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Methods of optimizing surgical intervention in esophago-gastric cancer

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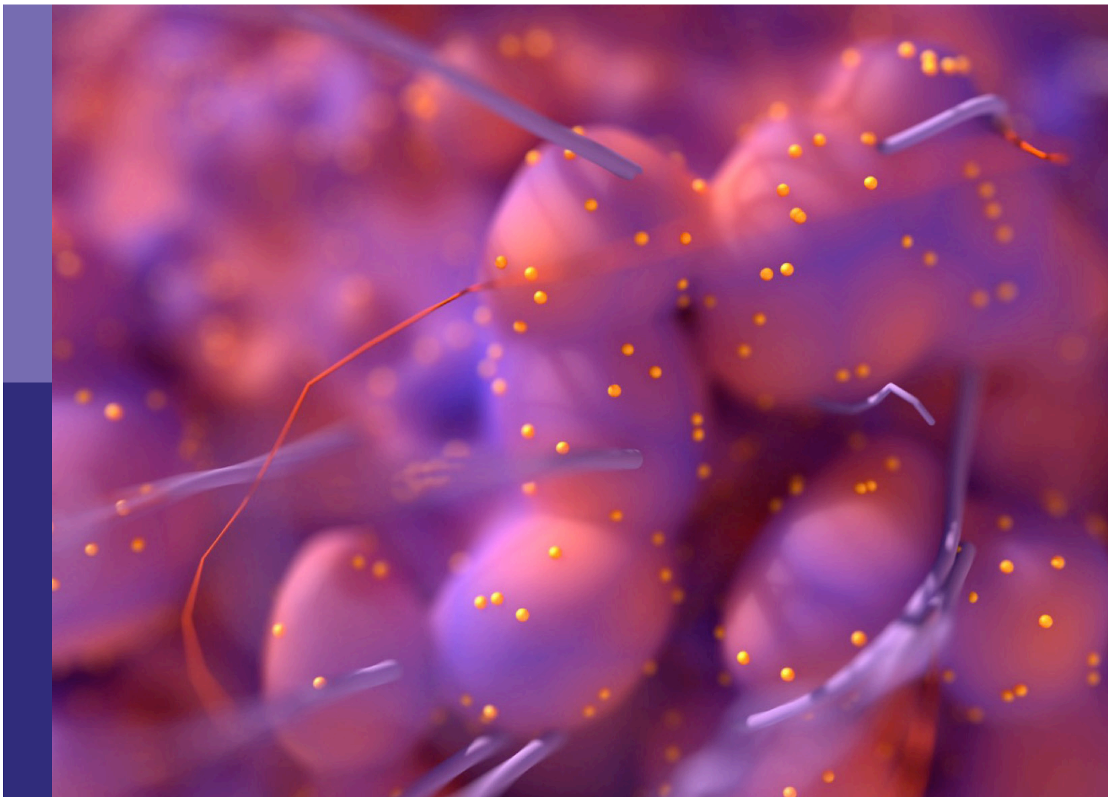

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Methods of optimizing surgical intervention in esophago-gastric cancer

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Optimal Extent of Transhiatal Gastrectomy and Lymphadenectomy for the Stomach-Predominant Adenocarcinoma of Esophagogastric Junction: Retrospective Single-Institution Study in China

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Background: The optimal extent of gastrectomy and lymphadenectomy for esophagogastric junction (EGJ) cancer is controversial. Our study aimed to compare the long-term survival of transhiatal proximal gastrectomy with extended periproximal lymphadenectomy (THPG with EPL) and transhiatal total gastrectomy with complete perigastric lymphadenectomy (THTG with CPL) for patients with the stomach-predominant EGJ cancer.

Methods: Between January 2004, and August 2015, 306 patients with Siewert II tumors were divided into the THTG group (n = 148) and the THPG group (n = 158). Their long-term survival was compared according to Nishi's classification. The Kaplan–Meier method and Cox proportional hazards models were used for survival analysis.

Results: There were no significant differences between the two groups in the distribution of age, gender, tumor size or Nishi's type ($P > 0.05$). However, a significant difference was observed in terms of pathological tumor stage ($P < 0.05$). The 5-year overall survival rates were 62.0% in the THPG group and 59.5% in the THTG group. The hazard ratio for death was 0.455 (95% CI, 0.337 to 0.613; log-rank $P < 0.001$). Type GE/E=G showed a worse prognosis compared with Type G ($P < 0.05$). Subgroup analysis stratified by Nishi's classification, Stage IA-IIB and IIIA, and tumor size ≤ 30 mm indicated significant survival advantages for the THPG group ($P < 0.05$). However, this analysis failed to show a survival benefit in Stage IIIB ($P > 0.05$).

Conclusions: Nishi's classification is an effective method to clarify the subdivision of Siewert II tumors with a diameter ≤ 40 mm above or below the EGJ. THPG with EPL is an optimal procedure for the patients with the stomach-predominant EGJ tumors ≤30 mm in diameter and in Stage IA-IIIA. For more advanced and larger EGJ tumors, further studies are required to confirm the necessity of THTG with CPL.

Keywords: esophagogastric junction, Siewert II adenocarcinoma, Siewert's classification, Nishi's classification, transhiatal gastrectomy, lymphadenectomy

INTRODUCTION

Epidemiological data show an increasing incidence of esophagogastric junction (EGJ) cancer (1–5). Because of the lack of a uniform definition and classification, EGJ cancer has sometimes been treated as distal esophageal cancer, sometimes as proximal gastric cancer, and sometimes as an entity separated from both esophageal and gastric cancer (6, 7). Obviously, EGJ cancer is distinguished from carcinomas of the lower esophagus or the upper stomach (6). Nevertheless, there are inconsistent prognoses among subtypes of EGJ cancer (8, 9). Siewert's classification (**Figure 1A**) (8, 9) defines three types of EGJ adenocarcinoma (Type I-III) with epicenters located within 5 cm proximal and distal to the anatomical cardia, regardless of tumor size. Type I tumors (lower-esophageal adenocarcinoma) are located 1–5 cm above the EGJ, irrespective of EGJ involvement. Type II tumors (cardia adenocarcinoma) are located between 1 cm above and 2 cm below the EGJ. Type III tumors (subcardial gastric adenocarcinoma) are located 2–5 cm below the EGJ with involvement of the EGJ and distal esophagus. In Japan, Nishi's classification (**Figure 1B**) (7, 8) was employed by the Japanese Classification of Esophageal Cancer and Gastric Cancer to define five types of EGJ cancer characterized by diameters of 40 mm or less and an epicenter within 2 cm proximal or distal from the EGJ, irrespective of histological type. The "E-G" terms of "E," "EG," "E=G," "GE" and "G" were used to describe the subtype according to the epicenter location at the rostral and caudal portions of the EGJ. In fact, EGJ cancer based on Nishi's classification corresponds to Siewert Type II-True cardia cancer according to the Japanese Classification of Esophageal Cancer and Gastric Cancer (**Figure 1**) (7).

Surgical resection of the primary tumor plus adequate lymphadenectomy remains a mainstay of therapy for resectable EGJ tumors. Special attention should also be paid to the surgical procedure. Based on previous studies of Siewert's classification (6, 9), there is consensus on the surgical treatment for Type I (transthoracic esophagectomy) and Type III (transhiatal extended gastrectomy). However, there is no consensus over the extent of gastrectomy and lymphadenectomy that could be a standard of care for Type II based on Siewert's and Nishi's classifications (8–14).

Considering the discrepancies among the classifications and survival data, our study compared the long-term survival of transhiatal proximal gastrectomy with extended periproximal lymphadenectomy (THPG with EPL) and transhiatal total gastrectomy with complete perigastric lymphadenectomy (THTG with CPL). As EGJ cancer corresponds to the description of Siewert II tumors, Nishi's definition "E-G" can be used to classify the subdivision of Siewert II adenocarcinoma into tumors located above or below the EGJ.

Abbreviations: EGJ, esophagogastric junction; THTG, transhiatal total gastrectomy; THPG, transhiatal proximal gastrectomy; EPL, extended periproximal lymphadenectomy; CPL, complete perigastric lymphadenectomy; HR, hazard ratio; CI, confidence interval; OS, overall survival; RCT, randomized clinical trial.

PATIENTS AND METHODS

Cohort

The study was approved by the Institutional Review Board of Nanfang Hospital, Southern Medical University. A total of 1918 patients with gastric or cardia adenocarcinoma underwent potentially curative gastrectomy at Nanfang Hospital, Southern Medical University, Guangzhou, China, between January 2004 and August 2015 according to the proposed standard for EGJ cancer from the Japanese gastric cancer classification (15) and treatment guideline (8, 16) (3rd and 4th Edition). The EGJ was defined as the border between the esophageal and gastric muscles. It was identified by one of the following clinical criteria: (a) the distal end of the longitudinal palisading small vessels in the lower esophagus at endoscopy, (b) the horizontal level of the angle of His shown by barium meal examination, (c) the proximal end of the longitudinal folds of the greater curve of the stomach shown at endoscopy or barium meal examination or (d) the level of the macroscopic caliber change of the resected esophagus and stomach. After the retrospective review of the institutional database including the medical records of these patients by two independent surgical oncologists, the following categories of patients were excluded from this study: 837 (43.6%) patients with distal gastric cancer and 733 (38.2%) patients with Siewert III, gastric upper and body cancer, transthoracic resection, squamous carcinoma, hospital deaths, surgical exploration only, chemotherapy alone, and endoscopic resection alone.

After the above exclusions, 348 patients with Siewert II tumors were enrolled. As the EGJ cancer corresponded to Siewert II cancer according to Nishi's definition (7, 8), Nishi's classification "E-G" was used to clarify the subdivision of Siewert II adenocarcinoma into tumors located above or below the EGJ (**Figure 1** and **Table 1**). Another 42 patients were excluded due to tumor size of >40 mm, R2 status or unavailability of follow-up data. Finally, 306 patients were eligible for this study. All tumors were classified as Type GE/E=G or Type G according to the epicenter location at the EGJ. The enrolled patients were divided into a THTG group and a THPG group based on the type of gastric resection with lymph node dissection (**Figure 2**). Histological type was defined as adenocarcinoma according to Siewert's classification (17, 18). All the patients provided written informed consent. All relevant data, including demographic information, location, "E-G" subtype, lymphadenectomy and gastrectomy were collected according to the tentative standard for junctional cancer of the Japanese Gastric Cancer (8) and Esophageal Cancer Society (7) and were in accordance with the ethics review board at the Southern Medical University and ethical standards of the Declaration of Helsinki.

Transhiatal Gastrectomy and Lymphadenectomy

The surgical procedures THPG with EPL and THTG with CPL were routinely undertaken according to the local surgeon's evaluation and preference. All the resection procedures of the parahiatal and lower mediastinal nodes included only the lymph nodes around the distal esophagus, which was accessed transhiatally. Since the two surgical procedures included different

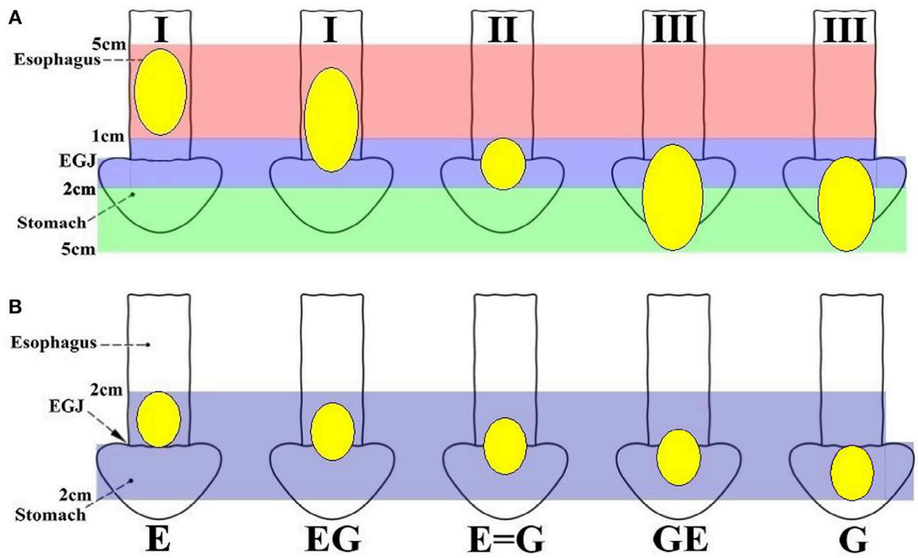

FIGURE 1 | Definition and classification of EGJ cancer according to the epicenter location. **(A)** Siewert's classification defines three types of EGJ cancers with epicenters situated between 5 cm proximal and distal to the EGJ, regardless of tumor size. Type I tumors (lower oesophageal adenocarcinoma) are located 1–5 cm above the EGJ, irrespective of EGJ involvement. Type II tumors (cardia adenocarcinoma) are located 1 cm above to 2 cm below the EGJ. Type III tumors (subcardial gastric adenocarcinoma) are located 2–5 cm below the EGJ with involvement of the EGJ and distal esophagus. Siewert's classification Types I, II and III should also be described for adenocarcinoma located in the lower esophagus or at the EGJ. **(B)** Nishi's classification defines five types of EGJ cancer with 40 mm or less in dimension that have an epicenter within 2 cm proximal or distal to the EGJ, irrespective of histological type. The terms "E, EG, E=G, GE, and G" were used to describe subtype depending on the epicenter location at the oral "E" and anal "G" portions of the EGJ. EGJ, Esophagogastric Junction.

TABLE 1 | EGJ cancer corresponds to Siewert II adenocarcinoma according to the epicenter location.

Definition	Epicenter	Oral E(Esophagus "+")			EGJ	Anal G(Stomach "-")		
	Zone	+5 cm	+2 cm	+1 cm	0 cm	−1 cm	−2 cm	−5 cm
Siewert (AC)	+5 ∼ −5 cm	1∼5 cm		1∼2 cm				2∼5 cm
Type I	E	Y	Y	N	N			
Type I	EG	Y	Y	Y	Y	N		
Type II	GE		N	Y	Y	Y	Y	N
Type III	G		N	Y	Y	Y	Y	Y
Nishi (AC/SC)	+2 ∼ −2 cm	Size ≤ 4 cm	2 cm	1 cm	EGJ	1 cm	2 cm	
Type E	E	N	Y	Y	Y	N		
Type EG	EG		N Y	Y	Y	Y N		
Type E=G	E=G		N	Y	Y	Y	N	
Type GE	GE			N Y	Y	Y	Y N	
Type G	G			N	Y	Y	Y	N

A quantitative comparison of epicenter location between Siewert's and Nishi's classifications. EGJ cancer corresponds to Siewert II adenocarcinoma according to the epicenter location. The calibrated and colored cells only illustrated the exact location of the epicenter in the EGJ region. In cancers located at the EGJ, the oral and anal portions of the EGJ are described as "E" and "G," respectively. The terms "E, EG, E=G, GE, and G" can be used depending on the epicenter location. EGJ, esophagogastric junction; AC, adenocarcinoma; SC, squamous carcinoma; Y, involvement; N, no involvement.

extents of lymphadenectomy and gastrectomy, the patients underwent precise assessment of tumor stages, with abdominal, and thoracic CT scans, endoscopy, upper gastrointestinal contrast, and laboratory tests before surgery. Patients who had positive lavage cytology and macroscopic peritoneal metastasis were considered incurable.

The THPG with EPL procedure consisted of proximal gastrectomy and extended proximal perigastric nodal dissection along the upper and middle portions of the stomach, esophageal hiatus, distal esophagus and suprapancreatic area, while the THTG with CPL procedure consisted of total gastrectomy and complete perigastric nodal dissection along the total perigastric portion, esophageal hiatus, distal esophagus, and suprapancreatic area.

Follow-Up

Long-term survival was the primary endpoint in this study. As of August 2015, the median follow-up duration was 69.2 months (95% CI 42.5–59.5). Thirty patients in the THTG group and 8 in the THPG group were lost to follow-up during this study. In

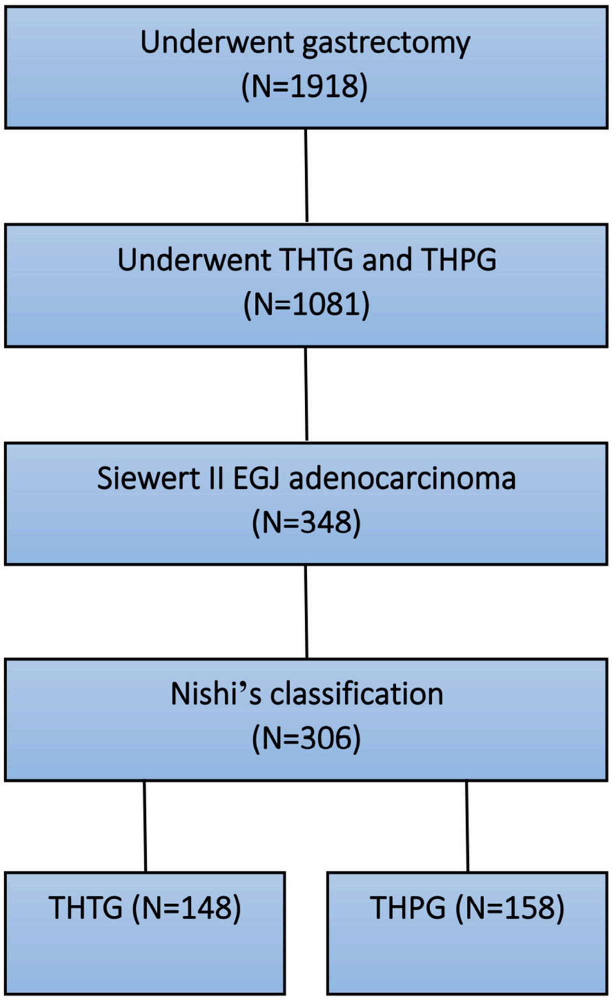

FIGURE 2 | Selection and grouping diagram for the patients with EGJ adenocarcinoma. EGJ, Esophagogastric Junction; THTG, Transhiatal Total Gastrectomy; THPG, Transhiatal Proximal Gastrectomy.

this study, the overall survival was measured from the date of surgery to the date of death from any cause or to lost follow-up. All in-hospital deaths and deaths within 1 month of surgery were excluded from the analysis. Patients who were still alive at the end of the study, lost to follow-up, or died of any cause were marked as censored data. Tumor staging was adapted from the 8th edition of AJCC/UICC system (AJCC, American Joint Committee on Cancer /UICC, Union for International Cancer Control).

Statistical Analysis

Data are presented as the means ± standard deviations for continuous variables and as number (%) for categorical variables. Continuous and categorical variables were compared using *t*-tests and chi-square tests, respectively. Survival curves were estimated using the Kaplan-Meier method and compared with the log rank test. Cox proportional hazards regression was used to identify the predictors associated with overall survival. Statistical significance was defined as a two-sided *P*-value <0.05. These statistical analyses were performed using IBM SPSS, version 25.0 (IBM, Armonk, NY, USA).

RESULTS

Comparison of Siewert's and Nishi's Classification

A comparison of Siewert's and Nishi's classifications is presented in **Table 1**. EGJ cancer corresponded to Siewert II tumor with a diameter of ≤40 mm. Nishi's classification is an effective method to clarify the subdivision of Siewert II tumors with a diameter of ≤40 mm into tumors located above or below the EGJ. The stomach- and esophagus-predominant cancers were designated as having their epicenters located at the rostral and caudal portions of the EGJ, respectively (**Figure 1** and **Table 1**).

Demographics and Pathologic Characteristics

A total of 306 patients with Siewert II adenocarcinoma of 40 mm or less in diameter were included in the retrospective single-institution study. The demographics and pathological characteristics of the two groups are provided in **Table 2.** Both THTG and THPG groups showed comparable demographics, including age, gender, body mass index, tumor size, pathological N0, E-G type, and extent of lymphadenectomy (all $P > 0.05$). Statistically significant differences were found in terms of pathological depth, positive nodal status, and TNM category ($P < 0.05$). The distribution of Eastern Cooperative Oncology Group performance scores (ECOG-PS) differed significantly between THTG and THPG ($P < 0.05$). THTG tumors were significantly more advanced in terms of Bormann and differentiation type ($P < 0.05$).

Long-Term Overall Survival

The median overall survival was 50.9 months (95% CI 42.5–59.5) for patients assigned to the THTG group and 81.1 months (95% CI 72.7–89.5) for those assigned to the THPG group. Thirty patients were lost to follow-up in the THTG group and 8 in the THPG group. The 5-year overall survival was 62.0% for all the patients in the THPG group and 59.5% in the THTG group ($P = 0.000$). The hazard ratio of death for THPG compared with THTG was 0.455 (95% CI, 0.337 to 0.613; log-rank $P < 0.001$; **Figure 3A**). Type GE tumors had a worse survival, the hazard ratio for death was 0.604 (95% CI, 0.450-0.811; log-rank $P = 0.001$; **Figure 3B**) compared with Type G tumors.

Subgroup analysis indicated significant survival advantages based on the subgroups of Stage IA-IIB ($P = 0.044$; **Figure 4A**) and IIIA ($P = 0.029$; **Figure 4B**), and tumors ≤ 30 mm ($P = 0.000$; **Figure 4D**) in favor of the THPG group compared with the THTG group but failed to show an advantage for Stage IIIB ($P = 0.211$; **Figure 4C**). In addition, more detailed subgroup analysis stratified by Type GE ($P = 0.002$) and Type G ($P = 0.000$), Well-differentiation ($P = 0.068$) and

TABLE 2 | Demographics and pathologic characteristics.

Characteristics	Total *N* = 306 (%)	THTG with CPL *n* = 148 (%)	THPG with EPL *n* = 158 (%)	*P*
Age(mean±SD)	57 ± 10.85	58 ± 10.10	56 ± 10.42	0.140
<65 years	222 (72.5%)	106 (34.6%)	116 (37.9%)	0.798
≥65 years	84 (27.5%)	42 (13.7%)	42 (13.7%)	
Gender				0.662
Male	248 (81.0%)	118 (38.6%)	130 (42.5%)	
Female	58 (19.0%)	30 (9.8%)	28 (9.2%)	
Body mass index	21.63 ± 3.13	21.54 ± 3.23	21.81 ± 2.95	0.591
Nishi's Classification				0.733
Type GE/E=G	148 (48.4%)	70 (22.9%)	78 (25.5%)	
Type G	158 (51.6%)	78 (25.5%)	80 (26.1%)	
ECOG-PS				0.000
PS 0	229 (74.8%)	92 (30.2%)	144 (47.1%)	
PS 1-2	64 (20.9%)	50 (16.3%)	14 (4.6%)	
Tumor size (mm)	25.44 ± 18.03	26.60 ± 18.12	24.61 ± 18.00	0.450
≤30mm	218 (71.4%)	90 (29.6%)	128 (41.8%)	0.874
>30mm	88 (28.6%)	38 (12.2%)	50 (16.3%)	
Bormann type				0.015
Type 1-2	106 (34.6%)	40 (13.1%)	66 (21.6%)	
Type 3-4	142 (46.4%)	80 (26.1%)	62 (20.3%)	
Type 5	58 (19.0%)	28 (9.2%)	30 (9.8%)	
Differentiation				0.000
G1-G2	132 (43.1%)	34 (11.1%)	98 (32.0%)	
G3-G4	166 (54.2%)	110 (35.9%)	56 (18.3%)	
Gx	8 (2.6%)	4 (1.3%)	4 (1.3%)	
pT category				0.000
pT1(M/SM)	8 (2.6%)	4 (1.3%)	4 (1.3%)	
pT2(MP)	22 (7.2%)	4 (1.3%)	18 (5.9%)	
pT3(SS)	10 (3.3%)	4 (1.3%)	6 (2.0%)	
pT4a(SE)	230 (75.2%)	100 (32.7%)	130 (42.5%)	
pT4b(SI)	36 (11.8%)	36 (11.8%)	0 (0%)	
pN category				0.000
pN0(0)	68 (22.2%)	28 (9.2%)	40 (13.1%)	
pN(+)	238 (77.8%)	120 (39.2%)	118 (38.6%)	
pN1(1-2)	62 (20.3%)	24 (7.8%)	38 (12.4%)	
pN2(3-6)	86 (28.1%)	34 (11.1%)	52 (17.0%)	
pN3a(7-15)	58 (19.0%)	34 (11.1%)	24 (7.8%)	
pN3b(≥16)	32 (10.5%)	28 (9.2%)	4 (1.3%)	
pTNM category				0.000
Stage-I	18 (5.9%)	6 (2.0%)	12 (3.3%)	
IA	6 (2.0%)	4 (1.3%)	2 (0.7%)	
IB	12 (3.9%)	2 (0.7%)	10 (3.3%)	
Stage-II	60 (19.6%)	22 (7.2%)	38 (5.6%)	
IIA	8 (2.6%)	2 (0.7%)	6 (2.0%)	
IIB	52 (17.0%)	20 (6.5%)	32 (10.5%)	
Stage-III	228 (74.5%)	120 (39.2%)	108 (39.7%)	
IIIA	130 (42.5%)	48 (15.7%)	82 (26.8%)	
IIIB	54 (17.6%)	32 (10.5%)	22 (7.2%)	
IIIC	44 (14.4%)	40 (13.1%)	4 (1.3%)	
Lymphadenectomy				0.183
D2/D2+	250 (81.7%)	116 (37.9%)	134 (43.8%)	
D1/D1+	56 (18.3%)	32 (10.5%)	24 (7.8%)	
Chemotherapy	176 (57.5%)	96 (31.4%)	80 (26.1%)	0.430
Neoadjuvant	40 (13.0%)	24 (7.8%)	16 (5.2%)	
Adjuvant	136 (44.4%)	72 (23.5%)	64 (20.9%)	

Tumor stage according to the American Joint Committee on Cancer, 8th Edition. ECOG-PS, Eastern Cooperative Oncology Performance Score; G1-G2, Well-differentiation; G3-G4, Poor-differentiation; Gx, Unknown; THTG, Transhiatal Total Gastrectomy; THPG, Transhiatal Proximal Gastrectomy; EPL, Extended Periproximal Lymphadenectomy; CPL, Complete Perigastric Lymphadenectomy.

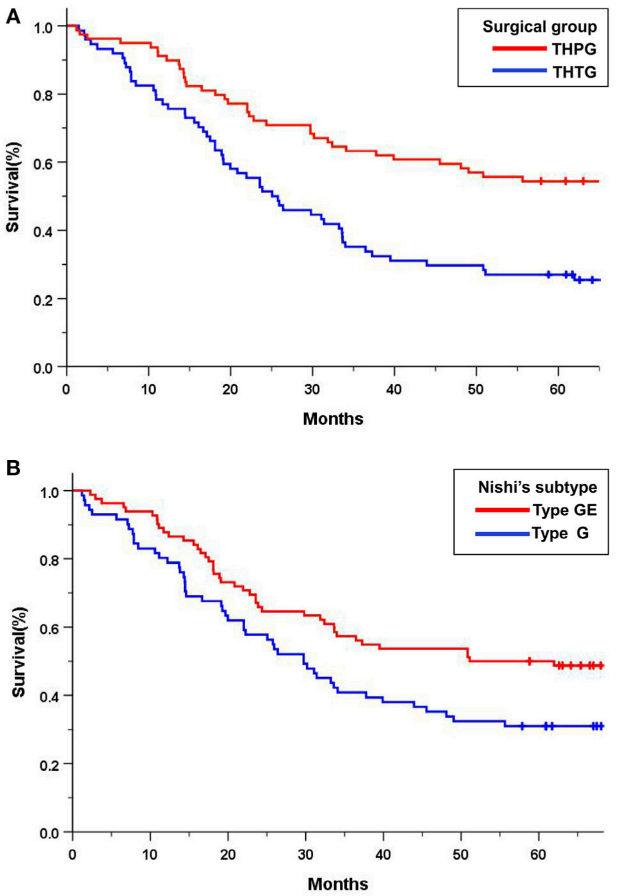

FIGURE 3 | Kaplan-Meier curves of overall survival in all the patients by treatment group and Nishi's classification. **(A)** THTG vs. THPG (HR = 0.455, 95%CI 0.337–0.613, log-rank $P = 0.000$); **(B)**. Type GE vs. Type G (HR = 0.604, 95%CI 0.450–0.811, log-rank $P = 0.001$). HR, Hazard Ratio; CI, Confidence Ratio; EGJ, Esophagogastric Junction; THTG, Transhiatal Total Gastrectomy; THPG, Transhiatal Proximal Gastrectomy; Type GE, and Type G, "E-G" subtype according to Nishi's classification.

Poor-differentiation ($P = 0.005$), ECOG-PS0 ($P = 0.003$), and D2/D2+ lymphadenectomy ($P = 0.000$) also yielded similar findings in favor of the THPG group (**Figures 5A–F**).

The potential predictors associated with OS in univariate analyses were analyzed by multivariate analysis using a proportional hazards model, to identify independent predictors associated with OS (**Table 3**). Ultimately, the following factors were determined to be the negative predictors: Type GE, THTG, D1/D1+, tumor size > 30 mm, Bormann type 3-4, pTNM category greater than Stage IIA. The strongest surgical predictors that were associated with OS were THPG and D2/D2+ lymphadenectomy.

DISCUSSION

The optimal extent of gastrectomy with lymphadenectomy in the EGJ cancer has been controversial. In this retrospective single institution study, we compared the long-term survival of transhiatal proximal gastrectomy with extended periproximal lymphadenectomy (THPG with EPL) and total gastrectomy with complete perigastric lymphadenectomy (THTG with CPL) for patients with the stomach-predominant EGJ cancer according to Nishi's classification. The findings demonstrated that THPG with EPL showed an advantage in survival compared with THTG with CPL for patients with EGJ tumors ≤30 mm in diameter and in Stage IA-IIIA. However, for more advanced and larger EGJ cancers (Stage IIIB), no survival benefit was demonstrated. As Type GE/E=G had a worse prognosis compared with Type G, Nishi's classification was an effective method to clarify the subdivision of Siewert II tumors with a diameter of ≤40 mm into tumors located above or below the EGJ line. We concluded that THPG with EPL should be considered as a specific modality to optimize the extent of gastrectomy and lymphadenectomy for individual patients with EGJ cancer ≤30 mm in dimension and in Stage IA-IIIA. However, for more advanced and larger EGJ tumors, further studies are required to confirm the necessity of THTG with CPL.

For EGJ tumors, tumor location, histological type, and tumor size are important for the selection of the surgical procedure in clinical practice. Therefore, an effective classification is particularly important. In most studies (6–8, 11) of EGJ cancer, the Siewert's classification is commonly used because it facilitates the selection of the surgical approach, especially for Type I and III tumors. However, there are considerable difficulties in the surgical approach, and the extent of gastrectomy and lymphatic dissection for Type II tumors (10), regardless of tumor size. This may be, in part, due to the imprecise definition of the gastric cardia, and also because it is difficult to identify its subtype when the tumor body is larger than 50 mm (7). Therefore, Nishi's definition was used, which determined that the diameter of the EGJ tumor was 40 mm or less and EGJ area was 2 cm above and below the cardia regardless of histological type. Considering the epicenter location at the rostral and caudal portion of the EGJ, EGJ cancer corresponds to Siewert II cancer according to the Japanese Classification of Esophageal Cancer and Gastric Cancer (**Figure 1**, **Table 1**). Based on the comparison between Siewert's and Nishi's classifications, we properly used the Nishi's classification to clarify the subdivision of Siewert II tumors into tumors located above or below the EGJ. Because 71.4% of Siewert II tumors had a diameter of ≤ 30 mm in this study, the finding showed a marked survival difference between Type GE/E=G and G. Nishi's classification is effective in clarifying the subclass of Siewert II tumors with a diameter of ≤40 mm into tumors located above or below the EGJ (**Figure 1**, **Table 1**).

Regarding differences between Siewert II and III tumors, comparisons of cases in Western and Eastern countries had inconsistent findings (1, 19, 20). In a prospective study from Germany by Siewert and colleagues, an almost equal distribution of Siewert I, II, and III EGJ cases was observed (21). In contrast, in Eastern countries, such as Japan and China, Type II-III tumors are more common (5, 16). In the current study, Type GE/E=G and G were almost equally common (48.4 vs. 51.6%, respectively).

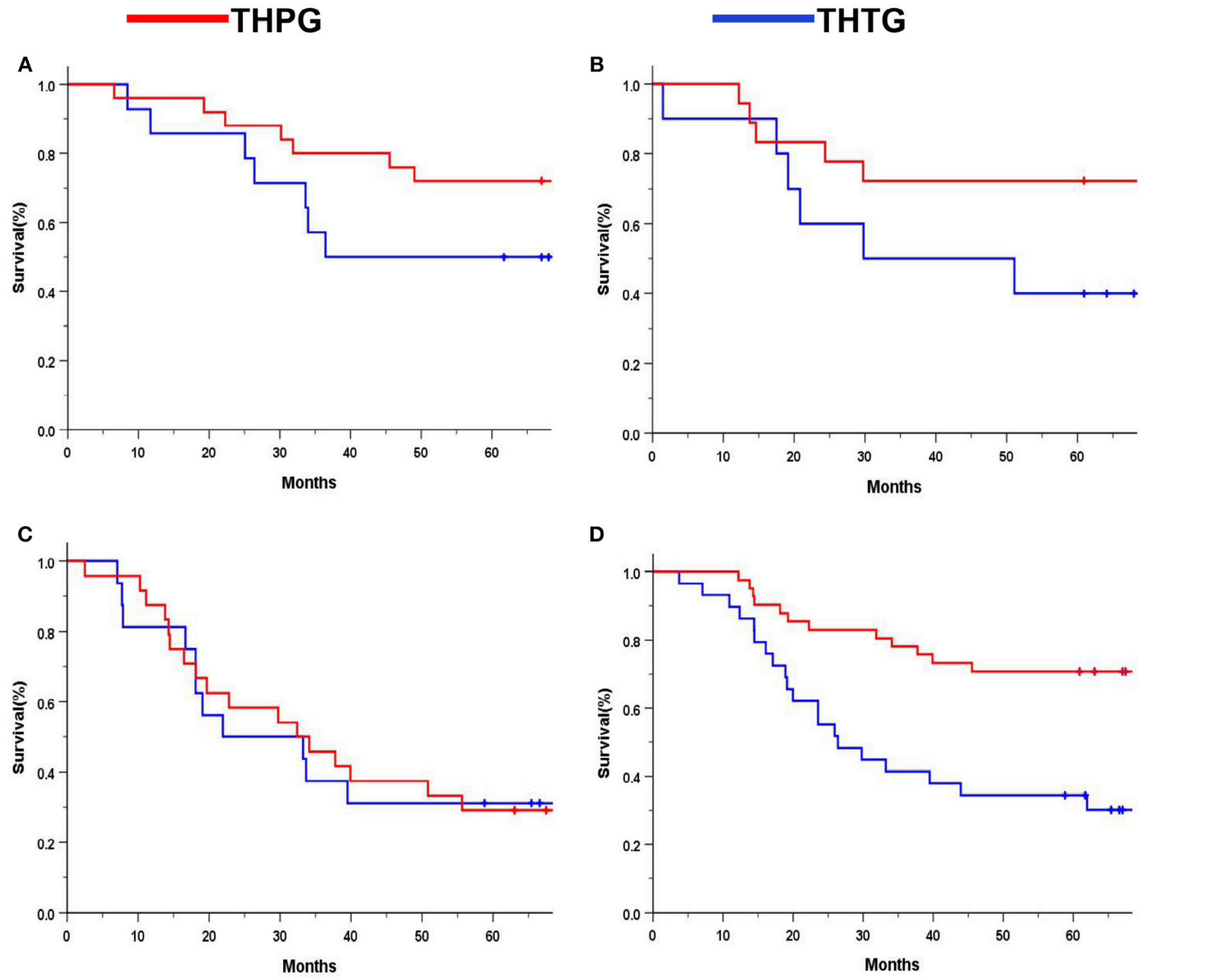

FIGURE 4 | Kaplan-Meier curves of subgroup analysis by treatment. **(A)** Stage IA-IIB (log-rank $P = 0.044$); **(B)** Stage IIIA (log-rank $P = 0.029$); **(C)** Stage IIIB (log-rank $P = 0.211$); **(D)** Tumor ≤30 mm (log-rank $P = 0.000$). EGJ, Esophagogastric Junction; THTG, Transhiatal total gastrectomy; THPG, Transhiatal proximal gastrectomy.

Multiple studies (21–24) have shown varied prognosis among patients with Type II and III cancers, and these observations were likely due to incomparable baseline characteristics (25). Some reports (13, 23) demonstrated that Siewert II cancer had a better survival than Siewert III cancer. In contrast, the other findings (20) showed no survival difference, and even a worse survival (26). However, in the present study, the univariate analyses confirmed that Type GE/E=G had a marked association with a worse prognosis compared with Type G. This finding was subsequently confirmed by the multivariate analysis. This finding actually suggested that esophageal invasion was a risk predictor for overall survival. It is important to highlight the limitation that the patients with tumors of >40 mm in diameter were excluded in the study according to Nishi's classification (27, 28), because these tumors undergoing THPG or even THTG are extremely likely to be incurable by surgery alone (29, 30).

The surgical approach for Siewert II and III tumors usually depends on the Siewert's classification (10). For patients with Siewert II disease, the RCT from the Netherlands (9) demonstrated that the transthoracic compared to the transhiatal approach was not associated with a survival benefit. The JCOG9502 RCT trial (11) also confirmed that the transthoracic approach should be abandoned due to increased morbidity and mortality, but no survival advantage was observed above the transhiatal approach for Siewert II and III cancers with esophageal invasion of ≤30 mm. Therefore, the extent of gastrectomy and lymphadenectomy seemed to be a controversial issue for Siewert II (6, 7, 12, 14, 18, 26–29).

