version 7 (GraphPad Software, San Diego, CA, USA).

Results

Baseline data

No significant differences in the baseline data including sex, age, T stage, N stage, TNM stage, Borrmann type, pathological type and

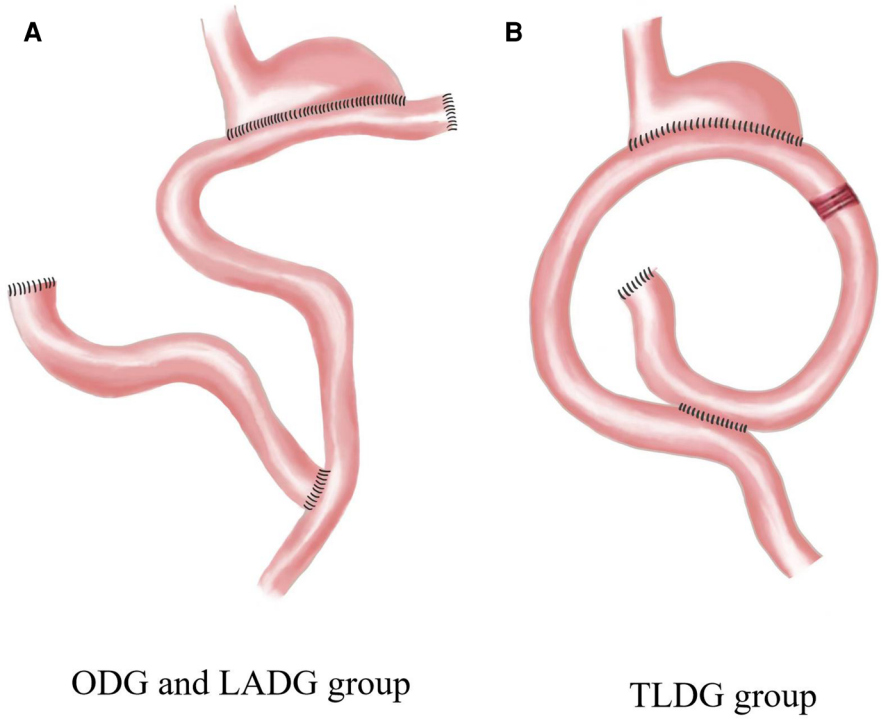

FIGURE 1
Gastrointestinal reconstruction. ODG, open distal gastrectomy; LADG, laparoscopic-assisted distal gastrectomy; TLDG, total laparoscopic distal gastrectomy.

preoperative comorbidities were found among the three surgical methods; however, tumour size and operation time showed statistically significant difference (Table 1). Preoperatively, no significant differences in the markers WBC, N, NLR, PLR, A and PNI were observed among the three surgical methods.

Inflammation indicators

At 1 day postoperatively, the WBC, N, NLR and PLR increased compared with their preoperative values. N and NLR in ODG, LADG and TLDG showed statistically significant difference ($P = 0.000$ and $P = 0.002$, respectively); however, PLR did not show significant statistical difference (Table 2). ΔN ($P = 0.001$) and ΔNLR ($P = 0.006$) showed significant statistical difference. LADG and TLDG were statistically different between ΔN ($P = 0.014$) and ΔNLR ($P = 0.020$). No statistically significant difference in ΔWBC and ΔPLR was noted among the three groups (Table 3).

At 1 week postoperatively, the WBC, N, NLR and PLR decreased but remained higher than their preoperative values. A significant difference in WBC ($P = 0.000$), N ($P = 0.000$) and NLR (Table 2C; $P = 0.007$) was observed among ODG, LADG and TLDG, but no significant difference in PLR was noted. The ΔWBC (2.97 ± 4.98 vs. 3.19 ± 3.88 vs. 4.37 ± 2.87; $P = 0.021$) was statistically significant. The difference between the two groups was that the ODG and TLDG could be statistically different from ΔWBC (2.97 ± 4.98vs. 4.37 ± 2.87; $P = 0.012$). The LADG and TLDG with regards to ΔWBC (3.19 ± 3.88vs. 4.37 ± 2.87; $P = 0.020$) was statistical difference. There were no significant statistical differences between ΔN, ΔNLR and ΔPLR in the three groups (Table 4).

Nutritional markers

At 1 day postoperatively, A and PNI decreased compared with the preoperative values. The differences in A ($P = 0.000$) and PNI ($P = 0.000$)(Table 2B), ΔA ($P = 0.001$) and ΔPNI ($P = 0.009$) among ODG, LADG and TLDG were statistically significant (Table 3). ΔA ($P = 0.001$) and ΔPNI ($P = 0.006$) increased in ODG and TLDG. A statistically significant difference in ΔA ($P = 0.003$) and ΔPNI ($P = 0.014$) was observed between LADG and TLDG (Table 3).

At 1 week postoperatively, A and PNI increased but remained lower than their values at 1 week preoperatively. The differences in A ($P = 0.016$) and PNI ($P = 0.022$) were statistically significant (Table 2C). The increase in the amplitude of ODG and TLDG there was significant at ΔA (6.61 ± 6.71 vs. 3.70 ± 4.86; $P = 0.004$) and ΔPNI (8.60 ± 7.42 vs. 5.62 ± 6.26; $P = 0.006$), LADG and TLDG was compared regarding ΔPNI (6.82 ± 5.49vs. 5.62 ± 6.26; $P = 0.046$) and was statistically significant. (Table 4).

Discussion

Comparison of the preoperative, 1-day postoperative and 1-week postoperative values of the inflammation index and

TABLE 1 Clinicopathological characteristics.

Characteristics	ODG($n = 85$)	LADG($n = 99$)	TDLG($n = 65$)	X^2orF	P
Sex					
Male	58	68	45	0.170	0.992
Female	27	31	20		
Age (years)	58.28 ± 12.36	58.66 ± 10.78	58.23 ± 9.91	0.155	0.925
Surgery Time (min)	205.68 ± 51.24	271.82 ± 57.00	231.14 ± 44.53	65.326	0.000
Tumor size (cm)	3.83 ± 1.71	3.17 ± 1.86	3.61 ± 2.40	10.890	0.004
T-Stage					
1	21	31	20	7.026	0.318
2	15	18	10		
3	15	12	17		
4	34	37	18		
N-Stage					
0	33	49	37	7.920	0.244
1	13	16	12		
2	17	13	6		
3	22	21	10		
TNM					
I	24	39	27	7.630	0.106
II	22	22	21		
III	39	38	17		
Pathology type					
Adenocarcinoma	64	76	51	0.250	0.993
Signet-ring cell carcinoma	6	6	4		
Other cancer[b]	15	17	10		
Differentiated					
Well	31	35	25	3.775	0.437
Median	11	23	13		
Poor[a]	43	41	27		
Borrmann type					
0	3	13	2	10.486	0.106
1	8	8	6		
2	25	33	18		
3	49	45	39		

[a]Poor: poor differentiated and undifferentiated.
[b]Other cancer: the mixed cancer of stomach cancer, intramucosal carcinoma, neuroendocrine carcinoma, medullary carcinoma, epithelioid carcinoma and adenosquamous carcinoma.

nutritional indicators among TLDG, ODG and LADG showed that the different surgical methods cause different levels of inflammation and nutrition, with TLDG causing the least trauma to the body.

We observed a minimum change in ΔNLR and ΔN preoperatively to 1 day postoperatively in TLDG, which indicates that TLDG has the weakest level of inflammatory response to the body. Moreover, the intensity of the postoperative inflammatory response can be determined primarily based on WBC and N; however, there are some disadvantages that the degree of surgery affects WBC and N to a greater extent. Therefore, we mainly used NLR, which more objectively reflects the level of inflammation of the body in different surgical methods, combined with the trend of WBC and N and the range of changes. Therefore, the intensity of inflammatory response in patients with radical distal gastric cancer is related to the type of surgery. Studies have shown that the extent of postoperative immune response is associated with surgically induced wounds. Immune response could induce systemic or local inflammation in the body, which in turn impairs the immune function of the body and increases the susceptibility to infectious complications (10–12). In a large meta-analysis with a large sample, Y. Jiang et al. (13) found that PLR is associated with low survival in patients with metastatic and non-metastatic solid tumours. Previous studies showed that the higher the NLR value in gastric cancer patients, the shorter the survival rate and overall survival time (12–14). However, we also observed from the results that the ΔPLR as an indicator of inflammation was not statistically significant, but it was consistent with the trend of inflammatory response changes, whereas the amount of TLDG was minimal. We suspect that patients with advanced gastric cancer have tumour cell growth that consumes platelets and that traumatic platelet consumption is associated with it. In addition, tumour-associated platelets secrete 5-hydroxytryptamine, platelet factor 4, tumour growth factor β and other particles, which adhere to vascular damage, thus maintaining the integrity of the tumour

TABLE 2 Characteristics with different surgeries at different times.

A Characteristics with different surgical of preoperative					
Characteristics	ODG ($n = 85$)	LADG ($n = 99$)	TDLG ($n = 68$)	H	*P*
WBC($\times 10^9$/L)	6.05 ± 1.85	6.20 ± 2.06	6.03 ± 1.52	0.070	0.966
N($\times 10^9$/L)	3.69 ± 1.68	3.71 ± 1.85	3.50 ± 1.17	0.419	0.811
A(g/L)	41.34 ± 5.45	42.65 ± 4.39	42.62 ± 3.44	4.323	0.115
NLR(N/L)	2.42 ± 1.91	2.30 ± 2.54	1.99 ± 0.94	2.306	0.316
PLR(PLT/L)	158.85 ± 83.29	146.56 ± 60.15	148.36 ± 77.09	0.465	0.793
PNI[5*L(*10^9/L)+A(g/L)]	50.25 ± 7.08	51.98 ± 5.62	52.12 ± 5.02	4.361	0.113
B Characteristics with different surgical of postoperative 1 day					
Characteristics	ODG ($n = 85$)	LADG ($n = 99$)	TDLG ($n = 68$)	H	*P*
WBC($\times 10^9$/L)	12.78 ± 4.47	12.20 ± 3.92	11.67 ± 3.05	2.246	0.325
N($\times 10^9$/L)	11.53 ± 3.99	10.57 ± 3.65	8.96 ± 2.26	16.874	0.000
A(g/L)	27.48 ± 5.67	30.39 ± 3.87	32.26 ± 3.45	36.118	0.000
NLR(N/L)	15.87 ± 8.32	14.88 ± 8.96	11.42 ± 4.86	12.725	0.002
PLR(PLT/L)	270.28 ± 114.59	268.56 ± 124.88	255.47 ± 112.27	0.709	0.701
PNI[5*L(*10^9/L)+A(g/L)]	31.64 ± 5.88	34.56 ± 4.30	36.65 ± 4.15	33.565	0.000
C Characteristics with different surgical of postoperative 1 week					
Characteristics	ODG ($n = 85$)	LADG ($n = 99$)	TDLG ($n = 65$)	H	*P*
WBC($\times 10^9$/L)	9.81 ± 2.57	9.01 ± 2.96	7.30 ± 2.02	36.757	0.000
N($\times 10^9$/L)	7.01 ± 2.34	6.55 ± 2.56	5.28 ± 1.51	26.404	0.000
A(g/L)	34.09 ± 4.34	35.14 ± 3.73	35.97 ± 3.45	8.319	0.016
NLR(N/L)	6.69 ± 3.41	6.09 ± 4.43	5.15 ± 2.79	10.005	0.007
PLR(PLT/L)	233.64 ± 116.88	227.02 ± 122.03	214.22 ± 110.58	1.063	0.588
PNI[5*L(*10^9/L)+A(g/L)]	40.24 ± 5.79	41.38 ± 4.81	42.28 ± 5.09	7.633	0.022

WBC, White blood cell count;, N, Neutrophils count; L, Lymphocytes count; PLT, Platelets count; A, Albumin.
NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; PNI, 5* lymphocyte (*10^9/L)+ albumin (g/L),.

TABLE 3 Comparison of change of indicators before surgery to postoperative 1 day.

Characteristics	ODG ($n = 85$)	LADG ($n = 99$)	TLDG ($n = 65$)	P_1	P_2	P_3	P_4
ΔWBC	6.73 ± 4.73	6.00 ± 3.53	5.64 ± 3.01	0.308	0.218	0.914	0.431
ΔN	7.01 ± 2.34	6.49 ± 2.56	5.46 ± 2.37	0.198	0.000	0.014	0.001
ΔA	13.86 ± 6.51	12.25 ± 4.59	10.35 ± 3.97	0.152	0.001	0.003	0.001
ΔNLR	13.45 ± 8.50	12.58 ± 9.55	9.43 ± 4.85	0.330	0.002	0.020	0.006
ΔPLR	111.42 ± 107.01	121.99 ± 123.55	107.12 ± 100.04	0.819	0.802	0.699	0.917
ΔPNI	18.61 ± 7.78	17.42 ± 5.49	15.46 ± 5.13	0.280	0.006	0.014	0.009

*P*1: *P* value after comparison between ODG and LADG.
*P*2: *P* value after comparison between ODG and TLDG.
*P*3: *P* value after comparison between LADG and TLDG.
*P*4: Compared ODG, LADG and TLDG after the *P* value.

TABLE 4 Comparison of change of indicators postoperative 1 day to postoperative 1 week.

Characteristics	ODG ($n = 85$)	LADG ($n = 99$)	TLDG ($n = 65$)	P_1	P_2	P_3	P_4
ΔWBC	2.97 ± 4.98	3.19 ± 3.88	4.37 ± 2.87	0.508	0.012	0.020	0.021
ΔN	3.98 ± 2.92	4.71 ± 3.93	3.34 ± 3.99	0.438	0.343	0.720	0.585
ΔA	6.61 ± 6.71	4.75 ± 4.92	3.7 ± 4.86	0.066	0.004	0.108	0.011
ΔNLR	9.18 ± 7.92	8.78 ± 9.53	6.28 ± 5.24	0.757	0.048	0.085	0.110
ΔPLR	36.64 ± 135.76	41.54 ± 168.40	41.25 ± 123.08	0.858	0.786	0.712	0.924
ΔPNI	8.60 ± 7.42	6.82 ± 5.49	5.62 ± 6.26	0.165	0.006	0.046	0.014

*P*1: *P* value after comparison between ODG and LADG.
*P*2: *P* value after comparison between ODG and TLDG.
*P*3: *P* value after comparison between LADG and TLDG.
*P*4: Compared ODG, LADG and TLDG after the *P* value.

vascular endothelium and promoting the progression of tumour cells (15).

From another perspective, the three surgical methods differ. Incision size, which has the most direct effect on the body, differs among the three surgical methods: the ODG incision is approximately 15 cm on average (largest); the LADG incision is about 8–12 cm; the TLDG incision is approximately 3–5 cm (smallest). The size of the incision during surgery is related to the extent of the inflammatory response and could induce the production and release of inflammatory mediators near the incision. In addition, studies have shown that inflammation due to wounds could increase the proliferation of mesothelial cells and increase the number of inflammatory cells (16) The inflammatory response to surgery stimulates the body to form cellular immunity; the infiltration of concentrated granulocytes, macrophages and myofibroblasts stimulates the release of a large amount of inflammatory mediators and cellular chemokines (17, 18). More interestingly, Krall et al. (1) established a standard experimental model of surgery and wound healing response and showed that distant metastasis linked tumour cell growth and wound healing cascade and that the recruitment of neutrophils and macrophages is followed by infiltration of myofibroblasts and extensive angiogenesis. Consistent with the results of our study, postoperative inflammatory markers in their study were elevated; however, because of the different surgical methods, the inflammatory response was different. The inflammatory index was the lowest in TLDG.

Nutrition, immunity, inflammation and cancer are closely linked to, which may in turn affect the survival prognosis of cancer patients (9, 19). Gastric cancer patients often suffer from symptoms such as weight loss, hypoproteinaemia, anaemia and malabsorption, which are related to the inhibition of humoral and cellular immune functions, changes in inflammatory response and wound healing (20–23). A is used to reflect the nutritional status of the body; however, there are many influencing factors, such as the effect of general anaesthesia drugs on the liver, causing a decrease in protein. Changes in the expression levels of A may be important markers reflecting the prognosis of patients with gastric cancer (24). Therefore, this study used PNI to assess the nutritional status of patients. This is calculated using serum albumin and is an objective indicator of malnutrition, but A is the most widely used and the easiest to study. PNI was used to assess perioperative immunonutrition status and surgical risk in patients undergoing gastrointestinal surgery (25). Studies have shown that low PNI means poor immunonutrition, which may affect the immunity of the organism to the tumour and increase the burden of the tumour, thus affecting the overall prognosis of advanced cancer. Moreover, Jiang et al. (26) suggested that low PNI is associated with poor prognosis of malignant solid tumours and is included in routine nutritional assessment of patients with advanced gastric cancer (26–31). In radical distal gastrectomy, most of the stomach, including tumours and normal tissues, is removed, leading to malnutrition, which greatly increases the risk of tumour recurrence. Surgical trauma may inhibit the body's fluid and cellular immune function and stimulate the body to produce inflammation and traumatic changes, resulting in poor nutrient intake; therefore, different surgical methods lead to different degrees of decline in nutritional indicators, which is consistent with our findings. ΔPNI and ΔA were observed to have the least change in TLDG from preoperative to postoperative 1 day (Table 3), indicating that this procedure is to minimise the loss of nutrients in the body. Perioperative gastric cancer patients are beneficial to nutritional recovery and enhance immunity against tumour recurrence.

In addition, we studied the changes of inflammatory index and nutritional index of different surgical methods at 1 week postoperatively. NLR, N and WBC were found to be statistically significant. Although PLR was not statistically significant, TLDG showed the lowest inflammation in the index status. PNI and A were found to be statistically significant in the nutritional indicators. This makes us more convinced that TLDG has the weakest effect on the level of inflammatory response in the body and has the least impact on the nutritional status of the body.

Although this study yields the above meaningful results, there were some limitations to the current study. First, this is a retrospective study. Despite strict inclusion and exclusion criteria, certain selection biases remained. Second, although postoperative PLR levels were elevated, they were not statistically significant, probably due to sample size problems. Third, this study did not evaluate the prognosis, but we will further study the prognosis.

Conclusions

The postoperative inflammatory response and nutritional status of patients with distal gastric cancer are related to surgery. TLDG has little effect on inflammatory response and nutritional status compared with LADG and ODG.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Fujian Provincial Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors contributed to the research conception and design. The first draft of the paper was written by XC. Data collection was performed by XC, CW, YL and XZ. Data calculation and analysis were performed by XC, CW, YL and XZ. The work was critically revised by XC, CW, YL, XZ, LZ, ZL, WZ, LL, CY and WL. All authors commented on previous versions of the paper, as well as

read and approved the final version. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Impact of neoadjuvant FLOT treatment of advanced gastric and gastroesophageal junction cancer following surgical therapy

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Introduction: Therapeutic treatment for advanced-stage (T_2–T_4) gastroesophageal junction (GEJ) and gastric cancer involves neoadjuvant chemotherapy with subsequent surgical intervention.
Method: Neoadjuvant oncological treatment for GEJ and gastric cancer previously consisted of the intravenous administration of epirubicin, cisplatin and fluorouracil (ECF) or epirubicin, cisplatin and capecitabine (ECX) combination (Group 1). The new protocol (FLOT, F: 5-FU, L: leucovorin, O: oxaliplatin, T: docetaxel), included patients with resectable GEJ and gastric cancer who had a clinical stage cT_2 or higher nodal positive cN+ disease (Group 2). Between 31 December 2008 and 31 October 2022, the effect of different oncological protocols in terms of surgical outcomes in cases of T_2–T_4 tumours were retrospectively evaluated. Results of randomly assigned patients from the earlier ECF/ECX protocol ($n = 36$) (Group 1) and the new FLOT protocol ($n = 52$) (Group 2) were compared. Effect of different neoadjuvant therapies on tumour regression, types of possible side effects, type of surgery, and oncological radicality of surgical procedures were analysed.
Results: When comparing the two groups, we found that in case of the FLOT neoadjuvant chemotherapy (Group 2, $n = 52$), complete regression was achieved in 13.95% of patients, whereas in the case of ECF/ECX (Group 1, $n = 36$), complete regression occurred in only 9.10% of patients. Furthermore, in the FLOT group, the mean number of lymph nodes removed was slightly higher (24.69 vs. 20.13 in the ECF/ECX group). In terms of the safety resection margin (proximal), no significant difference was found between the two treatment groups. Nausea and vomiting were the most common side effects. The occurrence of diarrhea was significantly higher in the FLOT group ($p = 0.006$). Leukopenia and nausea occurred more commonly with the old protocol

Abbreviations
GEJ, gastroesophageal junction; AJCC, Cancer Staging Manual: American Joint Committee on Cancer (AJCC) staging; TNM, The TNM Classification of Malignant Tumors; Stata, Statistical software for data science; ANOVA,: The Analysis Of Variance; ECF/ECX, Epirubicin, Cisplatin and Fluorouracil (ECF), or Epirubicin, Cisplatin and Capecitabin (ECX); FLOT, 5-FU, leucovorin, oxaliplatin, docetaxel; iv, intravenous; inf, infusion; *p.o*, per os; ASA, American Society of Anesthesiology) score; ECOG, Eastern Cooperative Oncology Group (ECOG) Performance Status; ECG, Electrocardiography; ECHO, heart ultrasound; MRI, magnetic resonance imaging; CT, computed tomography; TRG, tumour regression grade; CEA, Carcinoembryonalis antigen; CA 19-9, Cancer antigen 19,9; neoadjuvant KT, neoadjuvant chemotherapy; HGB, hemoglobin; HTK, hematocrit; pCR, pathologic complete response; HIPEC, hyperthermic intraperitoneal chemotherapy.

(Group 1). The rate of neutropenia was lower following FLOT treatment ($p = 0.294$), with the lack of grade II and III cases. Anaemia occured at a significantly higher rate ($p = 0.036$) after the ECF/ECX protocol.

Conclusions: As a result of the FLOT neoadjuvant oncological protocol for advanced gastro-esophageal junction and gastric cancer, the rate of complete tumour regression increased significantly. The rate of side effects was also appreciably lower following the FLOT protocol. These results strongly suggest a significant advantage of the FLOT neoadjuvant treatment used before surgery.

KEYWORDS

FLOT therapy, neoadjuvant treatment, advanced gastric tumour, gastroesophageal junction, surgery

Introduction

The incidence of GEJ or gastric cancers vary with different geographic locations. Based on a GLOBOCAN 2020 database, gastric cancer is the fourth leading cause of cancer related deaths. In 2020 about 1,1 M newly diagnosed cases were registered worldwide (1, 2).

The rates of primary esophageal adenocarcinoma and tumours of the gastroesophageal junction (Barrett's adenocarcinoma) are constantly on the rise (3, 4). As opposed to the Siewert–Stein topographical classification (I to III) used previously (5–7), the AJCC Cancer Staging Manual (8th edition TNM) classifies cardia tumours into two large groups based on their behaviour and management (8). The first group consists of patients previously included in the Siewert I and II classes, and their treatment should follow the principles to be used in patients with esophageal tumours. Patients in the prior Siewert III class now belong to the second group, where treatment used in gastric tumour patients should be employed.

Neoadjuvant oncological treatments have been used routinely around the world for several decades now. The first treatments were developed specifically so that tumours in an inoperable stage can be subjected to surgery after a favourable response (7). Treatments with modified indications were introduced later. In these cases, the objective was not only to achieve operability but also to preserve organs and achieve better oncological results (9, 10).

Many questions have arisen during the evolution of neoadjuvant treatments (11, 12). What should the indications be exactly, what should the treatment consist of, when should restaging assessments be performed, and what is the best time of surgery (6)? In this study, we evaluated the change in the chemotherapy component of the neoadjuvant therapy. Previous treatment with 3 cycles of ECF/ECX (epirubicin, cisplatin and fluorouracil [ECF], or epirubicin, cisplatin and capecitabine [ECX]) was replaced by 4 cycles of FLOT (5-FU, leucovorin, oxaliplatin, docetaxel) (13–15).

At our department, in accordance with the protocols used previously, neoadjuvant oncological treatment is indicated for stage T2–4 advanced gastric and cardia tumours, because of the size of the tumour, local spreading and/or lymph node involvement. This therapy has numerous advantages over the adjuvant treatment administered later. It has been demonstrated to decrease the size of the tumour (downsizing) and tumour regression may occur in case of a favourable response (downstaging). Downsizing and downstaging together contribute to an increased ratio of resectability and, with it, a higher chance of organ preserving surgery, which considerably improves the later quality of life of patients.

An argument for the preoperative treatment is that tissues have better blood and oxygen supply before the planned surgery, which improves their sensitivity to the treatment. At the same time, the regeneration ability is also better compared with the postoperative adjuvant therapy. The beneficial effect of neoadjuvant therapy on survival has been shown previously (16).

During our research, the effects of modifying the neoadjuvant oncological treatment protocol on tumour regression, the results of the surgical–oncological interventions, the number of lymph nodes removed, the resection margins and the surgical complications, as well as the side effect profile of the treatments, were evaluated.

Material and methods

Review Board of Human Investigations at the University of Szeged, Hungary, approval number: 117/2020-SZTE.

Neoadjuvant chemotherapy: Previously, patients received a combination of epirubicin, cisplatin and fluorouracil (ECF), and then they were switched to the combination of epirubicin, cisplatin, and capecitabine (ECX). During the ECF/ECX treatment, epirubicin 5 mg/m^2 (on Day 1), cisplatin 60 mg/m^2 (on Day 1), and 5-FU 200 mg/m^2 (or capecitabine 1,250 mg/m^2 orally, divided into two doses between Day 1 and Day 21) were administered every three weeks. The new pre-treatment was the FLOT therapy, the components and dosages of which were as follows:.

FLOT therapy:
F: 5-FU 2,600 mg/m^2 in 24-hour IV infusion on Day 1
L: leucovorin 200 mg/m^2 in IV infusion on Day 1
O: oxaliplatin 85 mg/m^2 in IV infusion on Day 1
T: docetaxel 50 mg/m^2 in IV infusion on Day 1
repeated every two weeks.

Study period

Data from gastric and cardia tumour patients receiving neoadjuvant therapy and then surgery at the Department of Surgery of the University of Szeged between 31 Dec 2008 and 31 Oct 2022 were evaluated during the research.

Patient inclusion criteria

The criteria for inclusion included disease resectability and an initial stage of at least T_2 (advanced), without distant metastases and with lymph node positivity (cN+).

Patient exclusion criteria

Exclusion criteria included potentially irresectable tumors with distant metastasis and patient unfit for neoadjuvant FLOT chemotherapy.

Patient demographics

Data from a total of 88 patients (35 females and 53 males) were evaluated. The ECF/ECX group (Group 1, $n = 36$) included 36 patients, whereas FLOT was administered to 52 patients (Group 2, $n = 52$).

The mean age of patients and its distribution by gender and treatment group were assessed. In addition, BMI and ASA of the patients were analysed by treatment group.

Investigations

As part of routine investigations, patients were subjected to oesophago-gastroscopy, sample collection for histology, oncological staging, laboratory tests, and consultation with an anaesthetist. Additional cardiac risk assessment was also performed (ECG, cardiac ultrasound), if it was required.

The T stage was determined using a CT/MRI scan and/or endosonography. No second, restaging MRI scan was performed after the different neoadjuvant oncological treatments.

The ratio of cases with endosonography performed increased over time.

Tumour marker measurements: CEA and CA 19-9 levels were determined in the laboratory before the start of treatment.

Decision by the tumour board

Decision on neoadjuvant treatment was made in each case by the multidisciplinary (oncology) tumour board. Provided that the patient accepted decision on pre-treatment, neoadjuvant chemotherapy could be initiated. Patients with metastatic or irresectable disease were excluded from this study.

Timing of surgery

The time to surgery (days) was evaluated both in patients receiving the ECF/ECX treatment protocol and in those subjected to the neoadjuvant FLOT therapy.

The type of further surgical treatment was also determined or much affected by the location of the disease.