In Asia, THTG with a more extensive lymphadenectomy is a fairly common procedure for EGJ tumors, regardless of tumor depth and size (31). However, unlike THTG, the THPG procedure removed only the periproximal nodes except for the lower perigastric lymph nodes. Therefore, we can conclude that the THTG based on a more extensive lymphadenectomy should provide a survival advantage over THPG. However, the current findings indicted no survival advantage in favor of THTG with CPL. The 5-year overall survival was 62.0% for the THPG group and 59.5% for the THTG group. As this was a retrospective

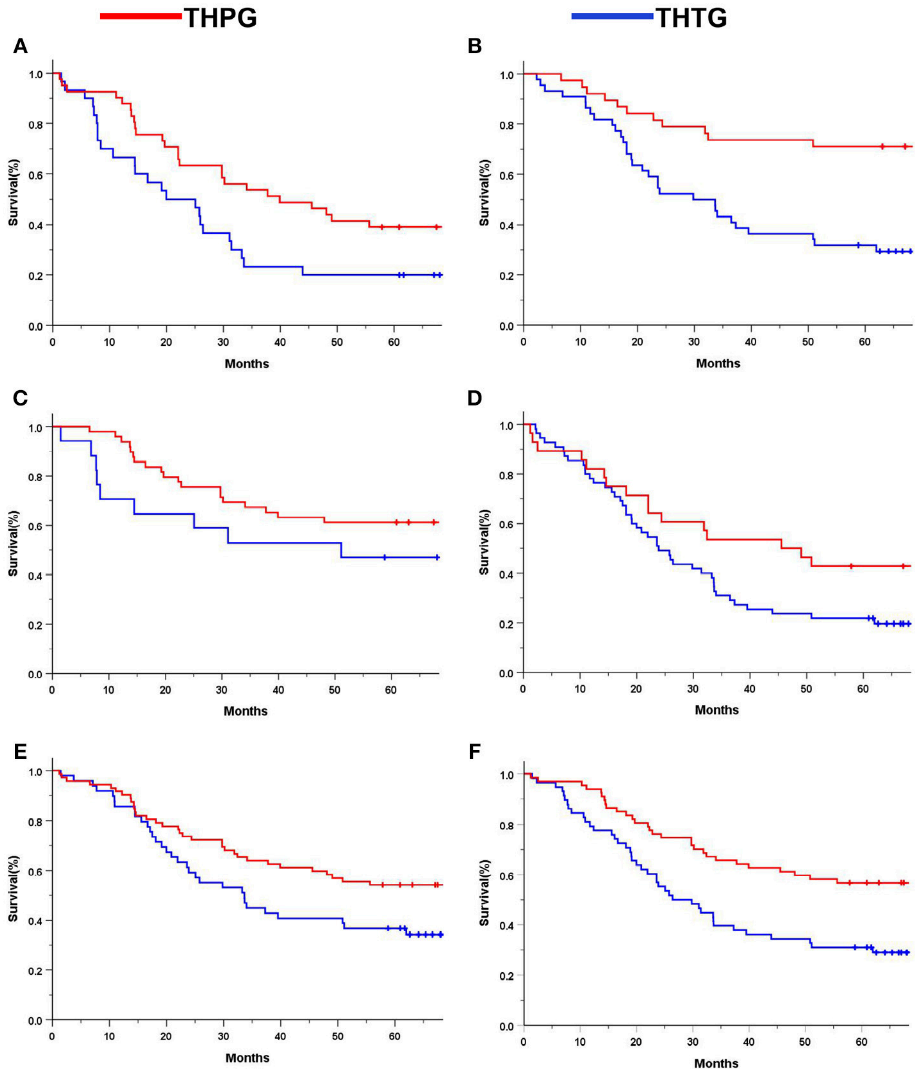

FIGURE 5 | Kaplan-Meier curves of subgroup analysis by treatment. **(A)**. Type GE (log-rank $P = 0.002$); **(B)** Type G (log-rank $P = 0.000$); **(C)** Well-differentiation (log-rank $P = 0.068$); **(D)** Poor-differentiation (log-rank $P = 0.005$); **(E)** ECOG-PS0 (log-rank $P = 0.003$); **(F)** D2/D2+ (log-rank $P = 0.000$). EGJ, Esophagogastric Junction; THTG, Transhiatal Total Gastrectomy; THPG, Transhiatal Proximal Gastrectomy; Type GE and Type G, "E-G" Subtype according to Nishi's classification; ECOG-PS, Eastern Cooperative Oncology Performance Score; D2/D2+, D2/D2+ lymphadenectomy according to the EGJ cancer with Type GE.

single-institution study with strict inclusion criteria, some characteristics was not well balanced between the groups. After adjustment of nine baseline variables (age, performance score, Nishi's type, tumor size, Borrmann type, differentiation, gastrectomy, lymphadenectomy, and pathological TN stage) with the use of Cox regression analysis, the finding was essentially unchanged. A more detailed subgroup analysis further confirmed the survival advantage of THPG for patients with EGJ tumors ≤30 mm in dimension and in Stage IA-IIIA ($P < 0.05$), which consisted of N0-2 categories with six positive nodes or less. This result may suggest that the THPG with EPL procedure not only removes the nodes likely to be violated in the Siewert II cancer with Stage IA-IIIA but also may reduce short- and long-term complications. The individualized subclass may not require THTG with CPL from the viewpoint of sufficient lymph node dissection (8, 12, 14, 28, 32–34).

Interestingly, no survival advantage to support either THPG or THTG in the subgroup of Stage IIIB consisted of pN3a-3b, while the IIIC subgroup consists of pN3b. N3a and N3b exceeding six positive nodes were found to be the most powerful risk predictor in the univariate analysis of this study. In light of the results, we can hypothesize that N3 represents an extensive nodal metastasis, not just an increase in the numbers of positive lymph nodes because positive nodes were harvested from each involved station. Therefore, the potential benefit of THTG depends not only on the number of positive nodes but also on the propensity for extensive nodal metastasis (29, 32, 35). This finding is consistent with recent studies (12, 14, 32, 36) showing that more than 90% of all the metastatic nodes

TABLE 3 | Cox proportional hazards models.

Predictors	Category	Univariate		Multivariable	
		HR (95%CI)	*P*	HR (95%CI)	*P*
Age(years)	<65	1		1	
	≥65	1.443 (1.056–1.972)	0.021	1.567 (0.929–2.644)	0.092
Performance score	PS 0	1		1	
	PS 1–2	2.328 (1.683–3.220)	<0.001	0.534 (0.273–1.045)	0.067
Nishi's definition	Type GE	1		1	
	Type G	0.604 (0.450–0.811)	0.001	0.508 (0.316–0.816)	0.005
Lymphadenectomy	D2/D2+	1		1	
	D1/D1+	1.893 (1.340–2.675)	<0.001	2.328 (1.357–3.993)	0.002
Gastrectomy	TH–TG	1		1	
	TH–PG	0.455 (0.337–0.613)	<0.001	0.468 (0.290–0.755)	0.002
Tumor size	≤30 mm	1		1	
	>30 mm	2.222 (1.504–3.284)	<0.001	2.028 (1.326–3.100)	0.001
Bormann type	Type 1–2	1		1	
	Type 3–4	1.809 (1.276–2.565)	0.001	2.186 (1.272–3.755)	0.005
	Type 5	1.971 (1.302–2.983)	0.001	4.216 (1.645–10.810)	0.003
Differentiation	G1–G2	1		1	
	G3–G4	2.184 (1.588–3.003)	<0.001	1.628 (0.961–2.759)	0.070
pTNM–category	I–II	1	<0.001	1	
	IIIA	2.062 (1.336–3.182)	0.001	1.946 (1.012–3.741)	0.046
	IIIB	2.995 (1.846–4.860)	<0.001	2.065 (1.032–4.132)	0.040
	IIIC	5.067 (3.096–8.294)	<0.001	2.115 (0.951–4.701)	0.066
pT–category	pT1–T2	1		–	–
	pT3	2.609 (0.905–7.524)	0.076		
	pT4a	2.920 (1.431–5.960)	0.003		
	pT4b	5.861 (2.681–12.813)	<0.001		
pN–category	pN0	1		–	–
	pN1	0.934 (0.516–1.691)	0.823		
	pN2	3.099 (1.935–4.962)	<0.001		
	pN3a	4.133 (2.526–6.760)	<0.001		
	pN3b	4.634 (2.652–8.098)	<0.001		
	pN1–3	2.634 (1.713–4.051)	<0.001		

Tumor stage according to the American Joint Committee on Cancer, 8th Edition. ECOG-PS, Eastern Cooperative Oncology Performance Score; G1-G2, Well-differentiation; G3-G4, Poor-differentiation; HR, Hazard Ratio; CI, Confidence Interval; THTG, Transhiatal Total Gastrectomy; THPG, Transhiatal Proximal Gastrectomy.

were distributed in the periproximal portion of the stomach, esophageal hiatus, distal esophagus, and suprapancreatic area. In contrast, the incidences of metastasis around the lower perigastric portion and greater curvature lymph nodes were <1%, even in patients with high dissection rates. Additionally, Siewert II/III cancer involving parapyloric nodes has a poor prognosis, similar to stage IV disease. This may explain why the THTG with CPL showed no survival advantage over THPG with EPL in the present study (28, 35). We can conclude that THTG with CPL along the lower perigastric nodes seems unlikely to offer significant survival benefits compared with THPG with EPL for the patients with Siewert II adenocarcinoma with a diameter of ≤40 mm because of rare nodal metastasis. The EPL along the proximal portion of the stomach, esophageal hiatus, distal esophagus, and suprapancreatic area may be the most essential step for the EGJ cancer, because D2/D2+ lymphadenectomy based on Type E-G of Nishi's definition was one of the strongest surgical predictors associated with OS for this study.

In this respective study, our results clearly showed that THTG with CPL provided no survival advantage over THPG with EPL for Siewert II adenocarcinomas with a diameter of ≤40 mm, at least, for EGJ tumors ≤30 mm in diameter and in Stage IA-IIIB. In addition, both Japanese and Dutch RCTs clearly confirmed that transthoracic lymphadenectomy provided no survival benefits over transhiatal lymphadenectomy for Siewert II adenocarcinoma. We did not aim to demonstrate that THTG with CPL was worse, since THTG with CPL may be a more thorough lymphadenectomy for more advanced and larger EGJ cancers accompanied by the distal perigastric lymph node metastasis (28). Accordingly, THPG with EPL should be considered as a specific modality to optimize the extent of gastrectomy and lymph node dissection for the individualized subgroup of EGJ cancer.

There are some limitations to this study. As it was a retrospective single-institution study with strict inclusion criteria, some characteristics were not well balanced between the groups. A selection bias concerning the surgical procedures might exist because limited surgical materials would be difficult to obtain. Despite this, the findings were sufficient to conclude that THPG with EPL was an optimal procedure for patients with the stomach-predominant EGJ tumors ≤30 mm in diameter and in Stage IA-IIIA.

CONCLUSIONS

Nishi's classification is effective to clarify the subdivision of Siewert II tumors with a diameter of 40 mm or less into tumors located above or below the EGJ. Transhiatal proximal gastrectomy is an optimal procedure for patients with EGJ tumors ≤30 mm in diameter and in Stage IA-IIIA. However, for more advanced and larger EGJ tumors, further studies are required to confirm the necessity of transhiatal total gastrectomy.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was carried out in accordance with the recommendations of the proposed standard for junctional cancer from the Japanese Gastric Cancer and Esophageal Cancer Society. This study was approved by the ethics review board of Nanfang Hospital, Southern Medical University. All study subjects provided written informed consent in accordance with the Declaration of Helsinki.

AVAILABILITY OF SUPPORTING DATA

The datasets generated and/or analyzed during the current study are not publicly available due to other ongoing studies but are available from the corresponding authors on reasonable request.

AUTHOR CONTRIBUTIONS

BZ, GL, and HL made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data. BZ, ZZ, DM, YL, JY, and YH contributed in drafting the manuscript or critically revising it for important intellectual content. All the authors approved the final manuscript submitted. Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. BZ should be considered as the first author. GL and HL contribute equally and should be considered as co-corresponding author.

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Esophageal Suspension Method for Hand-Sewn Esophagojejunostomy After Totally Laparoscopic Total Gastrectomy: A Simple, Safe, and Feasible Suturing Technique

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Background: Totally laparoscopic total gastrectomy (TLTG) not only is difficult to operate but also has high technical requirements and a long learning curve. Therefore, it has not been widely carried out yet, and esophagojejunostomy is one of its difficulties. Relevant studies have shown that intracorporeal hand-sewn esophagojejunostomy is safe, feasible and low-cost, but it is complicated and time-consuming and requires a high-suture technique. This study introduces a simple, safe and feasible hand-sewn technique.

Methods: The clinical data of 32 patients with the esophageal suspension method for hand-sewn esophagojejunostomy (suspension group) after TLTG were collected from February 2018 to June 2019. During the same period, 32 patients with traditional hand-sewn esophagojejunostomy (traditional group) after TLTG were used as the control group.

Results: The operative time, anastomosis time, exhaust time and hospitalization time of the suspension group were shorter than those of the traditional group. The intraoperative blood loss in the suspension group was less than that in the traditional group. There were no postoperative complications associated with the suspension group.

Conclusion: For those who have some experience in laparoscopic suture technique, the esophageal suspension method for hand-sewn esophagojejunostomy after TLTG is a simple, safe, and feasible suture technique.

Keywords: totally laparoscopic total gastrectomy, gastric cancer, esophageal suspension method, hand-sewn esophagojejunostomy, suture technique

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INTRODUCTION

Since 1994, when Kitano et al. (1) first reported laparoscopic assisted distal gastrectomy (LADG) for early gastric cancer, laparoscopic technology has continuously matured and improved. At present, laparoscopic distal gastrectomy (LDG) is a way to treat gastric cancer, and its safety and feasibility have been indicated (2–4). However, totally laparoscopic total gastrectomy (TLTG) is a difficult operation, has high technical requirements and has a long learning curve. Therefore, it has not been widely carried out yet, and esophagojejunostomy is its main difficulty (5, 6). Roux-en-Y anastomosis is the main anastomosis of digestive tract reconstruction after total gastrectomy (7, 8).

Currently, relevant literature (9–13) reports that esophagojejunostomy is mainly performed with circular and linear staplers. The former mainly includes the transorally inserted anvil (OrVil™), reverse puncture device (RPD), and purse-string suture method; the latter mainly includes functional end-to-end (FETE), overlap anastomosis, π-shaped esophagojejunostomy and semi-end-to-end anastomosis. Although the anastomosis technique has been continuously improved, there are still problems, such as difficulty in anvil implantation under the laparoscope, inaccurate esophageal cutting margins, and high price. In addition, related studies (14–17) have shown that intracorporeal hand-sewn esophagojejunostomy is safe, feasible and low-cost, but it is complicated and time-consuming and requires a high-suture technique. Therefore, it is particularly important to explore a simple, safe and feasible technique for hand-sewn esophagojejunostomy.

MATERIALS AND METHODS

Patients

The clinical data of 32 patients with the esophageal suspension method for hand-sewn esophagojejunostomy (suspension group) after TLTG were collected from February 2018 to June 2019. During the same period, 32 patients with traditional hand-sewn esophagojejunostomy (traditional group) after TLTG were used as the control group. There were 32 patients in the suspension group, including 22 males and 10 females. The average age was 63.34 ± 9.86 years, and the average BMI was 21.80 ± 2.55 kg/m^2. The tumor was located in the esophagogastric junction in 26 cases, including 10 cases of Siewert type II, 16 cases of Siewert type III, and in the middle of the stomach in six cases. The average follow-up time was 9.47 ± 2.83 months. There were 32 patients in the traditional group, including 24 males and eight females. The average age was 64.59 ± 10.90 years, and the average BMI was 22.42 ± 3.01 kg/m^2. The tumor was located in the esophagogastric junction in 23 cases, including five cases of Siewert type II, 18 cases of Siewert type III, and in the middle of the stomach in nine cases. The average follow-up time was 9.34 ± 4.62 months (**Table 1**).

Inclusion and Exclusion Criteria

The inclusion criteria of this study were as follows: 1. preoperative diagnosis was made by gastroscopy and pathology; 2. preoperative CT staging was $T_{1-2}N_{0-1}M_0$; 3. patients had no history of abdominal surgery; 4. patients did not have neoadjuvant radiotherapy or chemotherapy before surgery; 5. TLTG was performed by the same treatment group; 6. patients signed informed consent; and 7. it was approved by the ethics committee of our hospital. We excluded patients with severe heart, lung, kidney, and brain dysfunction, as well as coagulopathy and intolerance.

Operative Procedures

All patients underwent general anesthesia with tracheal intubation. A stomach tube and catheter were routinely inserted before operation. Patients were placed in the supine position with the two legs split. The operator stood on the left side of the patient, the first assistant stood on the right side of the patient, and the mirror holder stood between the patient's legs. The trocar was placed in a 5-hole method. After artificial pneumoperitoneum was established, a 10 mm trocar was placed under the umbilicus as the observation hole. The 5 mm trocars were placed in the left and right midline of the clavicle 2 cm above the umbilicus and 2 cm below the costal margin of the right anterior axillary line, respectively. The 12 mm trocar was placed 2 cm below the costal margin of the left anterior axillary line. The pneumoperitoneum pressure was maintained at 12–15 mmHg (1 mmHg = 0.133 kPa). Abdominal and pelvic conditions were routinely explored to rule out peritoneal implantation and distant metastasis. According to the requirements of radical gastrectomy, the perigastric vessels were isolated, and the corresponding lymph nodes were dissected with a harmonic scalpel. The duodenum and esophagus were cut with a linear cutting closure device, and the whole stomach specimen was taken through a semicircular incision around the umbilicus. The specimens were examined to ensure that the esophageal cutting edge was ∼2 cm, and the upper and lower cutting edges were confirmed to be negative by frozen sections and reconstruction was started.

Digestive Tract Reconstruction

The jejunum was disconnected with a linear cutting closure device at a distance of 10–15 cm from the ligament of Treitz. The proximal jejunum and jejunum at a distance of 30–40 cm from the anastomosis of the esophageal jejunum was anastomosed end-to-side through the specimen incision. A small incision ∼1.5–2 cm long was made at a distance of 3–5 cm from the distal jejunum to the stump and then put into the abdominal cavity. The pneumoperitoneum was established again. In the suspension group, the left and right sides of the proximal esophagus at a distance of 2 cm from the stump were suspended and fixed to the abdominal wall by the purse line or by the 3-0 Vichy line and purse line, respectively (**Figures 1**, **2**). A harmonic scalpel was used to dissect the proximal esophageal stump (**Figure 3**). The distal jejunum was lifted posteriorly through the transverse colon, and the 3-0 barbed line was used to suture the posterior wall of the esophagus and jejunum with continuous full-layer suture from left to right (**Figure 4**) and to suture the anterior wall of the esophagus and jejunum with continuous full-layer inverting suture from right to left (**Figure 5**). After the anastomotic suture was completed, the suspension suture was cut off (**Figure 6**). The stomach tube was placed in the distal jejunum and esophagojejunostomy was completed (**Figure 7**). In the traditional group, hand-sewn esophagojejunostomy was performed directly without esophageal suspension.

Observation Indicators

Operation indicators included operative time (from the insertion of the first trocar to the closure of the abdomen), anastomosis time (from the first suture to the end of anastomosis), and intraoperative blood loss. Postoperative recovery indicators included postoperative exhaust time and postoperative hospital stay. Postoperative complications included duodenal stump

TABLE 1 | Comparison of general characteristics and related indicators between the two groups of patients.

Factors	Suspension group (n = 32)	Traditional group (n = 32)	P-value
Sex (n)			0.581
Male	22	24	
Female	10	8	
Age (y)	63.34 ± 9.86	64.59 ± 10.90	0.632
BMI(kg/m^2)	21.80 ± 2.55	22.42 ± 3.01	0.378
Tumor location(n)			0.380
Esophagogastric junction	26	23	
Middle of stomach	6	9	
Operation Indicators			
Operation time (min)	185.81 ± 8.76	215.78 ± 8.08	< 0.0001
Anastomosis time (min)	26 (23.25, 27)	44 (41.25, 45)	< 0.0001
Intraoperative blood loss (ml)	98.28 ± 4.21	104.28 ± 5.51	< 0.0001
Postoperative Indicators			
Exhaust time (d)	3 (3, 3)	3 (3, 4)	0.016
Hospitalization time (d)	11 (10, 12)	11.5 (11, 12)	0.006
Postoperative Complications			
Anastomotic leakage [n (%)]	0 (0)	1 (3.13)	1.000
Follow-up time (mon)	9.47 ± 2.83	9.34 ± 4.62	0.897

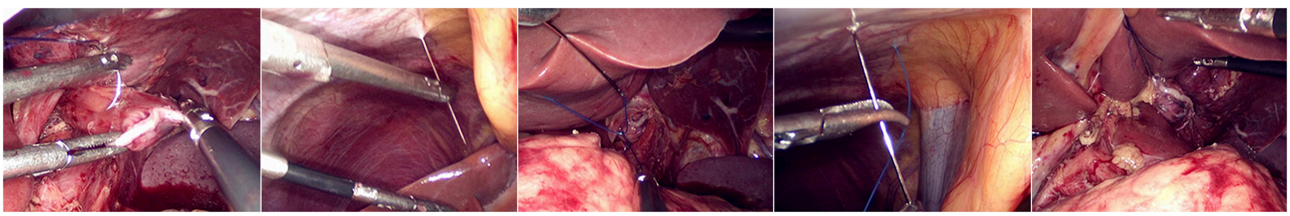

FIGURE 1 | Esophageal right side suspension and fixation.

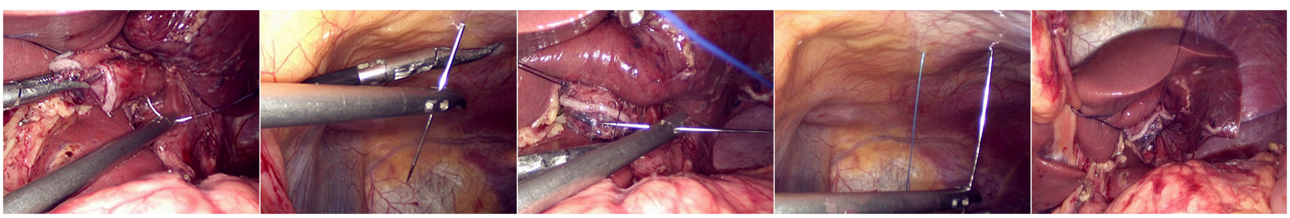

FIGURE 2 | Esophageal left side suspension and fixation.

leakage, anastomotic leakage, anastomotic bleeding, anastomotic stenosis, obstructive complications, and perioperative mortality.

Statistical Analysis

We used the single sample Kolmogorov-Smirnov test to test the normality of the data. If the quantitative data obeyed a normal distribution, it was described as the mean ± standard deviation; otherwise, it was described as the median and interquartile range. Quantitative data comparisons between the two groups were performed using the independent-samples t-test; otherwise, the Mann-Whitney U-test was used. Enumeration data comparisons between the two groups were performed using the chi-square test. A $P < 0.05$ was considered statistically significant. Data were analyzed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

There were no statistically significant differences in sex (P = 0.581), age (P = 0.632), BMI (P = 0.378), tumor location (P = 0.380), or follow-up time (P = 0.897) between the two groups; there were statistically significant differences in operation time (P

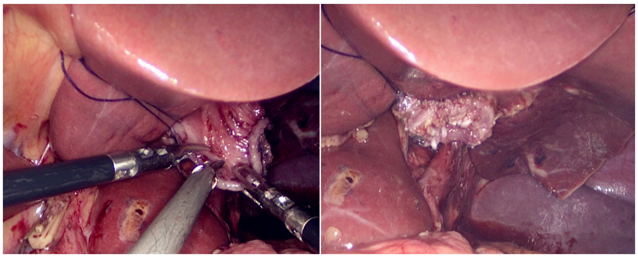

FIGURE 3 | Harmonic scalpel dissected the proximal esophageal stump.

< 0.0001), anastomosis time ($P < 0.0001$), intraoperative blood loss ($P < 0.0001$), exhaust time ($P = 0.016$), and hospitalization time ($P = 0.006$) between the two groups (**Table 1**). The results showed that the operative time, anastomosis time, exhaust time and hospitalization time of the suspension group were shorter than those of the traditional group, and the intraoperative blood loss in the suspension group was less than that in the traditional group. There were no postoperative complications associated with the suspension group. There was no statistically significant difference in postoperative complications between the two groups ($P = 1.000$). One case in the traditional group developed an anastomotic leakage and recovered after conservative treatment. There were no other postoperative complications associated with either group (**Table 1**).

DISCUSSION

In recent years, LDG has been widely accepted and carried out in clinical practice as a safe and feasible method for the treatment of gastric cancer. Compared with laparotomy, LDG has advantages such as fast recovery of gastrointestinal function, short hospital stay, mild pain, small incision and fewer complications (18, 19). Meanwhile, the incidence of the adenocarcinoma of esophagogastric junction (AEG) is on the rise worldwide (20, 21). According to the Japanese gastric cancer treatment guidelines (22), except for early cancer, the retained stomach can be larger than 1/2, proximal gastric resection is used, and the rest should be considered for total gastrectomy. However, TLTG not only is a difficult operation but also has high technical requirements and a long learning curve. Therefore, it has not been widely carried out yet, and esophagojejunostomy is one of its difficulties. Laparoscopic total gastrectomy is currently performed mainly by laparoscopically assisted surgery, which is used to complete the reconstruction of the digestive tract through assisted small incision. However, for patients with a thick abdominal wall, large anterior and posterior diameter, narrow subcostal angle and left liver hypertrophy, it is difficult to complete anastomosis. If forced to complete the reconstruction, it is necessary to extend the incision and strengthen the traction, which not only loses the advantage of being minimally invasive but also increases the incidence of pain and anastomotic ischemia in patients (9, 10, 23). Therefore, to solve this problem, the development of TLTG is particularly important. Relevant studies (24, 25) reported that total laparoscopic distal gastrectomy (TLDG) has certain advantages compared with LADG, such as fast recovery of gastrointestinal function, short hospital stay, mild pain, and small incision. Previous studies (26–28) have also shown that total laparoscopic gastrectomy (TLG) and laparoscopic intracorporeal anastomosis were safe and feasible. In addition, TLG in intracorporeal anastomosis had the advantages of high safety, less adhesion, rapid recovery, and small scars (29, 30).

At present, the related literature (9–13) reports that esophagojejunostomy is mainly performed with circular and linear staplers. In fact, a variety of techniques for esophagojejunostomy have emerged in recent years, but none of them was considered as the standard technique (31). Although the anastomosis technique has been continuously improved, there are still problems, such as difficulty in anvil implantation under the laparoscope, inaccurate esophageal cutting margins, higher incidence of total anastomotic complications and high price (9, 32). Studies (33, 34) reported that the purse-string suture method was a safe and reliable technique. However, the long operation time, high operation difficulty and high price limit its application (35, 36). However, intracorporeal hand-sewn esophagojejunostomy under visualization can not only ensure the tension at the anastomosis but also make the anastomosis more reliable. More importantly, this method does not require a long esophageal stump and can significantly improve the R0 resection rate. Because the anastomosis was performed after the specimen was removed, a frozen section could be used to confirm the negative cutting edge for anastomosis. In addition, the hand-sewn esophagojejunostomy can reduce the use of the device, thereby reducing the cost of surgery. Related studies (14–17) have shown that intracorporeal hand-sewn esophagojejunostomy is safe, feasible and low-cost, but it is complicated and time-consuming and requires a high-suture technique. Facy et al. (37) believed that the incidence of anastomotic leakage, anastomotic bleeding, and anastomotic stenosis was low after laparoscopic hand-sewn esophagojejunostomy with a barbed line, so it was safe. In addition, the safety of barbed line sutures has also been demonstrated in large-scale trials (38, 39). This study used a 3-0 barbed line for esophagojejunostomy. Only one case developed an anastomotic leakage and recovered after conservative treatment. The esophageal suspension method for hand-sewn esophagojejunostomy can make suturing simple and easy. Relevant studies (40, 41) showed that increased operative time could significantly lengthen hospital stay for patients who underwent a primary laparoscopic Roux-en-Y gastric bypass. Meanwhile, Carter et al. (42) indicated that prolonged operating time can predict longer hospitalization after laparoscopic gastric bypass operation. In addition, short exhaust time makes patients eat early to accelerate the recovery of patients after surgery, thus shortening the hospital length of stay. This study showed that the operative time, anastomosis time, exhaust time and hospitalization time of the suspension group were shorter than those of the traditional group, and the intraoperative blood loss in the suspension group was less than that in the traditional group. There were no postoperative complications in the suspension group. Our experience was that, for Siewert type II AEJ, 3-0 Vichy line and purse line were used for esophageal suspension and fixation, while Siewert type

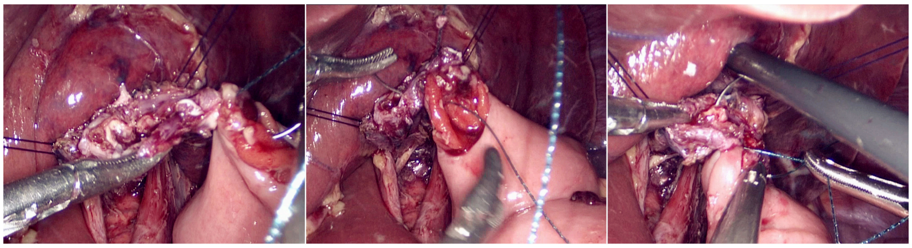

FIGURE 4 | Continuous full-layer suture of the posterior wall of the esophagus and jejunum from left to right using 3-0 barbed line.

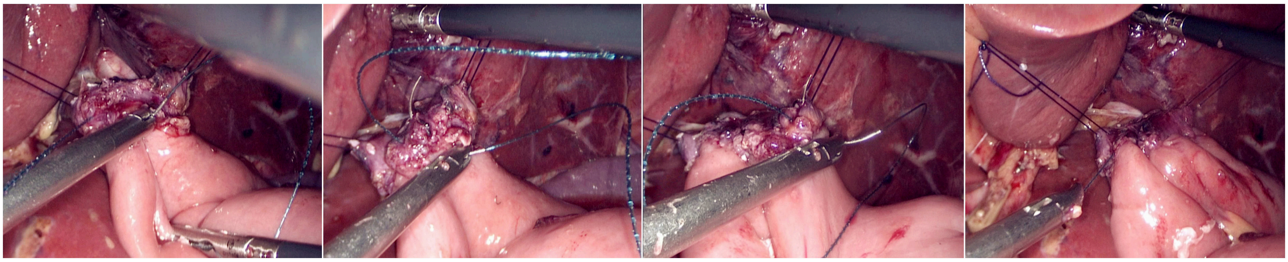

FIGURE 5 | Continuous full-layer inverting suture of the anterior wall of the esophagus and jejunum from right to left using 3-0 barbed line.

III AEJ can be directly suspended and fixed by purse line. We believed that compared with the traditional hand-sewn method, the esophageal suspension method has the following advantages: 1. esophageal suspension and fixation on both sides can not only provide a stable suture field but also provide better exposure in the surgical field and reduce the secondary injury of tissues caused by repeated turnover of the esophagus and jejunum during operation; 2. the esophageal suspension method has lower requirements on the free length of the esophageal stump, which reduces the incidence of tissue bleeding; 3. the esophageal suspension method for hand-sewn esophagojejunostomy has relatively lower requirements for laparoscopic suture technique, which makes the learning curve relatively short and shortens the operation time. In addition, it should be noted that when the esophageal was suspended and fixed, the tearing of the esophageal wall caused by too shallow of an esophageal suture and excessive fixation force should be avoided. This study has some limitations. This study was a single-center, small-sample study, and therefore, a multicenter, large-scale prospective randomized controlled trial is necessary.

In conclusion, for those who have some experience in laparoscopic suture technique, the esophageal suspension method for hand-sewn esophagojejunostomy after TLTG is a simple, safe and feasible suture technique, which has an important reference value for the wide development of TLTG in the future.

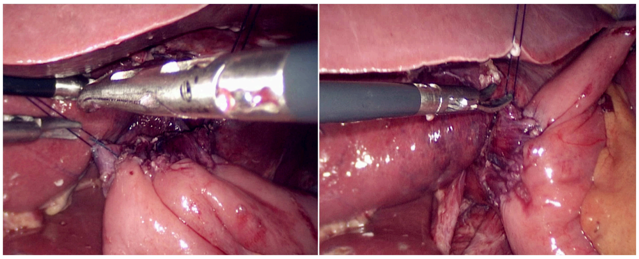

FIGURE 6 | Cut left and right suspension suture.

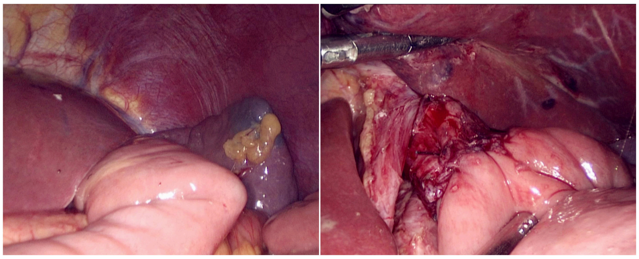

FIGURE 7 | Placing the gastric tube into the distal jejunum and completing the esophagojejunostomy.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Second Affiliated Hospital of Nanchang University.

The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CH and ZZ designed the study. CH, JZ, and ZL collected clinical data. CH and JH analyzed the data. CH wrote the manuscript with contribution from all authors. All authors read and approved the final version of the paper.

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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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Right Compared With Left Thoracic Approach Esophagectomy for Patients With Middle Esophageal Squamous Cell Carcinoma

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Background: In China, open surgical approaches for esophageal cancer (EC) can be divided into two techniques, the right- and left- transthoracic esophagectomy. Although there is an increasing number of instances that use the right side, the optimal surgical technique remains unclear. Based in a large cancer center with rich experience of both transthoracic side approaches, this study compared the long-term survival of patients treated by these two surgical techniques.

Methods: The patients included in this study underwent a right transthoracic esophagectomy (Right, McKeown) or left transthoracic esophagectomy (Left, Sweet, or chest neck dual-incision) for esophageal squamous cell carcinoma (ESCC) between January 2015 and October 2018. The overall survival(OS) rate and perioperative data between the two groups were then retrospectively analyzed.

Results: We included 437 patients who underwent Right ($n = 202$) and Left ($n = 235$) approaches for ESCC. There was a significantly longer median operative time (250 vs. 190 min, $P < 0.001$) and longer median postoperative hospital stay (17 vs. 14 days, $P < 0.001$) in the Right side group. The OS at 5-years was 49.9% in the Right group and 52.45% in the Left group; hazard ratio (HR) (95% CI): 1.002 (0.752–1.337), $p = 0.987$.

Conclusions: For middle thoracic ESCC without suspected lymph node metastasis in the upper mediastinum, the esophagectomy through the Left thoracic approach could achieve the same OS as the Right side, with better short-term outcomes.

Keywords: esophageal cancer, esophagectomy, survival analysis, squamous cell carcinama, surgery

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INTRODUCTION

Esophageal cancer (EC) is ranked as the sixth most common cause of cancer-related death in the world (1). Surgery is considered the best choice for EC, but in China, there is still a lack of consensus regarding the use of left and right thoracic transthoracic approaches, and debates have become increasingly complex over the past 5 years (2–6). This reflects previous debates in western countries regarding the transhiatal vs. transthoracic approach for EC (7, 8). This was resolved by a randomized control trial (RCT) that demonstrated there was no significant difference in overall survival (OS) between transhiatal and transthoracic approaches for EC (7, 8). However, an RCT by

Dr. Chen et al. in China concluded that the right transthoracic approach was better for patients with increased OS in esophageal squamous cell carcinoma (ESCC) (3). The study indicated that the extended radial lymphadenectomy of the right transthoracic approach has benefits in terms of survival (3). Despite these findings, a domestic online survey showed that only 27.8% of EC patients received an esophagectomy through the right thoracic approach in China in 2012 (9). Die to these RCT results and the advocation of the Chinese Anti-Cancer Association (9), the number of instances were the right thoracic approach is used is dramatically increasing in China. However, the left transthoracic approach has merits in that there is a lower risk of postoperative complications, shorter operation time, and faster recovery time (6, 10). Therefore, we performed a retrospective study, using a prospective database to compare right and left approaches to esophagectomy for middle thoracic ESCC conducted in a large-scale cancer center with extensive experience of the left thoracic approach.

PATIENTS AND METHODS

Patients

This study was approved by the ethics review committee of the Affiliated Cancer Hospital of ZhengZhou University Henan Cancer Hospital (approval number 2018138). The Thoracic Surgery Department of Henan Cancer Hospital has created a prospective database of the department with the help of the LinkDoc company. The details of patients were collected on the 1st day of hospitalization and included pretreatment examinations, treatment, and follow-up data.

The inclusion criteria of this study were: 1. consecutive patients with thoracic ESCC from January 1, 2015, to October 7, 2018; pathological T stage 1b-4 according to the 2009 American Joint Committee on Cancer (AJCC) TNM staging system; open transthoracic esophagectomy; and middle thoracic ESCC. We excluded patients for whom follow-up information was missing. They were divided into two groups, the Right group (McKeown) and the Left group (Sweet or chest neck dual-incision).

Each patient finished preoperational tests, including electronic ultrasound gastroscopy with a pathological examination, contrast thoracic and upper abdominal CT scanning, upper gastrointestinal contrast imaging, abdominal and cervical color ultrasound, emission computed tomography (ECT), pulmonary function test, electrocardiography, and other routine tests. If the positron emission tomography-CT (PET/CT) was accepted by patients, it was adopted. In total, $<10\%$ of patients accepted the PET/CT.

The surgical procedures were conducted by 10 surgeons in total, each of whom had extensive surgical experience in transthoracic esophagectomies on both the left and right sides. If there were no suspected positive lymph nodes in the superior mediastinum. The selection of the right or left approach was dependent on the informed choice of each surgeon. The definition of postoperative complications is outlined in **Supplementary Material 1**.

Surgical Procedures

Following the McKeown method for the Right approach to the procedure, the patient was initially placed in the left lateral decubitus, an incision was then made in the fourth or fifth intercostal space, the azygos vein was dissected, and the esophagus was mobilized. If the thoracic duct was injured it was removed, otherwise, it was preserved. Next, the patient was positioned in the supine position. An upper midline abdominal incision was made in the stomach, mobilized, and the left gastric artery was resected. A gastric conduit was constructed using linear staplers (EC60, Ethicon, Cincinnati, USA). The esophagus was then resected in the neck. The gastric tube was delivered through the thoracic cavity to the left side of the neck and a mechanical or hand-sewn cervical esophagogastric anastomosis was adopted.

In the Left approach to the procedure, a left-sided thoracic incision was made at the sixth or seventh intercostal space. The esophagus was then mobilized and resected. To access the abdominal cavity, the diaphragm was incised, the stomach mobilized, and a gastric tube was made. The residual stomach with the esophagus was removed. Finally, the gastric tube was delivered to the left side of the neck incision. A mechanical or hand-sewn cervical esophagogastric anastomosis was conducted.

In the right thoracic procedure, a total mediastinal lymphadenectomy was used. The bilateral recurrent nerve lymph nodes were resected. Except for the recurrent nerve lymph nodes, the two procedures could acquire the same lymphadenectomy. The middle and lower periesophageal, subcarinal, lower posterior mediastinum, perigastric, common hepatic, celiac arteries, and the left gastric artery lymph nodes were removed.

Follow-Up

After surgery, follow-up surveillance tests were every 3 months in the first 2 years, 6 months between 3 and 5 years, and every year after 5 years. The chest CT scans and abdominal/cervical color ultrasound were routinely tested. If a patient had special symptoms, they may have received other tests. OS was defined as the duration from the date of surgery to death.

Statistical Analysis

The Mann-Whitney U-test and the chi-square test were used to evaluate the association between the two groups in the clinicopathological variables. Kaplan-Meier curves were employed to analyze the OS. A multivariate analysis of survival was conducted using the Cox proportional hazards regression model. Covariates with clinical value and those factors with a $P \leq 0.2$ in the univariate analysis were included in the multivariate model. R language 3.4.1 for Windows was used to fulfill the statistical analysis. A value of $P < 0.05$ was considered statistically significant.

RESULTS

From January 1, 2015, to October 7, 2018, a total of 437 patients met the inclusion criteria and were included in the study. There were 202 (46.22%) patients in the Right group (McKeown) and 235 (53.78%) patients in the Left group (Sweet or chest neck

TABLE 1 | Baseline demograpic and clinical characteristics of patients of the entire cohort.

Variable	Caese ($N = 437$)	Surgical approaches (%)		*P*-value
		Right ($N = 202$)	Left ($N = 235$)	
Mean Age, median (range)	437 (100%)	63.5 (43–77)	65 (41–81)	0.136
Age *N* (%)				0.400
≥64	228 (52.17%)	101 (50.00)	127 (54.04)	
<64	209 (47.83%)	101 (50.00)	108 (45.96)	
Mean BMI, mean (*SD*)	437 (100%)	23.23 (3.03)	23.65 (3.02)	0.204
Sex *N* (%)				0.323
Female	138 (31.58)	59 (29.21)	79 (33.62)	
Male	299 (68.42)	143 (70.79)	156 (66.38)	
Smoking *N* (%) (3 missing data)				0.597
Never	224 (51.61)	101 (50.25)	123 (52.79)	
Ever/current	210 (48.39)	100 (49.75)	110 (47.21)	
Drinking *N* (%) (5 missing data)				0.942
Never	243 (56.25)	111 (56.06)	132 (56.41)	
Ever/current	189 (43.75)	87 (43.94)	102 (43.59)	
Medical insurance *N* (%) (2 missing data)				0.464
Rural cooperative medical care system	265 (61.43)	127 (63.18)	138 (59.74)	
Others (city residents and works, self-paying, social insurance, free healthcare, others)	167 (38.66)	74 (36.82)	93 (40.26)	
cT stage *N* (%)				0.601
T1b-2	134 (30.66)	58 (28.71)	76 (32.34)	
T3	268 (61.33)	129 (63.86)	139 (59.15)	
T4	35 (8.01)	15 (7.43)	20 (8.51)	
cN stage *N* (%)				0.828
N0	321 (73.46)	147 (72.77)	174 (74.04)	
N+	116 (26.54)	55 (27.23)	61 (25.96)	
Neoadjuvant treatment *N* (%)				0.519
Yes	72 (16.48)	36 (17.82)	36 (15.32)	
No	365 (83.52)	166 (82.18)	199 (84.68)	
Adjuvant treatment *N* (%)				0.338
Yes	219 (50.11)	96 (47.29)	123 (52.34)	
No	218 (49.98)	106 (52.22)	112 (47.66)	

MIE, minimally invasive esophagectomy; OE, open esophagectomy; N, number; SD, standard deviation; cT, clinical tumor; cN, clinical lymph nodes.

dual-incision). The clinical characteristics of patients in the two groups are listed in **Table 1**. Most of the patients in the study were male. The number of female participants, as well as age, BMI, smoking history, drinking history, and clinical N stage, were slightly higher in the left group than in the right group. The right group included a higher proportion of patients from the rural cooperative medical care system. A higher proportion of patients in the right group (17.82%), compared to in left group (15.31%), accepted neoadjuvant treatment, while a higher proportion of patients in the left group (52.34%), compared to in right group (47.29%), received adjuvant treatment. There was no statistically significant difference in the clinical characteristics of the two groups (**Table 1**).

Intraoperative and postoperative data are shown in **Table 2**. The median operation time was 250 min in the right group and 190 min in the left group ($P < 0.001$). During the operation, the mean blood loss was 236.61 ml in the right group and 220.54 ml in the left group ($P = 0.708$). The median lymph nodes retrieved were four higher in the right group than in the left group ($P = 0.002$). The level of anastomosis for the right and left group was comparable (cervical/thoracic: 201/0 vs. 221/9, $P = 0.8$). No patients died during their postoperative hospital stay nor the first 90 days after the operation. The patients in the left group had a significantly shorter postoperation hospital stay than the right group (median number of days: 14 vs. 17, $P < 0.001$). The anastomotic leakage rate in the right group was 1.98%, vs. 2.13% in the left group, without a statistically significant difference ($P > 0.999$). The pathological data between the two groups were without significant difference ($p > 0.3$) (**Table 2**).

The follow-up period ranged from 3 to 64.60 months. The median follow-up period was 33 months. For the whole cohort, the 5-years OS rate was 51.44% (95% CI: 45.86–57.71). The 5-years OS rate for the right group was 49.90% (95% CI: 40.90–60.87) and for the left group, it was 52.45%

TABLE 2 | Intraoperative and Postoperative characteristics of the two groups.

	Surgical approaches (%)		*P*-value
	Right (*N* = 202)	Left (*N* = 235)	
Intraoperative Data			
Median operative time (min)	250	190	<0.001*
Mean operative time (*SD*) (min)	293.02 (314.94)	201.77 (48.76)	<0.001*
Mean blood loss (*SD*) (mL)	236.61 (239.18)	220.54 (189.23)	0.708
Median lymph nodes retrieved (range) *N*	25 (8–60)	21 (8–54)	0.002*
R1/R2 resection *N* (%)	2(1.04)	0	0.238
Level of anastomosis *N* (%)			0.800
Cervical	201 (100)	221 (96.09)	
Thoracic	0 (0)	9 (3.91)	
Anastomosis method *N* (%)			0.001*
Manual anastomosis	85 (42.08)	123 (52.34)	
Mechanical anastomosis	105 (51.98)	111 (47.23)	
Semi-mechanical anastomosis	12 (5.94)	1 (0.43)	
Postoperative data			
Median postoperative hospital stay days (range)	17 (7–68)	14 (4–75)	<0.001*
Median mediastinal tube drainage days (range)	7 (3–34)	7 (3–28)	0.175
Myocardial arrhythmia *N* (%)	20 (9.90)	35 (14.89)	0.117
Pneumonia *N* (%)	34 (16.83)	26 (11.06)	0.081
Anastomotic leakage *N* (%)	4 (1.98)	5 (2.13)	>0.999
In hospital mortality/90-days mortality *N* (%)	0	0	NA
Pathological data			
pT stage *T* (%)			0.950
T1b	9 (4.46)	23 (9.79)	
T2	56 (27.72)	46 (19.57)	
T3	112 (55.45)	138 (58.72)	
T4	25 (12.38)	28 (11.91)	
pN stage *N* (%)			0.546
N0	111 (54.95)	143 (60.85)	
N1	56 (27.72)	61 (25.96)	
N2	27 (13.37)	25 (10.64)	
N3	8 (3.96)	6 (2.55)	
pTNM staging 7th *N* (%)			0.398
IA	6 (3.02)	11 (4.85)	
IB	33 (16.58)	43 (18.94)	
IIA	31 (15.58)	28 (12.33)	
IIB	40 (20.10)	52 (22.91)	
IIIA	40 (20.10)	43 (18.94)	
IIIB	17 (8.54)	17 (7.49)	
IIIC	32 (16.08)	33 (14.54)	

MIE, minimally invasive esophagectomy; OE, open esophagectomy; N, number; SD, standard deviation; NA, Not Available; pN, pathological lymph nodes; pTNM, tumor/node/metastasis.
**Statistically significant ($p < 0.05$).*

(95% CI: 45.64–60.27). There was no statistically significant difference between the right and left groups, $p = 0.987$ (**Figure 1**, **Table 3**). This conclusion is consistent with data produced by the multivariable Cox regression model (**Table 3**).

DISCUSSION

This retrospective study compared the long-term OS of two widely adopted surgical approaches for resectable thoracic ESCC in China. The data showed no difference in the 5-years OS of two groups of patients without suspected upper mediastinal lymph node metastasis in preoperation tests.

In China over the past 5 years, there has been discussion as to whether the left or right transthoracic approaches were better. In 2013, a national survey showed that only 27.8% of ESCC received the right transthoracic approach (9). However, after it was advocated by the Chinese Anti-Cancer Association (9), the use of the right approach dramatically increased. Henan Cancer Hospital is located in the highest incidence area of ESCC in China and is the largest cancer center in China, and the proportion of

TABLE 3 | Univariate and multivariate analyses of overall survival in 437 esophageal carcinoma patients.

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P*-value	HR	95%CI	*P*-value
Age (<64 vs. ≥64 years)	0.817	0.611–1.092	0.171	0.782	1.581–1.051	0.103
Gender (Male vs. Female)	0.944	0.696–1.280	0.712	0.756	0.502–1.137	0.179
Smoking (Yes vs. No) (3 missing data)	1.190	0.893–1.586	0.235	1.181	0.710–1.967	0.522
Alcohol (Yes vs. No) (5 missing data)	1.151	0.863–1.535	0.338	1.227	0.768–1.960	0.391
Medical insurance (Rural vs. Others)	1.110	0.822–1.498	0.495			
Blood loss (≤200 vs. >200 ml)	0.840	0.565–1.294	0.390			
Operation time (≤180 vs. >180 min)	0.821	0.580–1.162	0.265			
Lymph nodes retrieved (≤23 vs. >23)	1.112	0.834–1.484	0.469			
pT stage (T1–2 vs. T3–4)	2.059	1.431–2.963	0.0001			
pN stage (N0 vs. N1–3)	2.570	1.917–3.446	<0.0001*			
pTNM staging 7th (I, II vs. III)	6.438	0.327–0.587	<0.0001*	0.431	0.321–0.579	<0.001*
Surgical approach (R vs. L)	1.002	0.752–1.337	0.987	1.031	0.771–1.377	0.838

HR, Hazard Ratio; CI, confidence interval; pN, pathological lymph nodes; pTNM, pathological tumor/node/metastasis; R, minimally invasive esophagectomy; L, open esophagectomy.
**Statistically significant (p < 0.05).*

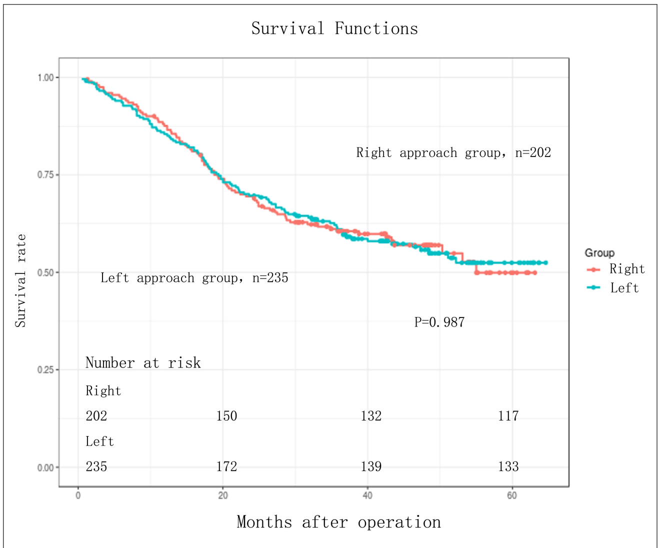

FIGURE 1 | Kaplan-Meier curves for comparison of overall survival between Right and Left in EC patients ($n = 437$). Overall survival (OS) between the two groups were without any significant difference (log-rank test, $P = 0.987$).

operations that have used the right approach has increased in recent years. In the Linkdoc database of our department, before January 1, 2015, the proportion of operations that used the right approach was 8.13%. In 2015, the proportional use of the right approach increased to 66.90%, and in 2017, the right approach accounted for 81.82%. Some studies have argued that the survival benefits of the right approach are because it involves a more radical lymphadenectomy of upper mediastinal lymph nodes. This was demonstrated by the RCT of Dr. Haiquan Chen et al. (3) in data that showed that the right approach is associated with increased OS in ESCC, particularly in those with lymph node involvement (HR, 0.632; 95% CI, 0.412–0.969, $P = 0.034$) and/or R1–2 resection margins (HR, 0.495; 95% CI, 0.290–0.848, $P = 0.009$) (2). As discussed here, the practices of Chinese thoracic surgeons have changed in response to this study, but the study itself is based on limited evidence.

In the long-term analysis by Chen (2, 3), the 3-years OS rates were 74 and 60% for the right and left approaches, respectively (HR, 0.663; 95% CI, 0.457–0.961; $P = 0.029$) (2). However, this trial has limitations, as the short-term analysis outlines that the mean operation time for the Sweet group was only 30 min faster than the Ivor-Lewis group, which is an unacceptable difference for most cancer centers with experience of the left approach procedure (10, 11). In contrast, the difference in median operation time in our left/right cohort reached 60 min. The difference in mean operation time reached 91.25 min. In the study by Chen, the median hospital stays for the Sweet group were 2 days ($p = 0.002$) longer than the Ivor-Lewis group, which is also unusual based on data from past studies (6, 10, 11). What is more, the total complications in the Sweet group were even higher than in the Ivor-Lewis group, 62 vs. 45% ($p = 0.04$) (2). This indicates that Chen et al. based their assessment of the benefits of the left approach from short-term data. The left approach has benefits which include a shorter operation time, fast recovery, fewer complications, and shorter postoperation stay (6, 10, 11), which accounted for the popularity of the Sweet procedure in China before 2013 (9). However, the data in the study by Chen does not reflect the short-term benefits of the left approach. Although it was an RCT, the results of the study by Chen should be carefully interpreted, especially in terms of the short-term results, which are different from those established by other studies (6, 10, 11). Except for the differences in approach to lymphanectomy of the left and right approaches, the surgical incision itself may affect the survival. With the same extent of lymphanectomy, another retrospective study has demonstrated that the MIE could achieve lower operative morbidity and long time survival benefits (12). The survival benefits may due to the different incisions.

The advocation of the survival benefits of the right side approach were mainly based on the radical resection of upper mediastinal lymph nodes (3, 9). The metastases rate of upper mediastinal lymph nodes was around 30% (13). The patients without suspected upper mediastinal lymph nodes, the negative predictive value of preoperative chest CT scan was 99.23% (14). Maybe some patients do not need superior mediastinal lymphanectomy.

The lymph nodes metastases of ESCC is an important prognostic factor. The number of positive lymph nodes (15), the ratio of positive lymph nodes (16), the number of total resected lymph nodes (17), have been suggested to have prognostic value. The radical lymphanectomy also has diagnostic value and more precise pathological stage classification to indicate the adjuvant treatment (18, 19). These may all contribute to OS benefits.

The treatment value of lymphanectomy is also still under debate (20–23). Hsu et al. have demonstrated that although 30% of ESCC had positive results for right upper mediastinal lymph nodes, there were no significant differences in survival rates between patients with or without lymphadenectomy of the right upper mediastinal (24), indicating that the lymph node dissection itself might not have benefits in terms of survival. It is therefore not appropriate to mix the different incisions with the different extents of lymphanectomy when discussing how these factors might influence survival. The left approach (Sweet or chest neck dual-incision) has been in existence for ∼80 years in China (25). It was the most used method chosen by thoracic surgeons before 2013 (9). One needs to be cautious when saying it has a better/worse impact on ESCC, especially for clinically negative lymph nodes of the upper mediastinum. This concept is also supported by Yang Ding et al. They found that for the middle and lower thoracic EC patients, with or without clinical lymph node metastasis, the surgical treatment through the right thoracic approach can achieve the same OS as the left thoracic approach (5).

The data used in this study was gathered from a prospective database. Our cancer center is a high-volume cancer hospital, located in an area with the highest incidences of EC worldwide, and the thoracic surgeons working there have a large amount of experience in using the left approach. Because the pretreatment parameters of the two groups in our study were without significant difference, the confounding biases of this study were well-controlled. However, this study did still have some limitations, particularly connected to the fact that it was a retrospective study. The LinkDoc data company was employed by our department to manage the database from 2015, meaning that long-term follow-ups still need further evaluation. At the time of publication, the information on the database including data on recurrence and postoperation complications were still under construction. Data on disease-free survival, local recurrence, and distant recurrence could not be analyzed as part of this study and we were not able to perform the Clavien-Dindo classification of postoperation complications.

The long-term oncological differences between the right and left approaches still need to be evaluated by a well-designed multicenter RCT in the future, and any changes in clinical practice should be based on further high-level evidence.

DATA AVAILABILITY STATEMENT

The datasets analyzed in this article are not publicly available. Requests to access the datasets should be directed to the ethics review committee of the Affiliated Cancer Hospital of ZhengZhou University/Henan Cancer Hospital.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The ethics review committee of the Affiliated Cancer Hospital of ZhengZhou University/Henan Cancer Hospital approved this study (Number. 2018134). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YZ and WX: conceived and designed the study. YZ, YL, XL, and RZ: performed the experiments. YZ and HS: analyzed the data, contributed reagents, materials, analysis tools, and wrote the paper. All authors contributed to the article and approved the submitted version.

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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.2020.536842/full#supplementary-material

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An Approach to Accelerate Healing and Shorten the Hospital Stay of Patients With Anastomotic Leakage After Esophagectomy: An Explorative Study of Systematic Endoscopic Intervention

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Objective: To explore the comprehensive role of systemic endoscopic intervention in healing esophageal anastomotic leak.

Methods: In total, 3919 consecutive patients with esophageal cancer who underwent esophagectomy and immediate esophageal reconstruction were screened. In total, 203 patients (5.10%) diagnosed with anastomotic leakage were included. The participants were divided into three groups according to differences in diagnosis and treatment procedures. Ninety-four patients received conventional management, 87 patients received endoscopic diagnosis only, and the remaining 22 patients received systematic endoscopic intervention. The primary endpoint was overall healing of the leak after oncologic esophageal surgery. The secondary endpoints were the time from surgery to recovery and the occurrence of adverse events.

Results: 173 (85.2%; 95% CI, 80.3-90.1%) of the 203 patients were successfully healed, with a mean healing time of 66.04 ± 3.59 days (median: 51 days; range: 13-368 days), and the overall healing rates differed significantly among the three groups according to the stratified log-rank test (P<0.001). The median healing time of leakage was 37 days (95% CI: 33.32-40.68 days) in the endoscopic intervention group, 51 days (95% CI: 44.86-57.14 days) in the endoscopic diagnostic group, and 67 days (95% CI: 56.27-77.73 days) in the conventional group. The overall survival rate was 78.7% (95% CI: 70.3 to 87.2%) in the conventional management group, 89.7% (95% CI: 83.1 to 96.2%) in the endoscopic diagnostic group and 95.5% (95% CI: 86.0 to 100%) in the systematic endoscopic intervention group. Landmark analysis indicated that the speed of wound healing in the endoscopic intervention group was 2-4 times faster at any period than that in the conservative group. There were 20 (21.28%) deaths among the 94 patients in the conventional group, 9 (10.34%) deaths among the 87 patients in the endoscopic diagnostic group and 1 (4.55%) death among the 22 patients in the endoscopic intervention group; this difference was statistically significant (Fisher exact test, P < 0.05).

Conclusion: Tailored endoscopic treatment for postoperative esophageal anastomotic leakage based on endoscopic diagnosis is feasible and effective. Systematic endoscopic intervention shortened the treatment period and reduced mortality and should therefore be considered in the management of this disease.

Keywords: esophageal cancer, anastomotic leak, endoscopic intervention, clips, sealants, perioperative complications

INTRODUCTION

As the seventh most commonly diagnosed cancer, esophageal carcinoma (EC) is associated with a dismal fatality rate, ranking as the sixth most common cause of cancer-related death (1). Once esophageal cancer is confirmed, radical resection is typically recommended, as it is of the most effective therapeutic approaches for select patients. Despite the considerable improvement in surgical conditions and skills, however, esophagectomies are still associated with various complications, of which anastomotic leakage is a disastrous postoperative complication that seriously affects patient quality of life due to both its high incidence (5-40%) and associated mortality (2-60%) (2–9). As a consequence, improvements in leak management are of vital necessity to reduce overall mortality.

Leaks after esophagectomy are defined as full-thickness gastrointestinal defects involving the esophagus, anastomosis, staple line, or conduit irrespective of the presentation or method of identification. Along with the development of esophageal anastomotic leakage (EAL), one consequence followed close on the heels of another. Firstly, EAL is the greatest risk factor for perioperative complication-related death, with up to 60% mortality rates, and the risk of death for patients with EAL is 3 times higher than that for those without EAL (7–11). Moreover, in the short run, it increases the length of hospital stay, prolongs the oral feeding time, contributes to the risk of anastomotic hemorrhage, and increases risk of reoperation. In the long run, a positive association between the occurrence of anastomotic stricture and the development of EAL was observed. EAL can also impair long-term survival, negatively impact surgical and oncologic outcomes and be related to cancer recurrence after surgical resection for esophageal malignancy (5, 7, 9–11).

The diagnosis or interference time of EAL explains the severity of this complication; more specifically, the most predominant risk factors for the subsequent clinical outcome are the patients' delay as well as the delay of diagnosis or even the absence of any interference, so it is undisputed that prompt diagnosis and immediate intervention are of vital significance to prevent further damage and to control the ensuing clinical development. Throughout the course of intervention, the use of a multidisciplinary diagnostic and treatment approach is undoubtedly highly important.

Traditionally, there are several methods used to detect EAL, of which routine contrast medium esophagography is widely utilized and has gained international recognition. In addition, direct surgical exploration, oral administration of methylene blue, and CT scans with or without oral contrast are extensively used. However, there is no consensus within the literature with regard to whether, when or which strategy should be used, even though their limitations are well documented. Some researchers have suggested that the routine use of contrast radiography be suspended, since it can be unreliable in the detection of anastomotic leaks, with a reported sensitivity between 40% and 66%, and aspiration pneumonia due to aspiration of the contrast agent was noted (12, 13). Meanwhile, operative exploration is limited by its high mortality rate; oral methylene blue may not be proper for diagnosing late EAL, as adhesions formed after esophagectomy may result in localized collection of the dye, making it difficult to identify EAL; and computed tomography (CT) scanning does not provide information about gastric conduit viability, so early ischemic or necrotic areas could be missed (12–16). As endoscopic techniques have begun to be applied clinically over the past decade, they have shown clear advantages (e.g., direct visualization and quantification of the defect, ability to determine gastric conduit viability, and both the sensitivity and specificity could reach up to 95-100%) (14–16).

In terms of treatment, the therapeutic strategies for this issue range from palliative treatment such as antibiotics and nutritional support to operative exploration and endoscopic management using stents, clips, glues, etc., or their combination. All of these efforts share the same goal: to close the breach and eliminate contamination. Traditional surgical repair has certain disadvantages, such as increased hospitalization costs and mortality and extended hospital stays, which obviously conflict with the notion of rapid rehabilitation surgery. Fortunately, minimally invasive endoscopic therapies may have advantages such as enhanced safety, minimal invasiveness, quicker recovery, lower treatment cost, etc., when compared with traditional open surgical methods (14–16).

However, clinicians remain reluctant to perform endoscopy after esophagectomy because of the theoretical risk of disrupting the anastomosis or worsening the EAL (17–19). In our cases, endoscopic intervention was found to aid in making a precise diagnosis and in deciding the most appropriate clinical strategy without increasing the incidence of complications and mortality. As highlighted in a recently published Position Statement of the European Society of Gastrointestinal Endoscopy, it is important to have a systematic approach for the diagnosis and treatment of GI perforations (20). Therefore, this investigation proceeded with the aim of evaluating the safety and efficacy of this new approach to diagnosing and treating anastomotic fistula and to assess the role of endoscopic intervention throughout the entire rehabilitation process of EAL.

PATIENTS AND METHODS

This was a single-center retrospective study conducted at our Thoracic Surgery Department. We analyzed our clinical databank and screened out all suspected EAL patients who had undergone esophagectomy between January 2012 and August 2019 at the Sun Yat-Sen University Cancer Center. To improve the homogeneity between the study groups, only patients with anastomotic leakage after esophagectomy due to malignant esophageal tumors were included. Other esophageal leaks, such as iatrogenic leakage, EAL from benign esophageal disease or following gastrectomy, were excluded. Other exclusion criteria were a prior history of esophageal surgery, cases managed by primary surgery, operation performed at another institution and incomplete medical records. The specific process of patient enrollment is shown in the flow chart (**Figure 1**).

Records were reviewed to collect patient demographics, tumor characteristics, preoperative chemoradiotherapy information, surgical procedures, diagnostic methods, leakage therapy regimens, clinical outcomes, mortality and complications.

Surgical Characteristics

A total of 3919 patients underwent esophagectomy during the evaluation period, of whom 203 were confirmed to have EAL and were included in the analysis (**Figure 1**). Among this population, 138 patients underwent open surgery, including 57 patients who underwent surgery according to the Sweet procedure, 61 patients who underwent surgery according to the McKeown procedure, and 20 patients who underwent Ivor-Lewis surgery. The remaining 65 patients underwent minimally invasive esophagectomy procedures such as the mediastinoscopic transmediastinal approach (n=3), thoraco-laparoscopic McKeown (n=42) and Ivor-Lewis (n=3) esophagectomy, and robot-assisted McKeown (n=17) with the aid of the da Vinci® system (Intuitive Surgical, Sunnyvale, CA). Construction was completed in 201 patients by gastric conduit and in 2 patients by colon interposition. The decision of surgical modality was made at the discretion of the surgeon performing the operation according to the patient's actual condition.

EAL Diagnosis and Intervention

Radiological contrast studies or endoscopy were routinely performed to screen for the existence of possible leakage at approximately day 7 after surgery. Once EAL was confirmed, the surgeon responsible for the respective case would decide on a treatment plan and initiate intervention. The specific diagnoses and intervention procedures of the 203 included patients are presented in **Figure 1**.

Conservative Treatment

Conservative approaches included nutritional support, gastrointestinal decompression through an intraoperatively placed gastric tube, perianastomotic drainage *via* a surgically placed prophylactic chest tube and systemic antibiotics. Supplemental nutritional support was generally provided through a preplaced jejunal nutrition tube during esophagectomy and occasionally through total parenteral nutrition support. Proton pump inhibitor (PPIS)-aided therapy was also included for gastrointestinal decompression, and the intraoperative indwelling gastric tubes were not pulled out until the anastomotic leakage healed. The leak cavity was flushed several times with irrigation fluids containing gentamycin in saline, with the same purpose as thoracic drainage to clear most of the pus. In accordance with the irrigation regimen, all patients received intravenous broad-spectrum antibiotics (2, 5, 9, 11).

Endoscopic Intervention

Endoscopic interventions were performed by veteran endoscopic surgeons. The endoscopic strategy was subdivided into two types: diagnostic and therapeutic. The location of the anastomosis and the lesion, the extent of the orifice, and the presence of pus were confirmed and evaluated during the diagnostic phase. Then, the leaks were subdivided into the following categories according to the Esophagectomy Complications Consensus Group (ECCG) classification (21):

Type I: Local defect requiring no change in therapy or treated medically.

Type II: Localized defect requiring interventional but not surgical therapy.

Type III: Localized defect requiring surgical therapy.

Then, the therapeutic phase was carried out at the discretion of the responsible surgeon according to the EAL characteristics found above. First of all, in the course of endoscopic intervention, whether the EAL was infected or not would be one of our major focuses. If the EAL was infected, we would irrigate the pus cavity with normal saline under the navigation of ultrafine gastroscopy, and then immediate suction and irrigation of the abscess cavity would be established by Endoscopic Transnasal Inner Drainage. Generally, the pus would exterminate in about 7-14 days, subsequent systematic endoscopic therapies would be carried out based on the status of patients and the results of endoscopic reexamination, the processes of drainage was not counted in the number of endoscopic sessions. If the EAL was not infected, the systematic endoscopic treatment would administrate directly. Treatment strategies included a 'wait and see' strategy (endoscopic diagnostic group), administration of tissue sealant, the use of an endoscopic clip or the application of combined therapy (endoscopic intervention group). Endoscopic treatment was systematically performed until an effective outcome was achieved or the patient died (6).

Details of intervention strategies in systematic endoscopic group is described as follows.

During the diagnostic procedure or the reexamination process, the depth of lesion was confirmed. If the depth of the wound was less than 1cm, the patient would be treated by

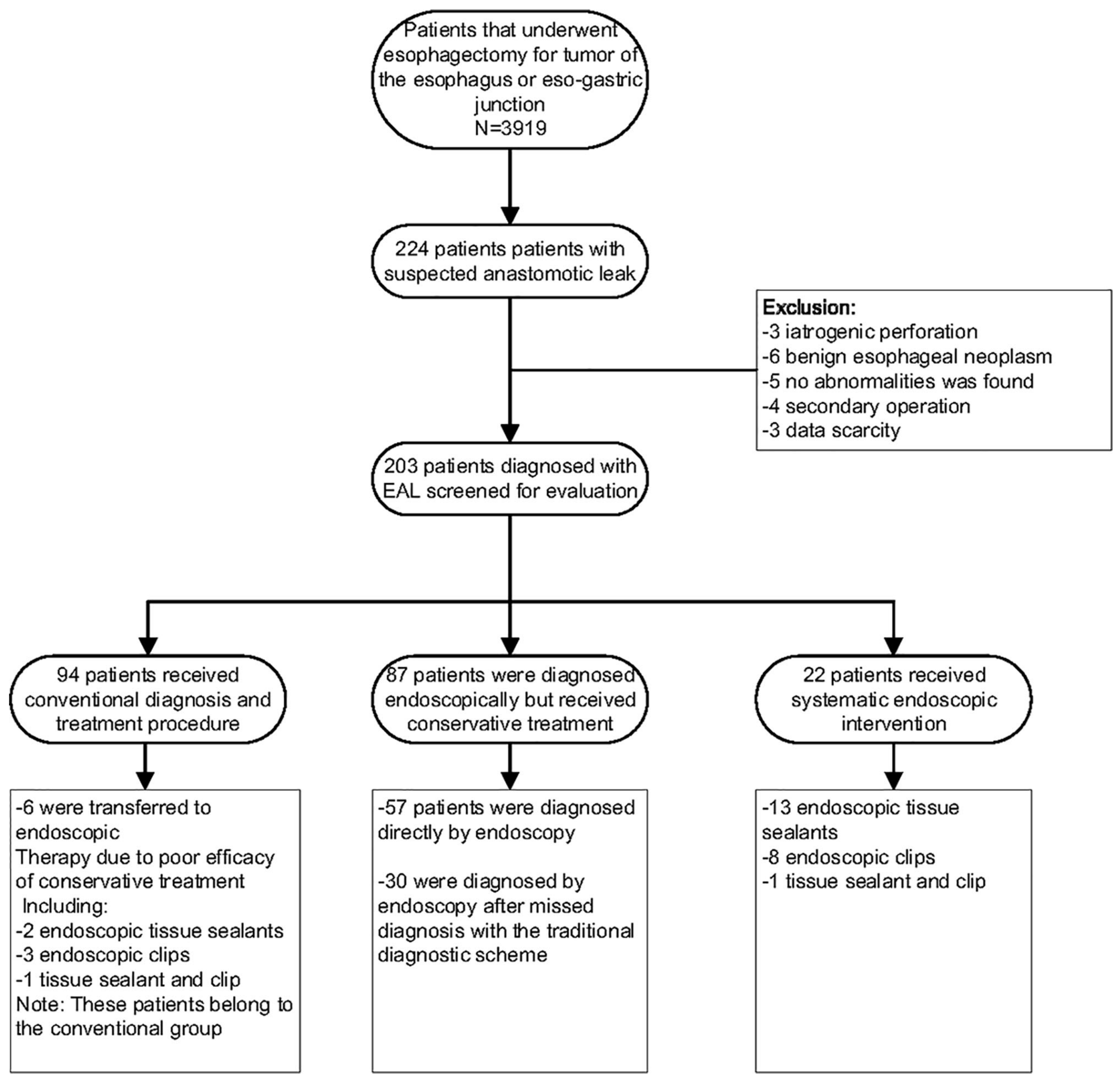

FIGURE 1 | Description of the selection of the studied population of patients.

endoscopic clips; otherwise, by biological tissue sealants to avoid the formation of residual cavity.

Endoscopic Clips

The first clip is proposed to place through the most distal part of the leak to the oral side successively as this prevents accidental snagging and drooping. Then, flushing the anastomosis with normal saline and observing whether there are bubbles, so as to judge whether it is closed completely. Lastly, checking the tension of the anastomosis. If the tension is high or the closure is incomplete, endoscopic review and following sessions will be administrated 7 days later.

Endoscopic Tissue Sealants

Firstly, we use a small endoscopic brush to clean the wound and make it bleed slightly, then spray sealants to fill the fistula and to stop the bleeding. The biological sealants consist two components, one component consists of the antifibrinolytic solution (aprotinin) and a protein concentrate (fibrinogen) derived from human plasma, and the other component includes human thrombin (or a bovine thrombin) and a calcium chloride solution. The two solutions are delivered in a dual-barrel syringe and combined at the site of desired application, through a double lumen catheter, to form a firm, white, rubber-like mass with strong adhesive properties within few seconds of being mixed.

Endpoints

The primary endpoint was the overall healing of leakages after oncologic esophageal surgery. Complete healing of the EAL was defined as patient recovery (no abnormality after oral feeding) after assessment with endoscopy or *via* follow-up X-ray or CT contrast study. The secondary endpoint was the time (in days) from surgery to recovery and the occurrence of adverse events (sinus formation, bleeding, anastomotic stenosis, etc.). Failure was defined as death or loss to follow-up.

Statistical Analysis

Primary data were managed and extracted from the hospital data management system and then analyzed by IBM SPSS Statistics version 25.0 (Inc, Chicago, Illinois, USA). Continuous variables are presented as the means ± standard deviations (SD), and categorical data are presented as numbers and percentages. Multivariable analyses with the Cox proportional hazards model were used to estimate the simultaneous effects of prognostic factors on healing. All eligible patients were included in the analysis of overall healing by the Kaplan–Meier method and the log-rank test to calculate corresponding *P* values. First, a univariate analysis using various factors associated with EAL healing time was performed. Next, to identify significant independent factors related to the time needed for EAL healing, multivariate Cox regression analysis was performed using factors identified as significant variables and selected potential confounding factors from the univariate analysis. Given that all patients in the endoscopic intervention group had healed within 90 days after surgery (except for one death on day 90), to explore the role of endoscopic technology in the healing process of EAL at different time periods from esophagectomy to rehabilitation, an exploratory analysis based on the landmark analysis method was performed according to landmark points of 30 days, 60 days, 90 days, and post-90 days, with the hazard ratio calculated separately for events that occurred each month after grouping and events that occurred between 90 days and the end of the follow-up period (22–24). We then performed a test for the interaction between treatment and time. In all time-to-event analyses (i.e., overall and landmark), for each type of event, data were censored at the time of the first event that occurred in a patient. Additionally, all patients were included in the complication assessment. Differences were considered to be statistically significant when the *P* value was 0.05 or less. All statistical tests were two-sided.

RESULTS

Patient Characteristics

A total of 224 patients were suspected of having EAL due to esophagectomy during the study period, of whom 21 were excluded from the study (**Figure 1**). The remaining 203 patients were included in the analysis (**Table 1** shows the baseline clinical data). Among these 203 patients, 94 patients received conventional diagnosis and treatment procedures (conventional group); of the other 109 patients, 87 patients (including one patient for whom endoscopic clipping was attempted but failed) were diagnosed endoscopically but received conservative treatment (endoscopic diagnostic group),

TABLE 1 | Basic characteristics of the 203 patients with EAL and Determinants of EAL postoperative overall healing in patients with EAL.

Factors	No. of patients	Univariate	Multivariate		
	(N=203)	*P* value	HR	95% CI	*P* value
Diagnosis and treatment procedure		**<0.001**			
conventional management[a]	94				
endoscopic diagnosis	87		1.67	1.20-2.32	0.002
systematic endoscopic intervention	22		2.81	1.70-4.63	<0.001
Sex (male vs. female)	167/36	0.734			
Age (year) (<62 vs. ≥62)	102/101	0.818			
Body mass index (kg/m2) (<22 vs. ≥22)	108/95	0.846			
ASA PS (II vs. III)	151/52	0.663			
Smoking index(package*years)(<25 vs. ≥25)	101/102	0.325			
Drinking history (yes vs. no)	69/134	0.949			
Diabetes Mellitus (yes vs. no)	23/180	0.120			
Hypertension (yes vs. no)	52/151	0.171			
Gastric ulcer and/or gastritis (yes vs. no)	144/59	0.485			
Tumor location (upper vs. middle vs. lower thoracic)	21/124/58	0.074			
Tumor staging (I vs. II vs. III vs. IV)	44/62/87/10	0.113			
Minimally invasive surgery (yes vs. no[a])	65/138	**0.003**	1.55	1.11-2.15	0.009
Postoperative fever (yes vs. no)	60/143	0.112			
Neo-adjuvant therapy (yes vs. no)	30/173	0.846			
Leak location (cervical vs. intrathoracic)	123/80	0.686			

HR, Hazard ratio; 95% CI, 95% confidence interval; ASA PS, American Society of Anesthesiologists classification of physical status.
[a]Reference category.
Bold values means the difference was statistically significant.

and 22 patients were diagnosed and treated by endoscopy directly (endoscopic intervention group) (**Figure 1**). There was no significant difference in clinical baseline among the three groups except age (**Table 2** shows the comparison of clinical characteristics according to the diagnosis and treatment procedures).

Diagnosis

Traditional radiological contrast studies (n=124) resulted in 30 missed diagnoses (omission diagnostic rate=24.19%) and 5 misdiagnoses among the EAL patients; hence, the sensitivity of traditional diagnostic methods was 75.81%. Comparatively, endoscopy correctly diagnosed the remaining 79 patients who underwent endoscopic examination directly due to suspected EAL with 100% accuracy. Moreover, endoscopy not only correctly identified the 5 false-positive patients from the radiological contrast study but also detected the 30 leaks that were missed.

Overall Healing

EAL was treated during hospitalization for all patients, and 173 (85.2%; 95% CI: 80.3-90.1%) of them successfully healed, with a mean healing time of 66.04 ± 3.59 days (median: 51 days; range: 13–368 days). The overall healing rates in the three groups differed significantly based on the results of the stratified log-rank test (*P*<0.001).

Table 3 shows the characteristics of EAL of the 22 study patients who underwent systematic endoscopic intervention.

The median healing time of EAL was 37 days (95% CI: 33.32-40.68 days) in the endoscopic intervention group, 51 days (95% CI: 44.86-57.14 days) in the endoscopic diagnostic group, and 67 days (95% CI: 56.27-77.73 days) in the conventional group (**Table 4**).

The univariate analysis showed a significant relationship between diagnosis and treatment procedure (conventional management vs. endoscopic diagnosis vs. systematic endoscopic intervention) and minimally invasive surgery (yes vs. no) (**Table 1**). Cumulative healing rates after surgery calculated with the Kaplan–Meier method and stratified by these significant factors are shown in **Figures 2A, B**.

The multivariate analysis results demonstrated that diagnostic and treatment procedures (conventional management vs. endoscopic diagnosis vs. systematic endoscopic intervention) and minimally invasive surgery (yes vs. no) were significant independent factors for EAL healing time (P<0.001 and P=0.009, respectively) (**Table 1**).

Landmark Analysis

The landmark analysis results indicated that the speed of wound healing in the endoscopic intervention group was faster than that in the conservative group at any period. The healing characteristics of the different groups at various landmark periods are illustrated in **Figures 3** and **4**. It was not difficult to find that the healing speed of the endoscopic intervention group was superior to that of the endoscopic diagnostic group, and the advantage was more prominent when compared with the conventional group, whose healing velocity was only one-third of its counterpart.

Landmark Analysis for the First 30 Days

Patients in the systematic endoscopic group had significantly lower rates of death than those in the endoscopic diagnostic group and the conventional group, while no obvious difference in fatality was observed between the endoscopic diagnostic group and the conventional group. In the weighted Cox proportional hazard regression model, the adjusted hazard ratio (HR) for healing in the endoscopic intervention group compared with the conventional group was 1.94 (95% CI, 0.68-5.51; P=.038), and that in the diagnostic group compared with the conventional group was 1.40 (95% CI, 0.66-3.00; P=.021). In this analysis, the

TABLE 2 | Comparison of clinical characteristics according to the diagnosis and treatment procedures.

Variables	Conventional management	Endoscopic diagnosis	Systematic endoscopic intervention	P value
Male	71(75.5%)	78(89.7%)	18(81.8%)	0.045
Age (years)	59.5	63.2	61.8	0.005
Body mass index (kg/m2)	22.3	21.5	22.0	0.211
Smoking index	507.6	497.2	429.6	0.802
Drinking history	32(34.0%)	30(34.5%)	7(31.8%)	0.972
Diabetes Mellitus	7(7.4%)	12(13.8%)	4(18.2%)	0.218
Hypertension	25(26.6%)	23(26.4%)	4(18.2%)	0.699
Gastric ulcer and/or gastritis	65(69.1%)	62(71.3%)	17(77.3%)	0.749
Tumor location				0.545
upper thoracic	12(12.8%)	6(6.9%)	3(13.6%)	
middle thoracic	58(61.7%)	52(59.8%)	14(63.6%)	
lower thoracic	24(25.5%)	29(33.3%)	5(22.7%)	
Tumor staging				0.058
I	13(13.8%)	23(26.4%)	8(36.4%)	
II	31(33.0%)	29(33.3%)	2(9.1%)	
III	46(49.0%)	30(34.5%)	11(50.0%)	
IV	4(4.2%)	5(5.7%)	1(4.5%)	
Postoperative fever	27(28.7%)	28(32.2%)	5(22.7%)	0.666
Neo-adjuvant therapy	11	16	3(13.6%)	0.443
Anastomosis infection	Unavailable	52(59.8%)	15(68.2%)	0.469
Leak size(mm^2)	Unavailable	52.34	52.09	0.992

TABLE 3 | Characteristics of EAL of the 22 study patients who underwent systematic endoscopic intervention.

Patient	Age and sex	Time to diagnosis (Days)	Location of anastomosis	Opening size (mm)	Infection of anastomosis	Number of sessions	Heling time (Days after surgery)	Clinical Outcome	Complication
13 Endoscopic sealants									
1	63; Male	7	Intrathoracic	10*9	yes	1(refusing following sessions)	90	Died	Died
2	57; Male	8	Intrathoracic	10*10	yes	1(refusing following sessions)	85	Discharged	None
3	69; Male	7	Intrathoracic	15*10	yes	3	73	Discharged	None
4	60; Male	7	Cervical	8*6	yes	2	52	Discharged	None
5	62; Male	7	Cervical	8*8	yes	2	51	Discharged	None
6	54; Male	7	Intrathoracic	3*3	no	4	44	Discharged	None
7	44; Male	10	Intrathoracic	4*4	no	3	37	Discharged	None
8	59; Male	7	Cervical	12*10	yes	1	36	Discharged	Stenosis
9	73; Male	4	Cervical	2*2	no	2	28	Discharged	None
10	57; Male	9	Intrathoracic	7*5	no	2	23	Discharged	None
11	50; Male	8	Intrathoracic	5*5	no	2	22	Discharged	None
12	66; Female	10	Intrathoracic	5*5	no	2	15	Discharged	None
13	50; Male	8	Intrathoracic	2*2	no	1	15	Discharged	None
8 Endoscopic Clips									
14	61; Female	7	Cervical	7*5	yes	2	78	Discharged	None
15	69; Male	7	Cervical	10*10	yes	3	69	Discharged	None
16	54; Male	7	Cervical	8*8	yes	2	46	Discharged	None
17	72; Male	8	Intrathoracic	15*3	no	4	38	Discharged	None
18	75; Male	7	Intrathoracic	4*4	yes	1	36	Discharged	None
19	71; Female	7	Intrathoracic	3*3	yes	2	35	Discharged	None
20	66; Female	7	Cervical	7*5	yes	1	33	Discharged	None
21	63; Male	7	Cervical	10*8	yes	1	32	Discharged	None
1 Combination Therapy									
22	65; Male	7	Intrathoracic	12*6	yes	1	39	Discharged	None

*Length *(and) Width.*

TABLE 4 | Overall healing the 203 patients with EAL.