Surgical treatment

During the two different neoadjuvant treatments, surgeries were performed by the same three surgeons experienced in gastric and esophageal surgery. Both open and laparoscopic procedures were performed, using standardised surgical techniques. The technique used was decided by the operating surgeon in each case. Total gastrectomy was carried out with open surgical technique only. Both open surgery and a minimally invasive technique (laparoscopic abdominal phase and thoracoscopy-assisted thoracic phase) were used for cardia resections. Upper midline laparotomy was used for total gastrectomies. Standard D2 lymphadenectomy was performed during both total gastrectomies and cardia resections. During the gastrectomies, a nasojejunal tube was inserted through the anastomosis, all the way below the level of the distal anastomosis, and early enteral feeding was started through it on postoperative day 2. The proximal anastomosis was an end to side esophagojejunal type, made with size 25 circular stapler. The end of the small afferent loop was closed with a linear stapler. The distant anastomosis was handsewn in one layer in the jejunum, 40 cm from the proximal anastomosis. These were end to side anastomoses. In case of cardia resections, a nasogastric tube was inserted into the gastric conduit through the esophagogastric anastomosis, with the purpose of decompression. During the abdominal phase, a jejunal catheter was also inserted to start early enteral feeding. For the minimally invasive cardia resections, the abdominal phase was performed laparoscopically. Main steps of the procedure: preparation of the greater curvature, gastric conduit formation using endoscopic staplers, complete lymphadenectomy, transhiatal mobilisation of the distal third of the esophagus, jejunal catheter insertion, abdominal drainage. After changing patient position, the thoracoscopy-assisted thoracic phase was performed. The proximal anastomosis was an end to side esophagogastric type, made with size 25 circular stapler. The end of the small gastric afferent loop was closed with a linear stapler. The specimen was removed using mini-thoracotomy. A nasogastric tube was inserted into the gastric conduit through the anastomosis, and two chest drains were left in place.

Follow-up

Patients were surgically followed up 1 week, 1 month and 1 year after being discharged. The mean follow-up of operable

patients was 26 months. At the same time, patients were receiving continuous oncological follow-up and care, and their follow-up is still ongoing to this day. Oncological follow-up is done according to the international protocols.

Studied parameters

1. Side effect profile analysis of oncological treatments:
   The different side effects of the two chemotherapies and their severity were assessed.
2. Comparison of CT images and pathological regression:
   We analysed how informative the CT scan performed after the neoadjuvant oncological treatment was, and how much it could determine the level of tumour regression. The analysis involved comparing the findings from the second CT scan with the TRG determined during the pathological assessment, and checking the level of correlation between the results.
3. Timing of surgery during the two treatment periods:
   The time from the different treatment methods to the surgeries was analysed.
4. Distribution of the surgical techniques in the two oncological periods:
   The ratio of minimally invasive to open surgeries was assessed in the periods corresponding to the two oncological protocols.
5. Assessment of perioperative complications:
   Results were also compared by the neoadjuvant treatment and the surgical technique used. The length of hospital stay (days), the rate of suture failure, as well as the incidence of impaired wound healing and wound suppuration were also assessed. Suture failure was established if contrast leak was revealed by the swallow test performed using a water-soluble contrast agent on postoperative day 7.
6. Pathological evaluation methods of the efficacy of the oncological treatment:

   6.1 TRG analysis: The efficiency of the neoadjuvant oncological treatment was confirmed with a pathological processing of the specimen obtained during the post-treatment surgery. In both periods, laparoscopic surgeries were compared with laparoscopic surgeries and open surgeries were compared with open surgeries for the studied parameters. The TRG–Mandard score was the most important studied parameter.

   6.2 Proximal resection margin: It was assessed if there was any difference in the distance from the tumour to the proximal resection margin between the oncological protocols and between the different surgical techniques.

   6.3 Lymph node status: The two oncological protocols and the two surgery types were assessed, respectively, for any difference in the number of regional lymph nodes removed.

Statistics

Statistical analyses were performed with STATA 16 program (StataCorp, College Station, TX 77845, United States). Continuous variables were checked for normality using the Shapiro–Wilk test. Two-sample *t*-test and one-way ANOVA were used to compare the means of two or more samples, respectively. If the distribution was not normal, then the Wilcoxon rank sum test or the Kruskal–Wallis test was applied. The proportions were analysed using the chi-squared test and Fisher's exact test. Henceforward, significant results are indicated using asterisks ($^{*}p \leq 0.05$; $^{**}p \leq 0.01$; $^{***}p \leq 0.001$). The abbreviation "NS" will be used for non-significant *p*-values.

Results

Patient demographics

Data from a total of 88 patients were evaluated in our research, with 36 patients in the ECF/ECX group (Group 1, $n = 36$) and 52 patients receiving FLOT (Group 2, $n = 52$).

There were 35 female and 53 male patients. Mean age was 61.65 years in women and 62.35 years in men. There was no significant difference in gender distribution between the ECF/ECX group (Group 1) and the FLOT group (Group 2). (Fisher's exact test; $p = 0.659$) As to mean age, there was a significant difference between the ECF/ECX group (Group 1) and the FLOT group (Group 2) (Student's *t*-test; $p = 0.0435$).

The mean body mass index of the patients in the two different neoadjuvant treatment groups was almost the same (25.50 in the ECF/ECX group vs. 25.90 in the FLOT group). There was no significant difference in the mean BMI between the ECF/ECX group (Group 1) and the FLOT group (Group 2). (Student's *t*-test $p = 0.6903$) (Table 1).

There was no significant difference between the ECF/ECX group (Group 1) and the FLOT group (Group 2) in ASA classification, including the ASA 1, ASA 2, and ASA 3 classes each (Fisher's exact test) (Table 2).

Tumour locations

The most frequent tumour location was the middle third of the stomach (in 32 out of 88 cases, 36.36%), and the tumours most often showed concentric, "napkin ring"-like spreading (Figures 1, 2).

TABLE 1 Mean BMI, mean age, and gender distribution by oncological protocol (ECF/ECX and FLOT).

Type of neoadjuvant therapy	ECF/ECX ($n = 36$)		FLOT ($n = 52$)		*p*-value
Age (with SD)	59.75 ± 11.59		64.48 ± 9.95		$p = 0.0435$ (Student's *t*-test)
Sex (no)	Female: 13	Male: 23	Female: 22	Male: 30	$p = 0.659$ (Fischer exact-test)
BMI (with SD)	25.45 ± 4.97		25.95 ± 5,07		$p = 0.6903$ (Student's t-test)

TABLE 2 ASA classification of patients by treatment group (ECF/ECX and FLOT).

ASA	ECF/ECX, $n = 36$	FLOT, $n = 52$	p-value (Fisher exact test)
1	5/36 13.89%	6/52 11.54%	NS
2	21/36 58.33%	25/52 48.07%	NS
3	10/36 27.78%	21/52 40.38%	NS
4	–	–	–
5	–	–	–

Radiological assessment results

A CT scan was performed in all 88 cases and a lesion could be diagnosed already with the CT scan in 66 cases (75.00%). A second CT scan after the completion of the treatment was performed in 66 cases (75.00%). An MRI scan was performed before the start of the treatment, during the previous oncological therapy (ECF/ECX) in 5.56% of the cases, whereas it was performed during the modified oncological therapy (FLOT) in 17.30% of the cases. No second MRI scan was performed after the different neoadjuvant oncological therapies. Certainly, this ratio has improved considerably in accordance with the international recommendations. The ratio of cases with endosonography performed increased over the study period. Endosonography was performed in 38.90% of the cases before the initiation of the previous oncological treatment protocol and in 59.60% of the cases before the modified oncological treatment (FLOT) (Table 3).

The laboratory measurement of CEA and CA 19-9 levels did not prove to be informative because of the too high SD values. In accordance with the literature, these markers have an emphasised role rather during follow-up.

Based on radiological imaging methods, patients usually had an N_0, N_1 or N2 lymph node involvement, with only 4 patients having a stage N_3 gastric tumour included in the study. In case of metastasis, the radiological picture of the distant metastasis was not typical and, therefore, the diagnosis of a metastasis could not be confirmed safely.

As to the initial T stage (including T_1, T_2, T_3, and T_4 each), there was no significant difference between the ECF/ECX group (Group 1) and the FLOT group (Group 2) (Fisher' exact test; $p = 0.082$).

The difference in the initial N stage between the ECF/ECX group (Group 1) and the FLOT group (Group 2) was not significant (Fisher's exact test; $p = 0.603$).

As to the initial M stage, there were no cases with distant metastasis in either the ECF/ECX group (Group 1) or the FLOT group (Group 2) (Figure 3).

Side effect profile analysis

a) Diarrhoea: A change in bowel habits is a very common side effect during chemotherapy. During ECF/ECX therapy, Grade 1 diarrhoea occurred in 2 out of the 36 cases (5.55%); Grade 2 diarrhoea was developed in 1 out of the 36 cases (2.78%); and Grade 3 diarrhoea was not reported. During the FLOT therapy, Grade 1 diarrhoea occurred in 10 out of the 52 cases (19.23%); Grade 2 diarrhoea was developed in 3 out of the 52 cases (5.77%); and Grade 3 diarrhoea was reported in 1 out of the 52 cases (1.92%). There was a significant difference between the ECF/ECX group (Group 1) and the FLOT group (Group 2) in the rate of diarrhoea (Grade 1, 2, and 3 diarrhoea each) (Fisher's exact test; $p = 0.006$).

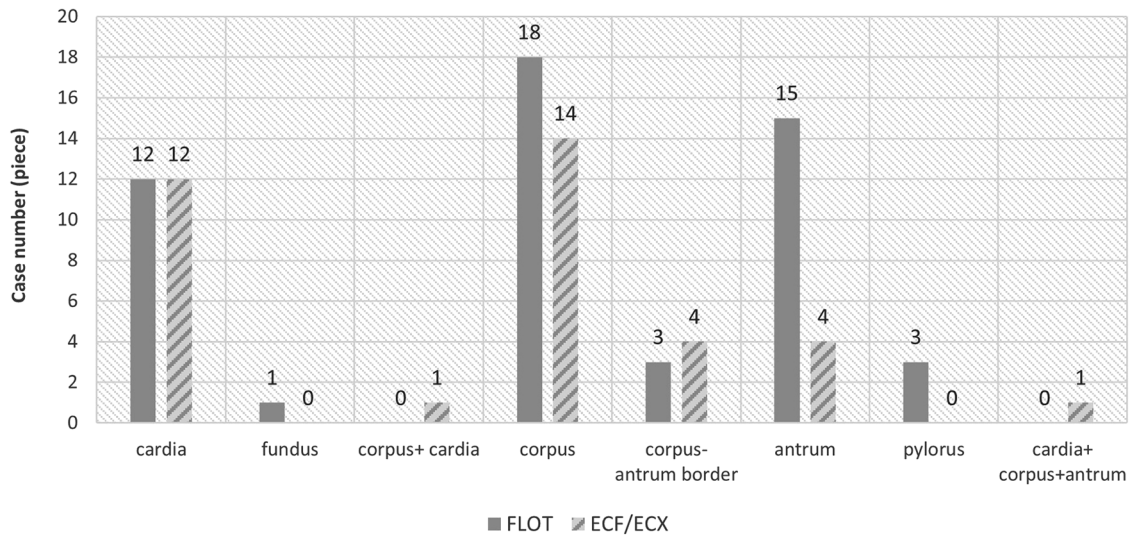

FIGURE 1
Location of gastric and gastric cardia tumours by treatment group (ECF/ECX and FLOT).

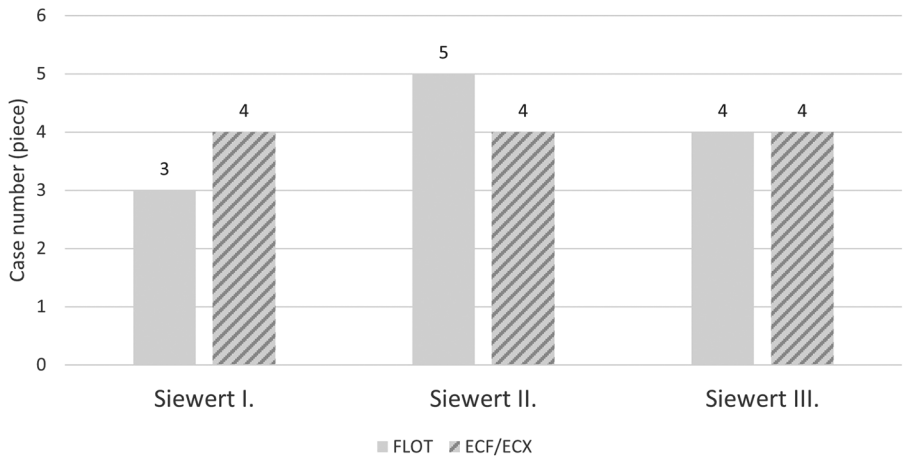

FIGURE 2
Location of cardia tumours according to the Siewert classification by oncological treatment group (ECF/ECX and FLOT).

TABLE 3 Imaging examinations performed by treatment group (ECF/ECX and FLOT).

Diagnostic procedure	ECF/ECX ($n = 36$)	FLOT ($n = 52$)
Endoscopy	29/36 80.56%	39/52 75.00%
Endosonography	14/36 38.89%	32/52 61.54%
CT	36/36 100.00%	52/52 100.00%
MRI	2/36 5.56%	9/52 17.31%

b) Weight loss: A small number of patients showed minimal weight loss during the intravenous chemotherapies. Whereas Grade 1 weight loss was reported in 2 out of the 36 cases (5.55%) in the ECF/ECX group, it occurred in 4 out of the 52 cases (7.69%) in the FLOT group. With regard to the side effect of weight loss, there was no significant difference between the ECF/ECX and the FLOT treatments (Fisher's exact test; $p = 1.000$).

c) Nausea: The leading symptom of intravenous chemotherapies. Nausea and vomiting were predominant in this study as well, occurring in both study periods. During the ECF/ECX treatment, Grade 1 and Grade 2 nausea occurred in 17 (47.22%) and 2 (5.55%) of the 36 cases, respectively, whereas during the FLOT treatment, the rates of Grade 1 and Grade 2 nausea were 11 (21.15%) and 2 (3.85%) of the 52 cases, respectively. There was no significant difference between the ECF/ECX and FLOT groups in Grade 1 and Grade 2 nausea and vomiting (Fisher's exact test; $p = 0.192$).

d) Neutropenia: No significant difference was demonstrated between the two oncological protocols in the production of cellular blood components. Neutropenia was slightly more common during the ECF/ECX treatment, which was associated with Grade 1, Grade 2 and Grade 3 neutropenia in 2 (5.55%), 1 (2.78%) and 1 (2.78%) of the 36 cases, respectively, whereas in the FLOT group, Grade 1 neutropenia occurred in 3 out of the 52 cases (5.77%). No Grade 2 or Grade 3 neutropenia was observed during FLOT treatment. Regarding neutropenia (including Grade 1, Grade 2, and Grade 3 cases), there was no significant difference between the ECF/ECX and FLOT treatments (Fisher's exact test; $p = 0.294$).

e) Anaemia: There was a significant difference in the rate of treatment-emergent anaemia. During the pre-treatment with ECF/ECX, patients developed Grade 1 and Grade 2 anaemia in 3 (8.33%) and 2 (5.56%) of the 36 cases, respectively. The FLOT therapy was not associated with Grade 1 anaemia but Grade 2 anaemia was observed in 2 out of the 52 cases (3.85%). (Cut-off values in males: haematocrit: 0.39%; haemoglobin: 133 g/L; in females: haematocrit: 0.36%, haemoglobin: 118 g/L.) There was a significant difference in the rate of anaemia between the ECF/ECX and FLOT treatments (Fisher's exact test; $p = 0.036$).

f) Peripheral neuropathy: The ECF/ECX treatment was not associated with Grade 1 peripheral neuropathy but Grade 2 peripheral neuropathy occurred in 1 out of the 36 cases (2.78%); with the FLOT pre-treatment, Grade 1 and Grade 2 peripheral neuropathy was developed in 10 (19.23%) and 1 (1.92%) of the 52 cases, respectively. The difference between the ECF/ECX and FLOT treatments in the rate of peripheral neuropathy was not significant (Fisher's exact test; $p = 0.192$).

g) Fever: During the pre-treatment with ECF/ECX, it occurred in 1 out of the 36 cases (2.78%), whereas in the FLOT group, it was reported in 1 out of the 52 cases (1.92%). The difference between the ECF/ECX and FLOT treatments in the rate of fever was not significant (Fisher's exact test; $p = 1.000$).

No other special, treatment-related complications were observed during either the ECF/ECX or the FLOT treatment (Table 5).

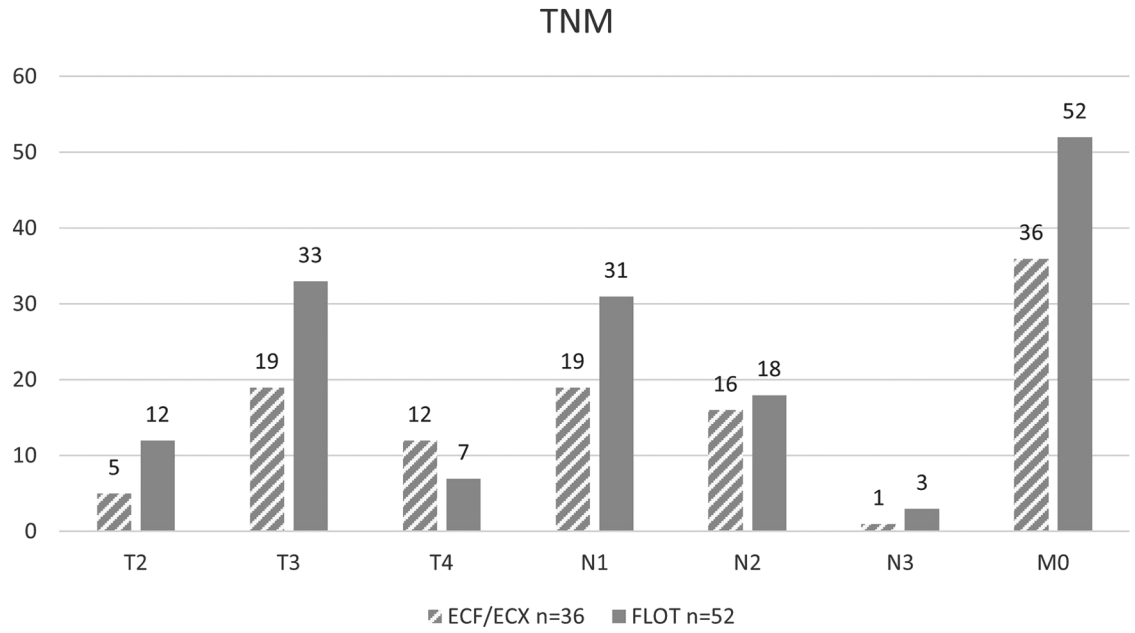

FIGURE 3
Initial TNM stage of the patients by oncological protocol (ECF/ECX and FLOT).

Comparison of CT images and pathological regression

In our study, clear improvement, regression was established in case of TRG 1-2. TRG 3-4 was deemed minimal improvement or unchanged status. TRG 5 meant no improvement. Based on the results, the tumour response, considering regression, found during the second, restaging CT scan correlated with the TRG in only 48.48% of the cases. Tumour response to the neoadjuvant oncological treatment was qualified, based on the follow-up CT scan, as better or worse (considering TRG 5 as progression only) than the result from the postoperative pathological assessment in 25.00% and 7.14% of the cases, respectively (Table 4).

These study results confirm the well-known fact that CT scans are not suitable for assessing the degree of tumour response to the oncological neoadjuvant treatment.

TABLE 4 Side effects of the neoadjuvant treatments in the ECF/ECX and FLOT groups.

Type of side effect	ECF/ECX, $n = 36$	FLOT, $n = 52$	p-value (Fisher's exact test)
Vomiting, Grade 1	17/36 47.22%	11/52 21.15%	$p = 0.192$
Vomiting, Grade 2	2/36 5.55%	2/52 3.85%	
Anaemia, Grade 2	3/36 8.33%	2/52 3.58%	$p = 0.036$
Anaemia, Grade 3	2/36 5.55%	0/52	
Diarrhoea, Grade 1	2/36 5.55%	10/52 19.23%	$p = 0.006$
Diarrhoea, Grade 2	1/36 2.78%	3/52 5.77%	
Diarrhoea, Grade 3	0/36	1/52 1.92%	
Neutropenia, Grade 1	2/36 5.55%	3/52 5.77%	$p = 0.294$
Neutropenia, Grade 2	1/36 2.78%	0/52	
Neutropenia, Grade 3	1/36 2.78%	0/52	
Peripheral neuropathy, Grade 1	0/36	10/52 19.23%	$p = 0.192$
Peripheral neuropathy, Grade 2	1/36 2.78%	1/52 1.92%	
Fever	1/36 2.78%	1/52 1.92%	$p = 1.000$
Weight loss	2/36 5.55%	4/52 7.69%	$p = 1.000$

Timing of surgery

In the two studied periods, surgery was performed a mean 6.12 weeks and a mean 5.82 weeks after the ECF/ECX and FLOT treatments, respectively. There was no significant difference in the time from the two different oncological treatments to the surgery.

TABLE 5 Clinical response based on CT/MRI findings in the ECF/ECX and FLOT groups.

Clinical response based on CT/MRI findings	ECF/ECX ($n = 36$)	FLOT ($n = 52$)
Not rated	7/36 19.44%	13/52 25.00%
Regression	15/36 41.67%	18/52 34.62%
Unchanged	10/36 27.78%	10/52 19.23%
Progression	4/36 11.11%	11/52 21.15%

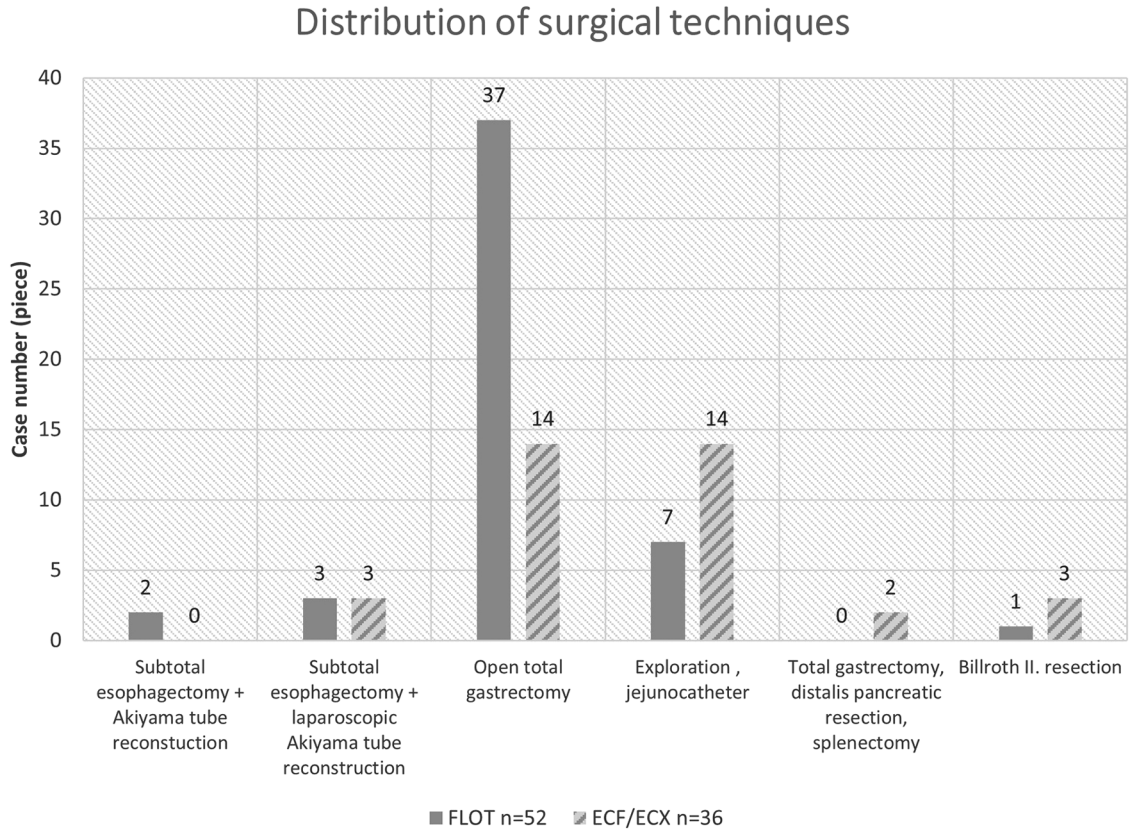

FIGURE 4
Distribution of the surgical techniques in the two oncological periods.

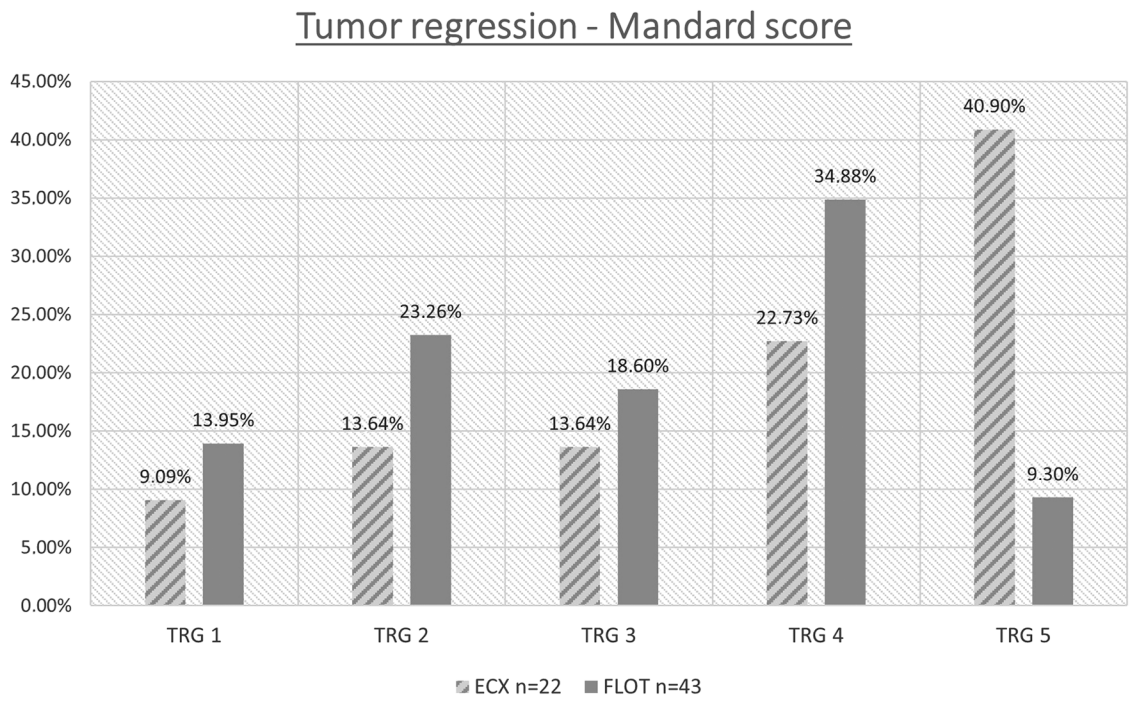

FIGURE 5
TRG values in the ECF/ECX and FLOT groups.

Distribution of the surgical techniques in the two oncological periods

Out of the 88 patients who went through surgery, 23 patients received no curative surgery because of complete technical and oncological inoperability (locally advanced status, carcinosis, spreading to adjacent organs).

Based on our results, the rate of laparoscopic procedures was 6.65% higher after the previous ECF/ECX neoadjuvant treatment (3/22) than following the FLOT pre-treatment (3/43) (Figure 4).

Assessment of perioperative complications

Anastomotic failure

When analysing complications, considering that our subject is esophageal surgery, the assessment of anastomotic failure has a special importance, not only with regard to the different neoadjuvant protocols but also to the two types of surgical intervention. The swallow test performed with a water-soluble contrast agent on the seventh postoperative day revealed some degree of contrast leak or a sign of anastomotic failure in 2 (9.09%) of the 22 cases in the ECF/ECX group and in 5 (11.63%) of the 43 cases in the FLOT group. As to anastomotic failure following a curative surgery, there was no significant difference between the ECF/ECX and FLOT treatments (Fisher's exact test; $p = 0.697$).

Repeat surgery, impaired wound healing

Immediate repeat surgery was required in one case among those with ECF/ECX pre-treatment, following an open surgery in a patient on dual anticoagulation therapy, because of diffuse bleeding; local haemostasis, hemostyptics, lavage, and drainage were given.

Wound suppuration as a complication occurred, overall, regardless of the type of surgery and the surgical technique used, in 8 out of the 36 cases in the ECF/ECX group (22.22%). It was reported in 8 (15.38%) of the 52 cases following the FLOT treatment. All cases of wound suppuration resolved to conservative therapy (local wound treatment, antibiotics), repeat operation was not required in either group. There was no significant difference in impaired wound healing between the ECF/ECX and FLOT treatments (Fisher's exact test; $p = 0.301$).

TABLE 6 TRG values in the ECF/ECX and FLOT groups. .

	ECF/ECX, $n = 22$	FLOT, $n = 43$	p-value (Fisher's exact test)
TRG 1	2/22 9.09%	6/43 13.95%	$p = 0.042$
TRG 2	3/22 13.63%	10/43 23.26%	
TRG 3	3/22 13.63%	8/43 18.06%	
TRG 4	5/22 22.73%	15/43 34.88%	
TRG 5	9/22 40.90%	4/43 9.30%	

Hospital stay

The mean length of hospital stay was 13 days in both the ECF/ECX group and the FLOT group.