	No. of patients	Healing rate	Median Healing time (95%CI)
Groups	(N=203)	*P*<0.001	
Conventional management	74/94	82.2%	67(56.27-77.73 Days)
Endoscopic diagnosis	78/87	89.7%	51(44.86-57.14 Days)
Systematic endoscopic intervention	21/22	95.5%	37(33.32-40.68 Days)
Total	173/203	85.2%	54(49.79-58.21 Days)

CI, Confidence Intervals.

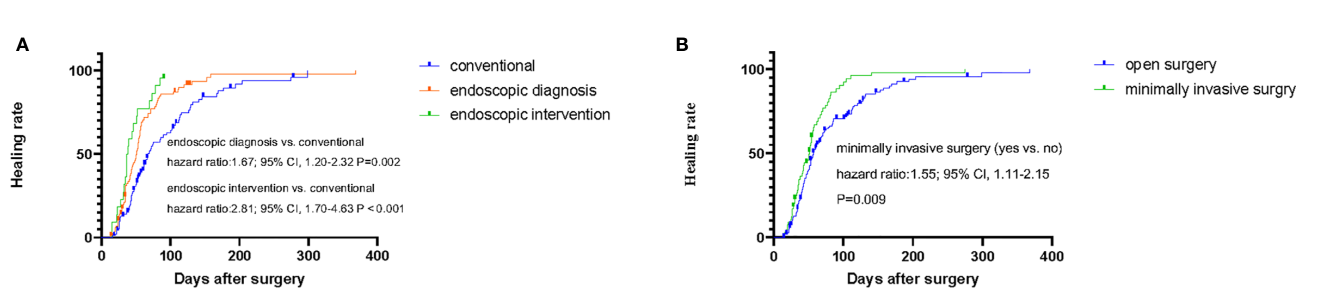

FIGURE 2 | (A, B) Kaplan–Meier curves for independent predictors of EAL healing.

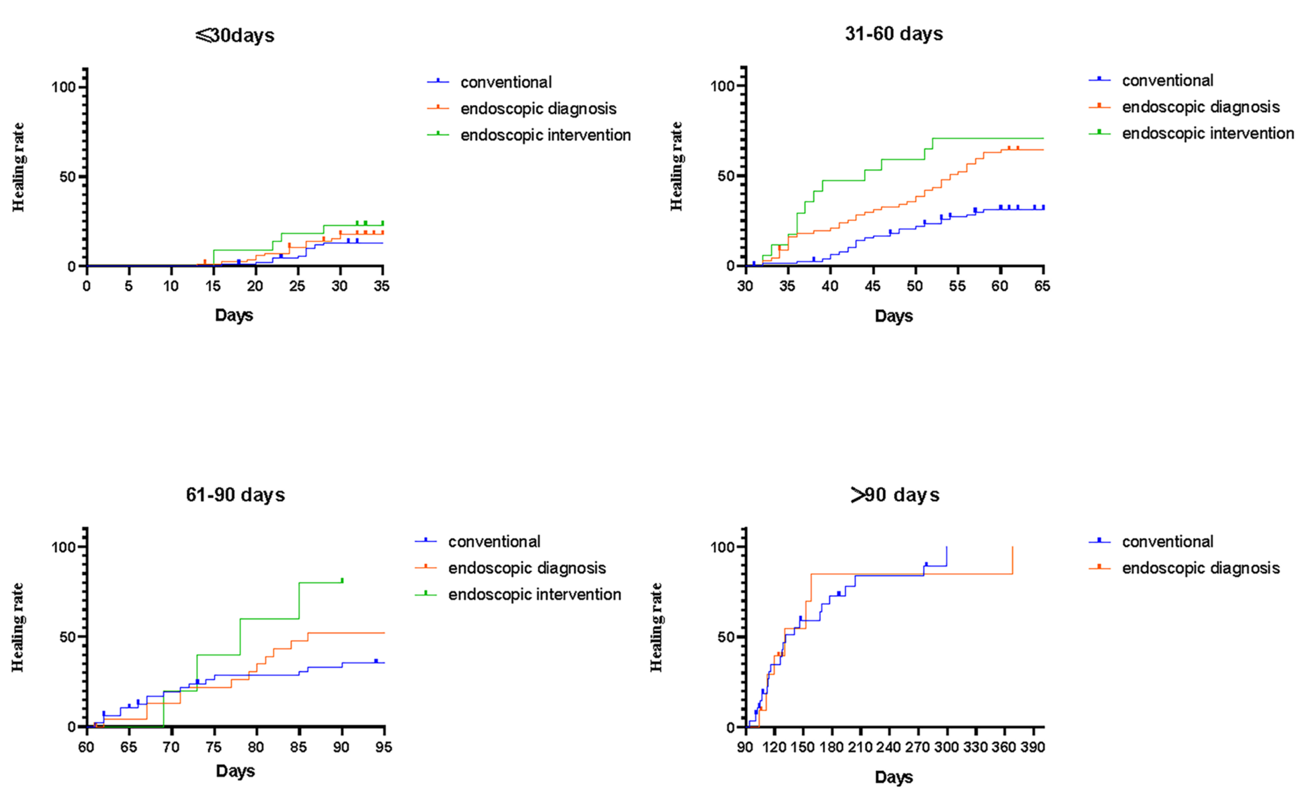

FIGURE 3 | The survival curves of Interventional vs. Endoscopic groups at different landmark period.

differences among the 3 groups were not statistically significant with regard to healing (**Figures 3** and **4**).

Landmark Analysis for 30-60 Days

Again, the possibility of death in the systematic interventional group was significantly lower than that of the conventional group; meanwhile, a similar advantage was found in the endoscopic diagnostic group when compared with the conventional group. Moreover, when compared with the traditional group, the endoscopic intervention group and endoscopic diagnostic group showed not only a significant reduction in the mortality rate but also a statistically significant increase in the recovery rate; the hazard ratios for healing were 3.86 (95% CI, 1.93-7.75; P<0.001) and 2.57 (95% CI, 1.56-4.25; P<0.001), respectively (**Figures 3** and **4**).

Landmark Analysis for 60-90 Days

A lower mortality rate was found in the endoscopic diagnostic group than in the conventional group, which had 4 fatal cases, yet the mortality rate seemed to be higher in endoscopic interventional group than in the remaining two groups; notably, only 5 patients were in the endoscopic interventional group during this period, which should be taken into consideration. During this period, the HRs for healing were 2.69 (95% CI, 0.89-8.10; P=0.08) in the endoscopic interventional group and 1.50 (95% CI, 0.71-3.18; P=0.29) in the endoscopic diagnostic group when compared with their counterparts (**Figures 3** and **4**).

Landmark Analysis for Post-90 Days

It should be noted that all patients in the systematic endoscopic group reached the study endpoints. As illustrated in **Figures 3** and **4**, during the period 3 months after surgery, the endoscopic diagnostic group and conventional group healed at very similar speeds, and the mortality rates were 3/11 (27.3%) and 6/28 (21.4%), respectively.

Mortality and Complications:

Of the 203 enrolled patients, there were 20 (21.28%) fatal cases among the 94 patients in the conventional group, 9 (10.34%) fatal cases among the 87 patients in the endoscopic diagnostic group and 1 (4.55%) fatal case among the 22 cases in the endoscopic intervention group; this difference was statistically significant (Fisher exact test, *P*=0.049<0.05).

Regarding compilations, 24 (25.53%) complications occurred in the 94 patients in the conventional group, 19 (21.84%) occurred in the 87 patients in the endoscopic diagnostic group, and 1 (4.55%) occurred in the 22 patients in the endoscopic intervention group, but the differences among the three groups were not statistically significant (Fisher's exact test, *P*=0.089>0.05).

Therefore, in conclusion, 30 patients died, and 44 patients developed EAL-related complications. The overall mortality and complication rates were 14.78% and 21.67%, respectively. The overall survival rate was 78.7% (95% CI: 70.3 to 87.2%) in the conventional management group, 89.7% (95% CI: 83.1 to 96.2%)

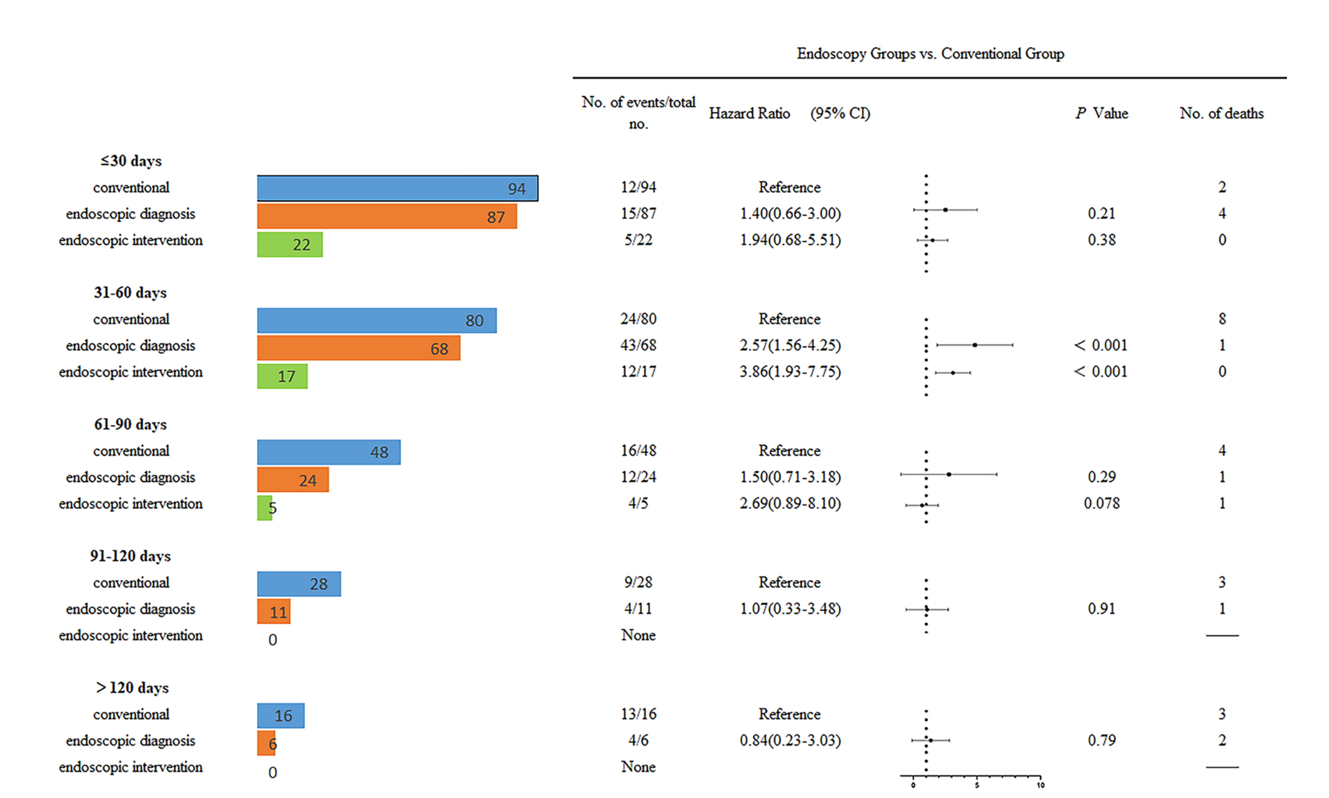

FIGURE 4 | Overall healing of patients with EAL based on landmark analysis and corresponding hazard ratios. The number of unhealed patients with EAL and the corresponding hazard ratios are shown at various time points for the groups. A total of 94 patients in the conventional group, 87 in the endoscopic diagnosis group, and 22 in the endoscopic intervention group; the corresponding numbers at 60 days were 48, 24, and 5, and the corresponding numbers at 90 days were 28, 11, and 0.

in the endoscopic diagnostic group and 95.5% (95% CI: 86.0 to 100%) in the systematic endoscopic intervention group (**Table 5**).

DISCUSSION

Post-esophagectomy anastomotic leakage or fistula is a serious and common complication in patients with esophageal carcinoma (2–5, 7, 9–11). Over the past decade, few studies have adequately assessed and evaluated the status of endoscopic technology for the diagnosis and treatment of EAL, and to the best of our knowledge, this paper is the first to discuss the relationship between EAL healing and the timeframe in which healing occurred, not just whether it was healed or not. We found that patients with EAL after endoscopic intervention may have the fastest healing speed at 30-60 days (1-2 months) after surgery based on the landmark analysis results (compared with the conventional management group and the endoscopic diagnosis group, HR values were 3.86 and 2.57, respectively). This may provide a reference to help clinicians make better clinical decisions at different time periods.

EAL can affect the operative efficacy of esophageal cancer, prolong hospital stays and increase postoperative mortality (2, 5–11). EAL can even impair patient quality of life, long-term survival of esophageal cancer and subsequent treatment of esophageal masses using strategies such as adjuvant chemoradiotherapy (2, 6, 8, 10, 25). Finally, because EAL potentially causes subsequent critical postoperative complications, such as intrathoracic abscess, tracheoesophageal fistula and hemorrhage, both predicting and

TABLE 5 | Mortality and Complications of the 203 patients with EAL.

Groups	No. of patients	Mortality	Complications			Total
	(N=203)		AS	SF	H	
Conventional management	94	20(21.28%)	19(20.21%)	2(2.13%)	3(3.19%)	24(25.53%)
Endoscopic diagnosis	87	9(10.34%)	14(16.09%)	3(3.45%)	2(2.30%)	19(21.84%)
Systematic endoscopic intervention	22	1(4.55%)	0	0	1(4.55%)	1(4.55%)
Total	203	30(14.78%)	33(16.26%)	5(2.46%)	6(2.96%)	44(21.67%)

AS, anastomotic stenosis; SF, sinus formation; H, hemorrhage.

treating EAL are clinically significant issues. Therefore, it is of vital importance to explore a safe and effective treatment model for EAL. The present study focused on the role of systematic endoscopic intervention in postoperative EAL detection and rehabilitation. Our study included patients with EAL following surgery for esophageal cancer at a specialized cancer center, representing a larger, more homogenous patient population.

Given the high incidence of anastomotic leakage and the severe harm it causes, most centers prefer to assess the anastomosis diagnostically before starting oral intake after esophagectomy. The use of endoscopy, however, has been questioned due to the theoretical threat of disrupting the anastomosis or aggravating EAL (17–19). At present, many surgeons in China still pay little attention to or are reluctant to attempt to address EAL by endoscopic means for fear of the possible complications mentioned above. Our findings show that properly performed endoscopic intervention does not cause injury to the anastomosis, and a certain number of studies have proven the safety of endoscopy (14–16); although an intraluminal pressure greater than 80 cmH2O is known to be required to disrupt the anastomosis, the intraluminal maximum insufflation at the anastomosis never exceeds 9 cmH2O and thus rarely disturbs blood flow in the conduit (14, 26–28).

Patients who underwent endoscopic diagnosis and/or intervention had lower probabilities of death and complications than the conventional group in our study (**Table 5**). It was found that the overall mortality was 14.78%. By comparison, the mortality rates presented in previous studies have ranged from 2.1% to 35.7% (2, 8, 9, 11, 29, 30).

Patients in the endoscopic diagnostic group vs. conventional group had a lower risk of death (odds ratio (OR) =0.43; 95% CI, 0.18-1.00); after adjustment by the Bonferroni method, however, there were no statistically significant differences between the groups with regard to mortality (P=0.067>0.01667). Patients in the endoscopic intervention group vs. conventional group also had a lower risk of death (odds ratio (OR) =0.18; 95% CI, 0.02-1.40), but again, no statistically significant difference was observed (P=0.119>0.01667). Regarding compilations, 24 (25.53%) complications occurred in the 94 patients in the conventional group, 19 (21.84%) occurred in the 87 patients in the endoscopic diagnostic group, and 1 (4.55%) occurred in the 22 patients in the endoscopic intervention group, but the differences among the three groups were not statistically significant (Fisher's exact test, P=0.089>0.05).

Moreover, the sensitivity and specificity of endoscopic assessment were superior to those of traditional methods. In our study, the sensitivity of traditional diagnostic methods was 75.81%, close to the previously reported CT diagnostic sensitivity of 71.4-80% (5, 12, 13, 26, 27), which is unsatisfactory. While endoscopy not only correctly identified the 5 false-positive patients evaluated by radiological contrast study but also determined 30 leaks that were missed in the radiological contrast study, and both the reported sensitivity and specificity of endoscopic diagnosis could reach 100% (16).

Additionally, the procedure is convenient, as it can be conducted at the bedside, even for patients on ventilation, without worsening an existing EAL. More remarkably, endoscopy is the only approach with the capacity to determine the viability of the gastric conduit and to grade the EAL according to the results of endoscopic observation, which will be highly valuable in making more accurate clinical decisions based on each individual, including the adjustment of the drainage strategy, the need for surgical treatment, the use of antibiotic regimens, adequate nutritional support, and so on. In summary, endoscopic diagnosis offers the advantages of possibly avoiding repetitive examinations, aiding in early diagnosis, guiding further treatments, improving the sensitivity and specificity, and reducing complications, which could make the treatment process more smoothly and accurately, and then enable patients to achieve better clinical outcomes.

With regard to the treatment, although we were interested in determining whether the EAL heals, we were more curious about when. To our knowledge, this paper is the first to discuss the outcome of anastomotic leaks in association with healing time rather than whether it healed based on the results of landmark analysis. Previous studies have reported 55.8-100.0% healing rates for EAL when treated with endoscopic strategies (31–50), while our research suggests that the healing rates could reach up to 95.5% if endoscopic management methods were implemented, and the number would still be near 90% if only endoscopic diagnosis was implemented [**Table 2** and **Figure 5** (31–50)].

Moreover, we elucidated the actual healing time and successfully identified two statistically significant independent factors associated with the time needed for healing EAL, of which different endoscopic strategies were included (**Table 1**).

Regarding how to reduce the healing time, endoscopy offered a satisfactory result. The goal of the landmark analysis method was to estimate the healing probabilities in each group at the landmark time in an unbiased way (22–24).The landmark analysis revealed that once the endoscopic intervention was administered, the superiority of endoscopic intervention compared with conventional management persisted until the leisure healed, and this advantage is most pronounced 1 to 2 months after surgery, which indicated that early intervention is of vital importance to the recovery process of EAL. Patients with EAL were found to heal faster than conservative patients even when only endoscopic diagnosis was conducted without systematic endoscopic intervention at the early stage; however, the superiority of the endoscopic diagnostic group compared with the traditional group before 90 days of follow-up was lost after 90 days. Of course, the healing time of EAL would be shorter if endoscopic intervention was added. Interestingly, it was found that if the patients in the endoscopic diagnosis group did not achieve clinical cure at an early stage when there was a healing advantage, their merits of rapid rehabilitation would nowhere to be seem as time goes by, put it another way, they would be found to have similar clinical outcomes as those in the conventional group at later stages of the follow-up, which provides a new perspective on the importance of early diagnosis of EAL, and suggests that patients with EAL may benefit from remedial endoscopic managements.

To summarize, our study provides new evidence that endoscopic therapy can offer an important prognostic benefit to EAL patients. Endoscopic intervention could be considered

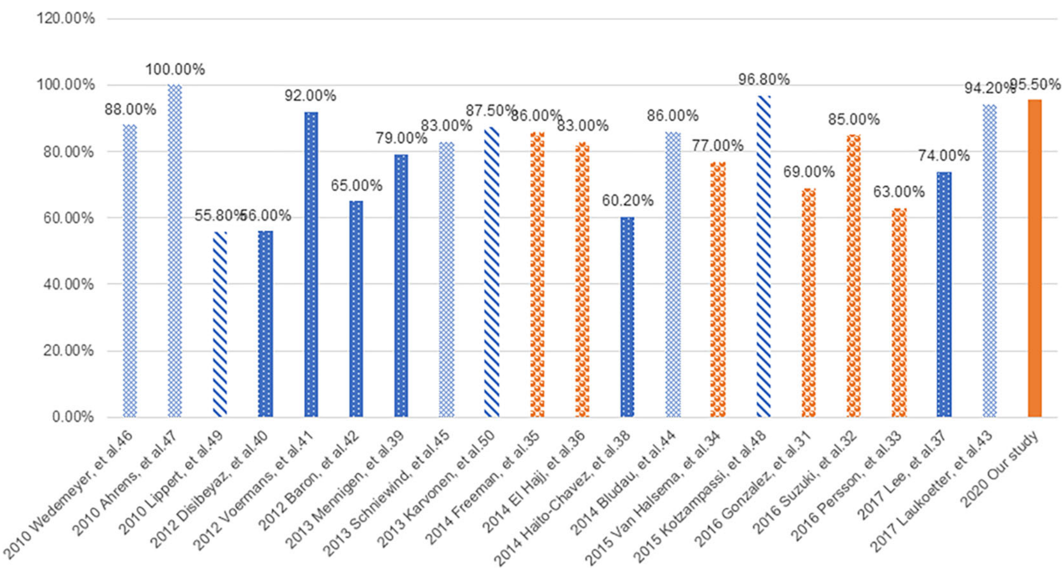

FIGURE 5 | Healing rates of EAL about part of previous studies.

superior to other regimens in managing anastomotic leakage at any period after esophagectomy. The landmark analysis results suggested that for EAL rehabilitation, endoscopic therapy can be attempted as a remedial measure at any period, even if endoscopic intervention was not employed at the early stage, since remedial endoscopy could shorten the healing time of EAL.

In terms of the clinical application of the results of this study, it is important to take into account the merits of a shorter healing time. Shortening the time needed for EAL healing has some potential clinical advantages, including reducing the incidence of subsequent critical postoperative complications and decreasing the cost of hospitalization due to the shortened hospitalization period. In addition, a shorter healing time allows for smoother coordination of the administration of adjuvant therapy when patients have cancers for which adjuvant therapy is indispensable.

The present study has several limitations. First, endoscopic vacuum-assisted closure (E-VAC) therapy was not carried out in our hospital; more specifically, E-VAC technology has not been widely used throughout China. E-VAC technology was first introduced in 2008 by Weidenhagen et al. (51) and has been proven to be safe and effective in some studies, with encouraging healing rates (93.3-93.5%) (52, 53). We look forward to using E-VAC technology in our hospital to help patients who have suffered from EAL. The second limitation is that the data for the present study were from a single institution, which may produce some bias in the preoperative management of patients, such as operative methods. In the future, these results should be validated in a multi–institutional, prospective, randomized, controlled trial using certain criteria, as mentioned above.

In summary, the results of this study suggest that systematic endoscopic intervention is an effective and safe method for the diagnosis and treatment of postsurgical leaks. This intervention leads to higher success rates and faster anastomotic healing and has the potential to reduce overall mortality. These findings could provide guidance for clinicians to promote earlier recovery from EAL.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

These authors contributed equally and share the first authorship. All authors contributed to the article and approved the submitted version.

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The Least Nodal Disease Burden Defines the Minimum Number of Nodes Retrieved for Esophageal Squamous Cell Carcinoma

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Background: Clinically, a single positive lymph node (SPLN) should indicate the least nodal disease burden in node-positive patients with esophageal squamous cell carcinoma (ESCC) and may also be used to define the minimum number of examined lymph nodes (NELNs) in ESCC patients.

Methods: Data from three Chinese cohorts of 2448 ESCC patients who underwent esophagectomy between 2008 and 2012 were retrospectively analyzed. Based on lymph node status, patients were divided into two groups: N0 ESCC and SPLN ESCC. A Cox proportional hazards regression model was used to determine the minimum NELNs retrieved to maximize survival for ESCC patients with localized lymph node involvement. The results were then validated externally in the SEER database.

Results: A total of 1866 patients were pathologically diagnosed with N0 ESCC, and 582 patients were diagnosed with SPLN ESCC. The overall survival rate of patients with N0 ESCC was significantly better than that of patients with SPLN ESCC (HR 1.88, 95% CI 1.64-2.13, P<0.001), but no significant difference was found between SPLN ESCC patients with ≥ 20 lymph nodes harvested and N0 ESCC patients (HR 1.20, 95% CI 0.95-1.52, P=0.13). Analysis of patients selected from the SEER database showed the same trend, and no significant difference was observed between N0 ESCC patients and SPLN ESCC patients with ≥ 20 lymph nodes retrieved (HR: 1.02, 95% CI 0.72-1.43, P=0.92).

Conclusions: A minimum of 20 lymph nodes retrieved should be introduced as a quality indicator for ESCC patients with localized lymph node involvement.

Keywords: esophageal squamous cell carcinoma, surgery, lymph node dissection, lymph node count, prognosis

INTRODUCTION

Esophageal carcinoma was the sixth leading cause of cancer-related mortality and the seventh most common cancer worldwide in 2018 (1). Squamous cell carcinoma is the predominant pathological type. It is an extremely aggressive gastrointestinal cancer with a poor prognosis. Even after radical surgical resection, the recurrence rate ranges from 43 to 53%, and the 5-year overall survival (OS) rate ranges from 15-20% (2). Lymph node metastasis is the most common mode of tumor spread and is an important prognostic factor (3, 4).

Esophagectomy with radical lymphadenectomy remains the standard treatment for operable esophageal squamous cell carcinoma (ESCC) patients. The possible presence of occult tumor dissemination is the rationale for radical systematic lymphadenectomy. The number of retrieved lymph nodes is regarded as a quality indicator for ESCC surgery (5, 6). Theoretically, the greater the extent of lymphadenectomy is, the more similar the survival outcomes between node-negative and node-positive ESCC patients. The authors speculate that a certain number of lymph nodes retrieved may allow SPLN ESCC patients to experience the same survival benefits as N0 ESCC patients; if so, this cutoff point should be defined as the minimum requirement for an adequate extent of lymphadenectomy. The aim of this study was to define the minimum number of examined lymph nodes (NELNs) harvested for ESCC patients with limited lymph node involvement.

PATIENTS AND METHODS

Patients in the Training Cohort

Between 2008 and 2012, ESCC patients who underwent radical surgical resection at three high-volume centers in China (West China Hospital, Shantou University Medical College and Sun Yat-sen University Cancer Center) were enrolled in this retrospective analysis. The analysis was limited to patients with negative lymph nodes (N0) and a single positive lymph node (SPLN) based on the postoperative histopathological examination. The exclusion criteria were as follows: (1) patients with nonsquamous cell carcinoma; (2) patients receiving neoadjuvant therapy; (3) patients with cervical esophageal cancer; and (4) patients with surgical-related mortality (defined as death occurring within 1 month of the operation). All patients underwent subtotal esophagectomy with two-field lymphadenectomy, including the Sweet, Ivor-Lewis or McKeown approach depending on the location and extent of the tumor. The study protocol was approved by our institutional review board (2019-441). Informed consent was waived because of the retrospective nature of the study.

Lymph nodes were identified and detached from the operative specimen by the surgeons during surgery. Lymph node metastasis was assessed by expert pathologists. The patients were followed up every 3 months for the first 2 years after surgery and then every 6 months for the subsequent 3 years. Thereafter, follow-up visits were conducted annually until death or June 2016. The primary outcome was OS. OS was defined as the time from surgery to the date of death or the last clinical visit. Patients who were alive at the last follow-up were censored for OS.

Patients in the Validation Cohort

ESCC patients who underwent esophagectomy and lymphadenectomy between 2004 and 2016 were selected from the Surveillance, Epidemiologic, and End Results (SEER) database to perform external validation. The exclusion criteria were as follows: patients with incomplete data, patients with nonsquamous cell carcinoma, patients who died within 1 month of the operation, and patients with distant metastasis. Ultimately, a total of 1316 ESCC patients from the SEER database who fulfilled the inclusion and exclusion criteria were eligible for the analysis.

Statistical Analysis

Continuous variables are described as the mean ± standard deviation (SD), and categorical variables are described as the frequency (%). Distributions' normality of the variables was checked by Lilliefors-test. The chi-square test or Fisher's exact test was used to compare the distribution of categorical variables between groups. Continuous variables were analyzed using Student's t test or the Wilcoxon rank-sum test. Univariate analysis was performed to examine the association between potential predictors and survival. Factors with $P < 0.25$ in the univariate analysis and believed to be associated with cancer-related deaths were entered into a multivariate Cox proportional hazards regression model. A backward stepwise elimination of variables was used to construct the final model. A two-sided P value < 0.05 was considered statistically significant.

Patients in this study were divided into two groups: ESCC patients with no lymph node metastasis (N0) and ESCC patients with an SPLN. N0 patients were defined as the reference group and were compared with SPLN patients with various numbers of harvested lymph nodes. To define the minimum NELNs that need to be removed, a multivariate analysis was performed and adjusted for potential risk factors. A certain number of lymph nodes was regarded as the minimum NELNs that needs to be removed when the OS analysis of SPLN patients with a certain number of lymph nodes retrieved showed no significant difference compared with that of N0 ESCC patients. We did the Kaplan-Meier survival curves by the log-rank test, which was used to analyze the differences between the curves. Data analysis was performed with SPSS version 24.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

Patient Characteristics

A total of 2448 ESCC patients in the training cohort were included in this study. Among them, 582 patients were diagnosed with an SPLN. And 1866 patients were diagnosed with N0 who were defined as the reference group. A total of 1316 patients from the SEER database fulfilled the criteria and were further analyzed in this study as the validation cohort. Among them, 1079 patients were diagnosed with N0 ESCC, and 237 patients were diagnosed with SPLN ESCC. The demographics and clinical characteristics of the training and validation cohorts are shown in **Table 1**.

Minimum NELNs for ESCC Patients With Localized Lymph Node Involvement

To maximize survival, a number of nodes need to be removed for ESCC patients with localized lymph node involvement. First, univariate analysis was performed. Age, sex, pT stage, tumor location, tumor differentiation and adjuvant therapy were identified as potential prognostic factors of ESCC patients (**Table 2**). Then, a Cox proportional hazards regression model for OS was generated between N0 and SPLN ESCC patients and adjusted for age, sex, pT stage, tumor location, tumor differentiation and adjuvant therapy (**Table 2**). N0 patients were defined as the reference group and were compared with SPLN patients with various numbers of harvested lymph nodes. Adjusted estimated hazard ratios for SPLN ESCC patients with different NELNs were shown in **Figure 1**. Patients with N0 ESCC had a significantly better OS rate than those with SPLN ESCC (HR 1.88, 95% CI 1.64-2.13, P<0.001, **Figure 2A**). However, no significant difference was found between SPLN ESCC patients with ≥ 20 lymph nodes harvested and N0 ESCC patients (HR 1.20, 95% CI 0.95-1.52, P=0.13, **Figure 2B**). Therefore, at least 20 lymph nodes must be resected for SPLN ESCC patients to maximize survival. Since SPLN ESCC indicates the least nodal disease burden, we speculate that 20 is the minimum number of lymph nodes that need to be dissected for ESCC patients with localized lymph node involvement.

There were 674 patients in the training cohort and 157 patients in the validation cohort had 20 or more lymph node dissection. Then, we validated whether the cutoff of 20 lymph nodes was also suitable for ESCC patients selected from the SEER database. Intriguingly, analysis of patients selected from the SEER database showed the same result: the OS of N0 ESCC patients was significantly better than that of SPLN ESCC patients (HR 1.68, 95% CI 1.42-1.98, P<0.001, **Figure 2C**). However, the OS rate of SPLN ESCC patients with ≥ 20 lymph nodes harvested was not significantly different from that of N0 ESCC patients (HR: 1.02, 95% CI 0.72-1.43, P=0.92, **Figure 2D**), which validated the results of the multicenter cohort described above.

Figure 3 shows OS according to the number of lymph nodes harvested. In detail, for SPLN ESCC patients with 0 to 19 lymph nodes retrieved, the 1-year, 3-year and 5-year OS rates were 78.7%, 61.2% and 31.3%, respectively. For SPLN ESCC patients with more than 20 lymph nodes retrieved, the 1-year, 3-year and 5-year OS rates were 86.6%, 56.7% and 41.8%, respectively (1-year the HRs with 95%CI was 0.59, 0.37-0.93; 3-year the HRs with 95%CI was 0.69, 0.53-0.91 and 3-year the HRs with 95%CI was 0.73, 0.57-0.94, **Figure 3A**). A trend of improved OS was also observed for SPLN ESCC patients from the SEER database (1-year the HRs with 95%CI was 0.43, 0.21-0.87; 3-year the HRs with 95%CI was 0.40, 0.25-0.62 and 3-year the HRs with 95%CI was 0.42, 0.27-0.63, **Figure 3B**). Therefore, more lymph nodes harvested during surgical resection predicts improved OS for SPLN ESCC patients.

COMMENT

The presence of lymph node metastasis affects the prognosis of ESCC patients (7). The latest UICC/AJCC staging system proposed pN classification based on the number of metastatic lymph nodes (8). Nodal disease burden includes not only the positive lymph nodes examined microscopically but also the occult tumor dissemination. Since the number of metastatic nodes cannot be assessed precisely before or during surgery, extensive lymphadenectomy could eradicate both overt metastasis and occult lymph node metastasis, which may result in a better prognosis and reduce stage migration (9–11). However, a greater number of retrieved lymph nodes may increase the risk of intraoperative and postoperative morbidity and the mortality rate (12). The optimal extent of lymph node

TABLE 1 | Demographics and clinical characteristics of the two cohorts.

Variables	Training cohort			Validation cohort		
	N0 (n = 1866)	SPLN (n = 582)	*P* value	N0 (n = 1079)	SPLN (n = 237)	*P* value
Age (Mean ± SD, years)	59.4 ± 8.5	59.5 ± 8.8	0.87	63.8 ± 9.6	63.5 ± 9.4	0.73
Gender (n, %)			0.02			0.33
Male	1417 (75.9%)	469 (80.6%)		651 (60.3%)	151 (63.7%)	
Female	449 (24.1%)	113 (19.4%)		428 (39.7%)	86 (36.3%)	
pTNM stage (n, %)			< 0.001			< 0.001
I/II	1721 (92.2%)	147 (25.3%)		858 (79.5%)	89 (37.6%)	
III	145 (7.8%)	435 (74.7%)		221 (20.5%)	148 (62.4%)	
NELN (mean ± SD)	15.6 ± 9.4	16.6 ± 8.7	0.02	14.4 ± 10.6	14.8 ± 10.7	0.71
pT stage (n, %)			< 0.001			< 0.001
pT1/pT2	762 (40.8%)	149 (25.6%)		560 (51.9%)	88 (37.1%)	
pT3/pT4	1104 (59.2%)	433 (74.4%)		519 (48.1%)	149 (62.9%)	
Differentiation (n, %)			0.06			0.006
Well/Moderate	1205 (64.6%)	351 (60.3%)		611 (56.6%)	111 (46.8%)	
Poor	661 (35.4%)	231 (39.7%)		468 (43.4%)	126 (53.2%)	

TABLE 2 | Univariate and multivariate cox regression analysis of independent prognostic factors for ESCC patients.

Variables	Univariate analysis				Multivariate analysis			
	Exp (B)	95% CI		*P* value	Exp (B)	95% CI		*P* value
		Lower	Upper			Lower	Upper	
Age	1.12	0.99	1.27	0.07	1.09	0.96	1.23	0.20
Gender	0.91	0.79	1.06	0.23	0.96	0.83	1.11	0.58
pT	1.94	1.69	2.23	< 0.001	1.92	1.66	2.21	< 0.001
Differentiation	1.22	1.07	1.38	0.002	1.28	1.13	1.46	< 0.001
Tumor location	0.90	0.77	1.04	0.13	0.85	0.74	0.99	0.03
Adjuvant therapy	1.00	0.87	1.14	0.98	0.86	0.75	0.98	0.03
LN metastasis	1.88	1.64	2.14	< 0.001	1.75	1.53	1.99	< 0.001

dissection for ESCC patients during esophagectomy has not been clearly defined (10, 13–15). In addition, since the increasing percentage of older patients may result in more patients considered marginal candidates for esophageal resection and not all of the patients may have the physiologic reserve to receive timely postoperative adjuvant therapy after surgery (16, 17), adequate resection is needed to reduce locoregional failure. Therefore, the optimal extent of lymphadenectomy needs to be determined for ESCC patients undergoing radical resection.

Lymphadenectomy strategy may be different for esophageal cancer patients with different lymph node status. According to Peyre et al. (18), the probability of systemic disease exceeds 50% when 3 or more nodes are involved and approaches 100% when 8 or more nodes are involved. Dr. Omloo and Hulscher et al. demonstrated that an extended lymphadenectomy did not provide survival benefit for esophageal cancer patients with more than 8 positive lymph nodes (19, 20). Therefore, a survival benefit may not be achieved through extended lymphadenectomy for patients with an advanced pN stage, and multimodality treatment may be needed (15). Regarding ESCC patients with localized lymph node involvement (especially SPLN ESCC patients), we speculate that they are still at a stage where they can be cured by surgery. In comparison with ESCC patients with two or more positive lymph nodes, SPLN ESCC patients may need the minimum NELNs harvested to maximize survival. Accordingly, we selected SPLN ESCC patients to investigate the minimum NELNs to maximize OS for ESCC patients with limited lymph node involvement.

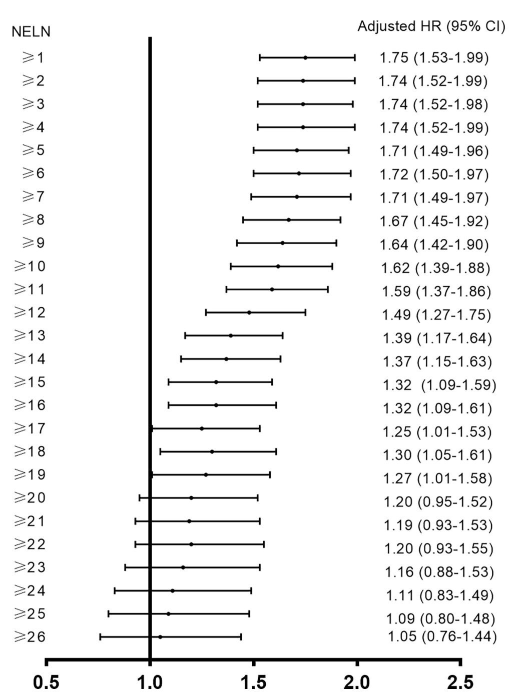

FIGURE 1 | Adjusted estimated hazard ratios for SPLN ESCC patients with different NELN (Reference group: N0 ESCC patients).

If clinically positive lymph nodes are suspected before surgery, neoadjuvant chemoradiation therapy followed by surgery is routinely recommended to maximize survival (12, 21, 22). CT, endoscopic ultrasound and positron emission tomography are the most common preoperative work-ups for ESCC patients. However, they are not precise enough to predict lymph node metastasis (23), and undetected nodal disease is usually encountered with upfront esophagectomy (24). Esophagectomy and sufficient lymph node resection are essential for accurate staging and improving survival, especially for ESCC patients with localized lymph node involvement.

Cut-point survival analysis is usually used to investigate the optimal cutoff point of the minimum NELNs to maximize survival for cancer patients (25, 26). However, our study is markedly different from previous studies. We utilized a novel method to investigate the minimum number of lymph nodes examined for patients with esophageal squamous cell carcinoma. We regarded ESCC node-negative patients as the reference group to investigate the minimum NELNs for overt metastasis and micrometastasis to be eradicated in SPLN patients. Ultimately, 20 lymph nodes was determined to be the minimum NELNs to maximize survival for SPLN ESCC patients; therefore, a total of 20 lymph nodes retrieved may be the minimum number of lymph nodes to eliminate nodal disease. Since SPLN ESCC patients have a lower potential for lymph node metastasis than other pN+ ESCC patients, we speculate that 20 might be the minimum NELNs for ESCC patients with a relatively low nodal disease burden.