Efficacy results of the oncological treatment

3.2.6.1. Tumour regression grade analysis

Data from the 65 operable patients were classified according to the 5 grades corresponding to the Mandard score, by oncological pre-treatment protocol. Complete tumour regression (TRG 1) was reported in a total of 8 cases, out of which 6 were the result of the modified neoadjuvant FLOT chemotherapy. Complete tumour regression occurred in 9.09% and 13.95% of the cases in the ECF/ECX and FLOT groups, respectively. (Figure 5 and Table 6) The modified oncological treatment (FLOT) resulted in a significantly higher rate of complete tumour regression (TRG 1) (Fisher's exact test; $p = 0.042$).

Proximal resection margin

Following open total gastrectomies, proximal resection margins showed a distance of 66.11 mm (ECF/ECX) vs. 54.36 mm (FLOT). There was no significant difference between the two oncological pre-treatments in the proximal resection margin following an open surgery (Mann–Whitney U test; $p = 0.9501$). The same was true for laparoscopic procedures, where there was no significant difference either (Mann–Whitney U test; $p = 0.500$).

Overall, regardless of the surgical technique used, R1 resection was achieved in 3 (13.64%) of the 22 cases in the ECX/ECF group and in 4 (9.30%) of the 43 cases in the FLOT group. The difference between the ECF/ECX and FLOT treatments in the achievement of R0 and R1 resection was borderline significant (Fisher's exact test; $p = 0.055$) (Table 7).

Number of removed lymph nodes

The mean total number of lymph nodes removed during the surgeries was 20.13 and 24.69 in the ECF/ECX and FLOT groups, respectively. The number of lymph nodes removed was further analysed by surgical technique. After pre-treatment with ECF/ECX, the mean number of lymph nodes removed was 19.63 and 23.33 during open surgeries and laparoscopic procedures, respectively. Following FLOT pre-treatment, the mean number of lymph nodes removed was 25.42 and 18.33 during open surgeries and laparoscopic procedures, respectively. There was no significant difference between the two oncological pre-treatments in the mean total number of lymph nodes removed. Mean number of positive lymphnodes were 5 in ECF/ECX group and 1,35 in FLOT group. As to the total number of positive lymph nodes removed, there was a significant difference between the two oncological pre-treatments (Mann–Whitney U test; $p = 0.0267$).

TABLE 7 Resection margins by oncological pre-treatment protocol.

	ECF/ECX, $n = 22$	FLOT, $n = 43$	p-value (Fisher's exact test)
R0	19	39	$p = 0.055$
R1	3	4	

Tumour marker measurement results

The laboratory measurement of CEA and CA 19-9 levels did not prove to be informative because of the high SD values. In accordance with the literature, these markers have an emphasised role rather during follow-up.

Discussion

The management of gastric tumours and tumours in the distal third of the oesophagus requires complex care, the main pillars of which are proper diagnostics, an oncological therapy continuously being advanced with new drugs and procedures, and a properly planned and performed surgical treatment (15). It is important to be able to support the efficiency of modified oncological treatments also with real-world results. Choosing the correct treatment strategy for gastric and cardia tumours, as well as tumours located in the distal oesophagus, warrants a multidisciplinary (tumour board) decision, and great experience and proficiency are required on the part of the surgeon (16). Today, relevant quality assurance principles can only be fulfilled with the regulated, regular operation of tumour boards.

Over the past decade, there has been a considerable change in approach, treatment strategies have been transformed, and classifications that are new from many aspects have been developed for oesophageal, cardia and gastric tumours. It suffices to mention the new classifications that appeared in the 7th edition of TNM and categorise positive lymph nodes (17, 18). The changes were needed because of the different prognostic groups based on the number of metastatic lymph nodes (19, 20).

TNM 8 also brought novelties in this field; the classic Siewert type I and II tumours mentioned previously are now considered oesophageal tumours and, correspondingly, their management follows the therapeutic algorithms used for oesophageal tumours (21, 22).

Neoadjuvant therapy has been part of the treatment for patients with advanced gastric, GEJ and oesophageal tumours for more than two decades now. Its justification is unquestionable, and any change in the treatment methods has a considerable impact also on surgery, among others (23).

However the type of neoadjuvant regimens differ by geographic locations of these patients. For patients with locally advanced esophageal and GEJ adenocarcinoma, one of the most commonly used treatment option consists of neoadjuvant chemoradiation with carboplatin/paclitaxel prior to surgery (CROSS study) (24).

Interestingly, while modifying the neoadjuvant treatment protocols, the addition of oxaliplatin (FLOT) resulted in a higher rate of pCR—as expected—, but neither improved survival or increased locoregional control can be reported yet (25).

There have been attempts at intensifying the FLOT treatment by administering 6 cycles of therapy instead of the usual 4 cycles. There was no significant difference in the number of perioperative complications. A higher rate of R0 resections and an improved ratio of metastatic/normal lymph nodes may be the advantages of the prolonged treatment but the "standard" is still the 4 cycles of treatment (26).

Further studies were conducted, among others, with a combination of the FLOT treatment, when spartalizumab was added to the four-drug treatment in the Phase 2 GASPAR study (27).

Previously as the combination of 5-fluorouracil with oxaliplatin or cisplatin were studied with lower toxicity compared to original FLOT protocol(FLAGS trial) (28).

In addition, the combination of FLOT and HIPEC was also assessed in multicentre randomised studies. Early recurrence with carcinosis and markedly poor prognosis is common after successful R0 resection of advanced tumours. In case of diffuse gastric and GEJ II–III tumours, patients also received intraoperative intaperitoneal cisplatin in one of the arms. The first patient was enrolled in 2021 (29).

During our study, not only did we assess the effects of the two different neoadjuvant oncological treatments on patients with gastric and cardia tumours, but we also evaluated the results by the type of surgery, where, aiming at complete homogeneity, results from open surgeries were compared only with those from open surgeries, and laparoscopic results were compared only with data from patients subjected to laparoscopy. The more favourable response of the tumour to the oncological treatment following FLOT therapy was confirmed in our patients based on the Mandard score. The better efficiency and effectiveness of the new combined chemotherapy, compared with the previous ECF/ECX treatment, can be measured well and in a standardised way based on TRG. The assessments clearly show that FLOT has favourable side effect profile and, what is more, that certain life-threatening side effects—occurring with ECF/ECX—are almost completely absent.

Based on the number of lymph nodes removed and the distances from the resection margins, the modification of the neoadjuvant treatment protocol did not increase "oncological radicality". Beyond its biological impact, the change in the oncological therapy also had an effect on the surgical treatment. Although this difference did not prove to be significant, it contributed considerably to an improvement in the ratio of oncological and technical operability. Certainly, there are still undecided questions such as that about the type of surgery for patients with a classic Siewert type II adenocarcinoma. Previously, tumours with a Siewert II location were considered a separate "entity" where a more aggressive behaviour resulted in a higher rate of recurrence than in the other two classes. Accordingly, surgical procedures as radical as possible were insisted on for such tumours (30). Statements by the two opposing parties can be found in the study results from the FREGAT working group and the CARDIA trial (31, 32). The question is whether adenocarcinomas in a Siewert II location should be treated with a) transhiatal extended total gastrectomy performed using a minimally invasive method, with complete D2 lymphadenectomy, or b) distal oesophageal resection and resection of the superior pole of the stomach (SPO) with gastric sleeve formation and, among others, mediastinal lymphadenectomy, and intrathoracic anastomosis (33, 34). An argument against transhiatal total gastrectomy is the high rate of positive oral resection margin (R1), which was 12% in the total

gastrectomy group and 5.9% in the SPO group. According to the study conducted at 21 centres in France, the mean survival was significantly longer in the total gastrectomy group (46 months in the TG group vs. 27 months in the SPO group) (FREGAT working group). The opposing party believes in transthoracic oesophageal resection completed with mediastinal lymphadenectomy. The emphasis is on mediastinal lymphadenectomy, since Siewert II adenocarcinomas—naturally, depending on their stage—may be associated with up to 10% of positive mediastinal lymph nodes. According to their investigations, total gastrectomies are associated with a higher rate of recurrence, a lower ratio of disease-free survival due to the positive, metastatic lymph nodes left in the mediastinum. Our position, which is based on our own results, agrees with the opinion and partial results of the CARDIA trial.

As to the surgery of malignant cardia tumours, thoracoscopy-assisted minimally invasive laparoscopy has been the "gold standard" treatment for almost a decade now (35–38). After the results from the TIME trial, the question in the surgery of cardia tumours is no longer whether minimally invasive procedures are justified but what method or technique should be used during them. Compared with open surgeries (39, 40), minimally invasive procedures are associated with less blood loss, less need for postoperative analgesia, and a considerably lower rate of pulmonary complications.

Nowadays minimally invasive surgery offers better survival and improved short-term postoperative outcomes in gastric and GEJ cancers compared to classic open procedures (41).

Patients may be mobilised earlier and the result is aesthetically better. The length of hospital stay can be decreased significantly. Within minimally invasive procedures, the results of robotic surgery are gradually improving, and the outcomes reported by expert centres are highly convincing. Numerous comparative studies have published their results (42).

The safe and oncologically equivalent use of robotic surgery is unquestionable but the results from additional ongoing, prospective, randomised, multicentre studies will help further analysis (43, 44).

Continuing with the analysis of the results from the two different pre-treatments, we observed slightly more favourable results overall in the FLOT group regarding passage disorders and wound suppuration among the complications reported during the immediate perioperative period, but these did not reach the level of significance. As to the highly important anastomotic failure, no true, significant difference could be shown between the two pre-treatment methods. The short-term benefits are unquestionable. Besides the favourable side effect profile and the slightly more favourable or at least unchanged perioperative and late postoperative complications, tumours show a considerably more favourable response to the modified oncological pre-treatment. To date, no reliable studies have been conducted to confirm any possible effect on long-term survival. We continue to collect and analyse relevant data.

In conclusion, there was a significantly higher rate of complete tumour regression when advanced gastric and cardia tumours were treated with the new FLOT neoadjuvant chemotherapy. The side effect profile of the new, modified treatment proved to be favourable compared with previous protocols. It can also be said that the modification of the oncological protocol also had an effect on the outcome of surgery, since there was an increase in the number of curative, oncologically correct R0 surgeries following the treatment.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study has been approved by the Board of Human Invastigations at the University of Szeged, approval number: 117/2020-SZTE. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Study concept: AP, GL, and AO; Study design: KB, ZS, ME, and ZH; Data acquisition: AM, ZS, AP, MV, and TN; Quality control of data and algorithms: AP, GL, and JO; Data analysis and interpretation: AP, LTi, LTo, and GU; Statistical analysis: TN, AP, and ZS; Manuscript preparation: AP, GL, AO, and JO; Editing: AP, GL, AO, and JO; Manuscript review: AP, GL, AO, and JO. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Endoscopic diagnosis and treatment in gastric cancer: Current evidence and new perspectives

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Gastric cancer is the fifth most common cause of cancer related deaths worldwide. Despite advancement in endoscopic techniques, the majority of the cases are diagnosed at late stage, when the curative treatment options are very limited. The early gastric cancer (EGC) on the other side is potentially curable, and in selected cases endoscopic resection techniques offer similar survival rates then surgical resection. The detection of EGC is endoscopically challenging and requires high quality examination. Recent data show that close to 10% of the gastric cancer cases had a previous negative endoscopy. This highlights the urgent need to improve the quality of the endoscopy services, what can be achieved by increasing the awareness of gastroenterologists and continuously monitoring the key performance indicators of upper gastrointestinal endoscopy. Newer endoscopic imaging techniques are also becoming commonly available to aid the detection of gastric premalignant lesions and EGC. High-definition endoscopy with image enhancement techniques is preferred over white light endoscopy to recognize these lesions, and they are also useful to determine the invasion depth of EGC. The endoscopic optical characterization of lesions is necessary for the selection of proper resection method and decide whether endoscopic resection techniques can be considered. Artificial intelligence systems aid the detection of EGC and can help to determine the depth of invasion. Endoscopic mucosal resection and endoscopic submucosal dissection requires centralized care and tertiary referral centers with appropriate expertise to ensure proper patient selection, high success rate and low adverse event rate. Appropriately scheduled endoscopic surveillance of high-risk patients, premalignant lesions and after resection of EGC is also important in the early detection and successful treatment of gastric cancer.

KEYWORDS

early gastric cancer, gastric premalignant lesions, missed gastric cancer, optical characterization, quality parameters of upper gastrointestinal endoscopy, endoscopic submucosal dissection

1. Introduction

Gastric cancer is the fifth most common cause of cancer related deaths worldwide (1). Despite advancement in endoscopic techniques, large proportion of the cases are diagnosed at late stage, when the curative treatment options are very limited. Early gastric cancer (EGC) on the other side is potentially curable, and in selected patient's endoscopic resection techniques offer similar survival rates then surgical resection. Early detection of gastric cancer can significantly improve the expected survival rate. The 5-year survival

rate of GC patients in most countries is approximately 20%, whereas that of early GC (EGC) can reach 90% (2). Upper gastrointestinal (UGI) endoscopy is the gold standard to diagnose gastric cancer. The detection of EGC is endoscopically challenging and requires high quality examination.

2. Endoscopic diagnosis and treatment of gastric cancer

2.1. Missed gastric cancer

Several studies indicate that similarly to colorectal cancer, a significant proportion of gastric cancers are so called interval cancers, which were missed during an earlier upper GI endoscopy. The time frame between the earlier endoscopy and the endoscopy which detected the cancer was usually within 3 years in most studies. Cancers detected within 1 year after a previous negative endoscopy are considered missed cancers, and those detected between 1 and 3 years are considered possible missed cancer. This is based on the doubling time of 2–3 years for gastric adenocarcinoma (3), which leads to the assumption that a cancer diagnosed within a year after a normal UGI endoscopy would almost certainly have been present as a macroscopic lesion at the time of the initial endoscopy and therefore had been missed.

An earlier meta-analysis of 10 studies, including 3,787 subjects showed that 12.9% of the patients had undergone upper GI endoscopy that missed cancer in the preceding 3 years, and 85% of these were gastric cancers (4). The possible explanations of the missed premalignant or malignant gastric lesions are inadequate supervision of trainees, lack of patient tolerance due to inadequate sedation, inappropriate follow up, errors in mucosal sampling and histopathologic interpretations. A more recent meta-analysis included 22 studies with a significantly higher patient number also explored the missing rate of gastric cancer. The author analyzed the data of 69.061 patients, and concluded that the missed gastric cancer proportion was 9.4% (5). In this study, younger age (<55 years), female sex, marked gastric atrophy, gastric adenoma or ulcer, and inadequate number of biopsy fragments were reported as predictive factors for diagnostic failure.

2.2. Quality of endoscopy

The problem of missed gastric cancer highlights the urgent need to improve the quality of the endoscopy services, which can be achieved by increasing the awareness of gastroenterologists and continuously monitoring the key performance indicators of upper gastrointestinal endoscopy. Appropriate patient preparation with administration of defoaming and mucolytic agents before/during endoscopy (6), and adequate inspection of the gastric mucosal surface are some of the main determinants of high-quality examination. Adequate inspection can be ensured with appropriate insufflation to flatten the mucosal folds, systematic inspection, and photo documentation.

To improve the detection of pathology, similarly to colonoscopy withdrawal time, it is also suggested to measure the duration of the examination. One of the key performance indicators of upper GI endoscopy in the recent ESGE Quality Improvement Initiatives is that the entire procedure should last minimum 7 min from scope intubation to extubation (7). This is based on the study of Teh et al., who showed that "slow endoscopist" (mean duration of endoscopy was 8.6 ± 4.2 min) was three times more likely to detect a neoplastic lesion (cancer and dysplasia alone) in the stomach compared to a fast endoscopist (mean duration of endoscopy was 5.5 ± 2.1 min, OR 3.42, 95% CI 1.25–10.38) (8). Another important key performance indicator is the accurate photodocumentation, which is believed to improve the quality of endoscopy, however no data supports this so far (7). Nowadays accurate and good quality image documentation is recommended by major endoscopic societies, and not only the abnormal findings, but the normal landmarks are also expected to be captured and incorporated to the hospital information systems (7, 9).

2.3. Optical characterization of gastric lesions

Appropriate endoscopic identification and characterization of suspicious lesions in the stomach is very important. The endoscopic optical characterization of lesions is necessary for the selection of proper resection method and decide whether endoscopic resection techniques can be considered. Focal erythema or whitish discoloration, irregular mucosal surface with protrusions, elevations or depressions, spontaneous bleeding and abnormal mucosal folds are the most important hallmarks of early gastric cancer.

These lesions should also be characterized by the Paris classification (10) as polypoid (type I), flat (type II) or excavated (type III) lesions. Flat, type II lesions also might have some elevation which is less than 1.3 mm (IIa), or they might be completely flat (IIb) or superficially depressed (IIc). Flat, depressed, or excavated lesions have significant higher chance of submucosal invasion, which influence the endoscopic resecability.

Further signs were also analyzed to determine the depth of invasion with conventional endoscopy. The non-extension sign is seen when the gastric wall is distended by insufflation, but a trapezoid elevation remains visible at the site of early gastric cancer. This indicates that the cancer is causing a deeper infiltration of the submucosa (500 µm or more), which is labeled as SM2. The specificity and sensitivity of the non-extension sign was 97.7% and 92.0% in a large cohort (11). These SM2 lesions are not suitable for endoscopic resection since the risk of lymph node metastasis is significant at this stage.

Newer endoscopic imaging techniques are also becoming commonly available to aid the detection of gastric premalignant lesions and EGC. High-definition endoscopy with image enhancement techniques is preferred over white light endoscopy to recognize these lesions, and they are also useful to determine the invasion depth of EGC. Image enhancement techniques or advanced endoscopic imaging are the narrow band imaging

(NBI, Olympus), Fuji intelligent chromoendoscopy (FICE, Fujifilm), blue laser imaging (BLI, Fujifilm), linked color imaging (LCI, Fujifilm), i-scan with surface enhancement, contrast enhancement and tone enhancement modes (Pentax). These advanced techniques are based on specific blue and green wavelengths to enhance the mucosal surface pattern and the mucosal/submucosal microvessels. These wavelengths correspond to the light absorption of hemoglobin, which result more contrast and better visualization of capillaries in the endoscopic image. These techniques increase the detection of early neoplastic lesions in the colorectal area and in the esophagus according to large number of studies, but less information is available for EGC. The usefulness of advanced imaging in the detection of EGC is still under discussion (6). High-definition white light endoscopy and NBI had similar detection rate of gastric cancer, but NBI performed better in the identification of intestinal metaplasia in a multicenter randomized controlled study (12). Data from another multicenter randomized controlled study show high rate of accuracy and specificity (>90%), but lower rate of sensitivity (60%) for depressed small (<1 cm) gastric cancer with magnifying NBI, and these values were significantly better than those of white-light endoscopy (13).

The Japanese Society of Gastroenterology and Japanese Gastric Cancer Association jointly advocate the magnifying endoscopy simple diagnostic algorithm for gastric cancer based on the vessel and surface (VS) classification system. A lesion with demarcation line between cancerous and normal mucosa plus irregular microvascular or surface pattern is highly suspicious for EGC (14). Demarcation line is the border of the lesion, where an abrupt change can be observed in the microvascular and microsurface pattern. Image-enhanced magnifying endoscopy is particularly useful in the diagnosis of differentiated-type early gastric cancer. Beside the VS classification system, other characteristic findings of EGC during magnifying endoscopy are also described in a recent review. These are the presence of white opaque substance, light blue crest, white globe appearance, vessel within epithelial circle pattern (15).

2.4. Artificial intelligence in the detection of early gastric cancer

Several studies have been published about the role and future perspectives of artificial intelligence (AI) in the detection of EGC, which were recently reviewed by Xiao Z et al. (16). Among these different systems, real time assistance is also available to ensure that the entire mucosal surface of the stomach is visualized during the endoscopy, what is a prerequisite for the detection of early neoplastic changes. The system was named as WISENSE (from the words of wise and sense) and was compared to the conventional endoscopy in a randomized controlled trial involving 324 patients. The rate of blind spots was significantly less using WISENSE than in the controls (5.9% vs. 22.4%, $p < 0.001$) (17). The Gastrointestinal Artificial Intelligence Diagnostic System (GRAIDS) is another real time tool developed by using more than 1 million endoscopic images taken from more than 80.000 patients. The system can detect upper GI cancer with sensitivity similar to that of expert endoscopist and superior to that of non-expert endoscopist in real time (18).

The invasion depth can be also evaluated by using convolutional neural network computer-aided detection, and it was shown that accuracy and specificity of this AI method is significantly better than that of experienced endoscopists (19). ENDOANGEL is also a real-time AI system that covers various aspects of EGC diagnosis, including detection with white light endoscopy, magnifying narrow band imaging, and predicting invasion depth (2). The specificity, accuracy, and positive predictive value of ENDOANGEL (93.22%, 91%, and 90%, respectively) were significantly higher than those of endoscopists (72.33%, 76.19%, and 70.56%, respectively), and its sensitivity and negative predictive value were slightly higher than those of endoscopists (2).

2.5. Endoscopic resection techniques

The identified and carefully characterized neoplastic lesions should be resected in an *en bloc* fashion (20, 21). The main endoscopic techniques are endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), both requires centralized care and tertiary referral centers with appropriate expertise to ensure proper patient selection, high success rate and low adverse event rate. Significantly higher R0 *en bloc* resection rates can be achieved by ESD; therefore, this is the recommended technique, especially for lesions larger than 10–15 mm. EMR is acceptable for smaller lesions with a very low probability of advanced histology. Non-lifting lesions are also not suitable for EMR, because it does not allow proper histological evaluation of EGC. ESD is suggested to be the first line resection technique for gastric neoplasia in cases with very low risk of deep submucosal invasion and lymph node metastasis. ESD in the stomach is recommended for dysplasia or intramucosal carcinomas of any size without ulceration or <30 mm if ulcerated. Well differentiated superficial or SM1 adenocarcinomas of size <30 mm, or poorly differentiated intramucosal adenocarcinomas of size <20 mm without ulceration can be also considered for ESD, but it should be based on individual decision, since the recommendation is weak (21).

ESD is technically demanding, requires significantly longer procedure time and carries higher risk of adverse events, mainly perforations, if compared to EMR (22). ESD offers an alternative for surgical resection for highly selected patients with EGC, since this technique is less expensive, and associated with less perioperative morbidity, faster recovery, shorter length of hospital stay and better quality of life, according to the most comprehensive meta-analysis (23). On the other hand, ESD is related with higher risk of recurrence, metachronous and synchronous cancer compared to surgery, therefore strict and close follow-up is advised after endoscopic removal.

This endoscopic resection technique became widely available in the Far East more than 10 years ago, and many Western endoscopist visited Japan to learn ESD. To further increase the availability of this advanced endoscopic procedure in Europe, ESGE developed a core curriculum for ESD practice to ensure

TABLE 1 Distinction between curative and noncurative endoscopic resection of early gastric cancers.

Main features	Low risk (curative)	High risk (noncurative)
R0, intramucosal, well to moderately differentiated	– any size without ulceration, or – ≤30 mm with ulceration	– >30 mm with ulceration
R0, SM1, well to moderately differentiated	– ≤30 mm and – no lymphovascular invasion and – no ulcers	– >30 mm or – lymphovascular invasion or – with ulceration
R0, intramucosal, poorly differentiated	– ≤ 20 mm and – no lymphovascular invasion and – no ulcers	– >20 mm or – lymphovascular invasion or – with ulceration

proper training, competence and maintain proficiency in the technique (24).

Depending on the histological features of the resected specimen, curative and noncurative resections should be discriminated, carrying low (<3%) and high risk of lymph node metastasis [Table 1 (21),]. Patients with noncurative, high risk resection should have complete staging after resection and additional surgical treatment should be offered. Further risk assessment of the endoscopic curability can be carried out by the eCura scoring system as it is suggested by the Japanese gastric treatment guidelines (25). The score can discriminate between low (0–1 point), intermediate (2–4 points) and high risk lesions, where lymphatic invasion is 3 points, and 1–1 point is added for tumor size >30 mm, SM2 status, venous invasion and positive vertical margin (26).

2.6. Risk stratification and surveillance

Appropriately scheduled endoscopic surveillance of high-risk patients, premalignant lesions and after resection of EGC is also important in the early detection and successful treatment of gastric cancer.

Helicobacter pylori infection is a well-known promoter of gastric carcinogenesis by inducing chronic inflammation, which leads to atrophic gastritis, intestinal metaplasia, dysplasia and finally intestinal-type gastric adenocarcinoma. Patients with chronic atrophic gastritis and intestinal metaplasia are at risk of gastric adenocarcinoma (27). The more severe and extensive are the atrophy and the intestinal metaplasia, the higher is the risk of early gastric cancers. Therefore, it is very important to correctly determine the stage and extension of these abnormalities, but conventional endoscopic visualization of atrophy and intestinal metaplasia correlates poorly with the histological findings. The best way to estimate the severity and extension of these changes is random biopsy sampling from the stomach, according to the Sydney protocol: 2 samples from the antrum, 2 from the corpus (small and large curvature in both case) and an additional sample from the incisura. The samples are evaluated according to the Operative Link of Gastritis Assessment (OLGA) and Intestinal Metaplasia (OLGIM) strategy (27).

Mild or moderate atrophy localized in the antral area does not require surveillance, while those patients who have severe atrophy or intestinal metaplasia in both antrum and corpus (OLGA/OLGIM III/IV stages) should be followed up with a high quality endoscopy and biopsies in 3 years interval (27). Those patients who have family history of gastric cancer may benefit a more frequent follow-up, e.g., every 1–2 years.

Endoscopic surveillance is advised 3–6 month after curative resection of EGC with high-definition white light and chromoendoscopy, and then annually. Other cross-sectional imaging methods (EUS, CT, MRI, PET) are not advised routinely in these cases (21).

3. Conclusions

The detection of EGC is endoscopically challenging and requires high quality examination. Recent data show that close to 10% of the gastric cancer cases had a previous negative endoscopy. This unfavorable phenomenon can be markedly reduced if the quality of endoscopic evaluation is improved. Newer endoscopic imaging techniques are also becoming widely available to help the optical characterization, which can be further enhanced by artificial intelligence. Real time AI systems capable to detect and characterize premalignant/malignant gastric lesions are becoming available in the foreseeable future. Proper endoscopic evaluation of EGC is also required for the adequate selection of resection techniques, since usually cross-sectional imaging methods are not able to identify and characterize these small malignant gastric lesions. ESD offers an alternative for surgical resection for highly selected patients with EGC. Appropriately scheduled endoscopic surveillance of high-risk patients, premalignant lesions and after resection of EGC is also important in the early detection and successful treatment of gastric cancer.

Author contributions

AV: contributed to conception of the mini review, wrote the manuscript.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Enhancing gastric cancer conventional chemotherapy effects by triple angiokinase inhibitor nintedanib in preclinical models

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Background: Gastric adenocarcinoma (GAC) is the fourth leading cause of cancer death worldwide. Systemic chemotherapy is a preferred treatment option for advanced and recurrent GAC, but response rates and survival prolongation remain limited. Tumor angiogenesis plays a critical role in GAC growth, invasion and metastasis. We investigated the antitumor efficacy of nintedanib, a potent triple angiokinase inhibitor for VEGFR-1/2/3, PDGFR-α/β and FGFR-1/2/3, alone or in combination with chemotherapy, in preclinical models of GAC.

Methods: Animal survival studies were performed in peritoneal dissemination xenografts in NOD/SCID mice using human GAC cell lines MKN-45 and KATO-III. Tumor growth inhibition studies were performed in subcutaneous xenografts in NOD/SCID mice using human GAC cell lines MKN-45 and SNU-5. The mechanistic evaluation involved Immunohistochemistry analyses in tumor tissues obtained from subcutaneous xenografts. *In vitro* cell viability assays were performed using a colorimetric WST-1 reagent.

Results: In MKN-45 GAC cell-derived peritoneal dissemination xenografts, animal survival was improved by nintedanib (33%), docetaxel (100%) and irinotecan (181%), while oxaliplatin, 5-FU and epirubicin had no effect. The addition of nintedanib to docetaxel (157%) or irinotecan (214%) led to a further extension in animal survival. In KATO-III GAC cell-derived xenografts carrying *FGFR2* gene amplification, nintedanib extended survival by 209%. Again, the addition of nintedanib further enhanced the animal survival benefits of docetaxel (273%) and irinotecan (332%). In MKN-45 subcutaneous xenografts, nintedanib, epirubicin, docetaxel and irinotecan reduced tumor growth (range: 68-87%), while 5-FU and oxaliplatin had a smaller effect (40%). Nintedanib addition to all chemotherapeutics demonstrated a further reduction in tumor growth. Subcutaneous tumor analysis revealed that nintedanib attenuated tumor cell proliferation, reduced tumor vasculature and increased tumor cell death.