It is important to externally validate the results of our study in other clinical settings, so we retrieved data from the SEER

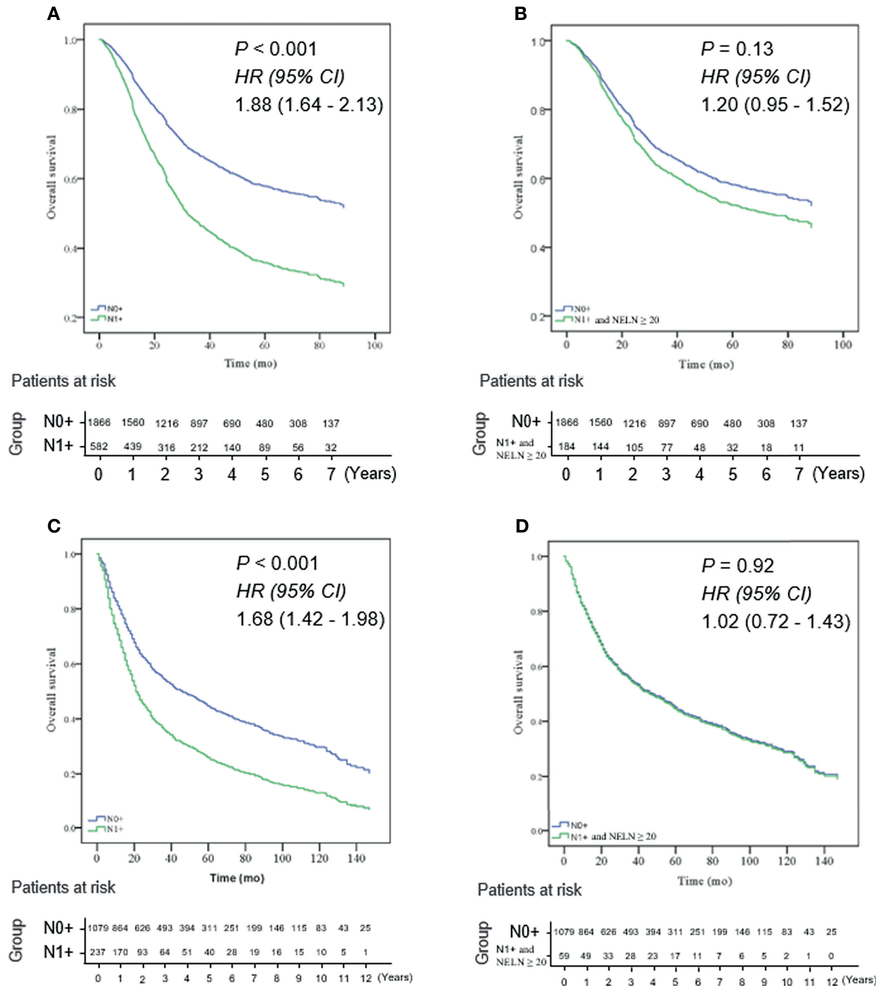

FIGURE 2 | **(A)** N0 ESCC patients had a significantly better OS rate than those with SPLN (N1 +) ESCC in the training cohort (HR 1.88, 95% CI 1.64 - 2.13, *P* < 0.001); **(B)** no significant difference was found between SPLN ESCC patients with ≥ 20 lymph nodes harvested and N0 ESCC patients in the training cohort (HR 1.20, 95% CI 0.95 - 1.52, *P* = 0.13); **(C)** OS of N0 ESCC patients was significantly better than that of SPLN ESCC patients in the validation cohort (HR 1.68, 95% CI 1.42 - 1.98, *P* < 0.001); **(D)** OS rate of SPLN ESCC patients with ≥ 20 lymph nodes harvested was not significantly different from that of N0 ESCC patients in the validation cohort (HR: 1.02, 95% CI 0.72 - 1.43, *P* = 0.92).

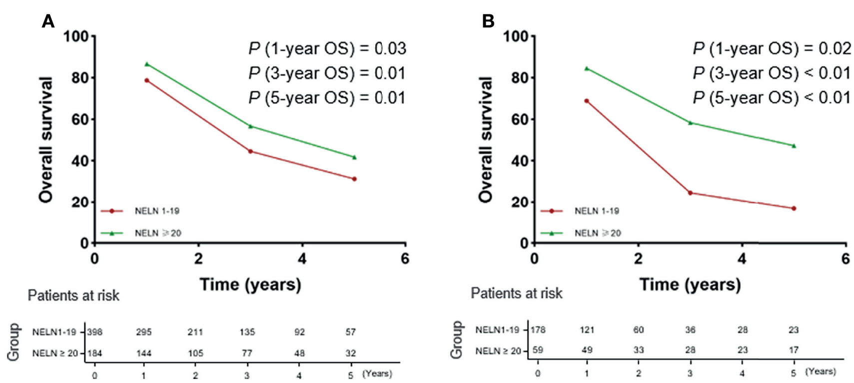

FIGURE 3 | 1-year, 3-year and 5-year OS rates of SPLN ESCC patients with 1-19 lymph nodes retrieved (Red line) and ≥ 20 lymph nodes retrieved (Green line). **(A)** the training cohort; **(B)** the validation cohort.

database for further analysis. Because the patients in the training and validation cohorts lived in two parts of the world, they had completely different clinicopathological characteristics. Intriguingly, patients selected from the SEER database showed the same trend as those in the base cohort. The results obtained from the validation cohort strengthen our research and indicate that our results have good universality. In clinical practice of upfront surgery for patients with ESCC, at least 20 lymph nodes should be resected and it may be a quality indicator.

The result of this multicenter study was validated externally by using data from the SEER database, but it has some limitations. This was a retrospective study, and no subgroup analysis was conducted on each pT stage because of the small number of SPLN patients. ESCC patients with negative nodes were defined as the reference group, but a number of patients with false negatives may have been included in the group. Therefore, 20 may be the minimum NELNs for pN+ ESCC patients with limited lymph node involvement. In addition, patients who received neoadjuvant were not included in this study. The present result may be applicable only to operable ESCC patients undergoing upfront surgery. Both neoadjuvant chemoradiotherapy and extensive lymph node dissection improve locoregional tumor control (27), so patients receiving neoadjuvant chemoradiotherapy might need extended resection, and a different lymph node dissection strategy may be needed. Further studies should investigate the minimum NELNs for ESCC patients receiving neoadjuvant chemoradiotherapy.

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 institutional review boards of each center approved this study. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

L-QC and J-HF contributed the idea and design. HZ and XY collected the data. All authors contributed to the article and approved the submitted version.

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A Machine Learning-Modified Novel Nomogram to Predict Perioperative Blood Transfusion of Total Gastrectomy for Gastric Cancer

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Background: Perioperative blood transfusion reserves are limited, and the outcome of blood transfusion remains unclear. Therefore, it is important to prepare plans for perioperative blood transfusions. This study aimed to establish a risk assessment model to guide clinical patient management.

Methods: This retrospective comparative study involving 513 patients who had total gastrectomy (TG) between January 2018 and January 2021 was conducted using propensity score matching (PSM). The influencing factors were explored by logistic regression, correlation analysis, and machine learning; then, a nomogram was established.

Results: After assessment of the importance of factors through machine learning, blood loss, preoperative controlling nutritional status (CONUT), hemoglobin (Hb), and the triglyceride–glucose (TyG) index were considered as the modified transfusion-related factors. The modified model was not considered to be different from the original model in terms of performance, but is simpler. A nomogram was created, with a C-index of 0.834, and the decision curve analysis (DCA) demonstrated good clinical benefit.

Conclusions: A nomogram was established and modified with machine learning, which suggests the importance of the patient's integral condition. This emphasizes that caution should be exercised regarding transfusions, and, if necessary, preoperative nutritional interventions or delayed surgery should be implemented for safety.

Keywords: gastric cancer, total gastrectomy, blood transfusion, nomogram, machine learning

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INTRODUCTION

Gastric cancer (GC) remains a significant health issue worldwide, and surgery is still the preferred treatment method. GC is the third leading cause of cancer-related deaths worldwide (1, 2). The increasing prevalence of upper and middle tumors, as well as the larger extent of resection and the difficulty of anastomosis in total gastrectomy (TG), has prompted scholars to focus on research related to TG (3, 4).

A significant proportion of patients requires blood transfusion during the perioperative period of gastrointestinal surgery, which has become a common treatment (4, 5). The preoperative nutritional status, tumor consumption, and intraoperative hemorrhage determine the need for perioperative blood transfusion. Studies have shown that whether it is gastrectomy or colorectal surgery, blood transfusion is a risk factor affecting the prognosis of patients (6). However, only a few studies have focused on the influence of blood transfusion on patients' short-term outcomes. Additionally, there is misuse or neglect of blood transfusion in addition to the variability of patients' conditions. Meanwhile, studies have indicated that the choice of blood transfusion depends on the details of the surgical procedure, preoperative hemoglobin (Hb), and tumor stage, among others, and blood transfusion therapy is still clinically significant for critically ill patients (7).

In the current environment affected by coronavirus disease 2019 (COVID-19), perioperative blood transfusion reserves are extremely limited; therefore, it is important to develop plans for perioperative blood transfusions. No study has provided guidance on the prediction of blood transfusion outcomes. Machine learning is an emerging technology for analyzing data, improving clinical decision-making, and establishing predictive models (8–10).

This study used readily available clinical data to build a predictive model identifying patients at risk of perioperative transfusion during TG. Furthermore, machine learning was used to simplify the model to obtain a streamlined and accurate prediction model. This model allows clinicians to actively prepare blood resources, advance preoperative interventions, and ensure the clinical safety of patients.

MATERIALS AND METHODS

Study Patients

This retrospective study collected the data of GC patients undergoing TG with D2 dissection at The First Affiliated Hospital of Soochow University from January 2018 to January 2021. **Figure 1** shows the patient selection process. A total of 513 patients were included according to the inclusion and exclusion criteria. The Ethics Committee of the First Affiliated Hospital of Soochow University approved this study. The protocol of this retrospective observational study involved minimal risk and did not present a threat to the health of the subjects.

Abbreviations: TG, total gastrectomy; PSM, propensity score matching; GC, gastric cancer; CONUT, control nutritional status; Hb, hemoglobin; TyG, triglyceride–glucose; C-index: concordance index; DCA, decision curve analysis; BMI, body mass index; PNI, prognostic nutritional index; ALB, albumin; LR, logistic regression; Tree, decision tree learning; XGB, extreme gradient boosting; RF, random forest; GBDT, gradient boosting decision tree; GBM, light gradient boosting machine; AUC, area under the curve; ROC, receiver operating characteristic; LADG, laparoscopy-assisted distal gastrectomy; CS, circle stapler; LS, linear stapler.

Inclusion and Exclusion Criteria

The inclusion criteria of this study were as follows: 1) preoperative or postoperative pathology consistent with gastric malignancy and 2) patients having undergone TG with D2 lymphadenectomy. The exclusion criteria were: 1) stage IV proven in any form; 2) palliative surgery; 3) combined organ removal; and 4) neoadjuvant chemotherapy.

Data Collection

In this study, blood transfusion, mainly perioperative blood transfusion, was defined as the transfusion from the first admission to discharge. Moreover, perioperative blood transfusion was mainly determined by the physician according to the patient's condition, with no specific criteria for blood transfusion and no strict regulations to regulate transfusion thresholds.

The following baseline data were collected: age, gender, body mass index (BMI), Hb at initial evaluation after admission and before discharge, preoperative controlling nutritional status (CONUT) score, preoperative triglyceride–glucose (TyG) index, preoperative prognostic nutritional index (PNI), preoperative prealbumin, and preoperative albumin (ALB). Data on the stapler used (line or circle stapler), surgical technique (open surgery or laparoscopic surgery), blood loss, operation time, nutrition feeding tube, cost, and hospital stay were also obtained. Simultaneously, concerning tumors, data on tumor size, T stage, N stage, number of lymph nodes, vascular invasion, and nerve invasion were collected. At the first admission, information on the preoperative status was extracted. Tumor size was measured with a combination of intraoperative conditions and postoperative pathology according to the long and short diameters of the tumor.

Data on early postoperative complications higher than grade II were collected according to the Clavien–Dindo classification within 30 days after surgery. Clinical symptoms and signs, CT, and endoscopy were used to diagnose the complications.

Statistical Analysis

Patients were categorized into two groups based on receiving or not receiving a blood transfusion. The patients in the two groups were matched using 1:1 propensity score matching (PSM). The age, gender, BMI, and the long and short diameters of the tumor were used to calculate the individual propensity score; the caliper value was set to 0.01.

In this study, six types of machine learning algorithms were assessed: logistic regression (LR), decision tree learning (Tree), XGBoost (XGB), random forest (RF), gradient boosting decision tree (GBDT), and light gradient boosting machine (GBM). XGB (extreme gradient boosting) is an improvement of the GBDT. It can be used not only for classification problems but also for regression problems. This algorithm uses positive lateralization to prevent overfitting and is a relatively novel algorithm.

Univariate and multivariate logistic regressions and machine learning were used to explore the relationship between the variables and blood transfusion. The results were displayed as odds ratios (ORs) and 95% confidence intervals (CIs).

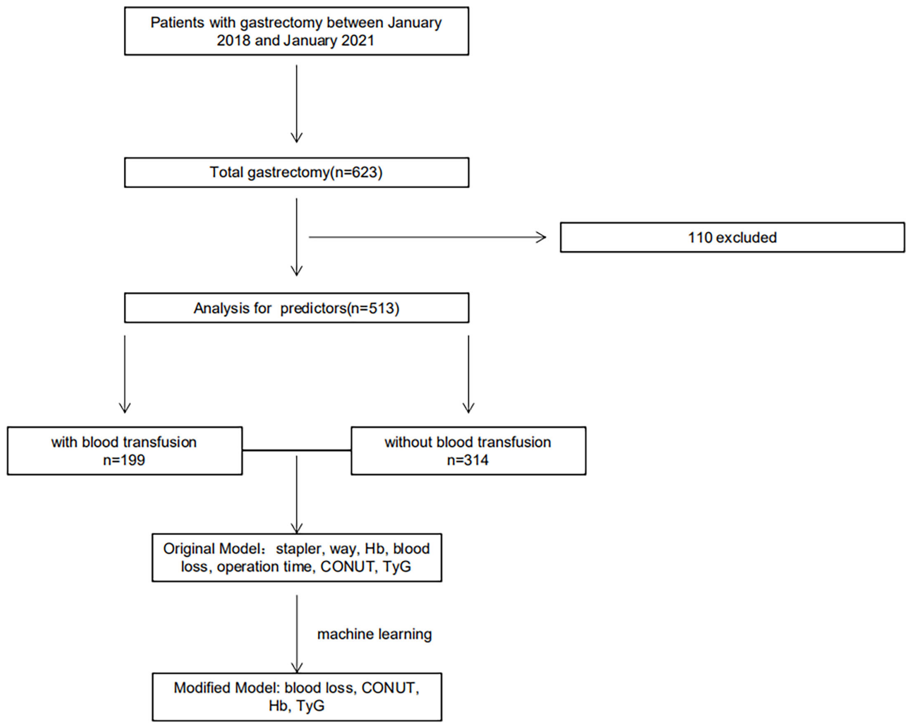

FIGURE 1 | Flowchart of the study. A total of 513 patients were included in the final study for perioperative transfusion-related analyses.

The concordance index (C-index) was used to measure the differences between the performance and the predicted results of the nomogram. The C-index correctly predicted the probability of positive events in a survival prediction model through a group of randomly selected patients. Moreover, calibration curves were used to compare the predicted results of the nomogram with the actual results, while the 45° line was used as the optimal model. The data were 7:3 randomly divided into the training and testing cohorts.

Continuous variables with normal distributions were presented as means and standard deviations, and categorical variables were presented as numbers (percentages). Statistical analyses were performed using Python 3.8.5, SPSS 26.0, and R software programs. A $p < 0.05$ indicated a statistically significant difference.

RESULTS

Clinicopathological Characteristics and Short-Term Outcomes of Patients

Figure 1 presents the flowchart of patient selection in this retrospective study. In total, 199 patients who had blood transfusion and 314 without blood transfusion were included in the study. As displayed in **Table 1**, 210 patients were successfully matched after PSM, with their clinical and pathological characteristics also shown. Based on the study design, the age, gender, BMI, and the long and short diameters of tumor were compared. The histogram demonstrated rigorous matching effectiveness (**Supplementary Figure S1**). Before PSM, the long and short diameters of tumor were significantly larger in the blood transfusion group than those in the non-transfusion group. Possible biases were reduced by PSM, with no significant differences between the groups in age, gender, BMI, and in the tumor long and short diameters after PSM.

Table 2 presents the differences in the short-term hospitalization results of the two groups regarding blood transfusions. There were no significant differences between the two groups regarding postoperative Hb, Hb changes, and percentages both before and after PSM ($p > 0.05$). In terms of postoperative recovery, the hospital stay in the non-transfusion group was shorter than that in the blood transfusion group. Moreover, the expenditures in the non-transfusion group were lower in terms of the total cost of hospitalization and disposable items for surgery ($p < 0.05$). The blood transfusion group exhibited a lower incidence of early postoperative complications before PSM ($p = 0.0115$), and there was a nearly significant difference between the two groups after using PSM to remove possible bias ($p = 0.0714$).

Risk Factors Associated With Blood Transfusion

Table 3 shows the differences in the clinical data between the two groups, including nutritional indicators, pathological data, and surgical outcomes. After PSM, the blood transfusion group had lower Hb ($p < 0.0001$) and higher TyG ($p = 0.0188$) than the non-transfusion group, with the blood transfusion group exhibiting a

TABLE 1 | Comparison of clinical and pathological data of the patients with PSM.

Variable	All patients (n=513)			Patients after matching (n=210)		
	With blood transfusion (n=199)	Without blood transfusion (n=314)	P	With blood transfusion (n=105)	Without blood transfusion (n=105)	P
Age (years)	66.21	66.34	0.9055	66.49	67.07	0.7177
Gender			0.1477			0.9999
Male	140	240		73	74	
Female	59	74		32	31	
BMI	22.52	23.09	0.0890	23.03	22.77	0.6005
Tumor long diameter	5.753	4.623	0.0003	4.449	4.386	0.8203
Tumor short diameter	4.182	3.483	0.0025	3.376	3.404	0.9068

BMI, body mass index.

TABLE 2 | Short-term outcomes of patients who had total gastrectomy (TG) before and after propensity score matching (PSM).

Variable	All patients (n = 513)			Patients after matching (n = 210)		
	With blood transfusion (n = 199)	Without blood transfusion (n = 314)	p-value	With blood transfusion (n = 105)	Without blood transfusion (n = 105)	p-value
Postoperative Hb	113.4	106.7	0.0006	108.7	110.6	0.4631
Hb change	–4.778	–9.257	0.0494	–7.986	–10.77	0.4608
Hb change (%)	0.69	–5.12	0.0232	–2.05	–6.13	0.3227
Hospital stay	16.79	15.16	0.0039	16.87	14.90	0.0252
One-time consumables for surgery	31,620	28,515	0.0022	32,495	27,388	0.0015
Total cost of hospitalization	74,638	63,947	<0.0001	76,773	61,939	<0.0001
Early postoperative complications			0.0115			0.0714
No	169	290		90	98	
Yes	30	24		15	7	

Hb, hemoglobin.

worse CONUT score ($p < 0.0001$). Regarding the nutritional indicators, such as PNI, prealbumin, and ALB, there was no statistical difference between the two groups after PSM in the pathological indicators, including vascular invasion, nerve invasion, T stage, and N stage.

Concerning surgery, a linear stapler was used more frequently, and patients in the blood transfusion group underwent more open surgery to complete the procedures ($p < 0.05$). Meanwhile, the operation time and the estimated blood loss were higher in the transfusion group compared to the non-transfusion group ($p < 0.05$). There were no significant differences between the two groups in the use of feeding tubes and the number of resected lymph nodes ($p > 0.05$).

Features were evaluated using univariate and multivariate analyses, which showed that the factors associated with blood transfusion were the stapler used, surgical technique, Hb, blood loss, operation time, CONUT, and TyG (**Figure 2**). The others were not significant risk factors. **Figure 3** further shows the area under the curve (AUC) for the stapler used, surgical technique, Hb, blood loss, operation time, CONUT score, and the TyG index.

Improvements Based on Machine Learning

The correlation analysis showed that the stapler used, blood loss, operation time, CONUT, and TyG were positively correlated with blood transfusion, with blood loss, CONUT, and TyG exhibiting a strong connection. Meanwhile, Hb and the surgical technique were negatively correlated with blood transfusion. Therefore, it is expected that the surgical technique and stapler used were related (**Figure 4**). To evaluate our model, we used the area under the receiver operating characteristic (AUC-ROC) curve. **Supplementary Figure S2** shows the performance of 6 machine learning algorithms. The logistic regression model performed the best (AUC = 0.879), while the decision tree performed the worst (AUC = 0.867). In addition, **Figure 5** shows the importance of seven factors in the XGB algorithm, with the order of importance from high to low: blood loss, CONUT, Hb, TyG, operation time, surgical technique, and the stapler used.

Combining logistic regression, correlation analysis, and XGB, we further screened for transfusion-related risk factors and considered blood loss, CONUT, Hb, and TyG as the main factors to modify the nomogram model.

Figure 6 shows the AUCs of the six algorithms after improving the model, considering only the four factors, which showed a similar trend to that before the improvements. The AUCs, ranged from high to low, were as follows: logistic regression, 0.851; gradient boosting decision tree, 0.841; light gradient boosting machine, 0.818; random forest, 0.817; XGBoost, 0.794, and decision tree, 0.665. Moreover, **Supplementary Figure S3** shows the differences in the ROC curves before and after improvement using the XGB algorithm, which were not statistically different (AUC = 0.796 *vs.* 0.794, p = 0.478).

TABLE 3 | Comparison of the clinical, pathological, and surgical data of patients.

Variable	All patients (*n* = 513)			Patients after matching (*n* = 210)		
	With blood transfusion (*n* = 199)	Without blood transfusion (*n* = 314)	*p*-value	With blood transfusion (*n* = 105)	Without blood transfusion (*n* = 105)	*p*-value
Preoperative Hb	104.2	126.3	<0.0001	101.3	124.5	<0.0001
CONUT score			<0.0001			<0.0001
0–1	33	139		15	45	
2–4	75	135		34	49	
5–8	64	37		37	9	
9–12	27	3		19	2	
TyG	8.565	8.234	<0.0001	8.476	8.268	0.0188
PNI	44.39	45.18	0.5316	48.17	45.30	0.2625
Prealbumin	186.7	204.2	0.0500	205.1	201.8	0.7171
ALB	35.63	37.83	0.0006	37.55	37.72	0.8589
Vascular invasion			0.2657			0.5487
Yes	82	114		34	30	
No	117	200		71	75	
Nerve invasion			0.7205			0.6743
Yes	83	136		42	45	
No	116	178		63	60	
T stage			0.0535			0.5363
1–2	24	58		15	12	
3–4	175	256		90	93	
N stage			0.3338			0.9370
0	52	102		33	30	
1	30	51		15	18	
2	48	72		27	27	
3	69	89		30	30	
Stapler			0.0054			0.0280
CS	142	257		81	93	
LS	57	57		24	12	
Surgical technique			<0.0001			<0.0001
Laparoscopy	66	185		36	70	
Open	133	129		69	35	
Blood loss			<0.0001			<0.0001
<200	102	246		48	87	
200–400	64	63		34	15	
>400	33	5		23	3	
Operation time	246.6	224.1	0.0097	252.6	211.8	0.0016
Nutrition tube			0.9485			0.4270
Yes	69	108		29	24	
No	130	206		76	81	
No. of total lymph nodes	29.90	21.71	0.3673	26.11	21.06	0.2907
No. of positive lymph nodes	8.13	4.867	0.3761	10.77	4.871	0.2387

Hb, hemoglobin; CONUT, controlling nutritional status; TyG, triglyceride–glucose; PNI, prognostic nutritional index; ALB, albumin; CS, circle stapler; LS, linear stapler.

Performance Assessment and Validation of the Nomogram

Based on the results mentioned above, we established a nomogram model using blood loss, CONUT, Hb, and TyG. By projecting the points corresponding to each variable to the "points" axis, the total scores were calculated to provide the corresponding prediction results (**Figure 7**). The discrimination power of the nomogram was appraised by the C-index. The C-index of the nomogram was 0.834. **Figure 8** shows the calibration curves of the cohort. The model demonstrated good consistency. The results of the decision curve analysis (DCA) for the blood transfusion nomogram before and after improvement were also presented, which suggested that the modified nomogram model had a considerable net clinical benefit that was not weaker than that of the original model.

The nomogram prediction model finally incorporated four predictors. The minimum calculated sample size was 365 cases, with 142 cases in the blood transfusion group. According to the sample size computation, the number of patients included in the present study was deemed sufficient. The incidence of blood transfusion in the present study was approximately 38.8%.

DISCUSSION

This study compared the short-term outcomes and economic costs of patients undergoing TG with or without blood transfusion. Simultaneously, potential variables for blood transfusion were analyzed, and the stapler used, surgical technique, preoperative Hb, blood loss, operation time,

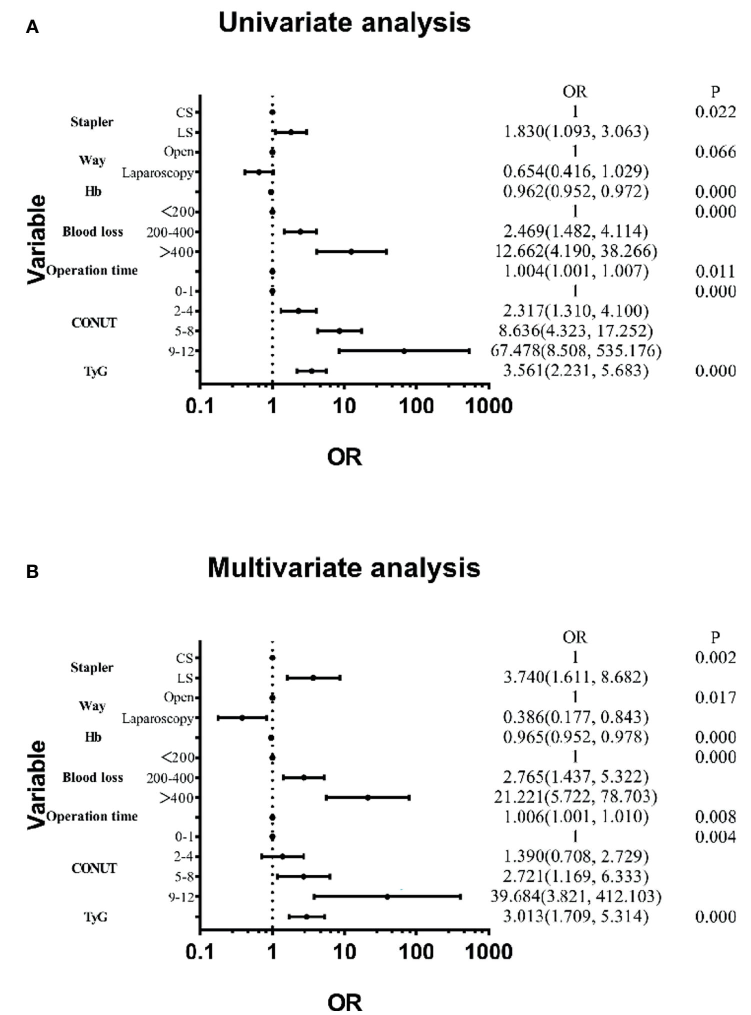

FIGURE 2 | **(A)** Results of univariate analysis. **(B)** Results of multivariate analysis.

CONUT score, and the TyG index were further explored. A streamlined nomogram was created including blood loss, CONUT, Hb, and TyG by combining the previous results, the correlation analysis, and the importance analysis of the XGB algorithm. In addition, a comparison with the original model showed that the performance of the modified model was not significantly weaker. The nomogram showed good diagnostic performance (C-index = 0.834). An internal verification was conducted, and the calibration curves demonstrated good model consistency. The DCA also showed clinical benefits that were no worse than those of the original model. Moreover, all the indicators were easily obtained, which reduced the patients' additional medical expenditure and medical behavior and made the application of the nomogram easier. Meanwhile, we found that potential preoperative nutritional indicators were incorporated, with an indispensable role in the nomogram. Thus, greater attention should be paid to the nutritional status of patients undergoing TG and nutritional intervention should be carried out, when necessary.

The effect of blood transfusion on the short- and long-term prognosis of patients undergoing gastric cancer surgery remains unclear. For some critically ill patients, especially those with unstable hemodynamics, blood transfusion is an important and a life-saving intervention (11, 12). On the contrary, research has shown a number of potential risks of blood transfusion, including allergic reactions, fever, hemolytic reactions, and volume overload. In addition, inflammatory reactions and blood transfusion usually worsen the prognosis of patients (13). Studies have also reported that patients are more likely to develop infections after blood transfusion, irrespective of clean or contaminated surgeries (14). There is also evidence that a patient's immune function is affected as blood transfusion might affect the body's immunosuppressive prostaglandins and the activity of heterogeneous T cells (15). In this study, the change in Hb was not pronounced in the transfusion group, but the elevated costs and the delay in discharge were significant. The seriousness of patients requiring blood transfusion and the complications after a blood transfusion may result in this outcome, indicating that blood transfusions

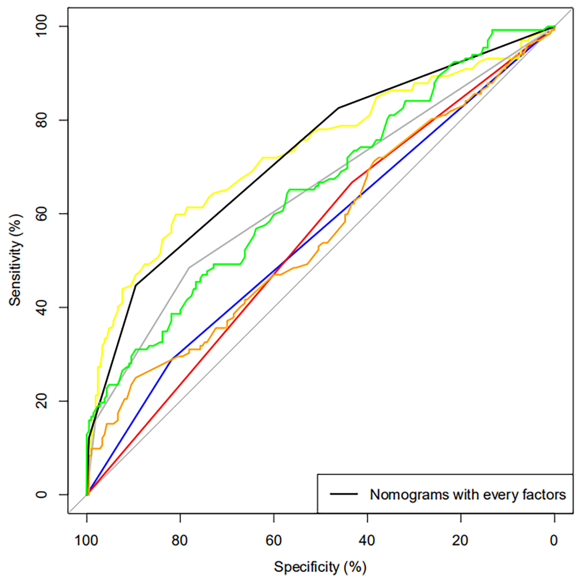

FIGURE 3 | Receiver operating characteristic (ROC) curve of blood transfusion based on logistic regression for each variable. *Blue*, stapler; *red*, surgical technique; *yellow*, hemoglobin (Hb); *gray*, blood loss; *orange*, operation time; *black*, preoperative controlling nutritional status (CONUT); *green*, triglyceride–glucose (TyG).

should be carried out with caution as they are likely to lead to unpredictable and adverse prognoses.

The relationship between blood loss and blood transfusion was apparent. The greater extent of resection and the difficulty of anastomosis in TG make it more important to pay attention to refinements in order to reduce bleeding. Since the first report of laparoscopy-assisted distal gastrectomy (LADG) in 1994, the safety and the feasibility of laparoscopic surgery have been confirmed in continuous practice (16–18). Compared with open surgery, laparoscopic surgery can perform lymph node dissection in a clearer field of view, increasing the safety of the operation; although it extends the operation time, the reduction in bleeding is significant. At the same time, with advances in surgical technology, total laparoscopic TG has gradually become popular, and the indications have continuously expanded (19). Furthermore, intraoperative blood loss has also been found to be possibly related to long-term prognosis in previous studies (6, 20). The close relationship between blood loss and blood transfusion, as well as the risk of distant metastases that may arise from blood loss, is worth considering. Hematogenous metastasis of tumors and suppression of antitumor immunity have been reported to be possibly related to this (21–23). It is still recommended to perform quantitative tests for blood loss, which will help in reaching a more accurate conclusion.

It is quite common for patients with upper–middle tumors to be affected by diet, necessitating more attention to the nutritional

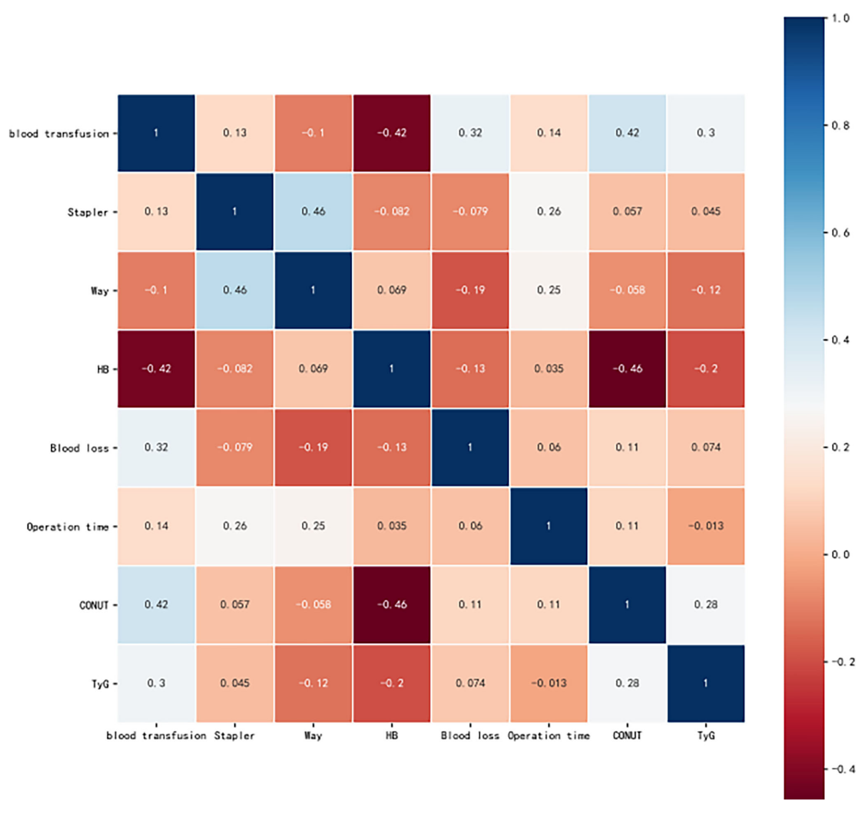

FIGURE 4 | Correlation between variables.

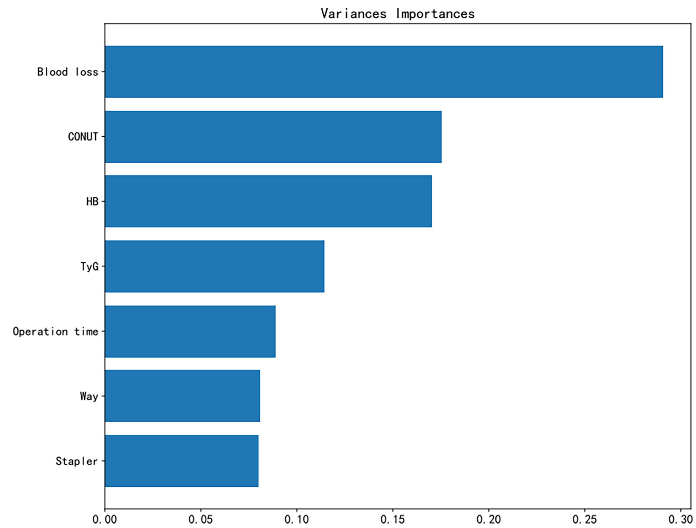

FIGURE 5 | Variable importance of the features included in extreme gradient boosting (XGB) for prediction of blood transfusion.

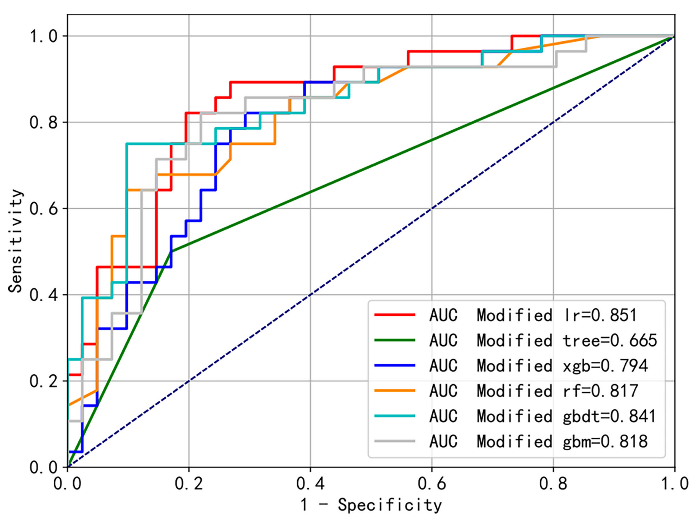

FIGURE 6 | Modified receiver operating characteristic (ROC) curves of the different machine learning algorithms predicting blood transfusion.

status. The CONUT score is a method used to evaluate patients' immune and nutritional status. It includes the serum albumin content, total cholesterol level, and the total number of peripheral blood lymphocytes, and the score is calculated based on the index content (24). Studies have shown that the CONUT score is closely related to the prognosis of various tumors (25). In gastric cancer, CONUT-related studies have focused on long-term prognosis (26–28). There are a few studies on the CONUT during hospitalization, but none of these studies found a relationship between CONUT and blood transfusion, so far. In terms of the indicators of composition, albumin is one of the most important references in the clinical assessment of the nutritional status of patients. Hypoproteinemia is often associated with anastomotic leaks, infections, and thoracoabdominal effusion (29–31). Total cholesterol level is often related to metabolism, antioxidant reserve, and inflammatory response (32–34). Lymphocytes are an important part of the human immune response system, helping to fight tumors by inhibiting the proliferation and migration of cancer cells (35). Taken together, the CONUT provides a comprehensive, easy-to-use scale enabling the assessment of the preoperative status.

Preoperative low Hb is the most important risk factor for perioperative blood transfusion (36). It was reported that severe anemia, Hb level of <9.0 g/dl, was associated with an increased odds of transfusion (37). Due to the characteristics of gastric

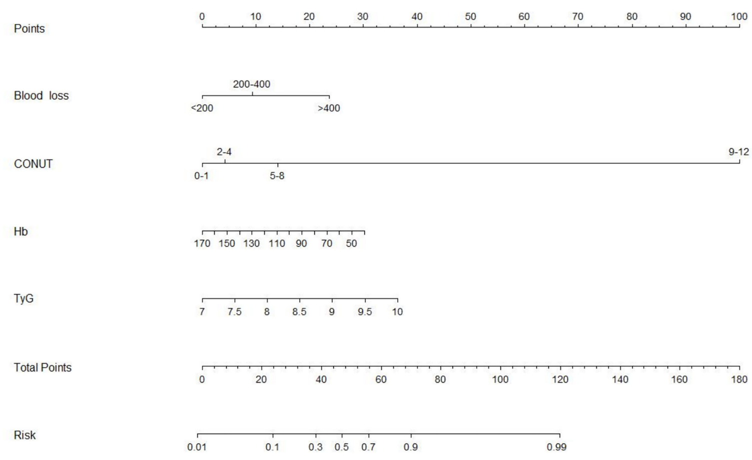

FIGURE 7 | Nomogram predicting the probability of blood transfusion.

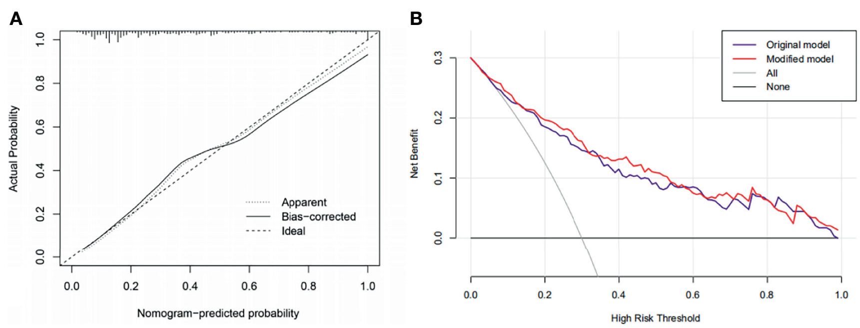

FIGURE 8 | **(A)** Calibration curves of the nomogram. **(B)** Decision curve analysis (DCA) of the original and the modified model.

cancer, many patients have anemia before surgery. In upper–middle and upper gastric cancers, in particular, obstruction is common, and the patient's compromised diet combined with the depletion of the tumor further worsens the anemic symptoms. Surgeons are usually not aware of the severity of tumoral anemia due to insufficient attention, resulting in less effective intervention. There is also a lack of accurate assessment of the extent of intervention, resulting in wasted blood resources or inadequate intervention. It is common knowledge that Hb is usually the primary indicator for transfusion, but this study showed that the assessment of transfusion is still a multifactorial process that requires considering multiple preoperative and intraoperative factors in order to achieve maximum efficacy.