Conclusion: Nintedanib showed notable antitumor efficacy and significantly improved taxane or irinotecan chemotherapy responses. These findings indicate that nintedanib, alone and in combination with a taxane or irinotecan, has the potential for improving clinical GAC therapy.

KEYWORDS

gastric cancer, chemotherapy, nintedanib, angiogenesis, combination therapy

Introduction

Gastric adenocarcinoma (GAC) is the fifth most common cancer and the fourth leading cause of cancer death worldwide (1). For primary metastatic or recurrent GAC, combination chemotherapy regimens lead to a small but clinically significant survival benefit, but median survival remains less than a year (2–6). The triple combination chemotherapy regimen FLOT (5-FU/leucovorin, oxaliplatin and docetaxel) demonstrated better overall survival (OS, 50 months) compared with the ECF/ECX (epirubicin, cisplatin, fluorouracil or capecitabine) group (35 months) as a perioperative therapy for GAC patients with locally advanced, resectable tumor (7). Thus, the FLOT regimen is now the standard regimen for a perioperative strategy of resectable GAC patients and is widely utilized for metastatic GAC, too. Meta-analyses indicate that GAC patients' survival can be improved by 2^{nd}-line therapy after failing 1^{st}-line chemotherapy (8, 9). The 2^{nd}-line therapy for GAC patients usually resorts to cytotoxic chemotherapy agents taxanes and irinotecan or the two molecular targeted agents trastuzumab and ramucirumab (10). The median OS of GAC patients receiving 2^{nd}-line therapy ranges from 3.6 to 10.9 months (11–13). Due to the low response rates of current standard therapies and the development of chemoresistance and toxicity (14), there is a compelling requirement for novel therapeutic options that can improve the outcomes of GAC.

Tumor angiogenesis is a crucial step in the pathogenesis of GAC, facilitating tumor growth, invasion and metastasis. Thus, targeting tumor angiogenesis has been a well-explored therapeutic approach for GAC (15). Angiogenesis is a complex process involving several growth factors and cytokines such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), tumor necrosis factor-alpha (TNF-α) and angiopoietins (Ang) (16). VEGF and its receptor 2 (VEGFR2)-mediated angiogenic signaling is the most extensively studied pathway in GAC because high levels of circulating and intratumoral VEGF are correlated with tumor aggressiveness and poor survival (17–19). Bevacizumab, the first agent targeting the VEGF axis, in combination with first-line chemotherapy showed some promising activity in several GAC phase II studies (20) but failed to demonstrate clinical efficacy in phase III (AVAGAST) study (21). Ramucirumab is a VEGFR2 monoclonal antibody, which blocks ligand binding and receptor-mediated pathway activation. Ramucirumab is an approved 2^{nd}-line treatment as monotherapy or in combination with paclitaxel for advanced GAC patients who have progressed after 5-FU and/or platinum-based chemotherapy (22, 23). Apart from monoclonal antibodies, several small molecule tyrosine kinase inhibitors (TKIs) targeting VEGF/VEGFR2 signaling were also evaluated in GAC (24). Among TKIs, only apatinib, a selective VEGFR2 inhibitor, demonstrated improved PFS and OS in chemotherapy-refractory advanced GAC patients (25).

Despite several studies evaluating anti-VEGF antiangiogenic therapies, improving OS remains a challenge for advanced GAC patients. The survival benefit of antiangiogenic therapies is short because tumors seem to develop several escape mechanisms including the upregulation of compensatory pathways by other angiogenic growth factors. In GAC, apart from VEGF, aberrant signaling of several other growth factors including FGF, PDGF, and IGF have been reported and correlated with poor prognosis (26). Further, the aberrant activation of these growth factor signaling pathways has been implicated in resistance and escape from anti-VEGF therapy (27), suggesting a possible benefit of multi-target antiangiogenic therapies in GAC. Nintedanib (Nin, Supplementary Figure S1) is a multi-TKI that targets the receptor kinase(s) of VEGF (IC_{50} 13–34 nM), FGF (IC_{50} 37–108 nM) and PDGF (IC_{50} 59–65 nM). It also targets other kinases such as RET, FLT-3 and Src in the low nanomolar range. In preclinical studies, nintedanib showed antitumor activity in several tumor types (28). In clinical studies, nintedanib combination with chemotherapy showed promising antitumor activity where other antiangiogenic agents failed to show a response suggesting that nintedanib might be superior in such settings (29, 30). Nintedanib is an approved treatment for non-small cell lung cancer (NSCLC) as well as idiopathic pulmonary fibrosis (30, 31).

Since several cytotoxic chemotherapeutic drugs generate only a moderate clinical response in GAC, there appears to be room for improvement in their efficacy by targeted agents. Multitarget antiangiogenic agents such as nintedanib may be more efficacious than single-target agents such as ramucirumab and apatinib but have not been widely explored in GAC, especially in combination with traditionally used chemotherapy drugs. Therefore, this preclinical study determined the most efficacious chemotherapeutics together with the antitumor activity of triple angiokinase inhibitor nintedanib in search for therapeutic combinations with enhanced antitumor efficacy in GAC.

Materials and methods

Cell culture and reagents

The human GAC cell lines KATO-III and SNU-5 were purchased from the American Type Culture Collection (ATCC, Rockville, MD). Human GAC cell line MKN-45 was purchased from Creative Bioarray (Shirley, NY). Cell lines were authenticated by ATCC (KATO-III, SNU-5) or Creative Bioarray (MKN-45) and were routinely screened to ensure the absence of mycoplasma contamination (InvivoGen, San Diego, CA). The characteristics of these GAC cell lines are presented in Supplementary Table 1. Cells were cultured in RPMI 1640 medium (Sigma Chemical Co. St. Louis, MO) containing 10% or 20% FBS and maintained at 37°C in a humidified incubator with 5% CO_2 and 95% air. Human gastric fibroblasts were purchased from ScienCell Research Laboratories (Carlsbad, CA) and cultured in a fibroblast specialty medium. Cytotoxic agents 5-FU, epirubicin (Epi), oxaliplatin (Oxa), docetaxel (Doc) and irinotecan (Iri) were purchased from the pharmacy at the Goshen Center for Cancer Care (Goshen, IN). Nintedanib was obtained from Boehringer Ingelheim Pharmaceuticals. The cell proliferation reagent WST-1 was purchased from Sigma-Aldrich.

Cell proliferation assay

In vitro cell proliferation assays were executed by adding the colorimetric WST-1 reagent. Four to five thousand cells were plated in each well of a 96-well plate in the regular growth medium, which was replaced after 16 hours with a 2% FBS-containing medium. The cells were treated with nintedanib, 5-FU, epirubicin, oxaliplatin, docetaxel and irinotecan, and incubated for 72 hours. Following the incubation, WST-1 reagent (10 µl) was added to each well. The cells were incubated for an additional 2 hours at 37°C. After incubation, the absorbance at 450 nm was measured using a microplate reader.

Tumor implant and *in vivo* tumor growth experiment

Animal experiments were performed following the Institutional Animal Care and Use Committee (IACUC) protocol approved by the Indiana University School of Medicine (South Bend, IN). Six-week-old female nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice were subcutaneously injected with human GAC MKN-45 cells (7.5 x 10^6) or SNU-5 cells (10x10^6). Ten days after tumor cell injection, all mice had a measurable tumor. Mice were then randomized (n=5 per group) to receive PBS (control), nintedanib (25 mg/kg, 5x wk), 5-FU (50 mg/kg, 2x wk), epirubicin (1 mg/kg, 2x wk), oxaliplatin (5 mg/kg, 2x wk), docetaxel (2 mg/kg, 2x wk) or irinotecan (10 mg/kg, 1x wk), for two weeks as previously described (32). The doses of nintedanib and chemotherapy agents were selected based on their clinically equivalent, safe and effective dose range described in the literature. Tumor size was measured twice per week and tumor volume was calculated using the formula V=1/2 (L x W^2), L=length and W=width.

Animal survival analysis

Animal survival studies were performed using 6-week-old female NOD/SCID mice as previously described (33). Briefly, the mice were intraperitoneally injected with MKN-45 cells (10x10^6) or KATO-III cells (10x10^6) and ten days after tumor cell injection, mice were randomized (n=6 to 8 per group) to receive PBS (control), nintedanib (25 mg/kg, 5x wk), 5-FU (50 mg/kg, 2x wk), epirubicin (1 mg/kg, 2x wk), oxaliplatin (5 mg/kg, 2x wk), docetaxel (2 mg/kg, 2x wk) or irinotecan (10 mg/kg, 1x wk), for next two weeks. The experimental procedure of animal survival experiments has been presented in Supplementary Figure S2. Animals were evaluated daily for any drug-related toxicities. After completion of treatment, mice were monitored daily and euthanized when moribund according to the predefined criteria, including sudden weight loss or gain (>15%), lethargy, inability to remain upright, and lack of strength (34). Animal survival was determined from the first day of treatment until death.

Immunohistochemistry and immunofluorescence analysis

Subcutaneous tumors were fixed in 4% paraformaldehyde, dehydrated with graded ethanol series (25%, 50%, 70%, 95% and 100%), embedded in paraffin and sectioned. The tumor sections (5 µm) were then deparaffinized with xylene and rehydrated through a graded ethanol series (100%, 95%, 70% and 50%) followed by heat-mediated antigen retrieval in citrate buffer. The sections were then blocked by CAS buffer for 20 minutes. The tumor sections were incubated for 20 minutes in CAS blocking buffer followed by overnight incubation at 4°C with 1:200 dilution of primary antibodies against Ki67 (rabbit polyclonal; Abcam, ab15580) or endomucin (rat monoclonal; Millipore Sigma, MAB2624). The tumor sections were washed with PBS and incubated with 1:200 dilution of secondary antibody conjugated with Cy3 (Jackson ImmunoResearch Laboratories, West Grove, PA) at room temperature for 40 minutes to visualize the antigen. Intratumoral apoptosis was analyzed by staining tissue sections with "Apoptag Red *In Situ* Apoptosis Detection Kit" according to the manufacturer's (Millipore, S7165) instructions. Tissues were then mounted with a solution containing 4',6-diamidino-2-phenylindole (DAPI) (Invitrogen, Carlsbad, CA). Fluorescence microscopy was used to detect fluorescent signals in five representative high-power field (HPF) per sample using an IX81 Olympus microscope and images were captured with a Hamamatsu Orca digital camera (Hamamatsu Corporation, Bridgewater, NJ) with a DSU spinning confocal unit using cellSens Dimension software (Olympus, Center Valley, PA). All the immunofluorescence experiments were normalized for exposure time.

Statistical analysis

The two-tailed Student's t-test (GraphPad Prism 7.0 Software, San Diego, CA) was used to analyze the statistical significance for the individual group comparison. For *in vivo* tumor growth studies, statistical analysis was executed by one-way ANOVA for multiple group comparisons and Student's t-test for the individual group comparisons. Nonparametric testing with log-rank group comparisons (GraphPad Prism 7.0) was applied for survival study statistics. *In vitro* cell proliferation data are expressed as the mean ± standard deviation. The statistical significance was determined based on the p-value between control and therapy groups (not significant, $p>0.05$; *$p<0.05$; **$p<0.01$; ***$p<0.001$; ****$p<0.0001$), and between nintedanib and combination therapy groups (not significant, $p>0.05$; $^{\#}p<0.05$; $^{\#\#}p<0.01$; $^{\#\#\#}p<0.001$; $^{\#\#\#\#}p<0.0001$). Similar to our recently published methodology about the sample size (35), we used G*Power 3.1 software for the power calculation in animal experiments. We used 6 to 8 mice per group in animal survival experiments and 5 mice per group in subcutaneous tumor growth experiments. With a sample size of 5 to 8 mice per group, a preset α value of 0.05, statistically significant differences in animal survival or tumor size of 40%, and a standard deviation of 20% could be detected at a power of greater than 80%. In this preclinical study, an external validation cohort was not planned.

Results

Improvement in animal survival by nintedanib and cytotoxic agents

Considering the fact that peritoneal metastasis is a hallmark of advanced GAC, we determined the efficacy of nintedanib and cytotoxic drugs in improving animal survival using the human GAC peritoneal dissemination model with MKN-45 cells (diffuse type, derived from the metastatic site, low *FGFR2* expression). Compared with controls (21 days), animal survival was significantly improved by nintedanib monotherapy (28 days, a 33% increase, p=0.0008). Among cytotoxic agent monotherapy, animal survival was not affected by oxaliplatin (18 days, p=0.75), slightly increased by 5-FU and epirubicin (both 24 days, a 14% increase, p=0.01), and markedly increased by docetaxel (42 days, a 100% increase, p=0.0008) and irinotecan (59 days, a 181% increase, p=0.0008). The addition of nintedanib did not increase survival in oxaliplatin (Oxa+Nin: 23 days, p=0.25), 5-FU (FU+Nin: 29 days, p=0.45) or epirubicin (Epi+Nin: 33 days, p=0.11), compared with nintedanib monotherapy. Importantly, there was a notable increase in animal survival by the addition of nintedanib to docetaxel or irinotecan compared with monotherapies: Doc+Nin (54 days, a 29% increase *vs* Doc, p=0.01; a 93% increase *vs* Nin, p=0.004) and Iri+Nin (66 days, a 12% increase *vs* Iri, p=0.007; a 136% increase *vs* Nin, p=0.0005) (Figure 1).

Animal survival was also evaluated in another GAC peritoneal dissemination model using KATO-III cells (diffuse type, derived from the metastatic site, *FGFR2*-amplified). In this experiment, median survival in PBS-treated controls was 22 days. Compared with controls, animal survival was not increased by oxaliplatin (20 days, p=0.49), but strikingly increased by monotherapy with nintedanib (68 days, p=0.002), 5-FU (35 days, p=0.041), epirubicin (39 days, p=0.007), docetaxel (62 days, p=0.002) and irinotecan (75 days, p=0.002). The addition of nintedanib to docetaxel and irinotecan exhibited a further improvement in animal survival: Doc+Nin (82 days, p=0.002 *vs* Doc, p=0.007 *vs* Nin) and Iri+Nin (95 days, p=0.006 *vs* Iri, p=0.002 *vs* Nin). However, nintedanib addition to 5-FU, epirubicin or oxaliplatin did not increase animal survival compared with nintedanib monotherapy (Figure 1).

Tumor growth retardation by nintedanib and cytotoxic agents

Antitumor efficacy of nintedanib and cytotoxic agents was further evaluated in subcutaneous xenografts using MKN-45 cells. Compared with rapid growth in tumor size in the control (PBS-treated) mice, single-agent 5-FU and oxaliplatin resulted in a small reduction in tumor growth, while nintedanib, epirubicin, docetaxel and irinotecan exhibited a marked tumor growth retardation. The combination of nintedanib with cytotoxic agents resulted in a remarkable synergistic tumor growth retardation effect (Figure 2A). Net increase in tumor volume, compared to controls (858 mm^3), was 216 mm^3 (nintedanib), 515 mm^3 (5-FU), 271 mm^3 (epirubicin), 517 mm^3 (oxaliplatin), 270 mm^3 (docetaxel), 108 mm^3 (irinotecan), 121 mm^3 (5-FU plus nintedanib), 8 mm^3 (epirubicin plus nintedanib), 118 mm^3 (oxaliplatin plus nintedanib), 110 mm^3 (docetaxel plus nintedanib) and -16 mm^3 (tumor regression, irinotecan plus nintedanib), respectively (Figure 2B). At the end of two weeks of therapy, the mean tumor weight in the control group was 1.61 g, which was reduced by the nintedanib treatment to 0.47g. The mean tumor weight in the single-agent chemotherapy groups was in the range of 0.35-1.23 g. In the nintedanib plus chemotherapy combination treatment groups, the mean tumor weight was in the range of 0.20-0.44 g (Figure 2C). There was no significant difference in the body weight in the control or therapy group animals indicating that there was no apparent treatment-related toxicity (Supplementary Figure S3).

In human GAC subcutaneous xenografts using SNU-5 cells (derived from malignant ascites), single-agent 5-FU and oxaliplatin had a small effect, while a significant reduction in tumor growth was observed with nintedanib, epirubicin, docetaxel and irinotecan monotherapy and nintedanib combination with all cytotoxic agents had a synergistic response (Figure 3A). This study demonstrated that compared to controls (523 mm^3), the net tumor growth was 187 mm^3 (nintedanib), 332 mm^3 (5-FU), 276 mm^3 (epirubicin), 430 mm^3 (oxaliplatin), 243 mm^3 (docetaxel), 139 mm^3 (irinotecan), 153 mm^3 (5-FU plus nintedanib), 141 mm^3 (epirubicin plus nintedanib), 215 mm^3 (oxaliplatin plus nintedanib), 63 mm^3 (docetaxel plus nintedanib) and 12 mm^3 (irinotecan plus nintedanib), respectively (Figure 3B). After two weeks of therapy, the mean tumor weight correlated with tumor growth inhibition data; it was 0.61 g in the control and 0.33 g in

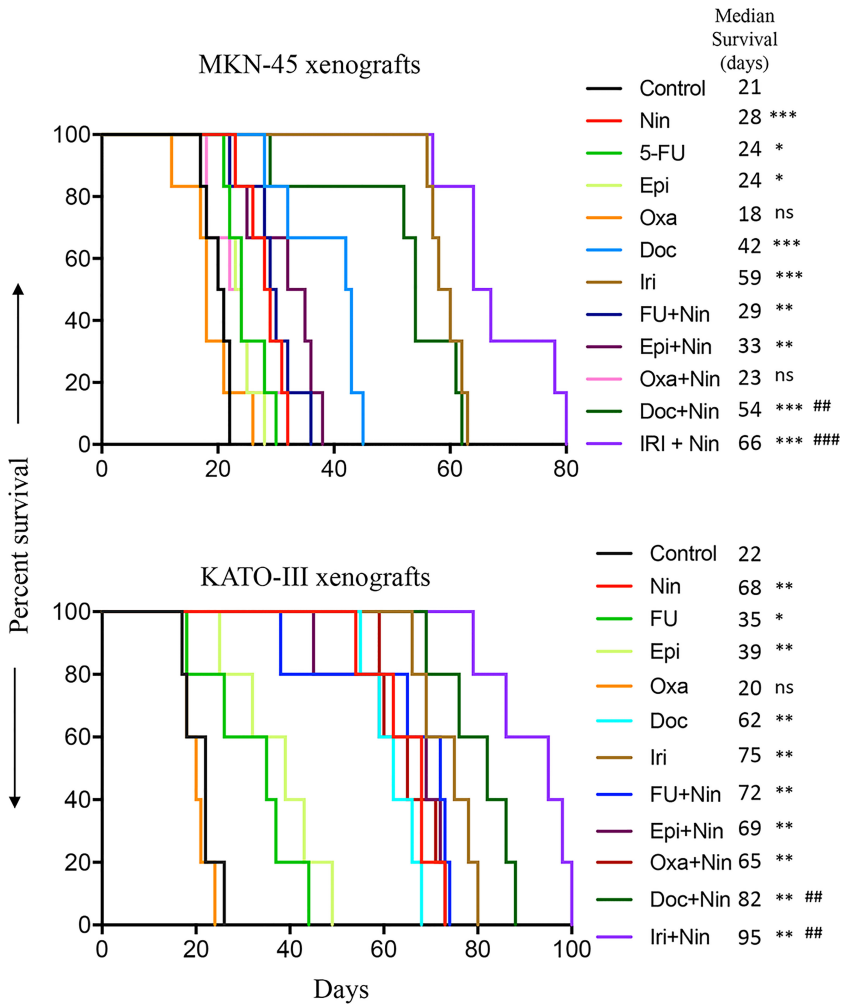

FIGURE 1
Animal survival benefits of nintedanib and cytotoxic agents. Animal survival analysis in MKN-45 (n=7) and KATO-III (n=5) cell-derived peritoneal dissemination xenografts. Ten days after tumor cell injection, mice were treated with nintedanib, 5-FU, epirubicin, oxaliplatin, docetaxel, irinotecan, or their combinations for two weeks. The curve represents the animal survival time from the start of therapy. Statistical group differences in survival time were calculated using log-rank testing. The statistical significance was determined based on the p-value between control and therapy groups (ns, not significant, p>0.05; *p<0.05; **p<0.01; ***p<0.001), and between nintedanib and combination therapy groups ($^{\#\#}$p<0.01; $^{\#\#\#}$p<0.001).

nintedanib. The mean tumor weight by single-agent chemotherapy was in the range of 0.31-0.55 g, while it further decreased by the nintedanib plus chemotherapy combination therapy exhibiting tumor weights in the range of 0.15-0.41 g (Figure 3C). Like the MKN-45 xenograft study, there was no treatment-related toxicity in different therapy groups (Supplementary Figure S3).

Effects of nintedanib and cytotoxic agents on tumor cell proliferation and tumor vasculature

We next investigated the biological impact of nintedanib and cytotoxic agents on GAC tissues. Ki67 staining to examine tumor cell proliferation in MKN-45 subcutaneous xenografts demonstrated that monotherapy with nintedanib and all cytotoxic agents reduced tumor cell proliferation, while combinations of nintedanib with cytotoxic agents were more effective than single agents. Again, the combination of nintedanib with docetaxel or irinotecan exhibited maximum inhibition in tumor cell proliferation. Compared to controls (100%), the intratumoral proliferative index, measured by calculating Ki67 positive cells over the total number of cells per HPF, was as follows: Nin (51.3±15.8%), 5-FU (59.7±16.9%), Epi (35.8 ±15.8%), Oxa (59.3±17.7%), Doc (54.3±13.6%), Iri (30.6±14.1%), 5-FU+Nin (49.9±24.5%), Epi+Nin (29.9±13%), Oxa+Nin (46.8 ±11.8%), Doc+Nin (20.9±12.5%) and Iri+Nin (13.4±7.3%) (Figure 4).

Assessment of the effects of therapies on tumor vasculature by endomucin staining revealed that nintedanib caused a remarkable decrease in microvessel density, while cytotoxic agents exhibited no significant change. Nintedanib combination with cytotoxic agents also led to a reduction in microvessel density compared with controls but this was not significantly greater than nintedanib monotherapy. Mean microvessel counts were as follows: Control (14±4.8), Nin (6.3 ±2), 5-FU (11.4±6.4), Epi (12.3±2.9), Oxa (10.9±5.9), Doc (9.3±2.8), Iri (11.2±2.8), 5-FU+Nin (5.8±2.8), Epi+Nin (4.6±2.8), Oxa+Nin (6.3 ±2.3), Doc+Nin (3.2±2.3) and Iri+Nin (2.9±2.1) (Figure 5).

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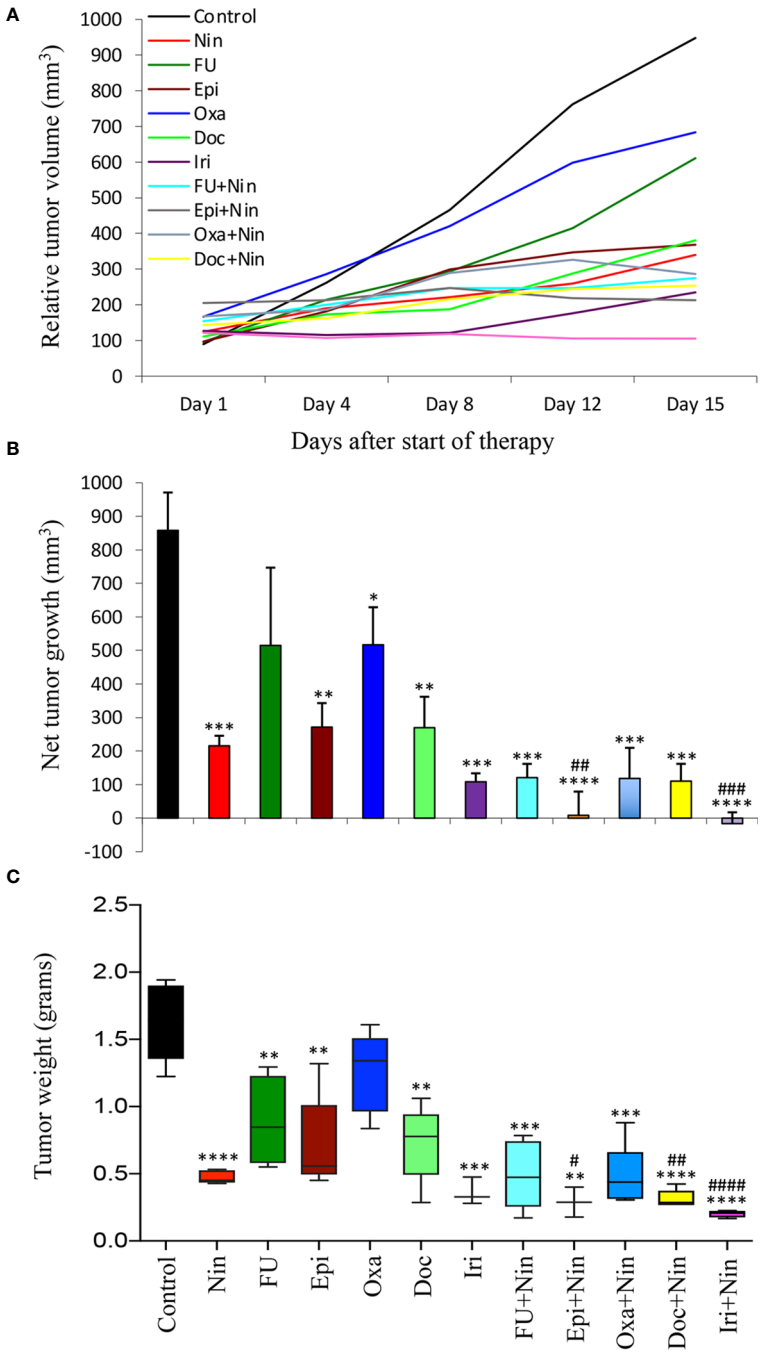

FIGURE 2
Tumor growth retardation by nintedanib and cytotoxic agents in MKN-45 cell-derived subcutaneous xenografts: Ten days after tumor cell injection, mice were treated with nintedanib, 5-FU, epirubicin, oxaliplatin, docetaxel, irinotecan or their combinations for two weeks. **(A)** Tumor size was measured twice a week during the therapy period using calipers and plotted. **(B)** Net growth in tumor size was calculated by subtracting tumor volume on the first treatment day from that on the final day. **(C)** On the final therapy day, tumors were excised, weighed, and the mean tumor weight was calculated in each group and presented as a Box plot. Student's t-test was done between control and therapy groups (*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001), and between nintedanib and combination therapy groups ($^{\#}$p<0.05; $^{\#\#}$p<0.01; $^{\#\#\#}$p<0.001; $^{\#\#\#\#}$p<0.0001). Data are representative of mean values ± standard deviation from at least 5 mice per group.

Effects of nintedanib and cytotoxic agents on tumor cell apoptosis

An investigation of the impact of nintedanib and cytotoxic therapies on tumor cell apoptosis in MKN-45 subcutaneous tumor tissues demonstrated that compared with controls (apoptosis index: 0.018), nintedanib was effective in inducing apoptosis (0.077). Except for oxaliplatin (0.024) other chemotherapy drugs also induced apoptosis in the following order: epirubicin (0.063), docetaxel (0.072), 5-FU (0.082) and irinotecan (0.107). Increase in intratumoral apoptosis in combinations of nintedanib with epirubicin (0.109), docetaxel (0.116) and irinotecan (0.15) were significantly higher than in single-agent treatment groups (Figure 6).