The TyG index is based on the study of triglyceride and insulin sensitivity in skeletal muscles and is calculated using fasting triglyceride and fasting blood glucose measurements. In addition, the latest research demonstrates that the TyG index is generally considered to be related to insulin resistance. Furthermore, several previous studies have explored the relationship between TyG and the occurrence and prognosis of various clinical diseases (38, 39). Our investigation suggests that an elevated TyG index increases the likelihood of blood transfusion preoperatively in patients undergoing TG. Obesity and inflammatory markers such as tumor necrosis factor-α and interleukin-6 were considered in relation to TyG; these factors can increase the difficulty of surgery and the possibility of blood transfusion (40, 41). There are also some reports on the relationship between TyG and diabetes and cardiovascular diseases, which may be related to vascular fragility, intraoperative hemostasis, and blood transfusion (42, 43). Furthermore, TyG has been reported to be a risk factor for non-alcoholic liver disease, influencing liver function and increasing the odds of blood transfusion. Recent research has shown that perioperative blood transfusion adversely affects the prognosis of patients; thus, more relevant studies are necessary to further clarify the comprehensive results of the correlation between the TyG index and blood transfusion and the long- and short-term prognosis. In brief, we attempted to demonstrate that an abnormally elevated TyG index has implications for blood transfusion, which provides new possible research directions to benefit patients.

The stapler used, the surgical technique, and the operation time had effects on perioperative blood transfusion. However, after further exploration, they were found to be less likely relevant. The choice of a circle stapler (CS) or a linear stapler (LS) is still worth investigating. CS is more commonly used in LADG and open surgery, while LS is more common in total laparoscopic surgery. LS is superior in terms of the size of anastomosis and the requirements for tunnels, while CS is more familiar to most clinicians. In addition, LS requires a higher esophageal separation in TG, which is very difficult in patients with huge tumors or obesity and may necessitate a blood transfusion. Furthermore, previous studies have reported a correlation between the increased duration of operation and blood transfusion (44). A longer surgery time usually means more difficulties encountered during surgery and a longer exposure time. A longer operative time has been demonstrated to be directly related to complications and reoperation (45).

Currently, there are requirements for blood transfusion; however, considering the lag of laboratory tests and the particularity of clinical changes, transfusion is still determined by the surgeon based on the patient's condition (46). With the effects of the COVID-19 pandemic, the number of blood donors dropped significantly. In the case of uncertain prognosis and a shortage of blood resources, blood transfusion should be carried out more cautiously for safety and the full use of blood resources. In this study, combined with surgery and basic conditions, it was found that some surgical options and the nutritional status are risk factors for patients with blood transfusion. When conflicts arise, the surgery can be delayed to actively prepare blood resources, formulate a more appropriate surgical plan, or provide nutritional support for patients to reduce the possibility of blood transfusion. In particular, adjusting the patient's preoperative general status is noteworthy in order to reduce the likelihood of transfusions and avoid a lack of blood resources that could lead to poor outcomes.

The present study comprehensively analyzed the prognostic factors for blood transfusion. Machine learning was used to establish a modified, accurate, and convenient nomogram prognostic model. However, the study still has some limitations. Firstly, this study was retrospective, and some unknown factors will inevitably lead to bias. Secondly, this was a single-institution study, and some patients were excluded for various reasons, possibly affecting the generalizability of this model. Therefore, more prospective, multi-institutional studies should be considered. In addition, the exact rationale for these, such as total cholesterol, lymphocyte count, and TyG with blood transfusion, has not been elucidated, and more basic research is worthwhile.

In conclusion, a nomogram was established and modified to predict the need for blood transfusion in patients undergoing TG. The exploratory discovery of the relationship between CONUT and TyG and blood transfusion provides a basis for further research. The nomogram is useful in guiding the surgeon's decision regarding blood transfusion, timely nutritional intervention, and making full use of clinical blood resources.

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 Ethics Committee of the First Affiliated Hospital of Soochow University. The patients/participants provided written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by JZ and LJ. The first draft of the manuscript was written by JZ and XZ. All authors commented on the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

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SYSTEMATIC REVIEW
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Indocyanine Green Fluorescence Using in Conduit Reconstruction for Patients With Esophageal Cancer to Improve Short-Term Clinical Outcome: A Meta-Analysis

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Objectives: This meta-analysis evaluated the short-term safety and efficacy of indocyanine green (ICG) fluorescence in gastric reconstruction to determine a suitable anastomotic position during esophagectomy.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyzes 2020 (PRISMA) were followed for this analysis.

Results: A total of 9 publications including 1,162 patients were included. The operation time and intraoperative blood loss were comparable in the ICG and control groups. There was also no significant difference in overall postoperative mortality, reoperation, arrhythmia, vocal cord paralysis, pneumonia, and surgical wound infection. The ICG group had a 2.66-day reduction in postoperative stay. The overall anastomotic leak (AL) was 17.6% (n = 131) in the control group and 4.5% (n = 19) in the ICG group with a relative risk (RR) of 0.29 (95% CI 0.18–0.47). A subgroup analysis showed that the application of ICG in cervical anastomosis significantly reduced the incidence of AL (RR of 0.31, 95% CI 0.18–0.52), but for intrathoracic anastomosis, the RR 0.35 was not significant (95% CI 0.09–1.43). Compared to an RR of 0.35 in publications with a sample size of <50, a sample size of >50 had a lower RR of 0.24 (95% CI 0.12–0.48). Regarding intervention time of ICG, the application of ICG both before and after gastric construction had a better RR of 0.25 (95% CI 0.07–0.89).

Conclusions: The application of ICG fluorescence could effectively reduce the incidence of AL and shorten the postoperative hospital stay for patients undergoing cervical anastomosis but was not effective for patients undergoing intrathoracic anastomosis. The application of ICG fluorescence before and after gastric management can better prevent AL.

Systematic Review Registration: PROSPERO, CRD:42021244819.

Keywords: esophagectomy, indocyanine green, anastomotic leak, meta-analysis, short-term outcome

INTRODUCTION

Esophagectomy is an important means of radical/curative treatment of esophageal cancer. Among the postoperative complications, anastomotic leakage (AL) after esophagectomy remains a risk of considerable morbidity and mortality. In high-volume centers, AL rates range from 5 to 40%, even up to 50% in some medical centers, despite surgical advances and preoperative optimizations (1–4). Among the risk factors affecting anastomotic integrity, poor perfusion is a factor that can be intervened upon surgically. Gastric tube blood supply is currently monitored clinically by monitoring blood vessel color, temperature, and arterial pulse to predict poor perfusion. However, these parameters cannot reliably and objectively reflect the level of perfusion, therefore they have limited predictive value (5, 6).

Thus, it would be useful to find valid parameters to evaluate the perfusion status. Indocyanine green (ICG) is a water-soluble three-carbon anthocyanin dye with a plasma half-life span of 3–5 min. ICG absorbs light at an excitation wavelength of between 750 and 800 nm while emitting light at longer emission wavelengths of 830 nm or more. Only a few patients developed anaphylactic shock after an intravenous injection of ICG. Regarding its safety concerns, ICG has been added to the rapid food and drug administration approval for clinical use (7, 8). Nowadays, the application of ICG fluorescence angiography in the resection of esophageal carcinoma and conduit reconstruction is being widely developed.

At present, ICG fluorescence has been widely used in liver surgery, sentinel lymph node biopsy of breast cancer, and gastric cancer. In the field of thoracic surgery, it is mainly used in the location of pulmonary nodules, determination of pulmonary segment boundaries during pulmonary segmentectomy, sentinel lymph node location in the thoracic cavity of lung cancer, intraoperative chest guide display, and gastric perfusion assessment (9–12). Previous meta-analysis has confirmed that ICG fluorescence is an objective and useful parameter for evaluating gastric microcirculation (13, 14). This study aimed to systematically review the existing literature to determine the value of ICG fluorescence for short-term efficacy, especially for preventing anastomotic leakage (AL), and to investigate whether there are differences in the efficacy of ICG among different anastomosis sites (intrathoracic versus cervical anastomosis), the sample size in the intervention group (<50 versus >50), and the intervention time (only after tube construction versus both before and after tube construction).

METHOD

A meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (PRISMA) (15). IRB approval and written consent were not required for this further analysis.

Literature Search Method

A search of PubMed, Embase, Web of Science, The Cochrane Library, Chinese National Knowledge Infrastructure, VIP Database, China Biology Medicine Disc, and Wan-fang database was conducted on 10 April 2021 by two independent researchers. The retrieval terms included ICG and esophagectomy. Both database subject heading fields (Emtree in EMBASE, MeSH in MEDLINE) and text word fields were searched. References of retrieved articles and reviews were also manually screened to obtain additional relevant studies.

Study Selection

The inclusion criteria included: (1) esophagectomy with gastric conduit reconstruction; (2) comparative study design: control group using color, temperature, and pulsation of vessels; experimental group using ICG to assess perfusion; (3) age ≥18 years; (4) sufficient clinical outcome data for further analysis; and (5) sample size ≥10. The exclusion criteria were as follows: (1) abstract or review; (2) data insufficient; (3) repeated publications; and (4) included in a multicenter study.

Quality Assessment

We used the Methodological Index for Non-Randomized Studies tool (MINORS) (score from 0 to 24). MINORS is a 12-point validated tool designed specifically to evaluate the methodological quality of non-randomized surgical trials. For the comparative studies, the ideal score was 24. A MINORS score below 12 indicates poor quality. A MINORS score above 18 indicates good quality (16, 17). Disagreements in the quality assessment were resolved through discussion.

Data Extraction

Data were extracted by two independent researchers (Z-NH and LH) and entered into an EXCEL file including author, published time, country, study design, BMI, sample size, gender, history of smoking, American Society of Anesthesiologists (ASA) status, histological type, preoperative albumin, preoperative comorbidity (including hypertension, diabetes mellitus, obstructive lung disease), neoadjuvant therapy, tumor location, pathological tumor category, TNM stage, anastomotic method (stapler/hand sewn), route of gastric conduit, operation type, operative time, intraoperative blood loss, AL number, other complications, postoperative hospital stay, and hospital cost.

Statistical Analysis

We used the inconsistency statistic (I^2) to evaluate the extent of heterogeneity. Relative risk was used to evaluate the binary variable and the weighted mean difference for the continuous variable. An I^2 value greater than 50% was considered to indicate substantial heterogeneity. A fixed model was used when I^2 <50%, and a random model was used when I^2 ≧50%. A 2-sided test at the 5% level was defined as indicating statistical significance. We only calculated the existing data and did not fill in the missing data. Subgroup and sensitivity analyses were conducted to find the heterogeneity source. Publication bias would be assessed by funnel plots, Begg's test, and Egger's tests. Statistical analysis was conducted with Stata version 15 (Stata Corp, College Station, TX, USA), and Revman 5.4.

RESULTS

Study Selection

Electronic database search results are available in the PRISMA flow diagram (**Figure 1**). From an initial total of 501 studies, 42 underwent full-text review, with 9 studies being included in our analysis (18–26). Many related publications focus on the flow dynamics of ICG perfusion.

Study Characteristics

A total of 1,162 patients from 4 countries were included in our analysis, of whom 419 patients underwent ICG. Although most of the publications were retrospective, there was only 1 prospective study. The sample size ranged from 40 to 285. There was some heterogeneity regarding the ICG dose, near-infrared system, operation type, and ICG intervention time. The ICG and near-infrared system were varied, which makes it difficult for further analysis. Detailed information about the included studies can be found in **Table 1**.

Five studies were assessed to be of good quality based on the MINORS, with scores of 19 or more. The other four studies were assessed to be of moderate quality, with scores of 13 or more (**Table 2**).

Baseline Characteristics

The age, body mean index, history of smoking, pathological type, diabetes mellitus, cardiovascular disease, obstructive lung disease, tumor location, pathological tumor category (T1–2/T3–4), TNM stage (I–II/III–IV), anastomotic procedure using a stapler, and gastric conduit through the posterior mediastinal were comparable in the ICG and control groups. However, the ICG group was lower in ASA I–II status (RR of 0.63, 95% CI 0.4–0.99), neoadjuvant therapy (RR of 0.59, 95% CI 0.41–0.85), and preoperative albumin (WMD −0.14 g/L, 95% CI −0.28–0.002).

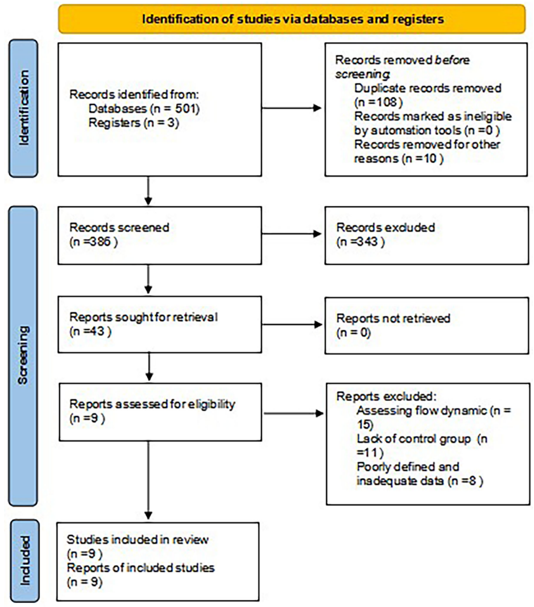

FIGURE 1 | PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

The ICG group underwent more thoracoscopy (RR of 2.73, 95% CI 1.40–5.37) and laparoscopy (RR of 2.17, 95% CI 1.18–3.96) (**Table 1**).

Short-Term Clinical Outcomes

The short-term clinical outcomes are summarized in **Table 3**. The operation time and intraoperative blood loss were comparable in the ICG and control groups. There was no

TABLE 1 | Baseline characteristics of included studies.

	Included studies	Heterogeneity		Model	Pooled effect	
		p	I2%		95% CI	*p*
Male	8	0.49	0	Fixed	0.93 (0.67-1.29)	0.49
Age	6	0.03	59.8	Random	0.07 (-0.08-0.22)	0.35
BMI	4	0.43	0	Fixed	0.12 (-0.08-0.31)	0.25
History of smoking	2	0.92	0	Fixed	1.12 (0.70-1381)	0.63
ASA I-II	3	0.1	51.7	Random	0.63 (0.4-0.99)	0.04
SSC	6	0.34	7.6	Fixed	0.98 (0.56-1.71)	0.94
Diabetes mellitus	3	0.86	0	Fixed	1.14 (0.78-1.66)	0.5
Cardiovascular disease	3	0.27	24	Fixed	1.08 (0.60-1.94)	0.79
Obstructive lung disease	3	0.63	0	Fixed	0.37 (0.13-1.03)	0.06
Neoadjuvant therapy	6	0.01	65	Random	0.59 (0.41-0.85)	0.004
Tumor in upper thoracic	3	0.07	62.6	Random	0.86 (0.51-1.47)	0.59
Pathological Tumor Category T1-2	3	0.13	51	Random	0.87 (0.57-1.32)	0.51
TNM stage I-II	4	0.006	75.6	Random	0.86 (0.60-1.23)	0.4
Thoracoscopy	6	0.72	0	Fixed	2.73 (1.40-5.37)	0.003
Laparoscopy	6	0.37	6.6	Fixed	2.17 (1.18-3.96)	0.01
Anastomotic procedure using Stapler	3	0.49	0	Fixed	0.99 (0.57-1.70)	0.97
Gastric conduit Through posterior mediastinal	6	0.51	0	Fixed	0.97 (0.44-2.17)	0.95
Preoperative albumin (mg/dl)	2	0.17	46.8	Fixed	-0.14 (-0.28–0.002)	0.047

TABLE 2 | Quality assessment by methodological index for non-randomized studies tool.

Author	Stated aim	Inclusion of consecutive patients	Prospective data collection	Endpoint appropriate for study	Unbiased assessment of study endpoint	F/U period approriate for study	Loss to follow-up <5%	Prospective calculation of study size	Adequate control group	Contemporary groups	Baseline aquivalence of groups	Adequate statistical analysis	Total score
Campbell et al. (26)	2	2	0	2	2	2	2	0	2	0	2	2	18
Dalton et al. (21)	2	2	0	2	2	2	2	0	2	0	2	2	18
Karampinis et al. (22)	2	2	0	1	2	2	2	0	2	0	2	2	17
Kitagawa et al. (25)	2	2	0	2	2	2	2	0	2	0	2	2	18
Noma et al. (23)	2	2	0	2	2	2	2	0	2	1	2	2	19
Ohi et al. (24)	2	2	0	2	2	2	2	0	2	1	2	2	19
Guo Jin-cheng et al. (20)	2	2	0	2	2	2	2	0	2	2	2	2	20
Song Xuantong et al. (19)	2	2	2	2	2	2	2	0	2	1	2	2	21
Rao-Jun Luo et al. (18)	2	2	0	2	2	2	2	0	2	1	2	2	19

significant difference regarding overall postoperative mortality, reoperation rate, arrhythmia rate, vocal cord paralysis rate, pneumonia rate, or surgical wound infection. However, the ICG group had a shorter postoperative stay, with a 2.66-day reduction (WMD, 95% CI −3.77–1.55, p = 0.000).

The overall AL rate was 17.6% (n = 131) in the control group and 4.5% (n = 19) in the ICG group. The overall RR for AL was 0.29 (95% CI 0.18–0.47, p = 0.000), suggesting that ICG was associated with a statistically significant decrease in rates of AL (**Figure 2**). The sensitivity analysis results did not indicate any publications with obvious heterogeneity (**Supplementary 1**). Subgroup analysis was conducted by anastomosis site, ICG group sample size, and intervention time. The application of ICG in cervical anastomosis significantly reduced the incidence of AL (RR of 0.31, 95% CI 0.18–0.52), but the application of ICG fluorescence in intrathoracic anastomosis did not significantly reduce the incidence of AL rate (RR of 0.35, 95% CI 0.09–1.43) (**Figure 3**). Regarding the sample size in the ICG group, publications with a sample size of >50 had a lower RR of 0.24 (95% CI 0.12–0.48). However, publications with a sample size of <50 still had a statistical RR of 0.35 (95% CI 0.18–0.68) (**Figure 4**). Regarding the intervention time of ICG, the application of ICG both before and after gastric construction showed a better RR of 0.25 (95% CI 0.07–0.89) (**Figure 5**).

Publication Bias

A funnel plot analysis based on AL was performed. The funnel plot was asymmetrical (**Figure 6A**), which suggested that smaller studies favoring control had been omitted. Thus, we further conducted the Egger's test (p = 0.65) (**Figure 6B**) and Begg's test (p = 0.47) (**Figure 6C**), which both indicated no potential publication bias. The trim and fill test was stable without any trim or fill (**Figure 6D**).

TABLE 3 | Summary of short-term clinical outcomes.

	Included studies	Heterogeneity		Model	Pooled effect	
		p	I2%		95% CI	*p*
Intraoperative blood loss (ml)	3	0.41	0	Fixed	-9.18 (-21.34-2.99)	0.14
Operation time (min)	4	0.21	33.1	Fixed	1.69 (-6.86-10.23)	0.7
Postoperative Hospital stay (d)	4	0.44	0	Fixed	-2.66 (-3.77–1.55)	0
AL	9	0.46	0	Fixed	0.29 (0.18-0.47)	0
Surgical Wound infection	2	0.32	0	Fixed	0.66 (0.29-1.49)	0.31
Pneumonia	5	0.51	0	Fixed	0.85 (0.59-1.23)	0.39
Vocalcord paralysis	2	0.27	17.9	Fixed	1.07 (0.98-1.16)	0.13
Arrhythmia	3	0.04	77.5	Random	0.73 (0.47-1.12)	0.15
Reoperation	7	0.70	0	Fixed	0.67 (0.20-2.22)	0.52
Overall mortality	9	0.28	20.5	Fixed	1.23 (0.45-3.39)	0.69

Al, anastomotic leak.

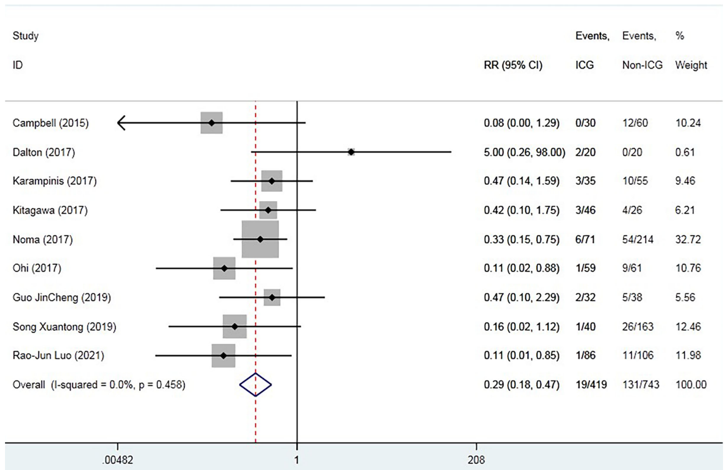

FIGURE 2 | Forest plot for anastomotic leak.

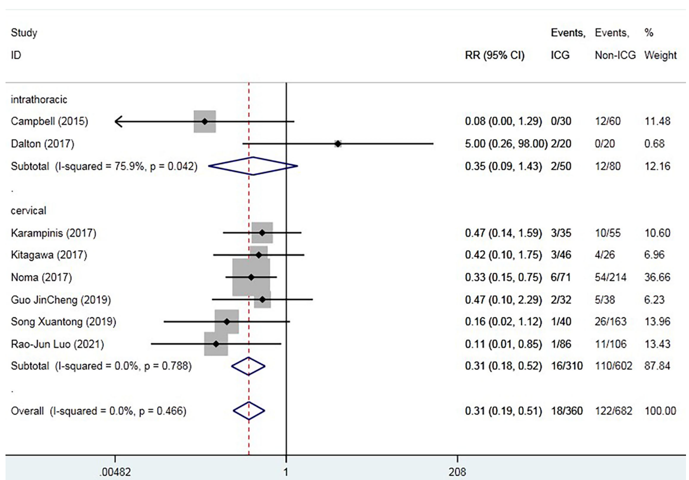

FIGURE 3 | Forest plot for subgroup analysis of anastomotic leak based on anastomosis site.

DISCUSSION

This is the first meta-analysis focused on the short-term outcome of ICG fluorescence. No ICG-related adverse events were reported in the included publications. Preliminary study results suggested ICG fluorescence did not increase the operation time or intraoperative blood loss. Overall postoperative mortality, reoperation rate, arrhythmia rate, vocal cord paralysis rate, pneumonia rate, and surgical wound infection were comparable between the ICG and control groups. There was an absolute risk reduction of 69% in the ICG group, which means the prevention of 55 patients in the ICG group from AL. ICG can effectively identify the sufficiency of gastric perfusion so that the surgeon can make an early decision if any adjustment of the gastric tube should be made. This is a promising finding and could explain the reduction in postoperative hospital stays.

The application of ICG could only prevent patients from undergoing cervical anastomosis but not intrathoracic anastomosis from AL (RR of 0.31, 95% CI 0.18–0.52). This contributed to the difference in AL rates between cervical anastomosis and intrathoracic anastomosis. Cervical anastomosis is associated with a significantly increased risk of AL. Biere et al. reported that cervical anastomosis could be associated with a higher leak rate (OR: 3.43; 95% CI: 1.09–10.78; p = 0.03) (27).

There is a consensus that cervical anastomosis requires the formation of a longer gastric tube, which must travel over a longer distance in the mediastinum with a higher tension. This in turn can impair the integrity of the blood vessels around the

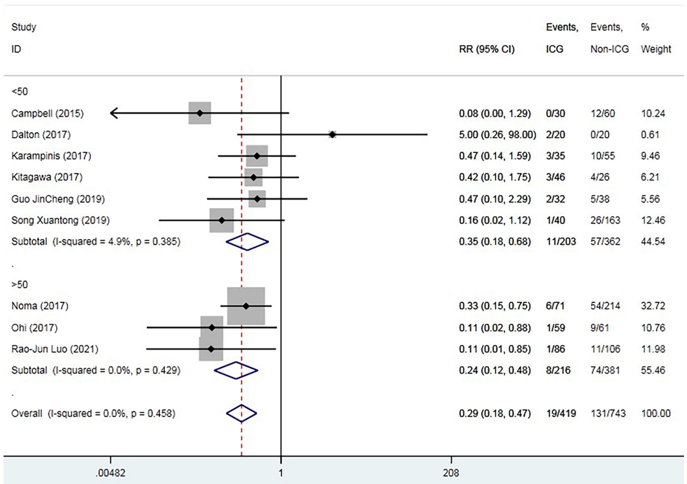

FIGURE 4 | Forest plot for subgroup analysis of anastomotic leak based on experimental group sample size.

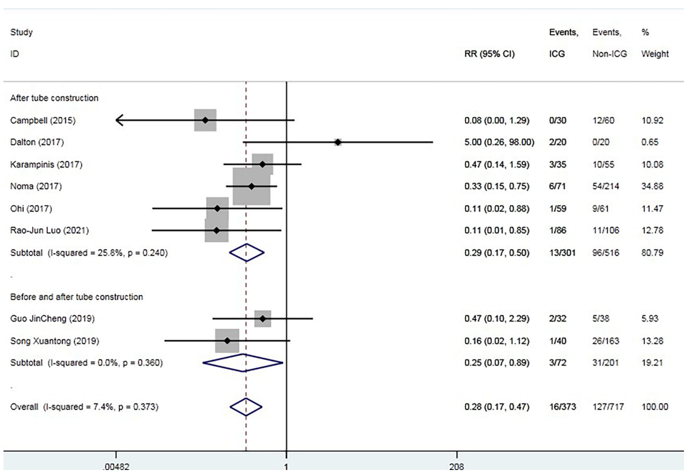

FIGURE 5 | Forest plot for subgroup analysis of anastomotic leak based on indocyanine green fluorescence intervention time.

gastric tube, leading to a greater rate of rupture and leakage (28, 29). For most intrathoracic anastomosis, the blood supply and tension are more likely enough. Thus, using ICG fluorescence to assess blood supply would not be helpful. Another explanation is that the low incidence of AL in intrathoracic anastomosis requires a larger sample size to confirm the validity of ICG.

Although most publications only applied ICG after gastric tube creation, our results showed that the application of ICG both before and after gastric creation showed a better RR of 0.25 (95% CI 0.07–0.89). Kitagawa et al. changed the intervention time from ICG after gastric tube creation to both before and after gastric creation to detect the border of the blood supply (25). Application of ICG before gastric tube creation could help surgeons detect the border of arterial supply and determine the cutting line. In terms of the practical use of ICG in clinical sites, there is no consensus on the dose of ICG. Doses ranged from 1.25 to 25 mg per bolus. The minimum dose can be measured clearly and reliably, but in some cases, it is too low. Higher doses may interfere with the second measurement because the background signal is still high. Slooter et al. recommended a 0.05 mg/kg/bolus dose, and after 15 min, new measurements could be taken (14). However, if we choose to assess gastric perfusion both before and after gastric construction, the total dose of ICG is 25 mg for a patient weighing 50 kg, which is the dose limit of ICG (30). Thus, we recommend 12.5 mg/bolus both before and after gastric construction.

Low volume of the institution and surgeon could be a risk factor of Al (31, 32). Regarding the sample size in ICG group,

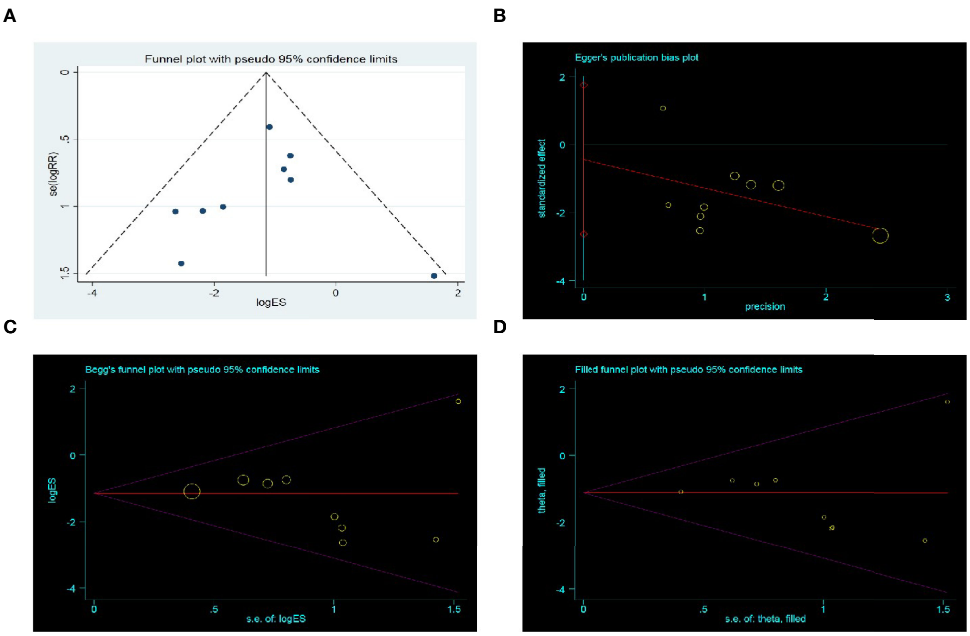

FIGURE 6 | Publication bias assessment. **(A)** Funnel plot; **(B)** Egger's test funnel plot; **(C)** Begg's test funnel plot; **(D)** Trim and fill funnel plot. Above four pictures were draw based on anastomotic leak rate.

publications with sample size <50 had a statistical RR 0.35(95% 0.18-0.68), and publications with sample size >50 had a lower RR 0.24(95% 0.12-0.48). This result indicated that application of ICG in gastric blood supply requires a learning curve. Hardy NP et al. conducted a questionnaire about the interpretation of near infrared perfusion imaging using ICG in colorectal surgery in 40 participants, and 70% felt > 10 cases were needed for competency in use with the majority of experts advocating > 50 (33). The learning curve of application of ICG in gastric perfusion is still unclear. Based on this subgroup analysis, application of ICG may have a short learning curve. It seems that, even in learning curve station, ICG application still could prevent patients from AL. Despite the expensive equipment, ICG fluorescence has potential popularization and application value.

Limitations

Despite the evidence-based findings, there still exist some limitations in our study, Methodological limitations include: (1) Only one study was prospective, and no randomized control trial (RCT) studies were included in meta-analysis. Based on the GRADE scales, the evidence is low. Thus, a well-designed RCT is necessary for further confirm the effect of ICG fluorescence. We would like to update this meta-analysis when there are more reliable studies, especially RCTs. (2) There were some minor differences in baseline data between the ICG group and control group, which may cause potential influence on the incidence of AL. (3) Most studies have not reported AL grading based on the Clavien-Dindo classification. Whether ICG fluorescence could prevent patients from severe AL is unclear. (4) The number of included publications on Ivor-Lewis (conducting intrathoracic anastomosis) is limited, more high-quality publications are necessary to confirm the usefulness of ICG fluorescence in intrathoracic anastomosis. (5) Few studies used ICG quantification to measure the blood flow speed, and most studies ignored the importance of venous congestion. How to reduce the AL rate in patients with poor perfusion is really a question (34). Recently, Takeda FR et.al reported the supercharged cervical anastomosis for esophagectomy procedure may reduce the occurrence of anastomotic leakage and improve perfusion in the anastomotic area via vein and arterial micro-anastomoses based on the ICG quantification technique (35).

Conclusion

The application of ICG fluorescence could effectively reduce the incidence of anastomotic leak and shorten postoperative hospital stay for patients undergoing cervical anastomosis, but not for patients undergoing intrathoracic anastomosis. The application of ICG fluorescence before and after gastric management can better prevent patients from AL. This prevention works both in large (>50 cases) and small (<50 cases) medical centers.

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

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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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.2022.847510/full#supplementary-material

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Selection of Digestive Tract Reconstruction After Partial Gastric Sparing Surgery in Patients With Adenocarcinoma of the Esophagogastric Junction of cT_2-T_3 Stage

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Objective: To investigate the appropriate reconstruction method of the digestive tract after partial gastric sparing surgery for adenocarcinoma of the esophagogastric junction of stage cT_2-T_3.

Methods: A retrospective analysis of the clinical data of patients with adenocarcinoma of the esophagogastric junction from January 2015 to January 2019 in the General Surgery Department of Zhengzhou University Affiliated Tumor Hospital was performed. Patients with intraoperative double tract anastomosis composed the double tract reconstruction (DTR) group, and patients with intraoperative oesophagogastrostomy with a narrow gastric conduit group composed the oesophagogastrostomy by a narrow gastric conduit (ENGC) group. We analysed and compared the short-term postoperative complications and long-term postoperative nutritional status of the two groups of patients.

Result: There were no statistically significant differences between the two groups of patients in terms of age, sex, preoperative haemoglobin level, albumin level, cT, cN, neoadjuvant therapy or not, pathological type and Siewert type. In terms of BMI and body weight, the ENGC group was higher than the DTR group, but the difference was not statistically significant ($p = 0.099$, $p = 0.201$). There was no significant difference between the two groups of patients in terms of upper resection margin, operation time, blood loss, tumor diameter, pT, pN and postoperative hospital stay. The gastric resection volume of the DTR group was much larger than that of the ENGC group, and there was a significant difference between the two ($p = 0.000$). The length of the lower resection margin of the DTR group was also significantly greater than that of the ENGC group ($p = 0.000$). In terms of surgical approach, the proportion of the DTR group with the abdominal approach was significantly higher than that of the ENGC group, and the difference between the two was statistically significant ($p = 0.003$). The postoperative exhaust time in the ENGC group was significantly shorter than that in the DTR group ($p = 0.013$). However, there was no statistically significant difference between the two groups in terms of anastomotic leakage, anastomotic bleeding, intestinal obstruction, abdominal infection, pneumonia, pancreatic leakage, lymphatic leakage,death within 30 days after surgery, or overall complications. In terms of anastomotic stenosis, the incidence in the ENGC group was higher than in the DTR group, and the difference was statistically significant ($p = 0.001$). There was no significant difference in oral PPI, haemoglobin or albumin levels in patients at 3 months, 6 months, or 12 months after surgery. Comparing reflux/heartburn symptoms at 3 months and 6 months after surgery, we found no statistically significant difference between the two, while in terms of reflux/heartburn symptoms at 12 months after surgery, the findings of the ENGC group were higher than those of the DTR group, and the difference was statistically significant ($p = 0.045$). In terms of poor swallowing, the ENGC group was always higher than the DTR group, and the difference between the two groups was statistically significant ($p < 0.05$). There was no statistically significant difference in body weight between the two groups at 3 months or 6 months after surgery. At 12 months after surgery, the body weight of the patients in ENGC group was significantly higher than that in the DTR group, and the difference between the two groups was statistically significant ($p = 0.039$).

Conclusions: For patients with cT2-T3 stage oesophagogastric junction adenocarcinoma with tumours less than 4 cm in diameter, ENGC anastomosis is recommended for patients with a high tumour upper boundary, with obesity, short mesentery, or disordered vascular arch, and for routine patients, DTR anastomosis is recommended.

Keywords: gastric cance, digestive tract reconstruction, double tract reconstruction (DTR), gastric anastomosis, tnm (8th edition)

INTRODUCTION

In recent years, the statistical results of clinical data from Europe (1), America (1), Japan and South Korea (2), and China (3) all show that the incidence of adenocarcinoma in the esophagogastric junction is increasing annually. In the past, total gastrectomy was usually performed by surgeons for advanced adenocarcinoma of the esophagogastric junction. With the increasing awareness of organ function protection, the majority of surgeons are seeking for the radical surgical treatment of adenocarcinoma of the esophagogastric junction, and at the same time, they are also actively seeking for the appropriate way to reconstruct the digestive tract (4). In terms of the radical treatment of tumors, it has been reported that the lymph node metastasis rates of No.4d, 12a, 5 and 6 patients with T_2-T_3 stage upper gastric cancer were 0.99%, 0.006%, 0 and 0 (5), respectively, indicating that the metastasis rates of distal perigastric lymph nodes in such patients were very low, suggesting that patients with T_{2-3} stage upper gastric cancer may not have dissected No. 4d, 12a, 5 and 6 lymph nodes. The results of this study also provide a theoretical basis for proximal gastrectomy in patients with stage T_{2-3} upper gastric cancer. A meta-analysis showed no significant difference of 5-year overall survival rate, recurrence rate between total gastrectomy and proximal gastrectomy for upper-third gastric cancer (6). At present, there are many ways to reconstruct the digestive tract after proximal gastrectomy, and different methods have their own advantages and disadvantages (7). Double tract reconstruction (DTR) can significantly reduce the incidence of reflux oesophagitis (8). However, this procedure involves more anastomotic sites, which theoretically increases the incidence of anastomotic leakage and the cost. Oesophagogastrostomy by a narrow gastric conduit (ENGC) is relatively simple and more suitable for patients with longer oesophagectomy times, but postoperative anastomotic stenosis often occurs. At present, there are few reports comparing DTR and ENGC. Therefore, the General Surgery Department of the Affiliated Cancer Hospital of Zhengzhou University conducted a retrospective study on the above situation to provide a basis for gastrointestinal surgeons to select appropriate digestive tract reconstruction methods for patients with oesophageal and gastric junction adenocarcinoma at stage CT_{2-3}.

OBJECTS AND METHODS

The general clinical data of patients with adenocarcinoma of the oesophagogastric junction in the general surgery department of the Affiliated Cancer Hospital of Zhengzhou University from January 2015 to January 2019 were retrospectively analysed. All patients underwent surgery by the same group of surgeons. One group was defined as the DTR group, while the other group was defined as the ENGC group. The short-term postoperative complications and long-term postoperative nutritional status were analysed and compared between the two groups. The entry criteria were as follows: (1) preoperative endoscopic pathology confirmed adenocarcinoma of the oesophagogastric junction; (2) the preoperative clinical T stage was cT_2-T_3; (3) the maximum diameter of the tumour evaluated by CT at the first diagnosis was ≤4 cm; (4) preoperative examination and intraoperative exploration showed no evidence of distant metastasis, with R0 resection being performed in both cases; and (5) the patients underwent radical proximal gastrectomy. The exclusion criteria included (1) severe patient heart and lung disease that could not tolerate radical surgery and (2) incomplete clinical case data. According to the above entry and discharge criteria, a total of 118 patients with oesophagogastric junction adenocarcinoma were included in this study – 60 patients in the DTR group and 58 patients in the ENGC group. This study was discussed and approved by the ethics committee of the hospital, and all the patients' family members signed informed consent for surgery.

METHODS

Anastomosis Method

In the DTR group, the jejunum was dissected approximately 15–25 cm from the distal end of the Treitz ligament. The end-to-side anastomosis of the oesophagus and the distal jejunum was completed with a circular stapler with diameter of 23–25 mm before transcolon. The anastomotic site was reinforced with continuous full-thickness barb suture, and the anastomotic site was embedded with a plasmomuscular layer to reduce tension. The jejunum stump was closed and embedded. The stapler base was placed in the jejunum approximately 15 cm from the distal end of the oesophagojejunal anastomosis, and a round stapler with diameter of 23–25 mm was placed through the residual stomach to complete the side-to-side anastomosis of the residual stomach and jejunum. The gastric stump was closed again with a straight-cut closure device, and the anastomotic stoma was reinforced by continuous full-thickness barb suture. Approximately 30 cm from the distal gastrointestinal anastomosis, the anastomosis between the proximal jejunum and distal jejunum was performed with a circular stapler with diameter of 23–25 mm . The anastomosis was reinforced by continuous full-thickness barbed suture, and the mesangial foramen was closed. The postoperative upper gastrointestinal contrast is shown in **Figure 1A**. In the ENGC group, a tubular stomach with a diameter of approximately 3 cm was made by using a linear cutting closure device, and the residual gastric closure line was embedded with absorbable thread. The bottom stapling seat of the circular stapler was placed at the oesophageal stump, the anterior wall of the appetizer was cut, the circular stapler with diameter of 25–26 mm was placed, and the end-to-end anastomosis of the oesophageal stump and stomach was completed. Absorbable sutures closed the incision of the anterior wall of the residual stomach, and barb sutures continued to strengthen the anastomotic site. The postoperative upper gastrointestinal contrast is shown in **Figure 1B**.