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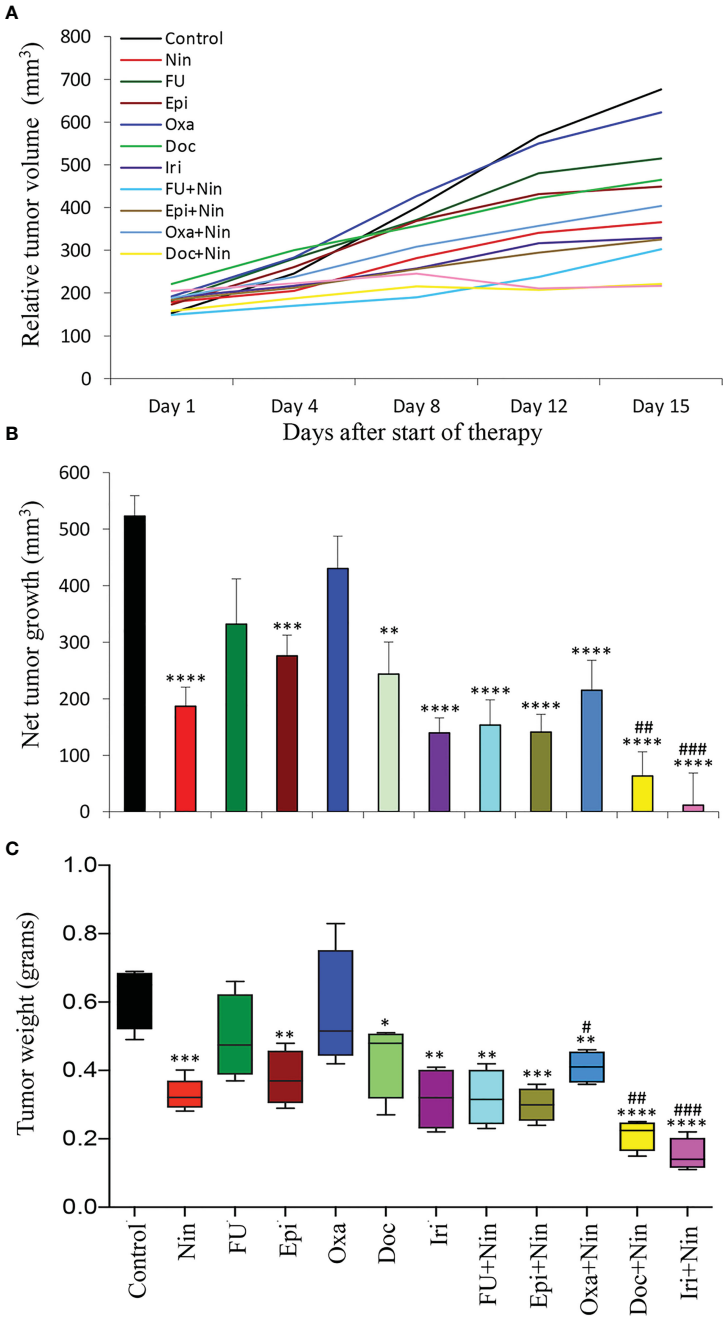

FIGURE 3
Tumor growth retardation by nintedanib and cytotoxic agents in SNU-5 cell-derived subcutaneous xenografts: Ten days after tumor cell injection, mice were treated with nintedanib, 5-FU, epirubicin, oxaliplatin, docetaxel, irinotecan or their combinations for two weeks. **(A)** Tumor size was measured twice a week during the therapy period using calipers and plotted. **(B)** Net growth in tumor size was calculated by subtracting tumor volume on the first treatment day from that on the final day. **(C)** On the final therapy day, tumors were excised, weighed, and the mean tumor weight was calculated in each group and presented as a Box plot. Student's t-test was done between control and therapy groups (*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001), and between nintedanib and combination therapy groups ($^{\#}$p<0.05; $^{\#\#}$p<0.01; $^{\#\#\#}$p<0.001). Data are representative of mean values ± standard deviation from at least 5 mice per group.

Effects of nintedanib and chemotherapy agents on *in vitro* GAC cell proliferation

Human GAC epithelial cells with different oncogenic mutations (MKN-45, KATO-III, SNU-5) and gastric fibroblasts were tested for growth-inhibitory effects by nintedanib and cytotoxic agents. Nintedanib had a significant growth inhibitory effect on these cell lines. Reduction in cell proliferation by nintedanib at 100 nM, 1 μM and 10 μM concentrations were 6%, 21%, 25% (MKN-45); 57%, 72%, 75% (KATO-III); 9%, 21%, 82% (SNU-5) and 8%, 4%, 92% (gastric fibroblasts) (Figure 7).

All cytotoxic drugs exhibited dose-dependent inhibition in the proliferation of GAC cells proliferation. Inhibition in cell proliferation at a medium dose (1 μM) in MKN-45, KATO-III,

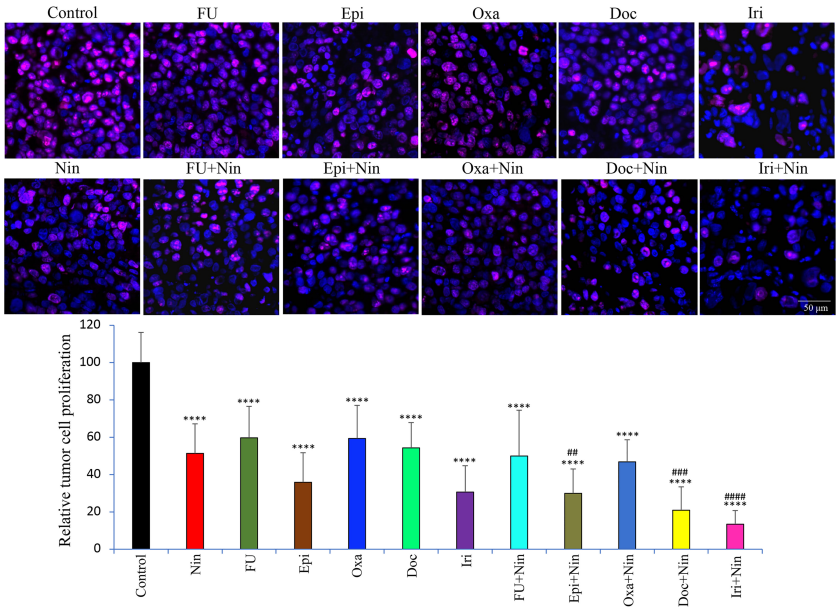

FIGURE 4
Effect of nintedanib and cytotoxic agents on tumor cell proliferation. Tumor sections obtained from the MKN-45 subcutaneous xenograft study after two weeks of treatment were used for the IHC analysis. Tissue sections were immunostained with Ki67 antibody and photographed under a fluorescent microscope. Ki67-positive cells were counted in five different high-power fields. The upper panel depicts merged images of cell nuclei stained with Ki67 (red) and DAPI (blue) illustrated at 20X magnification. Student's t-test was done between control and therapy groups (****p<0.0001), and between nintedanib and combination therapy groups ($^{##}$p<0.01; $^{###}$p<0.001; $^{####}$p<0.0001). The data are expressed as the mean ± standard deviation.

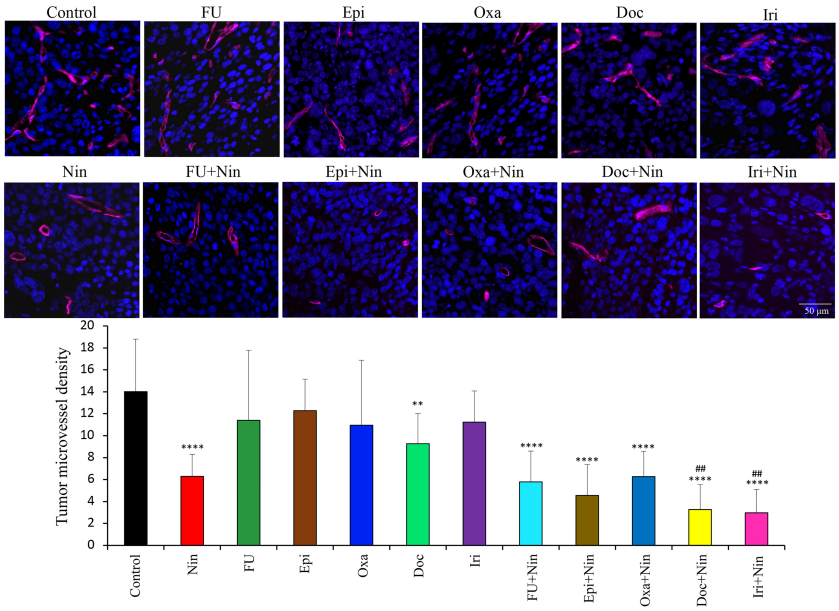

FIGURE 5
Effect of nintedanib and cytotoxic agents on microvessel density. Tumor sections obtained from the MKN-45 subcutaneous xenograft study after two weeks of treatment were used for evaluating intratumoral microvessel density. Tumor sections were stained with an anti-endomucin antibody and slides were photographed under a fluorescent microscope. Endomucin-positive vessels were counted within five different HPF in a blinded manner. The upper panel depicts merged images of endomucin-positive microvessel (red) and cell nuclei (DAPI, blue) illustrated at 20X magnification. Student's t-test was done between control and therapy groups (**p<0.01; ****p<0.0001), and between nintedanib and combination therapy groups ($^{##}$p<0.01). The data are expressed as the mean ± standard deviation.

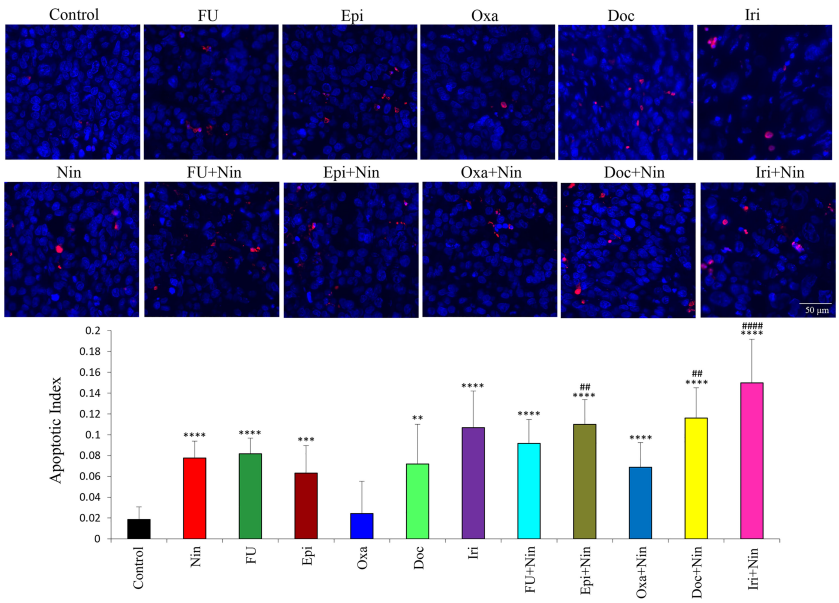

FIGURE 6
Effect of nintedanib and cytotoxic agents on tumor cell apoptosis. Tumor tissue sections obtained from the MKN-45 subcutaneous xenograft study after two weeks of treatment were stained with the TUNEL procedure. TUNEL-positive apoptotic cells were counted in five different high-power fields and slides were photographed under a fluorescent microscope. Student's t-test was done between control and therapy groups (**p<0.01; ***p<0.001; ****p<0.0001), and between nintedanib and combination therapy groups ($^{\#\#}$p<0.01; $^{\#\#\#\#}$p<0.0001). The data are expressed as the mean ± standard deviation.

SNU-5 and gastric fibroblast cells was 20%, 51%, 22%, 12% (5-FU); 35%, 42%, 89%, 65% (Epi); 0%, 32%, 33%, 0% (Oxa); 56%, 40%, 56%, 12% (Doc); 19%, 39%, 28%, 21% (Iri) (Figure 7). Notably, the combination of nintedanib with cytotoxic agents demonstrated additive effects, except for Oxa+Nin in SNU-5 cells, and inhibition in GAC cell proliferation at a medium dose (1 µM) in MKN-45, KATO-III, SNU-5 and gastric fibroblasts was 30%, 81%, 37%, 42% (5-FU+Nin); 77%, 85%, 96%, 70% (Epi+Nin); 30%, 76%, 25%, 32% (Oxa+Nin); 69%, 75%, 61%, 56% (Doc+Nin); 63%, 81%, 43%, 65% (Iri+Nin) (Figure 7).

Discussion

Chemotherapy remains the mainstay treatment for primary metastatic or recurrent GAC. However, cytotoxic regimens have to date all demonstrated limitations in clinical response and survival. Advancement in molecular profiling has paved the way for several novel therapeutic options for GAC patients with targetable oncogenic pathways including *HER2* amplification, *PIK3CA* mutation, JAK pathway, epithelial-mesenchymal transition, RTK amplification and angiogenesis (36). GAC development, relapse and metastatic dissemination critically depend on angiogenesis, which provides required nutrients, growth factors and oxygen. Tumor angiogenesis in GAC is regulated by several growth factors, growth factor receptors and cytokines (15). The FDA approval of molecular targeted agents, trastuzumab and ramucirumab, for advanced GAC, indicates the potential for growth-inhibitory and antiangiogenic treatments for improving GAC clinical therapy. Several studies indicated challenges in improving OS by anti-VEGF therapies in advanced GAC patients due to the implication of compensatory pathways by other angiogenic growth factors including FGF, PDGF, and IGF (26). These growth factor signaling pathways play a critical role in limiting the therapeutic potential of single VEGF-targeted therapy (27), indicating a potential for the multi-target antiangiogenic approach in GAC. Based on the triple angiokinase activity of nintedanib at low doses, we explored its antitumor efficacy as monotherapy and its potential to improve the response of conventional chemotherapy agents in diverse preclinical models of GAC.

Peritoneal metastasis is the most frequent form of metastasis in advanced GAC, and it is associated with poor prognosis (37, 38). We established two peritoneal dissemination xenograft models using human MKN-45 cells and KATO-III cells that closely resemble the clinical GAC progression pattern (39). Nintedanib exhibited noticeable improvement in animal survival in these two models, which was much higher in KATO-III xenografts compared with MKN-45 xenografts. Of note, this survival extension was observed after a limited treatment duration, without any maintenance therapy. Higher animal survival benefits by nintedanib in KATO-III xenografts can be attributed to the fact that KATO-III cells carry *FGFR2* gene amplification (40) rendering it susceptible to nintedanib's unique targeting profile that includes the FGF-FGFR signaling axis (28). Additionally, nintedanib also demonstrated a marked reduction in tumor growth in GAC cell-derived subcutaneous xenografts.

Gastric cancer is frequently diagnosed in more advanced stages except in Japan and Korea where some screening programs are being implemented. For late-stage or recurred GAC patients, systemic chemotherapy regimens including 5-FU/capecitabine,

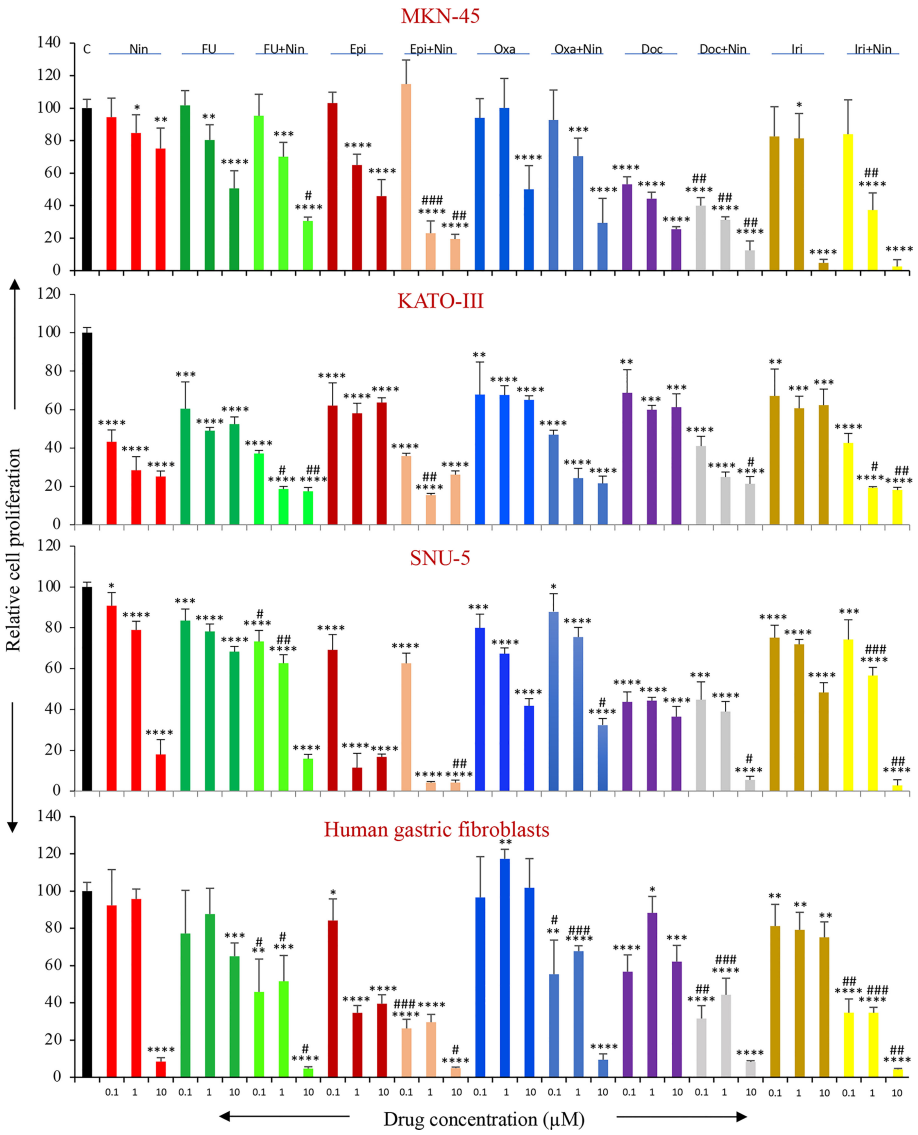

FIGURE 7
In vitro cell proliferation inhibition by nintedanib and cytotoxic agents. GAC cells (MKN-45, KATO-III and SNU-5) and human gastric fibroblasts were plated on 96-well plates and treated with nintedanib, 5-FU, epirubicin, oxaliplatin, docetaxel and irinotecan. After 72-hour incubation, WST-1 reagent (10 μl) was added to each well followed by additional incubation for 2 hours. The absorbance at 450 nm was measured using a microplate reader. The resulting number of viable cells was calculated by measuring the absorbance of color produced in each well. Student's t-test was done between control and therapy groups (*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001), and between nintedanib or respective cytotoxic therapy and combination therapy groups ($^{\#}$p<0.05; $^{\#\#}$p<0.01; $^{\#\#\#}$p<0.001). The data are the mean ± SD of quadruplicate determinations.

platinum compounds (cisplatin, oxaliplatin), taxanes (docetaxel, paclitaxel), epirubicin, and irinotecan have shown some benefit but an internationally accepted single standard chemotherapy regimen is still lacking. Among the five commonly used GAC chemotherapy drugs in this study, antitumor efficacy was low for oxaliplatin, moderate for 5-FU and epirubicin, and high for docetaxel and irinotecan, in the peritoneal dissemination xenograft models. In the subcutaneous xenograft models, 5-FU and oxaliplatin were moderately effective while epirubicin, docetaxel and irinotecan were highly effective. Beyond simple dosage and administration frequency, differential tumor responsiveness of various chemotherapy drugs in this study may be dependent on tumor histology, heterogeneity and growth rate. Another possibility for the mechanism of this differential effect of chemotherapy drugs is that the patient-derived cell lines used in these studies were previously exposed with 5-FU, epirubicin and oxaliplatin but not with docetaxel and irinotecan that have an established clinical track record as 2nd-line therapy in GAC (10).

Single-agent antiangiogenic therapies have dismal clinical benefits, supporting a combination therapy approach by combining angiogenesis blockade therapy with other conventional therapies, such as immunotherapy, radiotherapy and chemotherapy (41). In our studies, a combination of nintedanib with mechanistically different chemotherapies exhibited a marked increase in antitumor response compared with single-agent therapies. Among all the tested combinations, the antitumor efficacy was highest in the

combination of nintedanib with docetaxel and irinotecan. Consistent with our findings, a meta-analysis of randomized controlled trials showed significantly improved survival and anti-tumor activity with the combination of multitarget antiangiogenic agents and taxane-containing chemotherapy in advanced NSCLC (42). Further, the combination of irinotecan with multitarget antiangiogenic drugs has been shown to have a synergistic antitumor response in gastric cancer and colorectal cancer models (39, 43).

Tumor angiogenesis leads to leaky blood vessels, elevated interstitial fluid pressure (IFP) and low blood perfusion in the tumor microenvironment which provides barriers for drug delivery (44, 45). Although the mechanisms for nintedanib-led enhancement in chemotherapy response are not clear, IHC analyses of tumor tissues suggest a decrease in vessel density and an induction in tumor cell apoptosis as likely factors. Other possible mechanisms of nintedanib augmentation of chemotherapy response include a decrease in vessel wall permeability, normalization of tumor vasculature, decrease in IFP and an increase in perfusion (46). If an agent such as nintedanib can mediate similar benefits in experimental GAC therapy, independent from the cytotoxic agent utilized, it presents a promising tool for future GAC therapeutic combinations. Although genomic-directed stratifications and individualized approaches are reasonable thoughts for well-designed clinical trials in GAC, the agents used in this study, whether cytotoxic or in form of the multikinase inhibitor nintedanib, would not easily lend themselves to a mechanistically oriented genomic approach. In fact, since angiogenic activation in GAC progression reflects predominantly activation of autochthonous physiologic mechanisms, it should lend itself to a broader, less restricted therapeutic approach.

The crosstalk between angiogenesis and immunosuppression mechanisms within the tumor microenvironment and the therapeutic potential for the combination of antiangiogenic therapy and immunotherapy are now well-recognized (47–49). Based on the finding of this study, multitarget antiangiogenic combination therapy opens the avenue for the addition of an immunotherapy agent to achieve the best antitumor response in GAC. Although immunotherapy strategies are complicated in murine xenograft settings using human tumor cells, the addition of immunotherapy would be an interesting combination to explore in future studies.

In the background of multiple current clinical attempts for antiangiogenic combinations therapies in GAC, the present preclinical study demonstrates the higher antitumor activity of taxanes and irinotecan among several mechanistically different chemotherapy agents. This study also highlights the remarkable antitumor efficacy of the multitarget antiangiogenic drug nintedanib and a significant additive response of its combination with taxane and irinotecan. Thus, future clinical studies applying taxanes and/or irinotecan as cytotoxic drugs in combination with nintedanib to improve the clinical outcome of advanced GAC patients would appear sensible.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The animal study was reviewed and approved by The Institutional Animal Care and Use Committee (IACUC) of the Indiana University School of Medicine (South Bend, IN).

Author contributions

NA: Conceptualization, data curation, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, writing original draft, editing. MS, QK and CZ: Formal analysis, data curation, methodology. FH: Conceptualization, resources, editing. RS: Conceptualization, supervision, editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors NA and RS received funding support from Boehringer Ingelheim Pharmaceuticals to perform this research. FH was an employee of Boehringer Ingelheim RCV, Vienna, Austria, at the time of the study.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1145999/full#supplementary-material

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A novel technique for endoscope progression in gastroscopy resection: forward-return way for dissection of stromal tumor in the muscularis propria of the gastric fundus

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Background: The fundus of the stomach is a challenging region for endoscopic resection of gastrointestinal stromal tumors (GISTs), especially in the anterior wall of the fornix at the side of the greater curvature. This study aimed to introduce the Forward-Return Way (FRW) technique in gastric fundus operations and provide evidence of its advantages. The FRW technique allows the gastroscope to access the stomach fornix without entering the gastric antrum after passing through the gastric cardia. Using FRW, the gastroscope body makes a forward return along the wall of the posterior wall of the upper gastric body and the wall of the greater curvature.

Methods: The clinical data of patients with stromal tumors in muscularis propria at the gastric fundus (STMF) at the Fourth Hospital of China Medical University between May 2020- March 2021 were reviewed. The novel FRW technique was used in the procedures, and the beneficial effects, suitability, applicable lesion site, and success rates of FRW were analyzed.

Results: A total of 10 cases were reviewed, and the FRW technique was successfully performed in 7 cases (70%). The gastroscope's tip reached the area just below the gastric cardia, allowing endoscopists to successfully access all angles and sites of the stomach's fundus in all seven patients. The lesion was easily accessed, and the gastroscope was stable with good left-right and forward-backwards movements.

Conclusion: The FRW technique significantly facilitates the resection of the GISTs by aligning the endoscopy body movement direction with the observation direction. Gastrointestinal Stromal Tumor; forward-return of gastroscopy along the gastric body wall; muscularis propria; gastric fundus.

KEYWORDS

gastrointestinal stromal tumor, Forward-Return Way, muscularis propria, gastric fundus, common submucosal tumor

Background

Gastrointestinal stromal tumors (GISTs) are the most common gastrointestinal mesenchymal neoplasms and one of the clinically common submucosal tumors (SMT) of gastric origin (1, 2). Stromal tumors in muscularis propria (STMF) occur more at the fundus of the stomach, accounting for 51.5% of all GISTs sites (3, 4). The clinical presentation of STMF is nonspecific, with only a few patients experiencing gastrointestinal bleeding (5). Currently, complete resection of STMF is the best treatment (6), among other approaches, including traditional open surgery, laparoscopy, and gastroscopy dissection. However, many reports have demonstrated that gastroscopy dissection is the safest and most effective treatment for STMF of the fundus (4).

Several gastroscopy dissection techniques are used nowadays in clinical practice, including Endoscopic submucosal dissection (ESD) (7), endoscopic submucosal excavation (ESE) (8), endoscopic full-thickness resection (EFTR) (9, 10), submucosal tunnelling endoscopic resection (STER) (11), and the combination of EFTR and laparoscopic approach (4, 12–15). The fundus of the stomach is a challenging area for endoscopic resection of tumors in muscularis propria (16), especially when using ESD (17), ESE, or EFTR (18, 19). Additionally, endoscopic resection of lesions in the middle of the fornix and the anterior wall of the fornix is extremely difficult in clinical practice, especially the anterior wall of the fornix at the side of the greater curvature.

In some STMF cases, the removal procedure requires a U-turn of the distal tip of the gastroscope (20). In these cases, the progress of the tip is opposite to the moving direction of observation, and the body of the gastroscopy becomes suspended without support, making it difficult to operate and control. In 2016, Professor Zhi-Feng Zhao discovered the Forward-Return Way technique (FRW) during the endoscopic treatment of a patient with STMF and successfully completed the procedure. The FRW technique allows the gastroscope to access the stomach fornix without entering the gastric antrum after passing through the gastric cardia. Using FRW, the gastroscope body makes a forward return along the wall of the posterior wall of the upper gastric body and the wall of the greater curvature. The present study introduces this new endoscopy progression technique and the results of its applicability in practice.

Patients and methods

Subjects

The clinical data of STMF patients who accepted the new FRW technique at the Fourth Hospital of China Medical University from May 2020 to March 2021 were retrospectively analyzed. This study has been approved by our hospital's Ethics Committee (Ethics Approval No.: EC-2021-HS-001). All patients have been informed about the FRW technique and given their written consent before the procedure. This study was a retrospective study, not a clinical trial, so we did not register it on clinicaltrials.gov or other similar websites. All authors had access to information that could identify all the patients during or after data collection.

Case selection requirements: (i) gastroscopy revealing elevated mucosa at the fundus of the stomach; (ii) endoscopic ultrasonography revealing STMF; (iii) no history of gastric cardiac or gastric surgery; (iv) tolerance to general anaesthesia and tracheal intubation; (v) lesions diameter of ≤5 cm (21); (vi) patients who were informed with the new endoscopic technique and signed the consent form.

Exclusion Criteria (contraindications for endoscopic resection of gastrointestinal submucosal tumors (21)) were: (i) when an enlarged lymph node or distant metastasis lesion was identified; (ii) patients with a poor general health condition who could not tolerate endoscopic surgery; (iii) patients with bleeding and/or ulceration on the surface of the lesion; (iv) patients whose pathology results showed they were non-GIST patients.

Methods

The endoscopy progression technique

The FRW technique enables the gastroscope to pass through the gastric cardia without entering the gastric antrum while the endoscopy progresses continuously. The gastroscope body makes a forward return along the wall of the posterior wall of the upper gastric body and the wall of greater curvature to access the fornix of the stomach. When the gastroscope pushes forward, its tip moves towards the fundus of the stomach, and when the gastroscope pulls back, its tip moves away from the fundus. Thus, the gastroscope body is fixed in the upper gastric body by the stomach wall without being suspended. We called this endoscopy progression technique: Forward-Return Way (FRW). This new technique avoided the paradoxical movement in other advanced endoscopy progression skills, mainly the common U-turn. (Please refer to Figure 1).

Endoscopic resection

All endoscopic surgeries were performed following Professor Zhi-Feng Zhao's guidance on the FRW technique. The operators were senior endoscopists in our endoscopic treatment center with several years of experience in EFTR surgery. The patients underwent endotracheal intubation under intravenous anaesthesia before the endoscopic surgery. The anaesthesia of choice for the endoscopic surgeries of STMF was CO2 (22, 23). For the endoscopic resection of STMF, we mainly used EFTR (24).

Data collection

The following data were collected and analyzed: (i) basic information of patients; (ii) whether the FRW technique was

Abbreviations: GIST, endoscopic resection of gastrointestinal stromal tumors; FRW, Forward-Return Way; STMF, stromal tumors in muscularis propria at the gastric fundus; SMT, submucosal tumors; ESD, endoscopic submucosal dissection; ESE, endoscopic submucosal excavation; EFTR, endoscopic full-thickness resection; STER, submucosal tunnelling endoscopic resection.

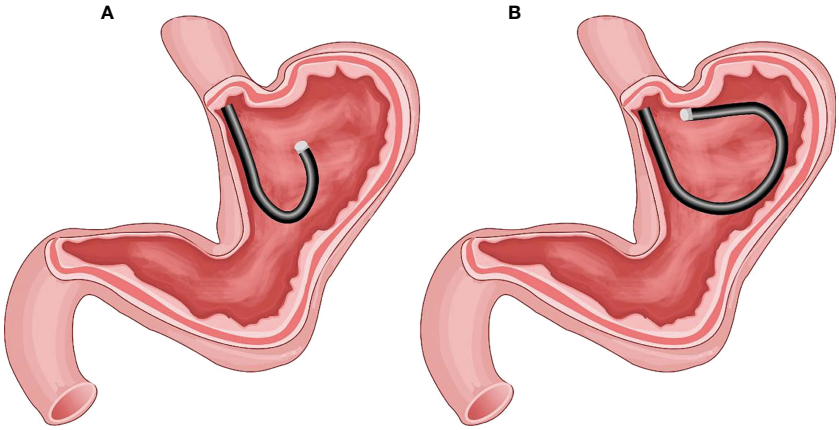

FIGURE 1
(A) The gastric fundus and cardia as observed by the traditional U-turn technique; the gastroscopy body is suspended without support. **(B)** Endoscopy progression just below the gastric cardia using the forward-return of gastroscopy along the greater curvature wall using the FRW technique; the gastroscopy body is supported by the gastric wall.

successfully performed; and (iii) the selected endoscopic method (after successful FRW). The lesion sites suitable for the FRW technique were selected according to the division of the gastric fundus and the lesion area, as shown in Figure 2. Moreover, the success rate, results, and operation characteristics of the FRW technique were analyzed.

Manipulating performance evaluation criteria after FRW implementation (Table 1)

Postoperative management

After the EFTR procedure, patients were confined to bed rest, food fasting, and water fasting for three days. The above measures and gastrointestinal decompression were performed for five days after EFTR. Parenteral nutrition was given during fasting, and continuous oral proton pump inhibitor and gastric mucosal protective agents were administered 6-8 weeks postoperatively. Patients were observed for complications of EFTR, including bleeding, perforation, and infection (25).

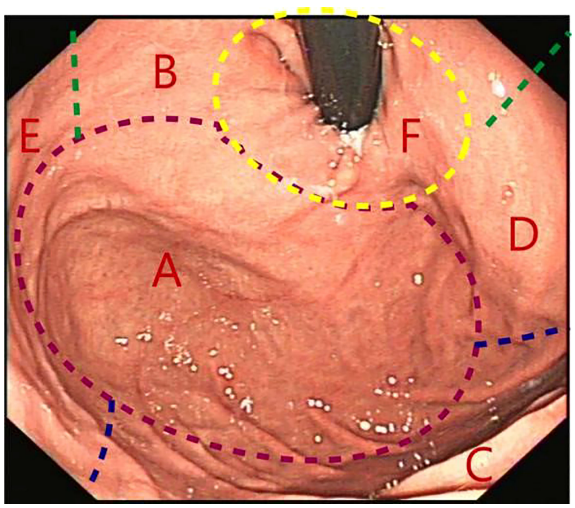

FIGURE 2
Gastric fundus subdivisions. **(A)** Fornix; **(B)** Lesser curvature of the stomach; **(C)** Greater curvature of the stomach; **(D)** Anterior wall; **(E)** Posterior wall; **(F)** Gastric cardia.

Follow-up

All patients were followed up regularly with gastroscopy examinations at 3, 6, and 12 months after the operation, and then they were checked once a year to monitor wound healing and to look for any residual or recurrent tumors.

Histopathological evaluation

H&E staining and immunohistochemical staining were conducted to identify the nature of the lesion and to examine any tendency to malignant transformation.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics 25.0 (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as `$X \pm s$. Categorical data were presented as numbers or percentages (%). *FRW handling performance score was expressed as* $X \pm s$.

Results

Patient information

A total of 112 cases diagnosed with STMF and treated in the Fourth Affiliated Hospital of China Medical University from 2016

TABLE 1 Manipulating performance evaluation criteria after FRW implementation.

Score	The direction of endoscopy body movement is the same as the direction of observation	Ease of instrument entry and exit	The flexibility of endoscopy body control	The ability to access and observe the lesion	Stabilization degree of endoscopy body at fixation and movement
2	Fully achieved	Easy (all devices pass easily and entry and exit freely)	Excellent (endoscopy body moves freely; various endoscopic movements are the same as in other parts)	Excellent (clear and stable visualization, like conventional visualization at other sites; various observations can be achieved)	Excellent (endoscopy body does not shake, almost unaffected by respiration or heartbeat.)
1	Partial achieved	Acceptable (various devices can pass through, but some devices have significant resistance when passing through)	Acceptable (there is instability in some directions of movement, but it meets the manipulating requirements)	Acceptable (Unstable visualization, but can perform various endoscopic procedures)	Acceptable (there is uncontrolled movement of the endoscopy body during the procedure, or it is influenced by respiration and heartbeat, but the procedure can be completed)
0	Not achieved	Not feasible (some instruments cannot pass through)	Poor (Severe limitation of endoscopy movement causing many procedures to be impossible)	Poor (difficult to maintain stable visualization, severely affecting manipulating, or unable to observe details during the procedure)	Poor (endoscopy body shaking, affected by breathing and heartbeat, or difficult to manipulate)

to 2020 were evaluated. Ten patients qualified for the FRW technique (2 males and 8 females), aged 57.6 ± 10.07 (46-78), with a lesion diameter of 0.5-5.0cm. The FRW technique was successfully performed in 7 patients (70%) and failed in 3 patients (30%). (See Table 2).

The results of the FRW technique application

Using the FRW technique, the tip of the gastroscope could access the location just below the gastric cardia in 7 out of 10 patients. All angles of the fundus of the stomach were operable in all 7 patients. Moreover, the FRW technique made accessing and observing the lesion much simpler without the need for paradoxical movement.

The suitable location for the FRW technique

The FRW technique allowed clear visualization of the lesions in the entire fundus area and the mucosa just below the gastric cardia. (Figure 3).

Operating characteristics of the FRW technique

The FRW technique was mainly used for submucosal injection and lesion dissection during the endoscopic treatment of STMF. However, post-resection trauma suturing was performed in a conventional endoscopy progression.

With the FRW technique, we were able to access and visualize the edge close to the pylorus (7/7), the edge close to the gastric cardia (7/7), and the left and right edges (7/7). The FRW technique can be applied at every site, and no obvious lesion site restriction was observed.

As for the Operational Performance Evaluation of the FRW technique, it was very accessible to navigate the tip of the gastroscope tip left or right using the small adjusting knobs. However, moving the gastroscope forward and backwards still showed moderate difficulty. The gastroscope's body makes a forward return along the gastric wall, keeping the gastroscopy's tip stable at all angles due to the support of the gastric wall. The gastroscope was stable at every angle without the need for an assistant to support the endoscope, and the operator could manually adjust the devices in the instrument channel to complete a variety of complex adjustments, cutting, and haemostasis. Since the gastroscopy's tip could access the lesion's edges with stable visualization, the details of each layer below the mucosa and above the lesion were clearly observed; however, water accumulation in the lesion area had certain interference. (See Table 3).

The dissector can be applied parallel to the muscularis propria, forming a good inclination angle during the dissection of the STMF (as shown in the view in Figure 3B), except for tumors at the posterior wall of the fundus. There was some resistance while progressing the instruments in the instrument channel using the FRW technique; however, this defect was the same as in the traditional U-turn technique.

Postoperative and follow-up results

The operation duration using the FRW technique was 47-122 min, and the hospital stay was 7.29 ± 0.49 (7-8) days.

TABLE 2 Case information.

Items	Details	Number of cases
Age	57.6 ± 10.07 (46-78) years	10
Sex	Male	2
	Female	8
Lesion diameter	0.5-5.0 cm	
Location	Middle of the fornix	1
	Greater curvature side of the anterior wall of the fornix	4
	The posterior wall of the fundus	1
	Greater curvature side of fundus	1
	Greater curvature side of the middle of the fornix	3
Successful FRW	7/10	70%
Surgical duration:	47-122 min	
Complications:	None observed	0
Length of hospitalization	7.29 ± 0.49 (7-8) days	

Postoperative histopathological evaluation revealed very low-risk stromal tumors in 8 cases and low-risk stromal tumors in 2 cases. No complications were observed, and all patients recovered well after the operation. No residual or recurrent tumors, metastasis, or death occurred during the postoperative follow-ups.

Discussion

The FRW technique is a novel direct endoscopy progression method with no paradoxical movement involved

Our team discovered the FRW technique during an STMF procedure. The present study summarises the operation method and success rate of the FRW technique based on practice and analysis of the results. Unlike the traditional progression method, in which the gastroscope's tip usually reaches the antrum first, the FRW technique uses the resistance of the posterior wall of the upper gastric body (near the junction with the fundus) and the greater curvature as the supporting force to progress the gastroscope along the arc from the posterior wall of the gastric body to the angular incisure, making a forward-return along the gastric wall. This route allows the gastroscope to access the fundus of the stomach and even access just below the gastric cardia (as shown in the view in Figure 3B). The fundus of the stomach can then be handled from all angles. As a result, there is no need for paradoxical movement, making it much easier for the operators to access the lesion for more visualization and handling during operation.

Additionally, when observing the fundus of the stomach using the FRW technique, we could clearly visualise the mucosa just below the gastric cardia. The gastroscope's tip had easy access to the lesion at a close distance, which can significantly benefit operating on lesions below the gastric cardia.

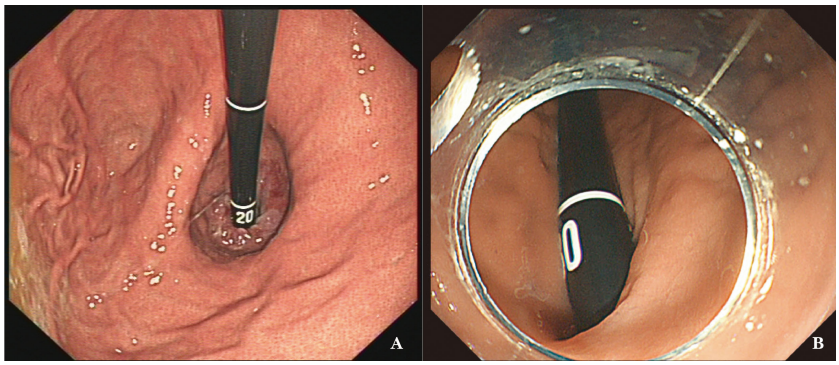

FIGURE 3
Two views of accessing subcardia using two methods. **(A)** Conventional metho**(D)** Due to the U-shaped reversal of the gastroscope and the limitation of the maximum angle of the gastroscope body, the view is directly facing the lesion at the subcardia or at the gastric fundus, resulting in an approximately vertical angle for the endoscopic knife; **(B)** FRW: Achieving a suitable angle with the lesion, allowing for closer proximity to the lesion.

TABLE 3 Evaluation of FRW manipulating characteristics.

Items \ Score	Average score	SD
The direction of endoscopy body movement is the same as the direction of observation	2.00	0
The ability to access and observe the lesion	2.00	0
The flexibility of endoscopy body control	1.43	0.54
Stabilization degree of endoscopy body at fixation and movement	2.00	0
Ease of instrument entry and exit:	1.00	0
Hemostatic clamp	0.71	0.49
Hemostatic forceps	0.71	0.49
Submucosal injection needle	2.00	0
Mucosotomy knife	2.00	0

Solutions to the challenges of endoscopic treatment of GIST in the gastric fundus

The fundus of the stomach is considered a challenging area for ESD (17), ESE, and EFTR (18, 19). Moreover, the ESD technique is complex and prone to perforation (26) because it intentionally destroys the full thickness of the gastric wall, causing perforation to remove the lesion then sutures the wound by nylon suture and or haemostatic clips (27). EFTR is one of the current endoscopic treatments for STMF is EFTR (16), which is why EFTR surgery was predominant in our surgeries (7/7).

Endoscopic operation on the gastric fundus is challenging, mainly due to the need for the traditional endoscopic progression method to be bent backwards (U-turn) to access and observe the fundus of the stomach completely. As a result, the direction of endoscopy body movement is opposite to the direction of observation (paradoxical movement), and the endoscopy body gets suspended, limiting the operating space for the fundus of the stomach (17). Furthermore, when the endoscope's body is suspended using the traditional U-turn technique, the forward injection force becomes greatly reduced, and the injection needle is perpendicular to the muscularis propria (as shown in the view in Figure 3A), making it difficult to find the submucosal space. Following the current commonly used technique, we found that endoscopic treatment of STMF lesions in the middle of the fornix and anterior wall of the fornix was extremely difficult, especially the anterior wall of the fornix at the side of the greater curvature. Thus, a better endoscopic technique was needed to observe, deliver surgical instruments, and operate on these difficult tumor sites.

The operating characteristics of the FRW technique

The FRW technique solves the problem of avoiding paradoxical movement. Furthermore, the stability score of the endoscopy body was 2 ± 0 points, which was excellent, demonstrating that this technique can achieve non-suspension of the endoscopy body and ensure its stability. Additionally, the handling of the endoscopy body and devices in the channel would not be significantly affected by respiratory and heartbeat beats. Finally, the FRW technique allowed easy access to the lesion and its observation.

The ease of device entry and exit using the FRW technique in the 7 patients was 1 ± 0 points, suggesting that the FRW technique had a certain impact on device entry and exit. The injection needle and mucosotomy knife were not affected (2 ± 0 points), while hemostatic forceps and hemostatic clips were significantly affected (0.71 ± 0.49 points). In 2 patients, the hemostatic forceps and hemostatic clips could not pass through the curved channel, and we had to complete the pre-insertion of the device by unbending the endoscopy body and then bending it again to reach the lesion. The difficulty of the passage of the device is mainly related to the long rigid part at the front end of the device and the large bending at the channel.

The flexibility score of the endoscopy body when using the FRW technique was 1.43 ± 0.54 points, but the movement coordination and comfort of the endoscopy body were still somewhat hindered. At present, the synchronization of front and back movement of the endoscopy body is relatively unaffected, but the accuracy is slightly affected. Furthermore, the small knob swing affects the left-right movement and angle adjustment of the endoscopy body.

Factors affecting the FRW technique

The success rate of the FRW technique was 70% in our clinical practice. Currently, the FRW technique can only be performed while patients are in the supine position and under general anaesthesia with endotracheal intubation. In the three cases where the FRW technique failed, we tried gastric cavity morphology after various gas volume adjustments and postural changes, including left lateral decubitus and supine positions, but FRW was still not applicable. Whether the failure cases were due to specific characteristics of the gastric fundus or other factors remains to be explored through a larger sample size. The present study had some limitations due to the small sample of STMF patients who qualified for the FRW technique. Therefore,

more large-scale observational studies are needed to further validate the FRW technique. Additionally, this study was not a randomised clinical trial with a large sample size since GIST is an uncommon disease. In future, we plan to conduct clinical trials for the FRW technique to confirm its reliability.

Conclusions

In summary, the clinical application of the FRW technique can greatly benefit the endoscopic treatment of gastric fundus stromal tumors. This method has distinct advantages in terms of accessing and observing the lesion, increasing the endoscopy body stability, and matching the endoscopy body movement with the direction of observation.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of The Fourth Affiliated Hospital of China Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

HM-G and YS collected the data and wrote the manuscript. SC, FM, YZ, and YY collected the data and revised the manuscript. Z-FZ was the leading surgeon who completed the procedures in this manuscript. He also revised the manuscript. LL checked all data and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1077201/full#supplementary-material

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Faster recovery and bowel movement after early oral feeding compared to late oral feeding after upper GI tumor resections: a meta-analysis

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Background: There were more than 1 million new cases of stomach cancer concerning oesophageal cancer, there were more than 600,000 new cases of oesophageal cancer in 2020. After a successful resection in these cases, the role of early oral feeding (EOF) was questionable, due to the possibility of fatal anastomosis leakage. It is still debated whether EOF is more advantageous compared to late oral feeding. Our study aimed to compare the effect of early postoperative oral feeding and late oral feeding after upper gastrointestinal resections due to malignancy.

Methods: Two authors performed an extensive search and selection of articles independently to identify randomized control trials (RCT) of the question of interest. Statistical analyses were performed including mean difference, odds ratio with 95% confidence intervals, statistical heterogeneity, and statistical publication bias, to identify potential significant differences. The Risk of Bias and the quality of evidence were estimated.

Results: We identified 6 relevant RCTs, which included 703 patients. The appearance of the first gas (MD = –1.16; $p = 0.009$), first defecation (MD = –0.91; $p < 0.001$), and the length of hospitalization (MD = –1.92; $p = 0.008$) favored the EOF group. Numerous binary outcomes were defined, but significant difference was not verified in the case of anastomosis insufficiency ($p = 0.98$), pneumonia ($p = 0.88$), wound infection ($p = 0.48$), bleeding ($p = 0.52$), rehospitalization ($p = 0.23$), rehospitalization to the intensive care unit (ICU) ($p = 0.46$), gastrointestinal paresis ($p = 0.66$), ascites ($p = 0.45$).

Conclusion: Early postoperative oral feeding, compared to late oral feeding has no risk of several possible postoperative morbidities after upper GI surgeries, but has several advantageous effects on a patient's recovery.

Systematic Review Registration: identifier, CRD 42022302594.

KEYWORDS

early oral feeding (EOF), upper GI surgery, meta-analysis, upper GI cancer, Eras

Introduction

Stomach cancer is the 5th most common cancer worldwide. It is the 4th most common cancer in men and the 7th most common cancer in women. There were more than 1 million new cases of stomach cancer in 2020. Concerning the stomach cancer, it causes 768,793/100,000 deaths worldwide. Esophageal cancer is the 8th most common cancer worldwide. It is the 7th most common cancer in men and the 13th most common cancer in women. There were more than 600,000 new cases of esophageal cancer in 2020. Esophageal cancer causes 544,076/100,000 deaths every year. Regarding tumors of the gastroesophageal junction, unfortunately we found little data. According to the latest 8th TNM classification, tumors of the gastroesophageal junction can be classified exactly as tumors of the stomach or stomach of the esophagus based on their location (1). After upper gastrointestinal surgeries, especially if the anastomosis is performed with the esophagus, the anastomosis failure rate is very high, reaching 9%–16% (2). For several decades, in upper GI resection surgeries in the postoperative period, inchoation of oral feeding was delayed to the seventh day in dread of occurring anastomosis insufficiency and generating systemic complications (3).

The human body produces up to 1 liter of saliva per day. This enzymatically active fluid, passes through the anastomosis, without triggering any anastomotic complication for the patient (4).

If the patient does not consume anything orally, the saliva is dense, its transit time increases, therefore it passes through the anastomosis slowly, possibly causing damage to the anastomosis.

Patients suffering from GI malignancies are often in an undernourished state. LOF (late oral feeding) protocol does not prove itself to be beneficial for the patient's nutritional state, while perioperative starvation provokes a severe catabolic state (5).

Enhanced recovery protocols for perioperative care, such as Enhanced Recovery After Surgery (ERAS), have gained wide acceptance. The concept of ERAS is to facilitate postoperative recovery and improve the quality of life. The postoperative oral feeding process is a fundamental component of the ERAS (6). EOF is defined by the start of oral feeding on the 1–3 postoperative days, while in the LOF feeding protocol, it starts 5–7 days after surgery. Despite several randomized clinical trials (RCTs) that have attempted to measure the benefits of EOF (early oral feeding), this protocol is not ubiquitously used. Early oral feeding (EOF) seems more profitable in the surgical profession to recover patients faster and decrease hospitalization time (7).

The aim is to compare the effect of early postoperative oral feeding and late oral feeding methods after upper gastrointestinal malignancy surgeries. For this express purpose, we performed a meta-analysis to compare the influence of the two diverse feeding strategies on postoperative recovery and to certify the safety and benefits of EOF.

We assume that early oral feeding does not increase the anastomotic insufficiency rate, nor the morbidity rate, while it has several beneficial effects on the general state and on the recovery time.

Methods

A meta-analysis was carried out using the population-intervention-control-outcomes (PICO) format. Those studies were selected where patients had surgery because of upper GI malignancy (P), and postoperative feeding methods were compared (I and C). Mortality, complications, length of hospitalization, first flatus, and defecation were compared, as the outcomes of different treatment groups (O). The meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Review (PRISMA) statement and it was registered in advance in the PROSPERO database. The registration number is CRD 42022302594.

Search strategy

The selection was conducted on electronic databases, including PubMed and Embase, and Cochrane. Restrictions were not applied. We started the search on the date of 1st of February 2021.

The search included the following keywords:

(((((upper GI OR upper gastrointestinal OR esophagus OR esophagus OR esophageal OR oesophageal OR stomach OR gastric) AND (surgery OR surgical OR operative OR operation OR resection)) OR (esophagectomy OR oesophagectomy OR gastrectomy)) AND ((enteral* OR oral*) AND (nutrition OR nutritional OR "oral feeding*" OR food))) AND random*.

Inclusion and exclusion criteria

We searched for studies, involving patients with upper GI cancers, including oesophageal and gastric tumors, and we excluded all the cases when the surgery was performed because of benign diseases.

In our analysis, we compared the effect of early postoperative oral feeding, compared to late oral feeding, after upper gastrointestinal surgeries.

Articles were included if they provided data on at least two feeding modalities on patients with either EOF or LOF or both reporting the outcomes mentioned above. Only randomized controlled trials were included. Non-English language studies, studies focusing on pediatric cases, and studies with combined interventions were excluded.

Selection process

The publications were processed by the EndNote X7.4 software (Clarivate Analytics, Philadelphia, PA, USA). Duplications were removed, and the remaining records were screened first by title,

second by abstract, and finally by full-text by two independent authors (DLS and DB).

Data extraction

Data were collected by two independent authors (DLS and AC) using an Excel (Office 365, Microsoft, Redmond, WA, USA) data sheet, based on predetermined criteria. Numerous binary variables outcomes were defined such as anastomosis insufficiency, pneumonia, wound infection, bleeding, ascites, rehospitalization, gastrointestinal paresis, and laryngeal nerve paresis. The appearance of the first gas, first postoperative defecation, and length of hospitalization were the outcomes of continuous variables.

Statistical analysis

The statistical analyses were made with R (R Core Team) Software (8). For calculations and plots, we used the meta (9) and dmetar (10) packages.

For dichotomous outcomes the odds ratio (OR) with a 95% confidence interval (CI) was used for the effect measure; to calculate the OR, the total number of patients in each group and those with the event of interest were extracted from each study. Raw data from the selected studies were pooled using a random effect model with the Mantel-Haenszel method (11–13). For the pooled results exact Mantel-Haenszel method (no continuity correction) was used to handle zero cell counts (14). In individual studies, the zero cell count problem was adjusted by treatment arm continuity correction (15).

In the case of continuous outcomes, the mean differences (MD) with 95% CI were calculated as effect size. The extracted values to calculate the mean difference were the sample size (N), the mean, and the standard deviation (SD) in each group. If the mean and SD were not reported, the median and the upper and lower quartilee, the minimum and maximum values were extracted. If the mean value was not available, it was estimated from the sample size, median, and range using the method proposed by Luo et al. (16). Similarly, if the standard deviation was not reported, it was estimated from the sample size, median, and range using the method of Wan et al. (17). If the study number for the given outcome was over five, the Hartung-Knapp adjustment (18, 19) was applied (below six studies no adjustment was applied).

To estimate τ^2 we used the Paule–Mandel method (20), and the Q profile method for calculating the confidence interval of τ^2 (21).

Statistical heterogeneity across trials was assessed utilizing the Cochrane Q test, and the I^2 values (22).

Forest plots and drapery plots (19, 23) were used to graphically summarise results. Where applicable we reported the prediction intervals (i.e., the expected range of effects of future studies) of results following the recommendations of IntHout et al. (19). A funnel plot of the logarithm of effect size and comparison with the standard error for each trial was used to evaluate publication bias. Publication bias was assessed with Egger's test using the Harbord method to calculate the test statistic (24).

Outlier and influence analyses were carried out following the recommendations of Harrer et al. (21) and Viechtbauer and Cheung (25).

Quality assessment

To estimate the quality of the articles two independent authors (DLS and ACS) used the Risk of Bias Assessment Tool version 2 by Cochrane, and the GRADE approach was applied to assess the certainty of evidence.

Results

We found 3,147 articles from Embase, Cochrane, and PubMed databases. We did not identify any additional articles from other sources. After the filter of duplication, title, and abstract, 77 articles remained. During the full-text filtering, we excluded 71 articles because they were not RCTs. We also excluded trials, which did not include patients with esophageal or gastric tumors and pediatric or animal experiments. We identified 6 relevant RCTs by full-text, which included 703 patients. The detailed steps of the selection process can be seen on the PRISMA flowchart (**Figure 1**).

Characteristics of the studies

The details of the characteristics of the studies were shown in the table below (**Table 1**).

Bowel movement

In the case of the first flatus or gas, a total of 5 studies (26–30) were selected for analyses covering a total of 604 patients. We found that the first flatus and gas appeared earlier in the EOF group (MD: −1.16; $p = 0.009$; 95% CI: [−1.82; −0.49]). The between-study heterogeneity was significant ($I^2 = 99\%$; $p < 0.001$) (**Figure 2**).

A total of 3 studies (26, 28, 30) were selected for the analyses of the first defecation covering a total of 442 patients. We found that first defecation appeared significantly earlier in the EOF group (MD: −0.91; $p < 0.001$; 95% CI: [−0.95; −0.86]). The between-study heterogeneity was not significant ($I^2 = 0\%$; $p = 0.676$) (**Figure 3**).

Length of hospital stay

A total of 5 (26–30) studies were selected for analyses covering a total of 605 patients. We found that the first flatus and gas appeared earlier in the EOF group (MD: −1.92; $p = 0.008$; 95%

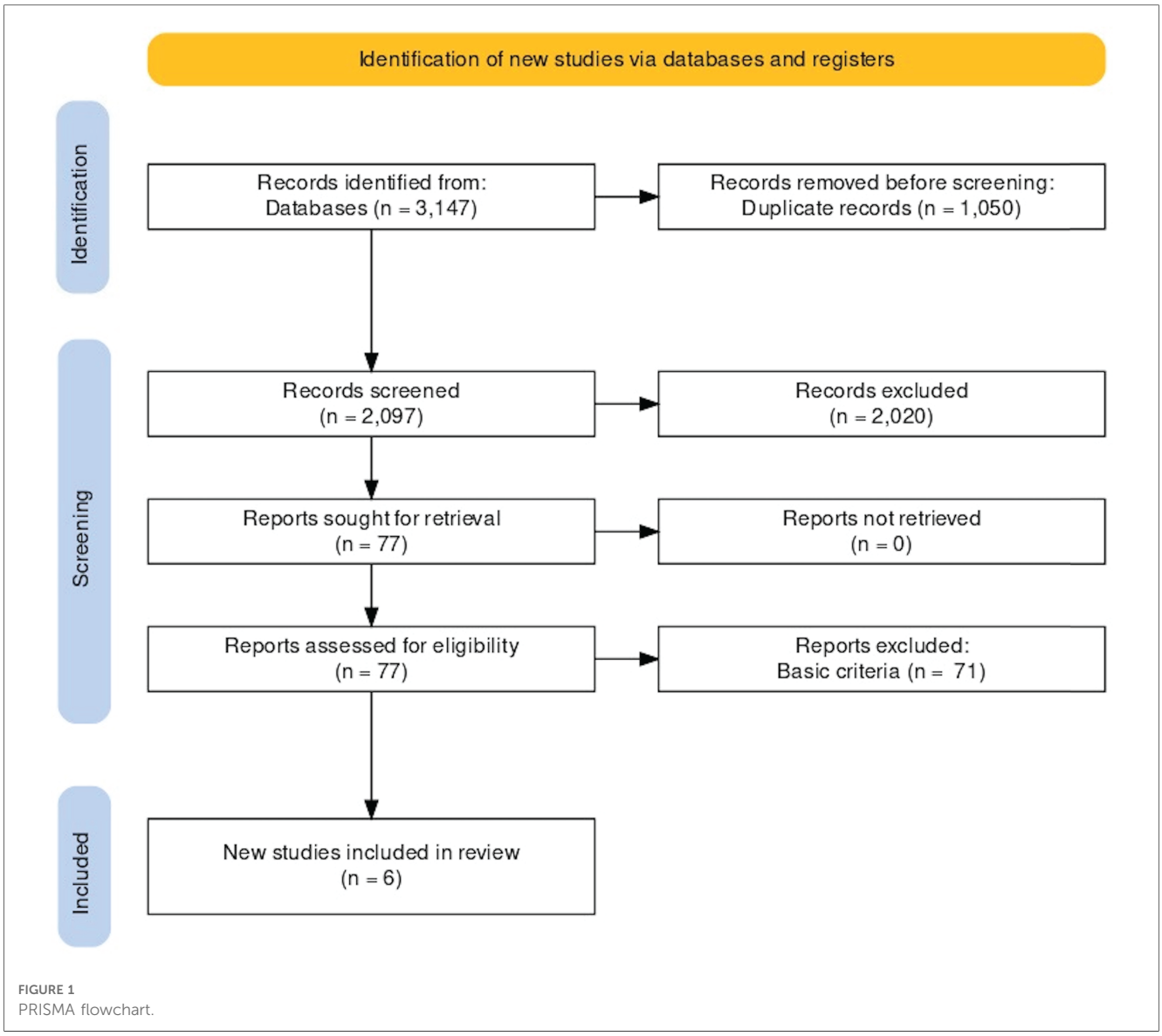

FIGURE 1
PRISMA flowchart.