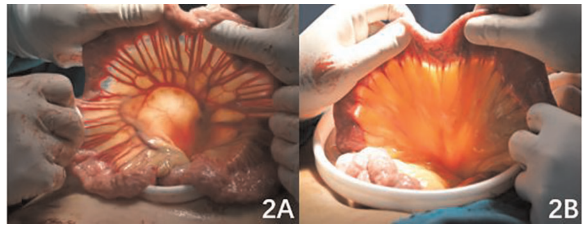

FIGURE 1. | Figure 1 A: postoperative upper gastrointestinal contrast in the DTR group; 1B: postoperative upper gastrointestinal contrast in the ENGC group.

Statistical Analysis

SPSS 22.0 software was used for statistical analysis, normally distributed data are represented, and the independent sample t test was used for comparisons between the two groups. The measurement data with a nonnormal distribution are expressed by months (range). Enumeration data are represented by the use case (%), and the χ^2 test was used for comparisons between groups. A nonparametric Z test was used to compare the nonnormally distributed data and grade data between the groups. $p < 0.05$ was considered statistically significant.

RESULTS

Comparison of General Information

There were no significant differences between the two groups in age, sex, preoperative haemoglobin level, albumin level, CT, CN, neoadjuvant therapy, pathological type or Siewer classification. In terms of BMI and body weight, the data of patients in the ENGC group was higher than those in the DTR group, but the difference was not statistically significant ($p = 0.099$, $p = 0.201$). The specific results are shown in **Table 1**.

Intraoperative and Postoperative Indicators

There were no significant differences between the two groups in terms of upper surgical margin, operative time, blood loss, tumour diameter, PT, PN or postoperative hospitalization time. The volume of gastrectomy in the DTR group was much larger than that in the ENGC group, and there was a significant difference between the two groups ($p = 0.000$). The length of the lower incisions in the DTR group was also significantly greater than that in the ENGC group ($p = 0.000$). In terms of surgical approach, the percentage of the DTR

TABLE 1 | General information.

Variables	DTR ($n = 60$)	ENGC ($n = 58$)	χ^2/t/Z	p
Age(years)	60.5 ± 9.7	62.5 ± 8.7	−1.250	0.214
Gender			1.250	0.264
Male	47	50		
Female	13	8		
BMI (kg/m^2)	21.4±2.8	22.2 ± 2.1	−1.663	0.099
Weight (kg)	65.5 ± 7.5	67.5 ± 9.2	−1.285	0.201
Hemoglobin (g/L)	121.9 ± 12.4	122.9 ± 8.2	−0.557	0.579
Serum albumin (g/L)	37.7 ± 3.7	38.2 ± 3.6	−0.771	0.442
cT			0.816	0.366
T_2	37	31		
T_3	23	27		
cN			0.136	0.713
N_0	29	30		
N_+	31	28		
Neoadjuvant chemotherapy			0.459	0.498
Yes	20	16		
No	40	42		
Differentiation			0.302	0.583
High-middle	28	30		
Low	32	28		
Siewert type			0.833	0.361
II	26	30		
III	34	28		

group choosing the abdominal approach was significantly higher than that of the ENGC group, and the difference was statistically significant ($p = 0.003$). The postoperative exhaust time of the ENGC group was significantly shorter than that of the DTR group ($p = 0.013$). The detailed results are shown in **Table 2**.

TABLE 2 | Comparison of intraoperative and postoperative conditions among two groups.

Variables	DTR ($n = 60$)	ENGC ($n = 58$)	χ^2/t/Z	p
Volume of the gastric specimen			−8.629	0.000
≥2/3	50	2		
½	10	46		
≤1/3	0	10		
Upper cutting margins (cm)	2.3 ± 1.6	2.6 ± 1.7	−1.056	0.293
Lower cutting margins (cm)	7.1 ± 2.2	5.1 ± 1.6	5.585	0.000
Operative approach			7.284	0.007
Abdominal approach	40	20		
Left combined thoracoabdominal approach	20	29		
Operation time (min)	143.9 ± 20.2	152.1 ± 26.8	−1.869	0.064
Intraoperative blood loss (ml)	128.0 ± 81.7	150.7 ± 68.4	−1.663	0.105
Tumor size (cm)	3.6 ± 1.1	3.8 ± 1.3	−1.102	0.273
pT			−1.146	0.252
T_1	5	3		
T_2	31	26		
T_3	20	24		
T_4	4	5		
pN			−0.391	0.696
N_0	31	32		
N_1	20	18		
N_2	7	7		
N_3	2	1		
First anal exhaust time (d)	3.4 ± 1.1	2.8 ± 1.3	2.524	0.013
Postoperative hospital stay (d)	10.7 ± 1.7	10.2 ± 2.7	1.718	0.088

Results of Complications in the two Groups

There were no significant differences in anastomotic leakage, anastomotic haemorrhage, intestinal obstruction, abdominal infection, pneumonia, pancreatic leakage, lymphatic leakage, death within 30 days after surgery or total complications between the two groups. The incidence of anastomotic stenosis in the ENGC group was higher than that in the DTR group, and the difference was statistically significant ($p = 0.001$). The specific results are shown in **Table 3**.

TABLE 3 | Comparison of postoperative complications among two groups.

Variables	DTR ($n = 60$)	ENGC ($n = 58$)	χ^2	p
Anastomotic leakage	0/60	1/58	1.043	0.492
anastomotic stenosis	1/60	12/58	10.886	0.001
Anastomotic bleeding	0/60	0/58	–	–
Ileus	2/60	0/58	1.967	0.496
Abdominal infection	1/60	1/58	0.001	1.000
Pulmonary infections	6/60	9/58	0.809	0.368
pancreatic leakage	2/60	0/58	1.967	0.496
lymphatic leakage	2/60	1/58	0.308	1.000
Death	0/60	0/58	–	–
Total complications	12/60	19/58	2.478	0.115

Postoperative Follow-up

There was no significant difference in oral PPI, haemoglobin or albumin levels at 3 months, 6 months or 12 months after the operation. There was no significant difference between the reflux/heartburn symptoms at 3 months and 6 months after surgery, while the reflux/heartburn symptoms at 12 months after surgery were higher in the patients in the ENGC group than in those in the DTR group, with a significant difference between the two ($p = 0.045$). In terms of adverse swallowing, the data of the patients in the ENGC group was always higher than those in the DTR group, and the difference between the two groups was statistically significant ($p < 0.05$). There was no statistically significant difference in the weight of patients in the 3 months and 6 months groups after surgery, while the weight of patients in the ENGC group was significantly higher than that in the DTR group 12 months after surgery, with a statistically significant difference between the two groups (p = 0.039). The specific results are shown in **Table 4**.

DISCUSSION

To completely remove the lymph nodes that may metastasize and to avoid severe reflux oesophagitis in patients after surgery, in the past, total gastrectomy combined with oesophagojejunostomy was often used by surgeons for advanced cancer of the oesophagogastric junction. However, after total gastrectomy, the digestive and absorption function of patients becomes severely impaired, leading to significant weight loss in patients later (9–11). Therefore, it is an urgent clinical problem for surgeons to preserve part of the gastric tissue and function. A multicentre retrospective study also found that for oesophageal and gastric junction cancer <4 cm in length, the rate of distal perigastric lymph node metastasis was very low, so transabdominal proximal gastrectomy was recommended (12). At present, the methods of gastrointestinal reconstruction after proximal gastrectomy include oesophageal gastric stump anastomosis (13), ENGC, Kamikawa anastomosis, jejunal interposition and DTR. According to the consensus of Chinese experts on the reconstruction of the gastrointestinal tract by proximal gastrectomy (2020) (14), the expert recommendation rate for ENGC was 81.8%, while the expert recommendation rate for DTR was 91.7%. A recent domestic study shows that most surgeons prefer DTR for gastrointestinal reconstruction after proximal gastrectomy (15). In clinical practice, it has been found that for patients with longer oesophageal invasion, DTR oesophagojejunal anastomosis is often limited by the length of the jejunal loop, and high tension anastomosis is likely to occur after anastomosis, which increases the occurrence of anastomotic leakage. Anastomotic stenosis also occurred in patients after ENGC surgery, but a comparative study on the clinical effects of the two anastomotic methods has not been reported.

After retrospective analysis of relevant research results, it was found that the weight and BMI of patients in the ENGC group were higher than those in the DTR group, indicating that the surgeon was more inclined to choose ENGC for obese patients. Patients with normal weight or underweight had longer mesentery and more regular vascular arches (**Figure 2A**). However, in obese patients, the small mesentery is usually shorter, and the classification of the vascular arch is disorderly (**Figure 2B**). The anastomotic site tension is heavier after high oesophageal jejunostomy, and ENGC anastomosis is typically selected. Therefore, ENGC is suitable for patients with greater body weight and a higher BMI. Patients in the DTR group had normal or lower body weight and longer mesentery length and did not have these problems. In patients in the DTR group, the volume of gastric excision was larger, while the volume of residual stomach was smaller, thus obtaining a longer lower incision margin. The difference between the two groups was statistically significant. In the patients in the ENGC group, oesophagogastric anastomosis did not have the problem of high tension at the anastomotic site, so it was suitable for patients with a higher upper margin of the tumour, and the upper margin was longer than that of DTR, but there was no

TABLE 4 | Comparison of postoperative follow-up among two groups.

Variables	DTR (n = 60)	ENGC (n = 58)	χ^2 /t	p
Reflux/heartburn				
3 m after surgery	5/60	8/58	1.749	0.186
6 m after surgery	6/60	13/58	3.364	0.067
12 m after surgery	4/60	11/58	4.020	0.045
Dysphagia				
3 m after surgery	2/60	12/58	8.496	0.004
6 m after surgery	2/60	13/58	9.676	0.002
12 m after surgery	1/60	6/58	3.980	0.046
PPI[a] therapy				
3 m after surgery	3/60	7/58	1.900	0.168
6 m after surgery	4/60	9/58	2.357	0.125
12 m after surgery	2/60	5/58	1.477	0.224
Weight (kg)				
3 m after surgery	55.7 ± 6.2	58.2 ± 8.7	−1.748	0.083
6 m after surgery	53.5 ± 5.7	55.8 ± 7.9	−1.770	0.079
12 m after surgery	60.7 ± 7.6	65.6 ± 7.3	−2.034	0.039
Hemoglobin (g/L)				
3 m after surgery	108.0 ± 10.5	107.0 ± 7.8	0.585	0.559
6 m after surgery	106.2 ± 10.7	104.4 ± 7.2	1.102	0.273
12 m after surgery	119.1 ± 8.3	120.5 ± 18.9	−0.547	0.585
Serum albumin (g/L)				
3 m after surgery	33.2 ± 3.6	33.6 ± 3.2	−0.619	0.537
6 m after surgery	31.7 ± 4.2	32.3 ± 4.4	−0.753	0.453
12 m after surgery	35.8 ± 3.9	36.5 ± 4.8	−0.784	0.435

aProton pump inhibitor.

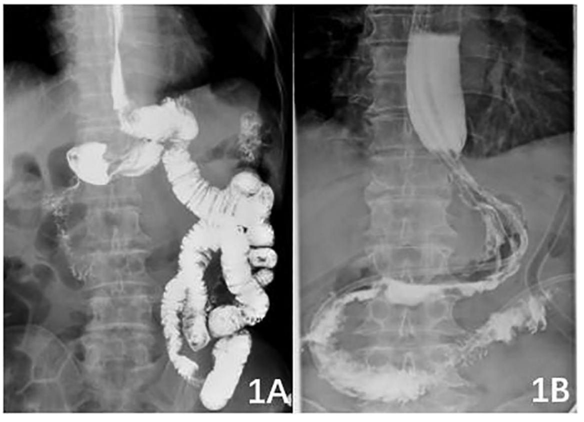

FIGURE 2. | Figure 2A: Relatively long mesentery with regular vascular arches; 2B: relatively short mesentery with disorderly vascular arches.

significant difference. Patients with Siewert II type had a higher tumour location, so the left thoraco-abdominal combined approach was selected to ensure adequate surgical margins, and high anastomosis was associated with anastomotic tension. The results of this study also showed that the left thoraco-abdominal combined approach was more commonly used in the ENGC group, while the transabdominal approach was more often used in the DTR group, but the difference between the two groups was not statistically significant. With the continuous improvement of surgical techniques and concepts over the years, although more patients in the ENGC group underwent the left thoraco-abdominal combined approach, there was no significant difference between the two groups in terms of operative time and amount of surgical bleeding. The results of this study showed that the exhaust time of patients in the ENGC group was shorter than that in the DTR group, and the difference was statistically significant. It may be that the small intestine was not disconnected in the ENGC group, which ensured the integrity of the small intestinal tract, so the intestinal function recovered faster and the patients' exhaust time was shorter. In terms of postoperative hospital stay, the ENGC group was slightly shorter than the DTR group, but there was no significant difference between the two groups.

In terms of postoperative complications, the incidence of anastomotic stenosis in the ENGC group was higher than that in the DTR group, and the difference between the two groups was statistically significant, which was also consistent with many domestic and foreign literature reports (16, 17). This may be related to the thicker gastric wall. After later endoscopic balloon dilation treatment, the adverse symptoms of swallowing in all patients can be significantly reduced (18). Therefore, our team mainly uses a continuous suture for one round to reinforce the anastomotic site after the completion of the anastomosis of the ENGC group during the operation and does not carry out plasmomuscular layer embedment to reduce the occurrence of anastomotic stenosis as much as possible. For the DTR group, the method of two-layer semianastomosis was continued; that is, after the whole-layer reinforcement of the oesophagojejunal anastomosis, the sarcomuscular layer was embedded in the anastomosis, and stenosis of the oesophagojejunal anastomosis was also rare in clinical practice. This study also found that there were no significant differences in anastomotic leakage, anastomotic haemorrhage, intestinal obstruction, abdominal infection, pneumonia, pancreatic leakage or lymphatic leakage between the two groups. Finally, in terms of total complications, although the data of the patients in the ENGC group were higher than those in the DTR group, there was no significant difference between the two groups, indicating that the operation safety of the two groups was essentially the same except for postoperative anastomotic stenosis.

Previous studies have found that the incidence of reflux/heartburn and adverse swallowing after ENGC is higher than that after DTR (19–21). The same results were also found in the follow-ups of this study. Patients in the ENGC group were worse than those in the DTR group in terms of reflux/heartburn and adverse swallowing, and the difference between the two groups was statistically significant. A study conducted by Japanese scholars (22, 23) found that the incidence of postoperative reflux oesophagitis confirmed by gastroscopy was significantly lower than the incidence of postoperative reflux symptoms. The present study also found that there was no significant difference in oral PPI between the two groups, indicating that in terms of subsequent quality of life, although the incidence of reflux/heartburn symptoms in the ENGC group was higher than that in the DTR group, most patients could tolerate the incidence and did not need PPI drug adjuvant therapy. The weight of patients in the ENGC group was higher than that in the DTR group, and it was found at follow-up that the weight of patients in the two groups still gradually decreased within 6 months after surgery, and there was no significant difference between the two groups. However, at the 12 months follow-up after surgery, the weight of patients in the ENGC group was found to be higher than that in the DTR group. One possible reason is that the majority of patients after gastrointestinal surgery decided to accept subsequent adjuvant chemotherapy, resulting in two groups of patients with 6 months post-operative weight loss. At the end of chemotherapy, the number of symptoms involving digestive tract reactions gradually decreased. In terms of weight gain, the weight difference between the two groups of patients gradually returned to baseline levels. Further study also found that there was no significant difference in haemoglobin or albumin level between the two groups in the postoperative follow-up of 3 months, 6 months and 12 months, which may be because the gastric antrum was retained in both groups, partial gastric function was retained, and the absorption of iron ions was not affected. In summary, the follow-up results indicated that the above anastomosis had the same effect on the recovery of digestive tract absorption function in the later stage, without obvious advantages or disadvantages.

In conclusion, ENGC anastomosis is recommended for patients with cT_2-T_3 oesophageal and gastric junction adenocarcinomas with a tumour diameter less than 4 cm and patients with a higher upper boundary of the tumour, obesity, short mesentery of the small intestine, or disorderly grade of the vascular arch. DTR anastomosis is recommended for conventional patients, including those with a transabdominal approach, a low upper boundary of the tumour, and a long mesentery. However, this study is only a single-centre retrospective study with a small sample, and the advantages and disadvantages of the two anastomotic procedures are compared. However, similar data need to be further confirmed in future studies involving larger samples and multiple centres.

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 Ethics Committee of Zhengzhou University

Tumpr Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JZ and YZ conceived the study. JZ performed the literature search and writing of the manuscript. JZ analyzed and interpreted the data. SL, CL, YC, PM, XZ and GH collected and assembled the data. X Z submitted the manuscript and YZ is the corresponding author. All authors contributed to the article and approved the submitted version.

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Robot-assisted esophagectomy may improve perioperative outcome in patients with esophageal cancer – a single-center experience

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Background: Although the introduction of minimally invasive surgical techniques has improved surgical outcomes in recent decades, esophagectomy for esophageal cancer is still associated with severe complications and a high mortality rate. Robot-assisted surgery is already established in certain fields and robot-assisted esophagectomy may be a possible alternative to the standard minimally invasive esophagectomy. The goal of this study was to investigate whether robot assistance in esophagectomy can improve patient outcome while maintaining good oncological control.

Material and methods: Data of all patients who underwent minimally invasive esophagectomy between January 2018 and November 2021 at University Hospital Mannheim was collected retrospectively. Patients were divided into two cohorts according to operative technique (standard minimally invasive (MIE) vs. robot-assisted esophagectomy (RAMIE), and their outcomes compared. In a separate analysis, patients were propensity score matched according to age, gender and histological diagnosis, leading to 20 matching pairs.

Results: 95 patients were included in this study. Of those, 71 patients underwent robot-assisted esophagectomy and 24 patients underwent standard minimally invasive esophagectomy. Robot-assisted esophagectomy showed a lower incidence of general postoperative complications (52.1% vs. 79.2%, p=0.0198), surgical complications (42.3% vs. 75.0%, p=0.0055), a lower rate of anastomotic leakage (21.1% vs. 50.0%, p=0.0067), a lower Comprehensive Complication Index (median of 20.9 vs. 38.6, p=0.0065) as well as a shorter duration of hospital stay (median of 15 vs. 26 days, p=0.0012) and stay in the intensive care unit (median of 4 vs. 7 days, p=0.028) than standard minimally invasive surgery. After additionally matching RAMIE and MIE patients according to age, gender and diagnosis, we found significant improvement in the RAMIE group compared to the MIE group regarding the Comprehensive Complication Index (median of 20.9 vs. 38.6, p=0.0276), anastomotic leakage (20% vs. 55%, p=0.0484) and severe toxicity during neoadjuvant treatment (0 patients vs. 9 patients, p=0.005).

Conclusion: Robot-assisted surgery can significantly improve outcomes for patients with esophageal cancer. It may lead to a shorter hospital stay as well as lower rates of complications, including anastomotic leakage.

KEYWORDS

minimally invasive esophagectomy, esophageal surgery, abdominothoracic esophagectomy, robotic surgery, DaVinci

Introduction

Esophageal cancer is the eighth most common cancer worldwide and an aggressive disease with a poor prognosis. The incidence of esophageal adenocarcinoma has been increasing especially in Western countries over the past decades as the incidence of risk factors such as obesity and gastroesophageal reflux disease has been rising rapidly (1, 2). At the time of diagnosis, more than 50% of patients present with unresectable or metastatic disease (3). This leads to poor 5-year overall survival rates of around 20%; in metastatic disease under 5% (4).

Outside of very early tumor stages, multimodal therapy has been established as a gold standard, including radiochemotherapy or chemotherapy, as well as surgical resection of the esophagus with the goal of complete tumor removal. Conventional (open), abdominothoracic esophagectomy was the first established technique for resection and often allows complete removal of the tumor, albeit with a high morbidity rate, most prominently anastomotic leakage and pulmonary complications secondary to thoracotomy (5).

In order to reduce complication rates and facilitate postoperative recovery, minimally invasive esophagectomy (MIE) was introduced. When compared to conventional esophagectomy, MIE results in lower blood loss, a lower rate of postoperative complications and perioperative morbidity in general, as well as improved quality of life (2, 6, 7). However, the higher cost of MIE and protracted learning curve as well as its technical complexity are obstacles in its implementation.

Recently, robot-assisted minimally invasive esophagectomy (RAMIE) has been introduced with the prospect of overcoming the technical limitations associated with MIE while maintaining good oncological outcomes (8). During RAMIE, the surgeon operates the robotic arms positioned at the patient from a console and benefits from an enlarged three-dimensional view of the operating field, a higher degree of freedom with the articulated instruments and stabilization of the naturally occurring tremor. Both the thoracoscopic and the laparoscopic parts of the procedure can be performed robotically, though in this study, we focused on the thoracoscopic part (esophagectomy, lymphadenectomy and esophagogastrostomy) while the abdominal part (formation of the gastric conduit) were performed as non-robotic laparoscopy (Figures 1, 2).

Although evidence comparing RAMIE to standard MIE is still limited, RAMIE has shown a lower blood loss as well as a shorter intensive care unit (ICU) stay while maintaining high rates of R0 resections when compared to MIE (8–10). A previously conducted systematic review also found that RAMIE provided similar short-term mortality rates (11). The need for specialized training in handling the robot as well as significant financial requirements for the acquisition and maintenance of robotic systems have however been holding back many hospitals from routinely using RAMIE.

In early 2018, RAMIE was introduced in the Department of Surgery of University Hospital Mannheim as an alternative to the standard minimally invasive surgery, both for tumors of the esophagus and the esophagogastric junction regardless of histologic subtype.

In this study, we report our experiences with robotic resection of esophageal cancer and investigate whether use of a surgical robot can improve patient outcome and reduce postoperative complications.

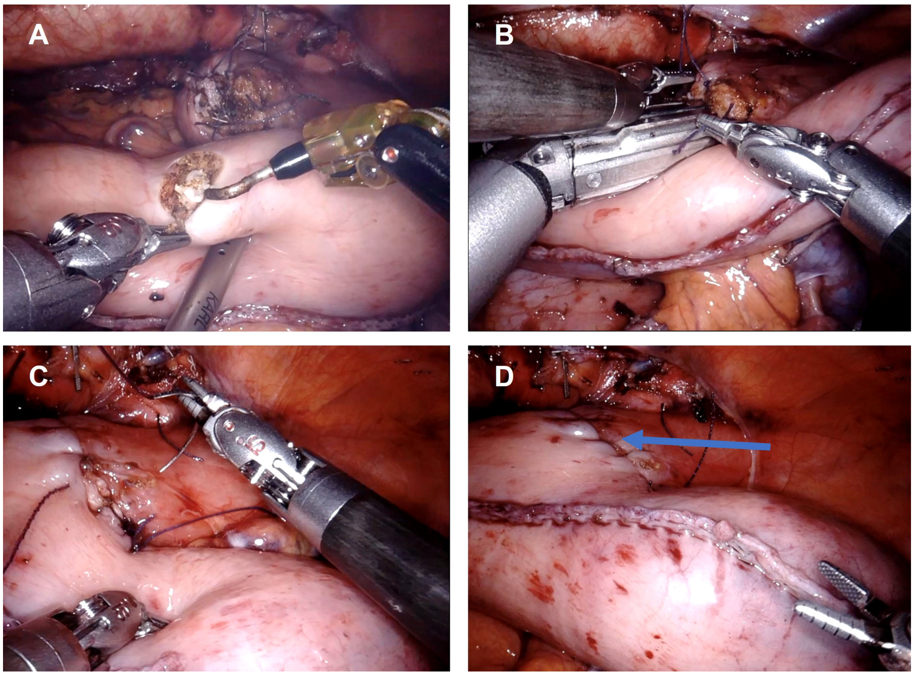

FIGURE 1
Robot-assisted linear stapled side-to-side esophagogastrostomy. **(A)** Opening of the gastric conduit. **(B)** Intrathoracic stapling of the anastomosis with the linear stapler. **(C)** Closure of the incision hole in esophagus and gastric conduit. **(D)** Completed side-to-side esophagogastrostomy (blue arrow indicates location of the esophagogastric anastomosis).

Material and methods

Patient selection and study design

A retrospective database was built containing all patients who underwent minimally invasive surgery for esophageal cancer or cancer of the esophagogastric junction (AEG) with curative intent between January 2018 and November 2021 (n=95). Patients who underwent laparotomy (n=9) or a combination of open and minimally invasive esophagectomy (n=8) were excluded from the study, as well as patients who received a two-stage surgical procedure (n=4) and patients with preoperatively diagnosed metastatic disease. In one patient liver metastases were detected during surgery.

Patients with Siewert type III adenocarcinoma of the esophagogastric junction (i.e. proximal gastric cancer not involving the esophagogastric junction), were not included in this study and treated following the gastric cancer protocol.

The study focused on postoperative complications as well as length of surgery, intraoperative blood loss, length of ICU and length of hospital stay.

This study was reviewed and approved by the ethics board II of Heidelberg University prior to its initiation (approval number 2020-803R).

Preoperative diagnostics and treatment

The tumor-node-metastasis (TNM) system was used for staging, which included endoscopy, endoscopic ultrasonography and a computer tomography (CT) scan of chest and abdomen. Only in cases in which the CT results suggested lymph node metastases not included in the standard lymphadenectomy or which would otherwise change the therapeutic strategy, a PET (positron emission tomography)/CT scan was performed. Biopsies were taken during endoscopy to determine histopathologic subtype and grading of the tumor. A multidisciplinary board discussed every case prior to treatment initiation.

Patient weight was recorded before neoadjuvant therapy and again on the day before surgery. The difference between those weights constituted the weight change during neoadjuvant therapy.

Preexisting conditions were classified into four categories: cardiovascular disease, pulmonary disease, diabetes and other malignancies besides esophageal cancer. Serum levels of albumin and cholesterol were routinely determined preoperatively and used as indicators for nutritional status (12–14).

Neoadjuvant therapy was given to patients with locally advanced tumors (cT3, cT4 or cN+) without the presence of distant metastases (cM0). Depending on tumor stage and

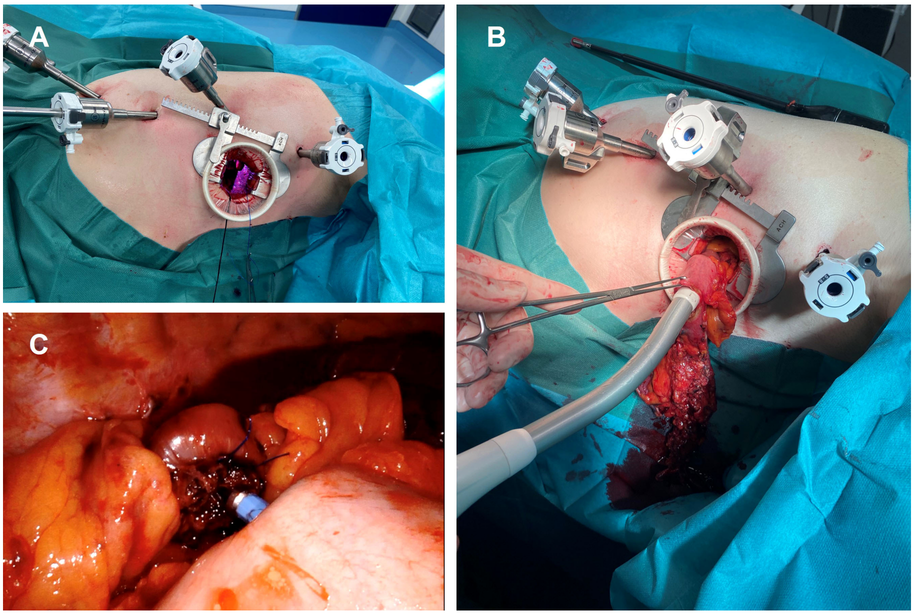

FIGURE 2
Robot-assisted circular stapled end-to-side esophagogastrostomy. **(A)** Thoracic port placement and small thoracotomy. **(B)** Insertion of the circular stapler into the gastric conduit. **(C)** Intrathoracic end-to-side esophagogastrostomy.

histopathologic type, patients preoperatively received either chemotherapy according to the FLOT protocol (15) (adenocarcinoma) or radiochemotherapy according to CROSS protocol (16) (squamous cell carcinoma (SCC)).

Patients with early-stage tumors (cT1-2N0) did not receive neoadjuvant therapy. Toxicity of neoadjuvant therapy was estimated using the National Cancer Institute's "Common Terminology Criteria for Adverse Effects" (CTCAE). We defined symptoms of grade three and higher, as well as all side effects that led to patient hospitalization, as severe toxicity (17, 18).

Operative techniques

The availability of the robotic system on the day of surgery determined whether MIE or RAMIE was performed. The same three surgeons operated on all of the patients, two of which were in training during the study period.

All esophagectomies were performed with an Ivor-Lewis (right thoracic) approach and consisted of a laparoscopy and a thoracoscopy. All patients in this study received an esophageal resection with two-field mediastinal and abdominal lymphadenectomy (D2 lymphadenectomy), reconstruction was performed as a gastric conduit and either side-to-side esophagogastrostomy with linear stapling technique (Figure 1) or end-to-side esophagogastrostomy using circular stapling technique (Figure 2). The anastomotic technique was changed from side-to-side linear stapling to end-to-side circular stapling in 2020 due to promising results of end-to-side circular stapling concerning anastomotic leakage and perioperative outcomes in several recent studies (19, 20). The anastomosis was mostly located intrathoracically. Two patients in the MIE group had a cervical anastomosis. In the RAMIE group, the DaVinci Xi system (Intuitive Surgical Inc, Sunnyvale, CA) was either used for the thoracoscopic part (n=60) or for both the laparoscopic and thoracoscopic parts (n=11). Operating time included repositioning of the patient between the laparoscopic and thoracoscopic parts as well as docking and undocking of the surgical robot. Blood loss during surgery was approximated by operating room personnel. The resected specimen was evaluated during routine pathological work-up by board-certified pathologists of the Department of Pathology of University Hospital Mannheim.

Postoperative management and complications

All patients were postoperatively transferred to either the intermediate care ward (IMC) or the ICU depending on the respiratory state of the patient. In this study, IMC and ICU stay will be summarized under the data point "length of ICU-stay".

Parenteral nutrition was used only when enteral food intake was not sufficient. All patients were encouraged to engage in physical activity according to their capabilities, starting on the day of surgery and supported by trained physical therapists.

Complications were categorized as either medical or surgical. Medical complications were divided into cardiac and pulmonary, the latter of which includes pneumonia. Under surgical complications, we summarized all complications that were related directly to the surgical procedure (e.g. postoperative hemorrhage). The incidence of anastomotic leakage as the most prominent surgical complication was analyzed separately.

If patients presented with elevated or increasing infectious parameters after postoperative day three (fever ≥ 38.5°C, leukocyte increase of ≥ 5,000/µl or total amount of ≥ 20,000/µl, CRP increase of ≥ 50mg/l or total amount of ≥ 200mg/l) an esophagogastroduoenoscopy (EGD) was performed. If no other reason was found for the elevated infectious parameters, prophylactic endoscopic vacuum therapy was started, even if no anastomotic insufficiency could be seen during EGD.

Postoperative complications are often ranked according to the Clavien-Dindo classification, a seven grade system in which higher grades indicate more severe complications (21). Usually only higher grades of complication (grades 2b or higher) in a patient are reported for statistical analysis, leading to an incorrect representation of the actual overall morbidity. To avoid this, we used the Comprehensive Complication Index (CCI) which is based on the Clavien-Dindo scores but includes all postoperative complications, weighted according to their severity, producing a score between 0 (no complications) and 100 (death) (22). An online calculator (https://www.assessurgery.com/) was used to calculate the CCI.

Follow-up was scheduled according to guidelines, with the first appointment two weeks after discharge.

Propensity score matching

To reduce bias due to confounding variables, propensity score matching (PSM) was performed. PSM included age, sex and histopathological diagnosis of the tumor (AEG I, AEG II, SCC). The Greedy matching algorithm was used to form matched pairs between the 71 patients receiving RAMIE and the 24 patients receiving MIE. A caliper width (maximum allowable difference in propensity scores) of 0.25 was used.

Statistical analysis

SAS statistical analysis software release 9.4 (SAS Institute Inc., Cary, NC, USA) was used for propensity score matching as well as other statistical analysis.

Qualitative variables were given as absolute and relative frequencies. Median and interquartile range (IQR) were calculated for non-normally distributed values. Mean and standard deviation (SD) were calculated for quantitative, normally distributed values.

Chi-square test was used for categorical variables. In cases of numbers lower than expected, Fisher's exact test was performed. Normally distributed data were compared using the Student's t-test. The Mann-Whitney-U-test was used for data not following a Gaussian distribution. All statistical tests comparing two groups were two-tailed. A *p*-value of <0.05 was considered statistically significant.

Results

A total of 95 patients were included in this study; 71 patients (74.7%) underwent RAMIE, while 24 patients (25.3%) underwent standard MIE. In the RAMIE group, in 11 patients the surgical robot was used for both the thoracoscopic and laparoscopic part, in 60 patients the surgical robot was used only for the thoracoscopic part.

Demographic and clinicopathological characteristics

The demographic data are presented in Table 1. The majority of patients (82.1%) were male with a mean age of 64 years. Most tumors were preoperatively identified as adenocarcinoma (AEG I in 43.2%, AEG II in 35.8%). In 60.0% of patients the tumor stage was identified as cT3 or higher, and in 68.4% of patients as cN+ (positive lymph node stage). The majority of patients (84.2%) received neoadjuvant therapy.

Baseline characteristics of both groups were statistically compared to ensure similarity. The only significant difference between both groups was the report of severe toxicity during neoadjuvant therapy, which was higher in the MIE group (71.4% vs. 25%, p=0.0077).

The histopathological postoperative data are presented in Table 2. No significant differences between the two groups were found in (y)pT, (y)pN and (y)pM statuses, the number of resected lymph nodes, the resection status or the ratio of positive to total number of resected nodes.

Perioperative data

Perioperative data of patients are presented in Table 3. There were no intraoperative complications.

The anastomotic techniques differed significantly between MIE and RAMIE (p=0.0406). Whereas 79% (n=19) of the patients in the MIE group received side-to-side linear stapling anastomosis, only 62% (n=44) in the RAMIE group received this anastomotic technique. 21% (n=5) of the MIE group received

TABLE 1 Demographic and clinicopathological characteristics.

	Total	Type of surgery		*p*-value
	n=95	RAMIE (n=71)	MIE (n=24)	
Sex				0.5471
male	78 (82.1%)	57 (80.3%)	21 (87.5%)	
female	17 (17.9%)	14 (19.7%)	3 (12.5%)	
Age, years (mean, [SD])	64.1 [10.3]	63.2 [10.1]	66.7 [10.5]	0.1503
Histopathology				0.2502
AEG I	41 (43.2%)	34 (47.9%)	7 (29.2%)	
AEG II	34 (35.8%)	24 (33.8%)	10 (41.7%)	
SCC	20 (21.1%)	13 (18.3%)	7 (29.2%)	
cT				0.9046
1	10 (10.5%)	8 (11.3%)	2 (8.3%)	
2	14 (14.7%)	10 (14.1%)	4 (16.7%)	
3	55 (57.9%)	42 (59.1%)	13 (54.2%)	
4	2 (2.1%)	1 (1.4%)	1 (4.2%)	
x	14 (14.7%)	10 (14.1%)	4 (16.7%)	
cN				0.0945
+	65 (68.4%)	45 (63.4%)	20 (83.3%)	
0	20 (21.1%)	16 (22.5%)	4 (16.7%)	
x	10 (10.5%)	10 (14.1%)	0 (0.0%)	
Neoadjuvant therapy	80 (84.2%)	59 (83.1%)	21 (87.5%)	0.7535
Toxicity	39 (48.8%)	25 (42.4%)	14 (66.7%)	0.0759
Severe Toxicity	16 (42.1%)	6 (25%)	10 (71.4%)	**0.0077**
Pre-existing conditions				
Cardiovascular	55 (57.9%)	40 (56.3%)	15 (62.5%)	0.6401
Pulmonary	15 (15.8%)	11 (15.5%)	4 (16.7%)	1.0000
Diabetes	10 (10.5%)	7 (9.9%)	3 (12.5%)	0.7094
Other malignancies	14 (14.7%)	11 (15.5%)	3 (12.5%)	0.3018
Nutritional status				
Albumin, g/dl (median, [IQR])	37.4 [34.7-39.8]	37.6 [35.3-39.9]	37.0 [32.6-39.5]	0.1956
Cholesterol, mg/dl (mean, [SD])	209.7 [49.9]	211.3 [51.7]	204.4 [44.2]	0.8242
Preoperative BMI, kg/m^2 (median, [IQR])	25.2 [22.6-27.9]	25.3 [22.8-27.9]	24.7 [22.0-27.6]	0. 6622

RAMIE, robot-assisted minimally invasive esophagectomy; MIE, minimally invasive esophagectomy; AEG, adenocarcinoma of the esophagogastric junction; SCC, squamous cell carcinoma; SD, standard deviation; IQR, interquartile range; p<0.05 are marked in bold.

end-to-side circular stapling anastomosis, whereas patients in the RAMIE group received this anastomosis in 38% (n=27).

Median duration of surgery did not differ significantly between RAMIE and MIE (395.0 vs. 399.5 minutes, p=0.6685). Patients who received RAMIE had a shorter overall length of stay (median of 15 vs. 26 days, p=0.0012) and a shorter ICU stay (median of 4 vs. 7 days, p=0.0280). The rate of general postoperative complications was also lower in the RAMIE group (52.1% vs. 79.2%, p=0.0198) which reflects in a lower Clavien Dindo Score (p=0.0188) and a lower CCI (median of 20.9 vs. 38.6, p=0.0065). More specifically, the rate of surgical complications (42.3% vs. 75.0%, p=0.0055) and anastomotic leaks (21.1% vs. 50.0%, p=0.0067) were significantly lower in the RAMIE group. There were no significant differences in anastomotic leakage rates between the different anastomotic techniques when comparing RAMIE and MIE (p=0.6885). There was no difference in medical complications (46.2% vs. 47.4%, p=1.0000).

In the entire study population, two patients died within 30 days after surgery. This equals a 30-day-mortality rate of 2.1%.

Propensity score matching

Patients in both groups were matched according to age, sex and histopathological diagnosis. The matched groups resulted in 20 pairs. Of these 40 patients, 36 (90.0%) were male, 14 (35.0%) had AEG type I tumors, 18 (45.0%) AEG type II and 8 (20.0%) SCC. The mean age of the RAMIE group was 64.4 and the mean age of the MIE group was 66.6.

In the preoperative data, we found a significant difference between the groups regarding the clinical lymph node stadium

TABLE 2 Histopathological data.

	Total	Type of surgery		p-value
	n=95	RAMIE (n=71)	MIE (n=24)	
TNM Classification				0.1764
(y)pT				
0	26 (27.4%)	23 (32.4%)	3 (12.5%)	
1	20 (21.1%)	15 (21.1%)	5 (20.8%)	
2	11 (11.6%)	9 (12.7%)	2 (8.3%)	
3	36 (37.9%)	23 (32.4%)	13 (54.2%)	
4	2 (2.1%)	1 (1.4%)	1 (4.2%)	
(y)pN				0.4317
0	59 (62.1%)	45 (63.4%)	14 (58.3%)	
1	23 (24.2%)	15 (21.1%)	8 (33.3%)	
2	10 (10.5%)	9 (12.7%)	1 (4.2%)	
3	3 (3.2%)	2 (2.8%)	1 (4.2%)	
(y)pM				0.4434
0	93 (97.9%)	70 (98.6%)	23 (95.8%)	
1	2 (2.1%)	1 (1.4%)	1 (4.2%)	
R-Status				0.3253
R0	90 (94.7%)	66 (93.0%)	24 (100%)	
R1	5 (5.3%)	5 (7.0%)	0 (0.0%)	
Lymph nodes				
Resected number (median, [IQR])	24 [19-34]	24.0 [19-34]	23.5 [18.5-32.3]	0.6342
Ratio of tumor affected to resected lymph nodes (median, [IQR])	0.0 [0.0-0.06]	0.0 [0.0-0.05]	0.0 [0.0-0.06]	0.7273

RAMIE, robot-assisted minimally invasive esophagectomy; MIE, minimally invasive esophagectomy; SD, standard deviation; IQR, interquartile range; p<0.05 are marked in bold.