CI: [−2.99; −0.85]). The between-study heterogeneity was significant ($I^2 = 97\%$; $p < 0.001$) (Figure 4).

Rehospitalization

A total of 5 studies (26–29, 31) were selected for analyses covering a total of 603 patients. We found that there is no statistically significant difference between the two groups (OR = 0.57; $p = 0.25$; 95% CI: [0.18; 1.80]). The between-study heterogeneity was not significant ($I^2 = 0\%$; $p = 0.47$).

Adverse events

Anastomosis leakage

A total of 4 studies (28–31) were selected for analyses covering a total of 539 patients. We found that there is no statistically significant difference between the two groups (OR = 0.98; $p = 0.98$; 95% CI: [0.33; 2.96]). The between-study heterogeneity was not significant ($I^2 = 0\%$; $p = 0.01$) (Figure 5).

Pneumonia

A total of 4 studies (26, 28, 29, 31) were selected for analyses covering a total of 549 patients. We found that there is no statistically significant difference between the two groups (OR = 0.95; $p = 0.88$; 95% CI: [0.51; 1.79]). The between-study heterogeneity was not significant ($I^2 = 0\%$; $p = 0.92$).

Wound infection

A total of 4 studies (26, 27, 30, 31) were selected for analyses covering a total of 520 patients. We found that there is no statistically significant difference between the two groups (OR = 1.59; $p = 0.48$; 95% CI: [0.44; 5.77]). The between-study heterogeneity was not significant ($I^2 = 0\%$; $p = 0.85$).

TABLE 1 Characteristics of the studies.

Author	Year of publication	Country	No of patients	Intervention	Surgery	Man/ Woman	Age	Follow-up (mean)
Hur et al.	2011	Korea	54	GE	Open laparotomy	33/21	–	28 days
Mahmoodzadeh	2014	Iran	109	UGI	Transthoracic esophagectomy/total gastrectomy with Roux-en-Y/partial gastrectomy with Billroth I or II or Roux-en-Y	29/25	65, 3	–
Sun et al.	2018	China	86	EE	MIE McKeown	52/34	62, 4	–
Wang et al.	2019	China	100	GE	Total laparoscopic radical gastrectomy	71/29	54, 22	–
Shimizu et al.	2018	Japan	74	GE	Distal gastrectomy (DG)	137/79	65, 45	–
					Total gastrectomy (TG)			
Sun et al.	2017	China	280	EE	MIE McKeown	195/85	63	24 weeks

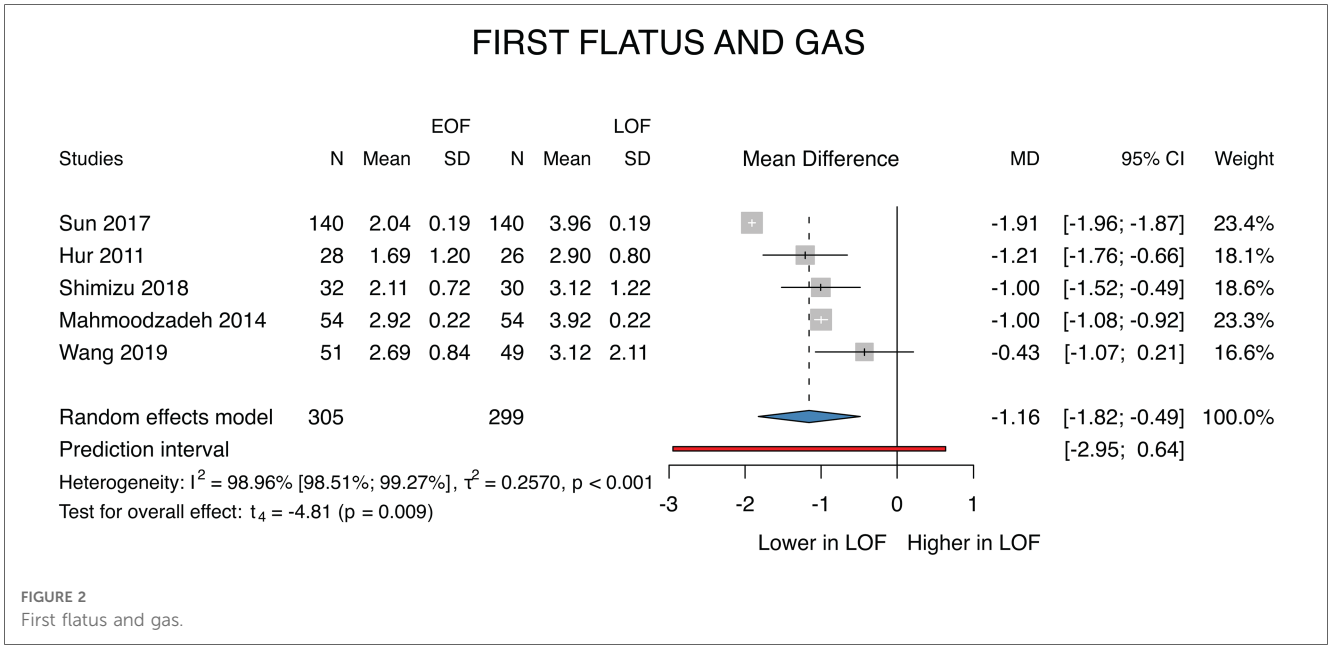

FIGURE 2
First flatus and gas.

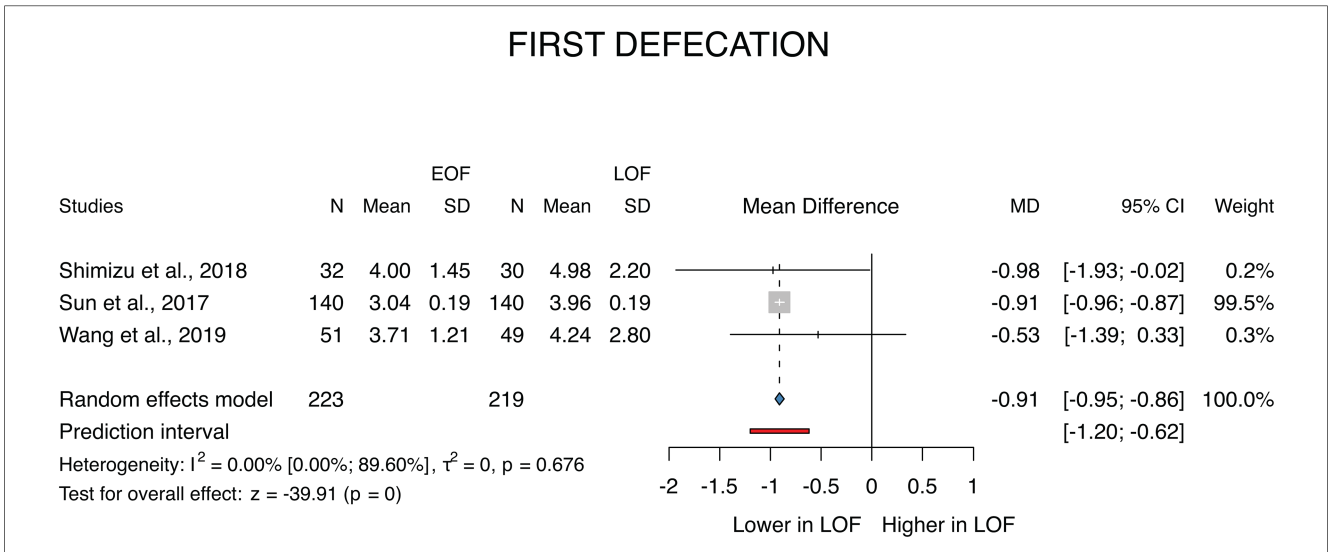

FIGURE 3
First defecation.

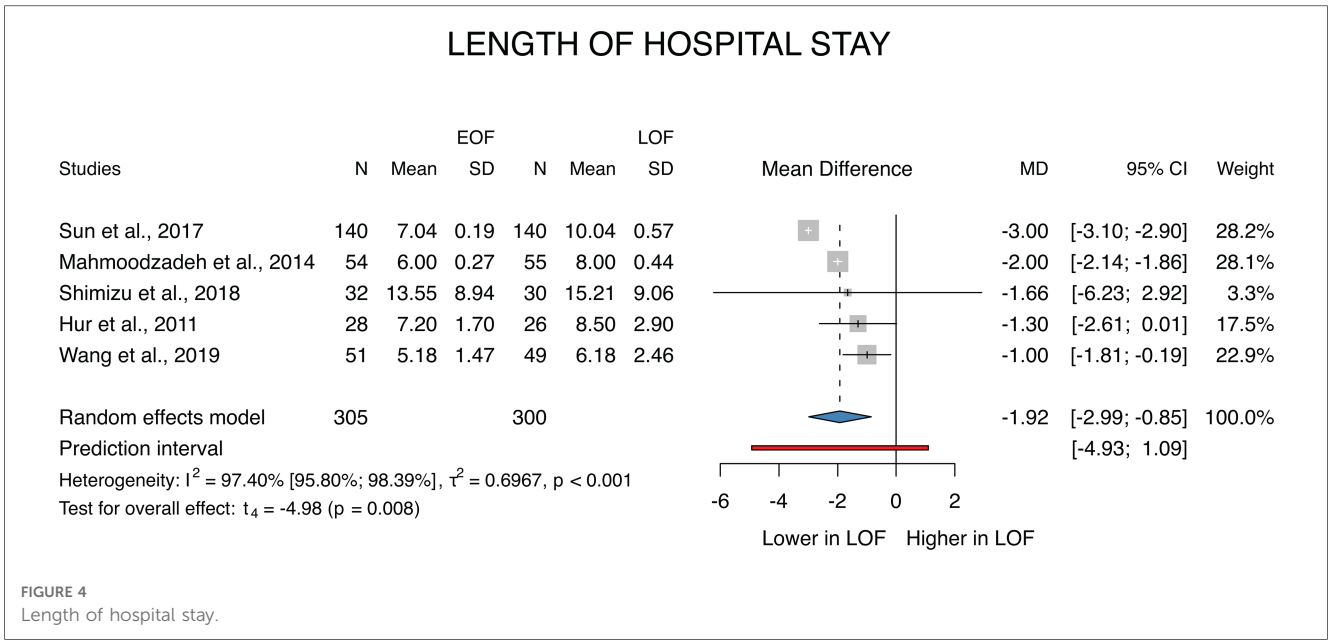

FIGURE 4
Length of hospital stay.

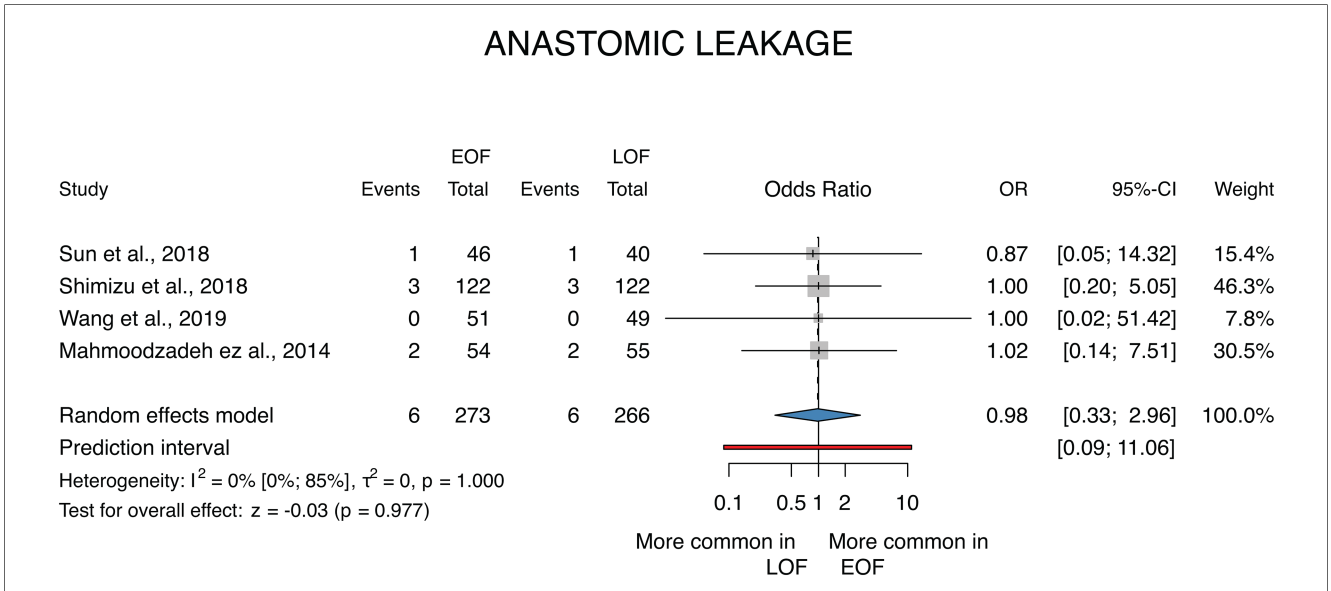

FIGURE 5
Anastomotic leakage.

Bleeding

A total of 4 studies (26–28, 30) were selected for analyses covering a total of 508 patients. We found that there is no statistically significant difference between the two groups (OR = 1.70; $p = 0.52$; 95% CI: [0.34; 8.61]). The between-study heterogeneity was not significant ($I^2 = 0\%$; $p = 0.92$).

Ascites

A total of 3 studies (26, 27, 31) were selected for analyses covering a total of 420 patients. We found that there is no statistically significant difference between the two groups (OR = 0.56; $p = 0.449$; 95% CI: [0.12; 2.52]). The between-study heterogeneity was not significant ($I^2 = 0\%$; $p = 0.82$).

Gastrointestinal paresis

A total of 3 studies (27, 28, 30) were selected for analyses covering a total of 228 patients. We found that there is no statistically significant difference between the two groups (OR = 0.55; $p = 0.43$; 95% CI: [0.12; 2.47]). The between-study heterogeneity was not significant ($I^2 = 0\%$; $p = 0.53$).

TABLE 2 D1, randomisation process; D2, deviations from the intended interventions; D3, missing outcome data; D4, measurement of the outcome; D5, selection of the reported result.

Outcome	ID	D1	D2	D3	D4	D5	Overall
First flatus and gas	Sun et al., 2017	Low	Low	Low	Low	Low	Low
	Hur et al., 2011	Low	Low	Low	Low	Low	Low
	Shimizu et al., 2018	Low	Low	Low	Low	Low	Low
	Mahmoodzadeh et al., 2014	Low	Low	Low	Low	Low	Low
	Wang et al., 2019	Low	Low	Low	Low	Low	Low
First defecation	Shimizu et al., 2018	Low	Low	Low	Low	Low	Low
	Sun et al., 2018	Low	Low	Low	Low	Low	Low
	Wang et al., 2019	Low	Low	Low	Low	Low	Low
Length of hospital stay	Sun et al., 2017	Low	Low	Low	Low	Low	Low
	Mahmoodzadeh et al., 2014	Low	Low	Low	Low	Low	Low
	Shimizu et al., 2018	Low	Low	Low	Low	Low	Low
	Hur et al., 2011	Low	Low	Low	Low	Low	Low
	Wang et al., 2019	Low	Low	Low	Low	Low	Low
Rehospitalization	Mahmoodzadeh et al., 2014	Low	Low	Low	Low	Low	Low
	Hur et al., 2011	Low	Low	Low	Low	Low	Low
	Sun et al., 2017	Low	Low	Low	Low	Low	Low
	Sun et al., 2018	Low	Low	Low	Low	Low	Low
	Shimizu et al., 2018	Low	Low	Low	Low	Low	Low
Anastomotic leakage	Sun et al., 2018	Low	Low	Low	Low	Low	Low
	Shimizu et al., 2018	Low	Low	Low	Low	Low	Low
	Wang et al., 2019	Low	Low	Low	Low	Low	Low
	Mahmoodzadeh et al., 2014	Low	Low	Low	Low	Low	Low
Pneumonia	Sun et al., 2017	Low	Low	Low	Low	Low	Low
	Mahmoodzadeh et al., 2014	Low	Low	Low	Low	Low	Low
	Sun et al., 2018	Low	Low	Low	Low	Low	Low
	Shimizu et al., 2018	Low	Low	Low	Low	Low	Low
Wound infection	Sun et al., 2018	Low	Low	Low	Low	Low	Low
	Wang et al., 2019	Low	Low	Low	Low	Low	Low
	Sun et al., 2017	Low	Low	Low	Low	Low	Low
	Hur et al., 2011	Low	Low	Low	Low	Low	Low
Bleeding	Hur et al., 2011	Low	Low	Low	Low	Low	Low
	Shimizu et al., 2018	Low	Low	Low	Low	Low	Low
	Wang et al., 2019	Low	Low	Low	Low	Low	Low
	Sun et al., 2017	Low	Low	Low	Low	Low	Low
Ascites	Hur et al., 2011	Low	Low	Low	Low	Low	Low
	Sun et al., 2017	Low	Low	Low	Low	Low	Low
	Sun et al., 2018	Low	Low	Low	Low	Low	Low
Gastrointestinal paresis	Hur et al., 2011	Low	Low	Low	Low	Low	Low
	Wang et al., 2019	Low	Low	Low	Low	Low	Low
	Shimizu et al., 2018	Low	Low	Low	Low	Low	Low
Recurrent laryngeal nerve injury	Sun et al., 2017	Low	Low	Low	Low	Low	Low
	Mahmoodzadeh et al., 2014	Low	Low	Low	Low	Low	Low
	Sun et al., 2018	Low	Low	Low	Low	Low	Low

Recurrent laryngeal nerve injury

A total of 3 studies (26, 29, 31) were selected for analyses covering a total of 475 patients. We found that there is no statistically significant difference between the two groups (OR = 0.96; $p = 0.9$; 95% CI: [0.51; 1.82]). The between-study heterogeneity was not significant ($I^2 = 0\%$; $p = 0.99$).

Risk of bias

ROB was assessed as low in all outcomes (26–31). The detailed estimation results are summarised in the table below (**Table 2**).

Grade

The quality of the evidence was estimated as moderate in all outcomes (26–31) because most articles originated from Asia, therefore we cannot standardize the results. The results of the GRADE were contained in the table below (**Supplementary Table S1**).

Discussion

In the case of operations performed for upper gastrointestinal tumors, the mortality and morbidity rates are very high, especially if the anastomosis is performed with the esophagus (2).

For decades, anastomosis failure was one of the most dangerous complications leading to other morbidities. Li et al. (32) described that EOF can increase the anastomosis leakage rate during open surgery, however, they worked with a small number of cases. Fearing this complication, the "nil per os" feeding method spread (3), however nowadays, MIE operations have become more common, because of several advantages (33), including the chance of anastomotic leakage does not increase during the EOF (32).

In recent years, it has been proven that the ERAS protocol has a beneficial effect on the prehabilitation and rehabilitation of patients, which includes early oral feeding after surgery as part of the multimodal care protocol (6), therefore the topic of EOF is becoming increasingly popular in literature. Previously 4 meta-analyses (32, 34–36) dealt with the comparative study of early and late oral feeding. They found the EOF is feasible and safe, especially in the case of MIE, however, they have some limitations, such as the small number of included studies, high heterogeneity between the groups, and complications that were not discussed in detail, therefore we investigate the topic again.

We prepared a meta-analysis based on the PRISMA protocol, in which we included 6 studies with the participation of 703 patients. In these studies, early (EOF) and late (LOF), oral feeding methods were used after oesophageal and gastric cancer surgeries, and then the results of the 2 groups were compared. In the EOF group, they were allowed to consume liquid on the second post-operative day orally, and then from the postoperative day on, they started giving formula, which is how the feeding method is structured. In the control group, for 5–7 days after the operation, the patients were not allowed to consume food orally, it was provided enterally or by other parenteral means.

As previously described, anastomotic leakage is one of the most common complications, associated with life-threatening infection and mortality, and influences the response of therapy, therefore, it is one of the most important outcomes. There was no significant difference between the EOF and LOF groups, based on our study. Li et al. (32) also found no significant difference in their meta-analysis between the two major groups. Because of the high heterogeneity, they performed subgroup analysis. This result, due to the small number of elements, should be addressed with some concerns. In the MIE subgroup, they found no difference, however, in the case of open surgery, the EOF can be associated with a higher risk of anastomosis leakage. The effect of the EOF depends on the site of the anastomosis. In the case of cervical anastomosis, the EOF can be at higher risk, however, in the thoracic subgroup, there was no significant difference (32). In gastric cancer surgery, Liu et al. found no difference between the EOF and the LOF group (35).

In the case of gastric cancer, He (34) and Liu et al. (35), found no difference in the case of overall complications, however, Xin et al. found that the EOF decreased the risk of postoperative complications (36). We investigated the postoperative complications of upper GI surgery separately, and we found no difference in bleeding ($p = 0.52$), wound infection ($p = 0.48$), ascites ($p = 0.45$), and gastrointestinal paresis ($p = 0.43$). He et al. also found no significance in feeding intolerance (0.62) (34).

However, we do not investigate the question due to a lack of data, He (34) and Xin et al. (36) found EOF can increase nutrition values, albumin ($p < 0.0001$), and prealbumin ($p < 0.001$) levels in case of gastrectomies. Xin et al. found a significant increment of immune indicators like CD3+ ($p = 0.0009$), CD4+ ($p < 0.00001$), CD4+/CD8+ (<0.00001), and NK cells (<0.00001) under the influence of EOF (36).

The appearance of the first flatus and gas is earlier in EOF, based on our investigation ($p = 0.009$; MD = −1.16 [−1.82; −0.49]), which is confirmed by He (34) and Liu et al. (<0.0001) (35), and we also found the first defecation comes earlier in EOF ($p < 0.001$, MD = −0.91 [−0.95; −0.86]).

The main advantage of applying the EOF is the shorter length of hospital stay, which our investigation ($p = 0.008$, MD = −1.92 [−2.99; −0.85]), and the meta-analyses by He (34) and Liu et al. (35) also confirmed ($p < 0.001$). Even though patients can be discharged earlier, the rate of rehospitalization does not increase ($p = 0.25$).

We found a lack of data, but logically the cost of hospitalization can decrease significantly, which He et al. also verified (MD: −4.21, $p < 0.001$) (34). Altman et al. examined the elements of the ERAS protocol and concluded that it can reduce hospital stay time and costs (1). Liu et al. also found that EOF can decrease the hospitalization cost ($p = 0.014$) (35) and Wang et al. estimated the difference at about 2,000 yuan (300 USD), however, the significance was not verified (30). An important element in reducing hospital stay is the length of stay in the intensive care unit, which can be reduced to a significant extent by starting oral feeding early, compared to the late-started feeding group (37).

Lower hospital costs can be achieved by reducing the length of stay in the intensive care unit. Roh et al. analyzed the length of hospital stay after a minimally invasive subtotal gastrectomy. In this study, the hospital length of stay in the early feeding group was significantly lower than that in the LOF group. However, the complication rate was not found to be higher in the EOF group (38).

In our analysis, we did not examine mortality as an outcome due to the small amount of available data, despite the fact that we planned to examine it in advance. A short-term 30-day follow-up of mortality was performed by Jang et al. (7) who found no difference in the mortality rate, however, no long-term follow-up was done in terms of this outcome. A 30-day follow-up was also carried out in the study published by Hur et al. (27), mortality as an outcome shows a long-term improving trend in the early feeding group, because the improvement of mortality indicators, such as acute phase proteins and the decreasing sepsis rate, reduce morbidity and thus mortality indicators. It can be said that the mortality rate can be indirectly reduced by using early oral feeding, which can be achieved through the reduction of morbidity factors and cannot be interpreted directly as an effect of oral feeding.

Quality of life is a very important aspect in addition to postoperative morbidities, although we could not analyze it due

to the small sample size and the high heterogeneity of the data, therefore it would be useful to measure QOL with one standard method, for example using the EORTC QLQC30 score system, in future studies.

Patients who have undergone upper GI surgery are often malnourished, which is also contributed to by the surgical metabolic stress. Weight loss and the weakening of the patient's physical condition have been shown an increased the mortality rate (39). Pre- and post-operative weight loss and body mass index have an impact on prognosis in patients with oesophageal cancer (39).

At the same time, this is also a factor, affecting the quality of life, which can be significantly improved by starting early oral feeding. Yang et al. investigated the effect of early oral feeding on the quality of life of patients who underwent minimally invasive oesophagectomy. They used Cancer-Quality of life Question-Core (QLQ-C30, version 3) and Oesophageal Cancer Module (QLQ-OES-18) questionnaires. They found that weight loss can be reduced and has a positive effect on early recovery, and can demonstrably improve the quality of life (40).

In the future, it would be necessary to widely use quality-of-life questionnaires as part of the ERAS protocol for patients undergoing upper gastrointestinal surgery. For example, Sun et al. used the EORTC QLQC30 questionnaire to assess the quality of life, it can be said that the EOF group had significantly better results compared to the LOF group (26).

Strength

We selected high-quality articles as there were only randomized controlled trials selected, therefore the risk of bias is low.

The definition of outcomes is homogenous, thereby increasing the quality.

The characteristic of patients was similar in the EOF and the LOF group.

Limitation

We were primarily interested in examining the EOF during oesophageal surgery, but unfortunately, due to the small number of RCTs, we had to combine it with gastrectomy, so in the end, we examined an integrated UGI group. Due to the rigorous criteria, a small number of cases were available. Another limitation is the averages had to be estimated in many places because it was not described precisely in the articles, and median values were not given in many places.

Mostly Asian and American articles were included, therefore the population of the patients was overwhelmingly Asian, while European and American were represented by only one article each. Thus, these results are only applicable to the European and American populations in a limited manner.

Due to the small number of cases and few studies, we did not separate the results of gastric tumor and oesophageal tumor patients during our meta-analysis but examined them in one group.

Implication for research

Recently, more and more articles deal with the advantages of EOF, but the number of RCTs is still small. In our meta-analyses some limitations emerge, therefore further large sample size randomized controlled investigation is needed in the topic of the esophagus and gastric resection, especially in cases of minimally invasive UGI surgery. Trials should originate from distinct countries so that the results can be standardized. This is the reason why we are planning on conducting a multicentric clinical research project involving multiple Hungarian medical institutions that handle UGI surgeries.

Implication for practice

In our meta-analysis, we proved that the use of EOF has many advantages, but does not involve significant complications. It reduces the length of hospital stay and contributes to a better immune status, which in itself reduces the development of postoperative complications and contributes to a faster recovery time. Anastomotic leakage can be a dangerous complication in connection with EOF, but we could not prove this risk. All in all, we can say that EOF has negligible risk, however, it is a safe way to improve the recovery of patients.

Conclusion

Our meta-analysis is more comprehensive and accurate than before, due to rigorous criteria. In conclusion, it can be said that oral feeding started early after surgery is safe even after upper gastrointestinal surgery. Based on our results EOF does not associate with higher morbidity especially anastomotic leakage, pneumonia, wound infection, bleeding, ascites, gastrointestinal paresis, and recurrent laryngeal nerve injury. The main advantages of the EOF are the appearance of the first flatus and defecation earlier, which means the recovery time of bowel function is more rapid. The risk of rehospitalization was similar in the investigated groups, and the time of hospital stay is also shortened in the EOF, which magnetifies lower cost. Even though many studies are still needed on this topic in the future, based on our results, we recommend the usage of EOF after upper GI surgery in practice, especially within the framework of the ERAS protocol, due to its many advantages and negligible complications.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

DS contributed to conception and design of the study, including establishing the selection process, data extraction and writing of the manuscript. PM accomplished the bio-statistical analyses and the interpretation of data, contributed to the writing of the manuscript. LS coordinated the process and lectured grammarly the manuscript, contributed to the writing of the manuscript. DB contributed to the selection strategy, data extraction, contributed to the writing of the manuscript. GB coordinated the process of forming the metaanalyses, was involved in the conceptualization, contributed to the writing of the manuscript. AC contributed to data extraction, helped with the risk of bias assessment, wrote the manuscript and assisted with the data presentation, contributed to the writing of the manuscript. CP was involved in the data extraction process and the interpretation of data, contributed to the writing of the manuscript. PH contiributed to the conception, helped the work with his suggestions, contributed to the writing of the manuscript. AP provided supervision and helped with the interpretation of the manuscript, contributed to the writing of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The reviewers GV and AP declared a shared affiliation with the author PH to the handling editor at the time of review.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2023.1092303/full#supplementary-material.

Supplementary Figure 1
Rehospitalization.

Supplementary Figure 2
Pneumonia.

Supplementary Figure 3
Wound infection.

Supplementary Figure 4
Bleeding.

Supplementary Figure 5
Ascites.

Supplementary Figure 6
Gastrointestinal paresis.

Supplementary Figure 7
Recurrent laryngeal nerve (RLN) injury.

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Prognostication and optimal criteria of circumferential margin involvement for esophageal cancer after chemoradiation and esophagectomy

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Purpose: Circumferential radial margin (CRM) involvement by tumor after resection for esophageal cancer has been suggested as a significant prognostic factor. However, the prognostic value of CRM involvement after surgery with neoadjuvant concurrent chemoradiotherapy (CCRT) is unclear. This study aimed to evaluate the prognostic value of and survival outcomes in CRM involvement as defined by the Royal College of Pathologists (RCP) and the College of American Pathologists (CAP) for patients with esophageal cancer undergoing neoadjuvant CCRT and esophagectomy.

Methods: A total of 299 patients with esophageal cancer who underwent neoadjuvant CCRT followed by esophagectomy between 2006 and 2016 were enrolled in our study. The CRM status of the specimens obtained was determined pathologically according to both the CAP and RCP criteria. Survival analyses were performed and compared according to the two criteria.

Results: Positive CRM was found in 102 (34.1%) and 40 (13.3%) patients according to RCP and CAP criteria, respectively. The overall and progression-free survival rates were significantly lower in the CRM-positive group than in the CRM-negative group according to both the RCP and CAP criteria. However, under multivariate analysis, in addition to pathological T and N staging of the tumor, only CAP-defined CRM positivity was a significant prognostic factor with adjusted hazard ratios of 2.64 (1.56-4.46) and 2.25 (1.34-3.78) for overall and progression-free survival, respectively ($P < 0.001$).

Conclusion: In patients with esophageal cancer undergoing neoadjuvant CRT followed by esophagectomy, CAP-defined CRM positivity is an independent predictor of survival. Adjuvant therapy should be offered to patients with positive CRM.

KEYWORDS

esophageal cancer, chemoradiotherapy, esophagectomy, circumferential radial margin, Survival

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Introduction

Esophageal cancer (EC) is a devastating disease with an increasing incidence worldwide, especially in the Western white population (1, 2). Surgery with or without radiotherapy and/or chemotherapy remains the treatment of choice for resectable EC. Nonetheless, even after en-bloc resection of the tumor, the loco-regional recurrence rates of EC are reported to be as high as 52% (3, 4). The TNM staging of EC defined by the American Joint Committee on Cancer (AJCC) is widely used for prognostication and therapeutic decision-making. In addition, various criteria have been suggested as independent prognostic factors after resection, including tumor size (5–8), tumor grade (6, 8), nodal involvement, lymph node ratio (9–13), and degree of tumor regression after neoadjuvant therapy (14).

The significance of the circumferential radial margin (CRM) status in EC has gained attention after the discovery of the association between CRM positivity and the incidence of local recurrence in colorectal and pancreatic cancer (15–17). Sagar et al. (18) first described the role of CRM in EC, showing that CRM involvement is associated with an increased risk of local recurrence. Further studies by the same group also showed that the presence of malignant cells within 1 mm of the CRM reduces median survival (19). Currently, there are two definitions of CRM involvement commonly used in clinical practice. The Royal College of Pathologists (RCP) defines a positive CRM as a tumor at or within 1 mm of the cut margin (20), whereas the College of American Pathologists (CAP) considers only the presence of a tumor at the cut margin as CRM-positive (21).

Neoadjuvant concurrent chemoradiotherapy (CCRT) before esophagectomy has been shown to improve R0 resection local control and survival compared to surgery alone (22) and is accepted as a standard of care for patients with locally advanced disease. However, the role and definition of CRM positivity after CCRT and esophagectomy remain unclear in the literature.

The purpose of the present study was to investigate the significance of CRM status in patients with EC undergoing esophagectomy after neoadjuvant CCRT and to examine the prognostic impact of CRM status according to the RCP and CAP criteria for overall and disease-free survival.

Methods

Patient selection and data acquisition

This study enrolled 299 patients diagnosed with EC who underwent esophagectomy after neoadjuvant CCRT at our institute between January 2006 and March 2016. The treatment plan was decided for each patient after discussion during a multidisciplinary meeting attended by the surgeon, oncologist, radiologist, physician, and nurse, according to the results of clinical staging.

Preoperative staging and routine evaluation for each patient included a computed tomography (CT) scan of the brain, neck, chest, and abdomen; upper gastrointestinogram; positron emission technology (PET) scan with CT; bronchoscopic examination; and endoscopic ultrasound (EUS). Tumor staging and grading were performed according to the 8th edition of the TNM classification of the AJCC (23).

All patients enrolled in the present study were followed up until death or five years after the initial treatment. Patient information was updated at six-monthly intervals in the first and second years after surgery and annually thereafter. Chest radiography, thoracoabdominal CT, and endoscopy were performed once or twice a year. If recurrence was suspected, the patients underwent PET/CT and endoscopic examination with biopsy.

The CRM status was analyzed separately according to criteria of the RCP and CAP from the pathological examination 1) RCP as a tumor at or within 1 mm of the cut margin (20), or 2) CAP as the presence of a tumor at the cut margin as CRM positive (21).

Operative procedure

The procedures used for performing esophagectomy were identical to those described in our previous study (24). Patients underwent open or minimally invasive McKeown (cervical) or Ivor Lewis (intrathoracic) esophagogastrostomy depending on the location and staging of the tumor. Three-field lymph node dissections were performed, including the bilateral supraclavicular, deep cervical, recurrent laryngeal area; tracheal bronchial region; and upper, middle, and lower paraesophageal regions. Laparoscopic or open gastric mobilization and gastric tube formation, along with lymph node dissection in the hiatus, lesser curvature, left gastric artery, and celiac trifurcation, were performed. Feeding jejunostomy was performed unless the patient had already undergone the procedure prior to CCRT.

Definitions and follow-up

Overall survival (OS) was computed as the period from the date of surgery to either the date of death or the last follow-up. Progression-free survival (PFS) was defined as the time from the date of surgery to the date of local recurrence or distant tumor relapse. The Royal College of Pathologists (RCP) defines a positive CRM as a tumor at or within 1 mm of the cut margin (20), whereas the College of American Pathologists (CAP) considers only the presence of a tumor at the cut margin as CRM-positive. Adjuvant therapy will be given if the lymph nodes were shown to have residual cancers. Post-op CCRT was the most common adjuvant therapy, which was added in the following multivariate analysis.

Statistical analysis

Progression-free and overall survival analyses were performed using the Kaplan–Meier method. Statistical significance was assessed using the log-rank test. Hazard ratios (HRs) and confidence intervals (CIs) were obtained at 95% significance. The independent variables analyzed included age, sex, use of neoadjuvant therapy, and tumor characteristics (histology, location, length, diameter, and T stage).

The x2 test was used to assess the statistical differences between CRM involvement and other categorical clinicopathological characteristics.

The Cox regression hazard model was used for multivariate analysis to assess the independent influence of CRM status and other covariates on tumor recurrence and overall survival. Results are presented as HRs with 95% CIs. Statistical significance was set at a $P < 0.05$ in 2-tailed tests.

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Results

A total of 299 patients with EC were enrolled in the current study. There were 102 (34.1%) and 40 (13.3%) patients with a positive CRM according to the RCP and CAP criteria, respectively. Patient and disease characteristics are summarized in Table 1.

The survival impact of each clinical and pathological variable in the univariate analysis is shown in Table 2. Among patients with a

TABLE 1 The summarized patient characteristics according to RCP and CAP criteria.

Characteristic	Total N=299	RCP			CAP		
		Negative N=197	Positive N=102	P-value	Negative N=259	Positive N=40	P-value
Age (year)				0.775			0.120
<50	48 (16.1)	32 (16.2)	16 (15.7)		45 (17.4)	3 (7.5)	
50-65	182 (60.9)	122 (61.9)	60 (58.8)		152 (58.7)	30 (75.0)	
>65	69 (23.1)	43 (21.8)	26 (25.5)		62 (23.9)	7 (17.5)	
Gender				0.078			**0.054**
Female	23 (7.7)	19 (9.6)	4 (3.9)		23 (8.9)	0	
Male	276 (92.3)	178 (90.4)	98 (96.1)		236 (91.1)	40 (100)	
pT stage				**<0.001**			**<0.001**
pT0	93 (31.1)	93 (47.2)	0		93 (35.9)	0	
pT1	32 (10.7)	31 (15.7)	1 (1.0)		31 (12.0)	1 (2.5)	
pT2	52 (17.4)	41 (20.8)	11 (10.8)		50 (19.3)	2 (5.0)	
pT3	108 (36.1)	28 (14.2)	80 (78.4)		80 (30.9)	28 (70.0)	
pT4	14 (4.7)	4 (2.0)	10 (9.8)		5 (1.9)	9 (22.5)	
pN stage				**<0.001**			**0.003**
pN0	190 (63.5)	146 (74.1)	44 (43.1)		173 (66.8)	17 (42.5)	
pN1	69 (23.1)	39 (19.8)	30 (29.4)		58 (22.4)	11 (27.5)	
pN2	30 (10.0)	9 (4.6)	21 (20.6)		22 (8.5)	8 (20.0)	
pN3	10 (3.3)	3 (1.5)	7 (6.9)		6 (2.3)	4 (10.0)	
CCRT				**<0.001**			**<0.001**
Pre	217 (72.6)	165 (83.8)	52 (51.0)		198 (76.4)	19 (47.5)	
Pre+Post	82 (27.4)	32 (16.2)	50 (49.0)		61 (23.6)	21 (52.5)	
COPD				0.414			0.581
No	293 (98.0)	194 (98.5)	99 (97.1)		254 (98.1)	39 (97.5)	
Yes	6 (2.0)	3 (1.5)	3 (2.9)		5 (1.9)	1 (2.5)	
Smoking				0.253			0.628
No	45 (15.1)	33 (16.8)	12 (11.8)		40 (15.4)	5 (12.5)	
Yes	254 (84.9)	164 (83.2)	90 (88.2)		219 (84.6)	35 (87.5)	
Complication				**0.026**			0.809
No	257 (86.0)	163 (82.7)	94 (92.2)		223 (86.1)	34 (85.0)	
Yes	42 (14.0)	34 (17.3)	8 (7.8)		36 (13.9)	6 (15.0)	
RT dose*		4174.70 ± 343.37	4195.18 ± 500.71	0.972	4180.18 ± 349.50	4190.63 ± 663.50	0.684
No of dissected lymphnodes*		41.96 ± 20.23	39.81 ± 21.21	0.339	41.72 ± 20.29	38.00 ± 22.27	0.131

*Mann Whitney Test.
Bold numbers represent that they are statistically significant.
CAP, College of American Pathologists; RCP, Royal College of Pathologists; CMR, Circumferential Radial Margin; CCRT, concurrent chemoradiation; Pre OP, preoperative; Pre + Post OP, preoperatively and postoperatively.

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TABLE 2 The survival impact of each clinical and pathological variable in the univariate analysis.

Characteristic	Total N=299	Overall survival HR (95% CI)	P-value	Progression-free survival HR (95% CI)	P-value
Age (years)					
<50	48	1		1	
50-65	182	0.89(0.56-1.41)	0.607	0.99(0.64-1.54)	0.965
>65	69	1.06(0.62-1.80)	0.833	1.07(0.65-1.77)	0.797
Sex					
Female	23	1		1	
Male	276	1.58(0.74-3.39)	0.237	1.66(0.82-3.38)	0.163
pT stage					
pT0	93	1		1	
pT1	32	1.73(0.90-3.32)	0.098	1.81(0.99-3.31)	0.053
pT2	52	1.95(1.11-3.45)	**0.021**	2.05(1.23-3.44)	**0.006**
pT3	108	3.73(2.32-6.00)	**<0.001**	3.54(2.29-5.48)	**<0.001**
pT4	14	5.90(1.70-12.90)	**<0.001**	6.09(2.92-12.72)	**<0.001**
pN stage					
pN0	190	1		1	
pN1	69	2.13(1.45-3.14)	**<0.001**	2.29(1.59-3.30)	**<0.001**
pN2	30	3.49(2.17-5.62)	**<0.001**	2.98(1.88-4.71)	**<0.001**
pN3	10	3.05(1.40-6.67)	**0.005**	4.35(2.17-8.71)	**<0.001**
CCRT					
Pre	217	1		1	
Pre+Post	82	1.86(1.33-2.62)	**<0.001**	2.17(1.58-2.99)	**<0.001**
COPD					
No	293	1		1	
Yes	6	2.50(1.10-5.70)	**0.029**	2.11(0.93-4.80)	**0.074**
Smoking					
No	45	1		1	
Yes	254	1.32(0.80-2.16)	0.278	1.21(0.77-1.92)	0.412
Complication					
No	257	1		1	
Yes	42	0.94(0.57-1.54)	0.794	0.75(0.46-1.23)	0.256
RCP-defined CRM status					
Negative	197	1		1	
Positive	102	2.93(2.90-4.10)	**<0.001**	2.73(1.99-3.75)	**<0.001**
CAP-defined CRM status					
Negative	259	1		1	
Positive	40	4.45(2.90-6.82)	**<0.001**	2.89(2.57-5.88)	**<0.001**

Bold numbers represent that they are statistically significant.
CAP, College of American Pathologists; RCP, Royal College of Pathologists; CMR, Circumferential Radial Margin; CCRT, concurrent chemoradiation; Pre OP, preoperative; Pre + Post OP: preoperatively and postoperatively; HR, hazard ratio.

positive CRM as defined by the RCP and CAP criteria, significantly more patients had an advanced T and N staging status and underwent adjuvant chemoradiation than among those with a negative CRM (P < 0.05). The presence of T3 disease and lymph node metastasis increased the risk of mortality and disease progression (P = 0.001 for OS and T3 status, and P < 0.005 for other variables both in OS and PFS).

The risk of mortality and disease progression was higher in patients with CAP-defined CRM positivity, with HRs of 4.45 (2.90-6.82; P = 0.001) and 2.89 (2.57-5.88; P = 0.001) for OS and PFS, respectively. The survival disadvantage of RCP-defined CRM positivity was also significant, with HRs of 2.93 (2.90-4.10; P = 0.001) and 2.73 (1.99-3.75; P = 0.001) for OS and PFS, respectively. Table 3 shows the multivariate analysis for patient survival.

In addition to T and N staging, the presence of a CAP-defined positive CRM strongly disadvantaged survival, with HRs of 2.82 (1.70-4.66; P < 0.001) and 2.36 (1.44-3.87; P = 0.001) for OS and PFS, respectively. When the CRM was defined by the RCP criteria, the difference became insignificant with HRs of 1.62 (0.95-2.78; P = 0.078) and 1.46 (0.89-2.40; P = 0.135) for OS and PFS, respectively (Supplementary Table 1). Figure 1 shows the survival curves according to CRM status based on the CAP criteria, with CRM positivity correlating with significantly lower OS and PFS (adjusted P < 0.05).

When we further classified the patients into three groups with circumferential margin uninvolvement, less than 1 mm, and involvement the significant survival difference persisted only between the patients with and without CRM involvement, although the survival curve of patients with a clear CRM of less than 1 mm was between the above-mentioned two groups of patients. Table 4 shows the results of the multivariate analysis, which includes the CRM status classified as CRM negativity, a clear

TABLE 3 Multivariate analysis for patient survival according to the clinical and pathological variables including CRM CAP criteria.

Characteristic	Total N=299	Overall survival HR (95% CI)	P-value	Progression-free survival HR (95% CI)	P-value
Age (years)					
<50	48	1		1	
50-65	182	0.88(0.54-1.44)	0.617	1.06(0.66-1.68)	0.819
>65	69	0.98(0.55-1.75)	0.956	1.29(0.74-2.24)	0.374
Sex					
Female	23	1		1	
Male	276	1.33(0.61-2.91)	0.470	1.41(0.68-2.92)	0.360
pT stage					
pT0	93	1		1	
pT1	32	1.27(0.64-2.52)	0.504	1.31(0.69-2.47)	0.410
pT2	52	1.68(0.93-3.04)	0.088	1.60(0.93-2.47)	0.093
pT3	108	2.26(1.32-3.88)	**0.003**	2.13(1.30-3.51)	**0.003**
pT4	14	2.38(0.95-5.95)	0.064	2.16(0.90-5.18)	0.086
pN stage					
pN0	190	1		1	
pN1	69	1.86(1.19-2.89)	**0.006**	1.97(1.29-3.02)	**0.002**
pN2	30	2.55(1.49-4.36)	**0.001**	1.86(1.11-3.13)	**0.019**
pN3	10	1.89(0.80-4.47)	0.149	2.10(0.95-4.65)	0.068
CCRT					
Pre	217	1		1	
Pre+Post	82	0.88(0.59-1.32)	0.541	1.12(0.76-1.65)	0.565
CAP-defined CRM status					
Negative	197	1		1	
Positive	102	2.82(1.70-4.66)	**<0.001**	2.36(1.44-3.87)	**0.001**

Bold numbers represent that they are statistically significant.
CAP, College of American Pathologists; RCP, Royal College of Pathologists; CMR, Circumferential Radial Margin; CCRT, concurrent chemoradiation; Pre OP, preoperative; Pre + Post OP, preoperatively and postoperatively.

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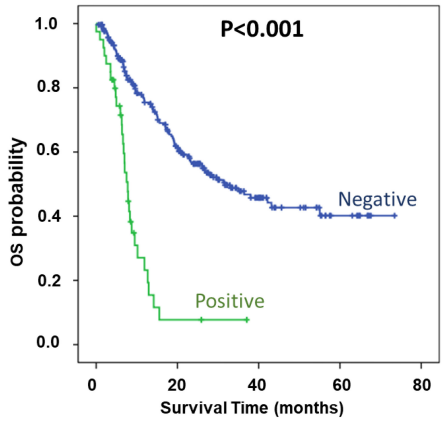
Overall Survival by CAP-defined CRM

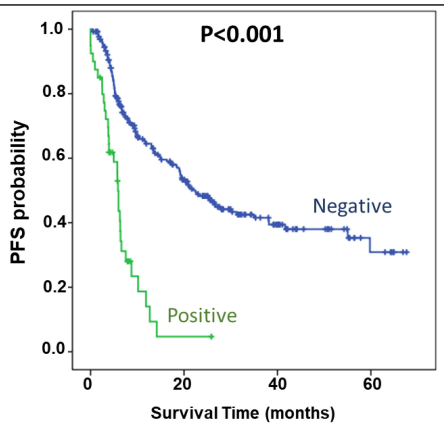
CAP	N	Events	Censored	Mean	Median	3-year OS(%)	Follow-up Duration Mean	Follow-up Duration Medain
Negative	259	110	149	40.48	31.63	47.8	31.61	29.50
Positive	40	30	10	9.85	7.77	7.7	22.80	25.87



No. at risk						
	Negative	259	117	39	10	0
	Positive	40	2	0	0	0

Progression-free Survival by CAP-defined CRM

CAP	N	Events	Censored	Mean	Median	3-year PFS(%)	Follow-up Duration Mean	Follow-up Duration Medain
Negative	259	129	130	33.27	21.97	41.5	31.09	28.40
Positive	40	31	9	6.81	5.87	N.R.	16.89	25.87



No. at risk					
	Negative	259	100	33	7
	Positive	40	1	0	0

FIGURE 1
The survival curves according to CRM status based on the CAP criteria which shows patients with CRM positivity correlating with significantly lower OS and PFS (P < 0.05). NR, Not Reached.

CRM of less than 1 mm, and CRM involvement. Patients with CRM involvement showed significantly lower chances of survival, with adjusted HRs of 3.35 (1.73-6.48; P < 0.001) and 2.63 (1.42-4.86, P = 0.002) for OS and PFS respectively. This correlation was not seen in patients with a clear CRM of less than 1 mm, with adjusted HRs of 1.62 (0.95-2.78; P = 0.078) and 1.46 (0.89-2.40; P = 0.135) for OS and PFS, respectively.

Discussion

Thus far, the literature has been contradictory on the significance of CRM status after esophagectomy, a fact largely attributed to the heterogeneity of the study populations (25). In addition, the different pathologic classification systems (RCP and CAP criteria) also make the prognostic effect of CRM difficult to evaluate (20, 21). Our study demonstrates that a CAP-defined positive CRM is a strong prognostic factor for patients with EC undergoing CCRT followed by radical esophagectomy and three-field lymph node dissection. However, although a similar trend was observed for RCP-defined CRM positivity in the multivariate analysis, it did not reach statistical significance.

The first study on CRM status in EC was published by Sagar et al. in 1993 (18), showing a possible association between a higher local recurrence rate and CRM involvement. In 2001, Dexter et al.

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TABLE 4 Multivariate analysis for patient survival according to the clinical and pathological variables including CRM with distance of margin.

Characteristic	Total N=299	Overall survival HR (95% CI)	p-value	Progression-free survival HR (95% CI)	p-value
Age(year)					
<50	48	1		1	
50-65	182	0.89(0.54-1.45)	0.640	1.06(0.66-1.69)	0.813
>65	69	0.98(0.55-1.75)	0.950	1.27(0.73-2.22)	0.393
Gender					
Female	23	1		1	
Male	276	1.36(0.62-2.96)	0.444	1.42(0.69-2.96)	0.344
pT stage					
pT0	93	1		1	
pT1	32	1.28(0.64-2.55)	0.484	1.32(0.70-2.48)	0.399
pT2	52	1.64(0.90-2.98)	0.108	1.57(0.91-2.72)	0.105
pT3	108	1.92(0.98-3.77)	**0.058**	1.93(1.05-3.55)	**0.035**
pT4	14	2.01(0.77-5.54)	0.149	1.99(0.79-5.01)	0.142
pN stage					
pN0	190	1		1	
pN1	69	1.85(1.18-2.88)	**0.007**	1.96(1.28-3.00)	**0.002**
pN2	30	2.52(1.47-4.32)	**0.001**	1.86(1.10-3.12)	**0.020**
pN3	10	1.86(0.79-4.42)	0.158	2.08(0.94-4.60)	0.072
CCRT					
Pre	217	1		1	
Pre+Post	82	0.86(0.57-1.30)	0.463	1.10(0.74-1.63)	0.648
CRM					
Uninvolved	197	1		1	
≦1mm	62	1.27(0.71-2.27)	0.418	1.17(0.69-1.99)	0.565
Involved	40	3.35(1.73-6.48)	**<0.001**	2.63(1.42-4.86)	**0.002**

CMR, Circumferential Radial Margin; CCRT, concurrent chemoradiation; Pre OP, preoperative; Pre +. Post OP, preoperatively and postoperatively.

(19) reported the first large-scale study on the impact of CRM involvement on the OS of 135 patients with EC. A meta-analysis by Wu et al. (26) found that the results of these studies were influenced by the heterogeneity of the patient populations, including varying T staging and the use of neoadjuvant therapy. A subgroup analysis by Khan et al. showed that CRM involvement yielded a statistically significant survival disadvantage only in T3 tumors (6). A later study by Griffiths et al. (27) revealed that the CRM status affects prognosis in patients with a low ratio of involved metastatic lymph nodes, whereas it is not a prognosticating factor in patients with a high metastatic lymph node ratio. The role of CRM status is also influenced by neoadjuvant therapy. As the above-mentioned study by Khan etal, the prognosticating significane of CRM for T3 disease was less evident once the patient received neoadjuvant chemoradiation (6). However, Shah et al. (28) reported that CRM involvement is an independent prognostic factor after deoadjuvant chemotherapy. Chao et al. (29) also reported an association between CRM status and local recurrence and survival rates in patients with ypT3 disease status after neoadjuvant CCRT.

Neoadjuvant CCRT has been adopted as a standard of care for improving the survival of patients with surgically treated locally advanced EC (22). The presence of a positive CRM after neoadjuvant therapy, especially after CCRT, represents poor response to neoadjuvant therapy and failure of complete surgical resection, leading to poor survival outcomes. However, CRM positivity, as defined by the RCP criteria, has previously been demonstrated to be 36 to 55% (18, 19, 28).

Three-field radical lymph node dissection with a mean of 41 dissected lymph nodes was performed. The association between CRM positivity and lymph node metastasis was significant in our patients. After adjusting for T and N staging status, CAP-defined CRM positivity remained a significant prognosticating factor, in contrast with RCP-defined CRM positivity. Furthermore, when patients were classified into three groups, that is, those with a clear CRM, those

with a clear CRM of less than 1 mm, and those with CRM involvement, a significant survival difference was observed only between patients with and without CRM involvement. These results were compatible with the findings of Brac et al., indicating that CAP-defined CRM positivity was a significant prognostic factor for OS and PFS in patients receiving upfront esophagectomy without neoadjuvant therapy (30). Similarly, Depypere et al. reported that CAP-defined CRM positivity can precisely predict the OS and PFS in patients with ypT3 tumors after neoadjuvant CCRT and esophagectomy (31). Histologically, most of these patients had adenocarcinoma (118/163, 72.4%), and two-field lymph node dissection was performed. In contrast, all our patients had squamous cell carcinoma and underwent three-field lymph node dissection during esophagectomy following neoadjuvant CCRT.

After adjusting for other significant prognostic factors, including T and N staging, CAP-defined CRM positivity remained prognostic for the entire patient population in our study. The prognostic value of CRM involvement is, therefore, greater after radical lymph node dissection and neoadjuvant chemoradiation (32). Adjuvant therapy might therefore be prescribed on the basis of CAP-defined CRM positivity rather than the RCP criteria. What is new in our work compared to the present literature is that, in addition to pathological T and N staging of the tumor, only CAP-defined CRM positivity was a significant prognostic factor with adjusted hazard ratios of 2.64 (1.56-4.46) and 2.25 (1.34-3.78) for overall and progression-free survival, respectively ($P < 0.001$).

Recently, a global prospective randomized trial, CheckMate 577, demonstrated that the use of nivolumab, an adjuvant immune-checkpoint inhibitor, improves the PFS of patients with EC after neoadjuvant chemoradiation and complete esophagectomy (R0 resection) (33). It must urgently be determined whether this strategy provides a survival advantage even in CRM-positive patients, where the prognosis is poor.

This was a large cohort study conducted by a single surgical team on patients with squamous cell carcinoma after neoadjuvant chemoradiation with long-term follow-up. However, this study is limited by potential selection bias, varying surgical treatment methods, and the neoadjuvant protocol used. Further studies are required to determine whether these findings can be applied to patients with other tumor cell types, two-field lymph node dissection, and after neoadjuvant chemotherapy or immunotherapy.

Conclusion

The CRM status, defined by CAP criteria, plays a vital role in OS and PFS in patients with EC after neoadjuvant CCRT and radical esophagectomy. Further adjuvant treatment may improve the currently poor survival outcomes of patients with CAP-defined CRM involvement after neoadjuvant CCRT and esophagectomy.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Research Ethics Committee review board of the Taiwan University Hospital (202202085RINA). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

AP wrote the first draft of the manuscript. K-CC, S-WK, M-WL, H-CL, P-MH, Y-HL, H-PW, M-LH, C-HC, C-HH, T-CH, F-MH and S-LL collected data, reviewed and edited. J-ML contributed to design of the study and edit. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1111998/full#supplementary-material

SUPPLEMENTARY TABLE 1
Multivariate analysis for patient survival according to the clinical and pathological variables including CRM RCP criteria.

SUPPLEMENTARY TABLE 2
Number of dissected lymph nodes.

SUPPLEMENTARY TABLE 3
Radiation therapy dose (cGY).

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