(cN) with 50.0% of patients in the RAMIE group vs. 85.0% of patients in the MIE group being staged as cN1 (p=0.0173). This did not reflect in the postoperative pathological staging (pN) which was not significantly different (p=0.8606). The difference in toxicity of neoadjuvant therapy was less pronounced after matching (42.9% vs. 68.4%, p=0.1420). Nevertheless, the rates of severe toxicity during neoadjuvant treatment remained significantly different between RAMIE and MIE (0 vs. 9 patients, p=0.0050). In the postoperative data, we found that the CCI (median of 20.9 vs. 38.6, p=0.0276) remained significantly lower in the RAMIE group after matching. Also, the rates of anastomotic leakage remained significantly lower in the RAMIE group (20% vs. 55%, p=0.0484). A non-significant tendency favouring RAMIE over MIE could be seen concerning overall postoperative complications (55.0% vs. 85.0%, p=0.0824) and surgical complications (50.0% vs. 80.0%, p=0.0958). ICU stay, overall hospital stay, Clavien Dindo Score, blood loss and other variables were not significantly different after matching.

Discussion

The here presented findings suggest that robot-assisted surgery might positively influence the outcome of cancer patients undergoing esophageal resection. Patients who underwent RAMIE had a significantly shorter hospital stay and ICU stay, as well as a lower rate of postoperative complications as reflected in lower Clavien Dindo and CCI scores than patients who received standard MIE. More specifically, rates of surgical complications and anastomotic leaks were lower in the RAMIE group, although only anastomotic leakage rates remained significantly lower after matching. The procedure itself is safe with no intraoperative complications. Oncological results were comparable to MIE.

Several studies comparing RAMIE and MIE have found no significant difference in the report of postoperative complications (9, 23–27). In contrast, our study shows a lower incidence of overall and surgical complications in RAMIE and no difference in medical complications. This could be due to the technical advantages of a surgical robot when operating in narrow spaces such as the mediastinum. The anastomoses in both patient groups were mostly performed as thoracic anastomoses, which has been connected to a lower incidence of anastomotic leakage than cervical anastomoses (28). To eliminate bias as much as possible, we matched patients according to gender, age and diagnoses, using propensity score matching. Also, after matching the CCI and anastomotic leakage rates remained significantly lower in the RAMIE group.

A recently published retrospective and propensity score matched analysis by Babic et al. reported similar results comparing RAMIE and hybrid minimally invasive

TABLE 3 Perioperative data.

	Total	Type of surgery		p-value
	n=95	RAMIE (n=71)	MIE (n=24)	
Characteristics of surgery				
Length of surgery, minutes (median, [IQR])	395.0 [360.5-449.0]	395.0 [351.0-448.5]	399.5 [367.5-456.0]	0.6685
Blood loss, ml (median, [IQR])	275 []	250 [200-400]	400 [200-500]	0.1258
Blood transfusion	9 (9.9%)	5 (7.6%)	4 (17.4%)	0.2228
Anastomotic technique				**0.0406**
Linear stapling	63 (66.3%)	44 (62.0%)	19 (79.2%)	
Circular stapling	32 (33.7%)	27 (38.0%)	5 (20.8%)	
Length of stay, days				
ICU (median, [IQR])	4 [3-9]	4 [3-6.5]	7 [4-18.5]	**0.0280**
Total (median, [IQR])	17 [11-28]	15 [11-25.5]	26 [13.8-61]	**0.0012**
Complications				
Any complication	56 (59.0%)	37 (52.1%)	19 (79.2%)	**0.0198**
Clavien Dindo				**0.0188**
0	39 (41.1%)	34 (47.9%)	5 (20.8%)	
1	1 (1.1%)	0 (0.0%)	1 (4.2%)	
2	10 (10.5%)	9 (12.7%)	1 (4.2%)	
3a + 3b	29 (30.5%)	19 (20.0%)	10 (41.7%)	
4a + 4b	12 (12.6%)	6 (6.3%)	6 (25.0%)	
5	4 (4.2%)	3 (4.2%)	1 (4.2%)	
CCI (median, [IQR])	20.9 [0-43.2]	20.9 [0-27.9]	38.6 [19.1-55.6]	**0.0065**
Surgical complications	48 (50.5%)	30 (42.3%)	18 (75.0%)	**0.0055**
Anastomotic leakage	27 (28.4%)	15 (21.1%)	12 (50.0%)	**0.0067**
Anastomotic technique				0.6885
Linear stapling	18 (18.9%)	10 (14.1%)	8 (33.3%)	
Circular stapling	9 (9.5%)	5 (7.0%)	4 (16.7%)	
Medical complications	31 (41.7%)	21 (29.6%)	10 (41.7%)	0.3181
Cardiac complications	16 (16.8%)	10 (14.1%)	6 (25.0%)	0.2228
Pulmonary complications	22 (23.2%)	15 (21.1%)	7 (29.2%)	0.4157

RAMIE, robot-assisted minimally invasive esophagectomy; MIE, minimally invasive esophagectomy; SD, standard deviation; IQR, interquartile range; ICU, intensive care unit; CCI, comprehensive complication index; p<0.05 are marked in bold.

esophagectomy. Although the analyzed groups (RAMIE and hybrid surgery) were different to our study, Babic et al. also reported significantly shorter ICU stay and less complications in the RAMIE group. After propensity score matching, they could not find significant differences concerning anastomotic leakage rates, but a strong trend favoring RAMIE could be shown as well (29).

We found no significant difference in intraoperative blood loss which matches some previously published studies although there have been widely varying results concerning this topic in recent literature (26, 30). For the cohort in this study, the total length of hospital stay as well as ICU stay was significantly shorter in the RAMIE group. This might be due to reduced intra- and postoperative pain which could be achieved because the robotic arms are able to bend inside the chest and therefore produce less pressure on the ribs and the surrounding nerves (31). Intraoperatively reduced pain can lead to reduced stress of the patient and therefore might lead to better hemodynamic status during the procedure (32). The shortened ICU and hospitals stay is beneficial to the patient and reduces hospital expenditures, which in the long run could offset the higher cost of acquiring and maintaining a robotic system.

It is important to note that some studies include docking und undocking of the robot in the operating time while others do not, which leads to significant discrepancies in operating times (367 to 693 minutes) (33). The here presented operating times include the robot docking and undocking as well as repositioning of the patient for the thoracoscopic part of the procedure. The operating time in our RAMIE group is comparable to the operating times of other studies using a transthoracic approach and including the docking times of the robot into their operating times (34).

The existing evidence on the number of resected lymph nodes is ambivalent. Many studies have shown that RAMIE yields significantly higher numbers of resected lymph nodes than MIE (9, 26, 30, 35). Others have found no significant difference in number of lymph nodes resected between MIE and RAMIE, which reflects the findings in our study (8, 24, 25). This seems unsurprising, as the extent of lymphadenectomy between MIE and RAMIE is identical in our practice. Additionally, the influence of a more extensive lymph node resection on the oncological outcome is not clear. Park et al. reported no difference in 5-year survival rate between groups who received RAMIE and MIE, even though lymph node yield was higher in the RAMIE group (35).

RAMIE remains a technically challenging surgery that requires time and experience. It has been suggested that surgeons must perform between 20 and 70 robot-assisted operations to achieve proficiency (36). The cohort in this study has a relatively high rate of postoperative anastomotic leakage. During the trial period, two of the three surgeons performing the procedures were still in training for MIE and RAMIE, possibly explaining this increased rate of anastomotic leakage. Also, the anastomotic technique was changed in 2020 from linear side-to-side stapler anastomosis to end-to-side circular stapler anastomosis. Recently published results from the EsoBenchmark database indicate lower rates of anastomotic leakage for end-to-side circular stapler anastomoses (37). Despite these data, the change of anastomotic technique may have led to an even longer learning curve and therefore to higher complication rates. Matching this hypothesis, our analysis revealed no improvement of anastomotic leakage rate after introducing circular stapling anastomosis.

To increase the reliability of our results we performed propensity score matching. Unfortunately, the anastomotic technique could not be included into the matching as this resulted in too few matching pairs. As the comparison of anastomotic leakage between linear and circular stapling revealed no significant differences, the results of our analysis still can be interpreted as reliable.

The lower rate of anastomotic leakage in RAMIE indicates that the learning curve may be steeper in RAMIE and reflects the technical challenges of an intrathoracic, minimally invasive anastomosis without the increased flexibility of the robotic system. Another advantage of using a surgical robot is the two-person operating console that allows a learning surgeon to closely attend the surgical field and observe the technique of the operating surgeon.

This study has some limitations. Data were collected retrospectively. Surgery was not always performed by the same surgeon, which could directly influence the outcome, as different surgeons have different levels of surgical expertise and different learning curves.

Our analysis did not include long-term survival, which is an important factor when considering the surgical technique. Future research should focus on high-volume, multi-center, randomized, controlled trials comparing MIE to RAMIE, some of which are currently ongoing (38–40). Especially the currently recruiting ROBOT-2 trial might reveal interesting results in comparison to our study, as it is also conducted in German hospitals and especially the secondary outcome measures are comparable to the investigated variables of our cohort (40).

Our findings suggest that use of a robot-assisted surgery is safe and can positively impact the outcome of esophageal resection in esophageal cancer patients in terms of length of hospital stay and complications.

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 Ethics Committee II, Medical Faculty Mannheim, Heidelberg University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JB: study design, data collection and interpretation, writing and drafting of the manuscript. LE: data collection and interpretation, writing and drafting of the manuscript. SyB: statistical analysis, critical revision of manuscript. CW: statistical analysis, critical revision of manuscript. NR: data interpretation, critical revision of manuscript. AB: data interpretation, critical revision of manuscript. CR: study design, data interpretation, critical revision of manuscript. MO: study design, data interpretation, critical revision of manuscript. SB: study design, data collection and interpretation, critical revision of manuscript. SS: study design, data interpretation, critical revision of 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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The safety of neoadjuvant chemotherapy combined with non-tube nofasting fast-track surgery for esophageal carcinoma

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Our non-tube no fasting (early oral feeding and no nasogastric tube) fast-track surgery (FTS) was safe and effective to combine with neoadjuvant chemotherapy for McKeown minimally invasive esophagectomy. In addition, the two groups were similar in terms of the recovery time, hospital discharge day, and early resumption of oral feeding.

Objectives: To evaluate the safety of early oral feeding (EOF) combined with neoadjuvant chemotherapy (NAC) of esophagectomy.

Summary Background Data: Our non-tube no fasting (early oral feeding and no nasogastric tube) fast-track surgery (FTS) was safe and effective for primary surgery esophageal cancer patients.

Methods: We retrospectively evaluated consecutive patients who underwent non-tube no fasting and McKeown minimally invasive (MIE). They were divided into two groups: one received NAC, and the other received primary surgery. Complications after the operation, postoperative CRG complications, operative time, operative bleeding, and length of stay were evaluated.

Results: Between 01/2014 and 12/2017, there hundred and eighty two consecutive patients underwent MIE with total two-field lymphadenectomy under the non-tube no fasting fast-track surgery program. A total of 137 patients received NAC, and 245 accepted primary surgery. Propensity score matching was used to compare NAC patients with 62 matched patients from each group. The NAC group had a similar number of total complications as the primary surgery group (32.26% in the primary surgery group vs. 25.81% in the NAC group; p=0.429) and had the same median postoperative hospitalization duration (8 days, p=0.723).

Conclusions: After McKeown MIE, the patients receiving NAC combined with "non-tube no fasting" FTS had a similar incidence of postoperative complications outcomes as those without NAC. In addition, the two groups were similar in terms of the recovery time, hospital discharge day, and early resumption of oral feeding.

KEYWORDS

esophageal cancer, fast track surgery, neoadjuant chemotherapy, minimally invasive esophagectomy, short term outcomes

Introduction

Esophageal cancer has a high incidence rate in China. Surgical treatment is the primary method to cure local advanced resectable esophageal cancer. However, it presents high morbidity and mortality, even in high-volume centers. The National Oesophago-Gastric Cancer Audit reported a morbidity rate of 3.2% and mortality rate of 29.7% for esophagectomy (1). If the patient has anastomotic leakage, the posthospital stay can be increased up to 43 days (1).

To reduce the morbidity, mortality and hospitalization duration of these patients, the concept of fast-track protocols after surgery was initially introduced by Kehlet in 1997 (2). It was soon successfully adopted in gastric and colon surgery (3). However, it was difficult to introduce to esophagectomy. Fasting prohibited fast-track surgery (FTS) in esophagectomy. Seven years after the initial FTS concept, it was introduced to esophagectomy by Cerfolio et al. (4) In 2011, our team reported the first application of early oral feeding and non-nasogastric tube (non-tube no fasting) FTS for esophagectomy (5). It soon caused considerable controversial in fear of anastomotic leakage. However, the most difficult aspect was combining this approach with preoperative treatment. In the review by Gemmill, all 10 studies excluded patients undergoing neoadjuvant treatment, which may increase anastomotic leakage (6).

More than ten years have passed since the first attempt of "non-tube no fasting" FTS after esophagectomy. We also wanted to confirm its safety and feasibility in combination with NAC for MIE. The short term outcomes of neoadjuvant chemotherapy (NAC) and primary surgery were compared for EC patients with "non-tube no fasting" FTS.

Methods

General information

The study was approved by the Ethics Review Committee of the Affiliated Cancer Hospital of ZhengZhou University/Henan Cancer Hospital (number 2016ct081).

In this study, the inclusion criteria were as followed: 1.consecutive patients ESCC patient who underwent surgery between 3 January 2014 and 29 December 2017. 2. with R0 resected ESCC. 3.Surgery was performed in the strict one of the thoracic surgery department of Henan Cancer Hospital. Exclusion criteria: 1.Patients who remained in the intensive care unit (ICU) for more than 1 day. 2.Patients with bilateral recurrent laryngeal nerve (RLN) injury. Preoperative tests included enhanced abdominal and cervical color ultrasound, thoracic and upper abdominal computed tomography (CT) scanning, endoscopic ultrasound (EUS), pathological examination, emission computed tomography (ECT) and other routine examinations.

Surgical procedures

All patients underwent MIE surgical approaches, as previously described (7, 8). Briefly, the left lateral decubitus position was adopted, and four ports were inserted into the thoracic cavity. The azygous vein was divided, and the esophagus was mobilized. The right and left recurrent laryngeal nerve and subcarinal and lower mediastinal nodes were harvested. For the abdominal part, the patient was placed in the supine position, and five ports were inserted into the abdominal cavity. The stomach was mobilized, and a gastric conduit was made by using linear staplers (EC60, Ethicon, Cincinnati, OH, USA). The left gastric artery, common hepatic artery, and splenic lymph nodes were removed en bloc. A hand-sewn cervical anastomosis approach was adopted for esophagogastric anastomosis on the left side of the neck (9). The thoracic duct was preserved normally. A chest drainage was put in thoracic and abdominal cavity (10).

Follow-up

During the first 2 years, the patients visited our patient department or were followed up by phone every 3 months. From the third year to the fifth year, follow-up occurred every six months, and from the sixth year, follow-up occurred annually. Follow-up examinations included chest CT scans and abdominal and cervical ultrasound. Other examinations were performed based on the patient's symptoms. The date from surgery to the first date of neoadjuvant treatment was defined as overall survival (OS). May 3, 2020, was the last follow-up date. Not all the patients did their follow up in out patient department. Some of the patients were follow-up by research nurse of our department by phone and all of them were follow-up by LinkDoc company for our hospital.

Statistical analysis

The Mann–Whitney U test and the chi-square test were adopted to compare the clinicopathological qualitative variables between the two groups. Student's t test was used for quantitative data, and Fisher's exact test was used for categorical variables. IBM SPSS statistics version 23 (IBM Corporation, Armonk, NY, USA) was employed for statistical analysis. A p value/0.05 was considered statistically significant. To reduce the bias between the two groups, propensity score (PS)-matched analysis was adopted. The matched variables included age, sex, BMI, clinical TNM stage, history of disease, surgical time, bleeding volume during surgery, and performance status score.

EOF group

On the morning of the first day after the operation, the patient was allowed to sip liquid. If the patients had no symptoms of nausea, vomiting or aspiration. Then the patients could start to consume food at will after fifty chews for every bite of food before swallowing (11). This was monitored by nurse for the first time and then by caretaker.

The basic nutrition for EOF patients was parenteral nutrition, including glucose, amino acids and fat emulsion, which offered 1000 to 1500, 800 to 1000, and 500 to 800 kilocalories (kcal) on POD1, POD2, and POD3, respectively. Oral feeding was started on POD1. The Harris-Benedict formula was used to calculate the required caloric intake of each patient by dieticians. Nutrition education was provided by dieticians. The nurse would emphasize the need for strict aspiration precautions. On POD1, more liquid diet was encouraged, such as porridge, milk, and juice. Semiliquid foods and soft solid foods were provided from POD2, such as cakes, boiled eggs, rice, steamed bread and noodles. The fifty chews per bite of food method was required to ensure patients chewed the food completely and that it had been transformed into a semiliquid state. Normally, parenteral nutrition is removed on POD4 or POD5.

Traditional group

In the traditional group, nasogastric and nasoenteral feeding tubes were used. The patients received nutrition *via* a nasoenteral feeding tube from POD 1. Parenteral nutrition was also adopted. Normally, the nasogastric and nasoenteral feeding tube was removed on POD 7, and the patients resumed oral feeding under the guidance of dieticians.

Results

From 01/2014 to 12/2017, a total of 382 consecutive patients met the inclusion criteria; 137 patients received NAC, and 245 underwent primary surgery. Beginning in 2014, an increasing number of patients received NAC and underwent "non-tube no fasting" FTS (Figure 1). At the same time, the total complication rate in both groups declined year by year (Figure 2). A total of 124 matched patients were retained after PS matched analysis. Each group had 62 patients (Table 1). The baseline demographics of the 124 patients after PS matching analysis are summarized in Table 1. The primary clinical data were comparable. The patients in the primary surgery group had a slightly earlier pathological stage (P=0.077), and those in the NAC group were slightly younger (P=0.184).

The intraoperative and postoperative outcomes and total complication rates are shown in Table 2. No deaths occurred in either of the groups in the hospital or at 90 days after surgery. The median postoperative hospital stay and most objective recovery data were not significantly different (median 8 days in both groups, p=0.723). The median number of chest tube drainage days was 6 in both groups (p=0.131). These FTS-related protocol were in the same manner as those in our previous RCT (5). The mean operation time was 200 min in the primary surgery group and 222.5 min in the NAC group ($P < 0.001$). The median number of lymph nodes retrieved in the primary surgery group was lower than that in the NAC group (9 fewer nodes, $P < 0.001$). The pathological data were compared between the two groups, showing a p value of 0.049 (Table 2).

The primary surgery and NAC groups showed no significant differences in terms of CRG complications and other complications (Table 3). The rates of anastomotic leakage in the primary surgery group and NAC group were 0 and 1.61% (1/6), respectively, representing a difference of -1.61% (95% CI -5.3% to 8.59%). The rates of unilateral RLN injury in the primary surgery group and NAC group were 6.45% (4/62) and 0, respectively, representing a difference of 6.45% (95% CI -0.57 to 15.45). The most common complication was pneumonia, which occurred in 11.29% (7/62) of primary surgery patients and in 9.68% (6/62) of NAC patients, representing a difference of 1.61% (95% CI -9.79% to 13.07%). Moreover, no notable differences in Clavien–Dindo grade complications were observed between the 2 groups. Two patients (3.23%) in the primary surgery group and 1 patient (1.61%) in the NAC group required reoperation (difference of 1.61%; 95% CI -5.74% to 9.52%). These patients were determined

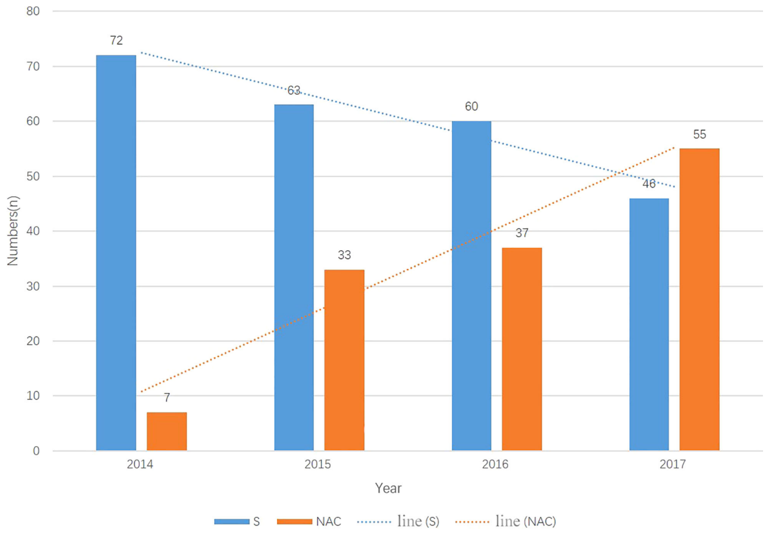

FIGURE 1
The number of patients in two groups each year from 2014-2017. The number of primary surgery patients droped every year meanwhile the muber of NAC patients increased every year. N, number; S, primary surgery; NAC, neoadjuvant chemotherapy.

to have Clavien–Dindo grade IIIb complications. In the two patients in the primary group, one experienced bleeding at the neck incision, and the other experienced bleeding in the chest cavity. The patient in the NAC group was suspected to have mechanical intestinal obstruction. However, after abdominal exploration, no remarkable findings were observed. He was finally diagnosed with several intestinal tympanites. The 3 patients recovered quickly after surgery.

Discussion

It is challenging to adapt esophagectomy to FTS. The most controversial part of FTS for EC is the resumption of early oral feeding in cases of anastomosis leakage and aspiration pneumonia (6). Ten years have passed since Dr Li first attempted to resume oral feeding in patients on POD1. Bohle et al. (12) reported that NAC was a risk factor for anastomotic

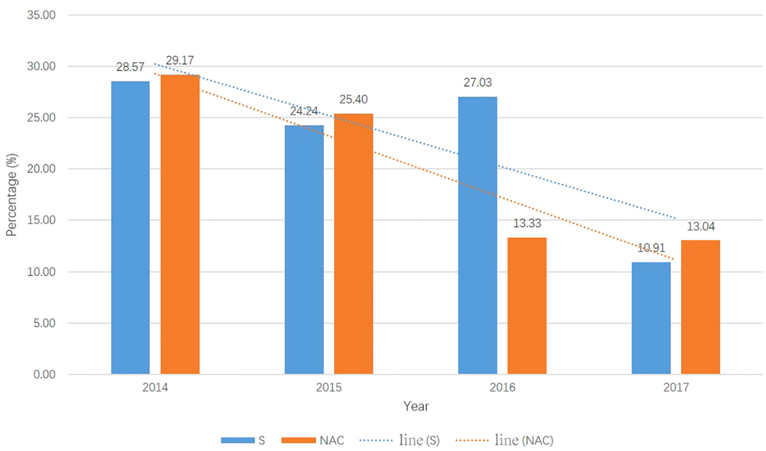

FIGURE 2
The total postoperation complication rate in two groups each year from 2014-2017. The total complication rates were droped year by year in both groups. S, primary surgery; NAC, neoadjuvant chemotherapy.

TABLE 1 Baseline demograpic and clinical characteristics of esophageal carcinoma patients after PMS.

Variable	S (N = 62)	NAC (N = 62)	*χ2/F/W*	*P* value
Mean Age(range)	62.10 (45-78)	60.34 (37-72)	1.336	0.184
Mean BMI(SD)	23.42 (3.54)	24.22 (3.12)	-1.178	0.241
Sex N(%)			0.911	0.340
Male	39 (62.90)	44 (70.97)		
Female	23 (37.10)	18 (29.03)		
History N(%)			0.525	0.469
No	37 (59.68)	33 (53.23)		
Yes	25 (40.32)	29 (46.77)		
cTNM stage N(%)			5.139	0.077
I	11 (17.74)	9 (14.52)		
II	35 (56.45)	25 (40.32)		
III	16 (25.81)	28 (45.16)		
Adjuvant treatment N(%)			0.704	0.402
Yes	17 (27.42)	13 (20.97)		
No	45 (72.58)	49 (79.03)		

PMS, propensity matched score; S, surgery; NAC, neoadjuvant chemotherapy; SD, +/-; N, number; F, F-test(joint hypotheses test); W, Wilcoxon-test; cTNM, clinical tumor lymph nodes metastasis stage.

leakage. Due to the risk of complications, initially, we could only dare to perform the "non-tube no fasting" FTS in primary surgery patients. Step by step, we have tried to combine it with neoadjuvant treatment. Most resectable EC patients need to receive preoperative treatment. If this approach cannot be combined with comprehensive treatment, then "non-tube no fasting" FTS is futile. The trial conducted by Cunningham et al. (13) reported no increase in complications when using NAC and

TABLE 2 Intraoperative and Postoperative Outcome.

	S (N = 62)	NAC (N = 62)	χ2/F/W	P value
Intraoperative data				
Mean operative time(SD) (min)	200(130-310)	222.5(150-350)	1223.5	<0.001*
Thoracic duct ligation(%)	14(22.58)	11(17.74)	0.451	0.502
Mean blood loss(SD) (mL)	67.26(42.59)	77.645(43.14)	-1.349	0.180
Median lymph nodes retrieved (range) N	24(15-56)	33(15-64)	1191	<0.001*
Postoperative data				
Complication N(%)	20(32.26)	16(25.81)	0.626	0.429
Median postoperative hospital stay days (range)	8(6-94)	8(5-34)	1852.0	0.723
Median Chest tube drainage days (range)	6(4-93)	6(4-31)	1626.5	0.131
Readmission to ICU N (%)	2(3.23)	1(1.61)	NA	1.000
Pathological data				
Type of carcinoma N(%)			0.121	0.989
Squamous cell carcinoma	55(88.71)	54(87.10)		
Adenosquamous carcinoma	2(3.23)	2(3.23)		
Adenocarcinoma	4(6.45)	5(8.06)		
Small cell carcinoma	1(1.61)	1(1.61)		
Median positive lymph nodes retrieved (range) N	0(0-12)	0(0-14)	1849	0.683
pTNM/ypTNM staging 8th N(%)				
pCR	NA	7(11.29)	NA	0.049*
I	17(27.42)	15(24.19)		
II	28(45.16)	26(41.94)		
III	17(27.42)	14(22.58)		

S, surgery; NAC, neoadjuvant chemotherapy; N, number; F, F-test(joint hypotheses test); W, Wilcoxon-test; SD, +/-; ICU, Intensive Care Unit; NA, Not Available; pTNM, pathological tumor/node/metastasis; *Statistically significant (p<0.05).

TABLE 3 The postoerative complications in two groups.

Variable N (%)	S (N = 62)	NAC (N = 62)	Difference (95% CI)	χ2	P value
Respiratory Complications (total)	11 (17.74)	10 (16.13)	1.61 (-11.78-14.97)	0.057	0.811
Pneumonia	7 (11.29)	6 (9.68)	1.61 (-9.79-13.07)	0.086	0.769
Atelectasis	0	1 (1.61)	-1.61 (-4.37-8.59)	NA	1.000
Pleural effusions	2 (3.23)	2 (3.23)	0 (-8.14-8.14)	NA	1.000
Pneumothorax	2 (3.23)	1 (1.61)	1.61 (-5.74-9.52)	NA	1.000
Cardiac complications (total)	1 (1.61)	1 (1.61)	0 (-7.1-7.1)	NA	1.000
Myocardial arrhythmia	1 (1.61)	1 (1.61)	0 (-7.1-7.1)	NA	1.000
Gastrointestinal complications (total)	2 (3.23)	2 (3.23)	0 (-8.14-8.14)	NA	1.000
Anastomotic leak	0	1 (1.61)	-1.61 (-4.37-8.59)	NA	1.000
Intestinal obstruction	0	1 (1.61)	-1.61 (-4.37-8.59)	NA	1.000
Delayed gastric emptying	2 (3.23)	0	3.23 (-3.06-11.02)	NA	0.496
Other complications					
Bleeding	2 (3.23)	0	3.23 (-3.06-11.02)	NA	0.496
Urinary tract infection	1 (1.61)	0	1.61 (-4.37-8.59)	NA	1.000
Wound infection /Fat necrosis	1 (1.61)	1 (1.61)	0 (-7.1-7.1)	NA	1.000
Unilateral RLN	4 (6.45)	0	6.45 (-0.57-15.45)	NA	0.119
Clavien-Dindo grading system					
I	2 (3.23)	3 (4.84)	-1.61 (-6.81-10.38)	NA	1.000
II	12 (19.35)	7 (11.29)	8.06 (-4.87-20.9)	1.554	0.213
IIIa	4 (6.45)	5 (8.06)	-1.61 (-8.48-11.85)	NA	1.000
IIIb	2 (3.23)	1 (1.61)	1.61 (-5.74-9.52)	NA	1.000
Unscheduled readmission within 60 days	0	0	NA	NA	NA
In-hospital mortality	0	0	NA	NA	NA
90 days mortality	0	0	NA	NA	NA

N, number; S, surgery; NAC, neoadjuvant chemotherapy; CI, confidence interval; NA, Not Available; RLN, recurrent laryngeal nerve.

FTS. Nomoto et al. reported NAC was related to a poorer preoperative condition, however it did not worsen the short-term outcomes (14). Based on their results, we tried the combination of NAC and FTS, and we found that our "non-tube no fasting" FTS approach could be extended; therefore, we added NAC with caution. As shown in Figure 1, we found that the number of patients undergoing the combination of "non-tube no fasting" FTS and NAC has increased year over year. Finally, in this study, we demonstrated that the total number of postoperative complications (p=0.425) did not increase in the combined patients. From 2014-2017, NAC was not an exclusion criterion for "non-tube no fasting" FTS. After 2017, the most of the patients received NAC without consideration of FTS.

In the present study, we attempt to summarize and demonstrate the safety of NAC in combination with "non-tube no fasting" fast-track surgery. Our study showed that the combination of NAC with "no tube no fasting" fast-track surgery after McKeown MIE did not increase the incidence of anastomotic leakage (the difference rate was -1.61% (95% CI -5.3% to 8.59%)) or pneumonia (the difference rate was 1.61% (95% CI -9.79% to 13.07%)). The results of this study were consistent with the results of our previous study, although only 31.1% (87/280) of the patients received NAC.

The other aspect was the efficacy of the NAC and "non-tube no fasting" FTS combination. A short postoperative hospital stay is one of the most important recovery outcomes and the most desirable outcome of FTS. In the current study, the NAC combined with FTS group had the same median discharge day as the FTS group (8 days, p=0.723). The length of stay was also consistent with other esophageal FTS studies (6). In our study, the discharged patients returned home to resume their leisure activities and activities of daily living. The fast recovery time may also be a benefit of MIE (8, 15). All patients resumed oral feeding on POD1 in both groups, with acceptable and equivalent rates of anastomotic leakage observed. This demonstrates the efficacy of the combination of NAC and "non-tube no fasting" FTS.

Regarding other data, the NAC combined group had a significantly longer surgical time (200 min vs. 222.5 min, p<0.001). Although 22.5 min is insignificant in our daily clinical practice, it indicates that NAC may prolong the surgical time. This result was different from the findings reported in our previous study (7). However, in the present study, the data were all from one medical team, so this might be more reflective of the increased surgical difficulty due to NAC. NAC causes tissue fibrosis, inflammation and tissue edema (12, 16), all of which might contribute to the prolonged surgical time. In the NAC combined group, more lymph nodes were harvested during the operation (median 33 vs. 20, p<0.001). As the pCR rate of NAC was approximately 10% (17), more lymph nodes tended to shrink rather than disappear. This may make lymph node dissection easier and allow for more lymph nodes to be harvested. Additionally, the ease of decision making may explain why the RLN injury rate in the combined group was significantly lower than that in the primary surgery group, 4/62 versus 0/62, respectively, and the difference rate was 6.45% (95% CI -0.57% to 15.45%).

In the present study, we demonstrated that NAC combined with "non-tube no fasting" FTS was equal to "non-tube no fasting" FTS in terms of the incidence of pulmonary complications, and the rates of postoperative complications, unscheduled readmission, hospital mortality and 90-day mortality were not affected. Taken together, our results showed that the NAC combined with "non-tube no fasting" FTS is safe and does not affect the hospital discharge day, as indicated by our previous RCT with little NAC data.

Limitations

As a single-center retrospective study, our study could not avoid natural biases. Moreover, in the current study, although PSM was adopted, some differences may have led to selection bias; for example, patients with a better performance status were more likely to receive preoperative treatment. Second, this study was performed in the highest-incidence EC area worldwide in a high-volume cancer hospital in Henan Province. A total of 997 esophagectomy procedures were performed for esophageal cancer during 2015 in our department, so the learning curve and surgical experience may be quite different from those of a low-volume center in a low-incidence area. Further exploration is needed to determine whether this approach is truly suitable for centers with limited experience. Third, this study used MIE hand-sewn cervical anastomosis. We did not know if the mechanical anastomosis also work? Fourth, similar to Japan, we were more likely to adopt NAC rather than NACR, so the number of NACRs was too limited to draw any conclusions. Finally, the total number of patients was limited. Therefore, we excluded NACR patients. This topic still needs to be addressed in the future.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. Requests to access these datasets should be directed to Jing Ding, dingjing201305@163.com.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Review Committee of the Affiliated Cancer Hospital of ZhengZhou University/Henan Cancer Hospital (number 2016ct081). The patients/participants provided their written informed consent to participate in this study.

Author contributions

YZ and WX designed the study. YL, XL, HS, ZW and YZ performed the surgical treatment and fast track surgery. WH and SL analysed the data, and YZ and WH wrote 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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Prophylactic cholecystectomy: A valuable treatment strategy for cholecystolithiasis after gastric cancer surgery

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The main treatment for gastric cancer is surgical excision. Gallstones are one of the common postoperative complications of gastric cancer. To avoid the adverse effects of gallstone formation after gastric cancer surgery, we reviewed the causes and risk factors and mechanisms involved in gallstone formation after gastric cancer surgery. The evidence and value regarding prophylactic cholecystectomy (PC) during gastric cancer surgery was also reviewed. Based on previous evidence, we summarized the mechanism and believe that injury or resection of the vagus nerve or changes in intestinal hormone secretion can lead to physiological dysfunction of the gallbladder and Oddi sphincter, and the lithogenic components in the bile are also changed, ultimately leading to CL. Previous studies also have identified many independent risk factors for CL after gastric cancer, such as type of gastrectomy, reconstruction of the digestive tract, degree of lymph node dissection, weight, liver function, sex, age, diabetes and gallbladder volume are closely related to CL development. At present, there are no uniform guidelines for the selection of treatment strategies. As a new treatment strategy, PC has undeniable advantages and is expected to become the standard treatment for CL after gastric cancer in the future. The individualized PC strategy for CL after gastric cancer is the main direction of future research.

KEYWORDS
gastric cancer, cholecystolithiasis, prophylactic cholecystectomy, cholecystectomy, risk factors

Introduction

Since Majoor and Suren first discussed the phenomenon of cholecystolithiasis (CL) after gastrectomy in 1947 (1), it has been confirmed that CL is one of the major postoperative complications of gastric cancer and that its related complications seriously threaten the life and health of patients (2). The incidence of CL after gastrectomy was reported to be 10-25% (3–8) and has been increasing in recent years (3, 9), being significantly higher than that in the general population (15-25% vs. 2.2-5.0%) (2, 10, 11). However, many issues remain unclear or disputable, such as the main, specific pathophysiological mechanism of gallstone formation after gastric cancer surgery; the risk factors for CL development after gastric cancer surgery; which strategies are the most appropriate treatments for CL after gastric cancer surgery; and whether prophylactic cholecystectomy (PC) should be performed. Because the above issues are controversial, we present a review from seven aspects and put forward our views, as follows.

Causes and mechanism of CL development after GC surgery

Vagus nerve disconnection

The vagus nerve is the source of power for the movement of the gallbladder. Studies have confirmed that vagal nerve injury is an important cause of CL after gastric cancer surgery (12), and the 5-year follow-up incidence of CL after vagal nerve dissection is 9%-21% (13). Ihasz et al. (14) found that 34% of the patients in vagectomy group who received gastrectomy had impaired gallbladder systolic function, and 65% had virtually no gallbladder systolic function.

Studies have shown that the vagus nerve trunk has an important regulatory effect on the absorption and metabolism of nutrients (15), and damage to the hepatic and biliary branches of the vagus nerve causes the gallbladder to lose its innervation, changes the dynamic function of the gallbladder, and increases the tension of the Oddi sphincter, which promotes the development of CL (16). Cattey et al. (17) confirmed that the pyloric one-gallbladder reflex was lost after antral gastrectomy, thus inhibiting gallbladder contraction and easily causing CL. This also confirms that the reflex mechanism between pylorus and bile duct is involved in the formation of CL (18).

Changes in the secretion of intestinal hormone

Cholecystokinin (CCK) can cause gallbladder contraction, Oddi-sphincter and duodenal relaxation (12). The main mechanism of gallbladder contraction is the release of CCK, even after gastrectomy (19). After gastrectomy, the secretory function of gastric mucosa is reduced or even lost; gastric acid is lacking; and after the digestive tract is reconstructed, food is redirected directly into the jejunum without passing through the duodenum, resulting in reduced CCK release (20), thereby promoting the development of CL. In addition, pancreatic hormone, gastrin, glucagon, motility hormone (21), substance P (SP), etc., can induce gallbladder contraction, while somatostatin (SS) and vasoactive intestinal peptide (11) can inhibit gallbladder contraction. These hormones interact with each other and eventually lead to CL development.

Changes in the composition of bile

The development of CL after gastric cancer surgery is closely related to changes in gallbladder physiology and changes in bile stone-causing components (5). Most CL cases after gastric cancer surgery involve bile pigment stones (3) and their formation is mainly related to biliary tract infection and cholestasis. Chijiiwa et al. (22) evaluated the gallbladder bile, bile lipid composition, and bile redness in patients who had previously undergone gastrectomy. The stone-causing difference between calcium and ionized calcium was compared, and it was found that ionized calcium and unconjugated bilirubin were significantly increased. These results showed that gallbladder bile tended to contain pigment stones after gastrectomy were an important factor for CL formation, which may be caused by the elimination of gallbladder contraction by gastrectomies and the inactivation of gallbladder bile as well as the mixture of gallbladder bile and fresh hepatic bile, resulting in hypersaturation of the mucosal surface and increasing the tendency toward salt precipitation and gallstone formation.

Oddi sphincter dysfunction

The dysfunction of the Oddi sphincter may be related to the hepatobiliary branch of the vagus nerve injury, and also related to the release change of gastrointestinal hormones. Nabae et al. (13) recorded Oddi sphincter motility after vagus nerve transection and found that the base pressure of the Oddi sphincter is significantly reduced, but the amplitude is increased. But after meal ingestion, the contraction of the Oddi sphincter increases, and the frequency slows down. This partly explains the cause of CL after gastric cancer surgery.

In conclusion, vagal nerve injuries, include the vagus trunk, hepatobiliary branch of the vagus nerve, upper digestive tract movement and pyloric-bile duct reflex, changes in the secretion of intestinal hormone and the composition of bile, and Oddi sphincter dysfunction are the main causes and closely related to CL development after gastric cancer surgery. Based on the above evidence, we summarized the mechanism as shown in Figure 1. We believe that injury or resection of the vagus nerve or changes in intestinal hormone secretion can lead to physiological dysfunction of the gallbladder (23) and Oddi sphincter, and the lithogenic components in the bile are also changed, ultimately leading to CL (12, 14, 16, 18, 20, 24).

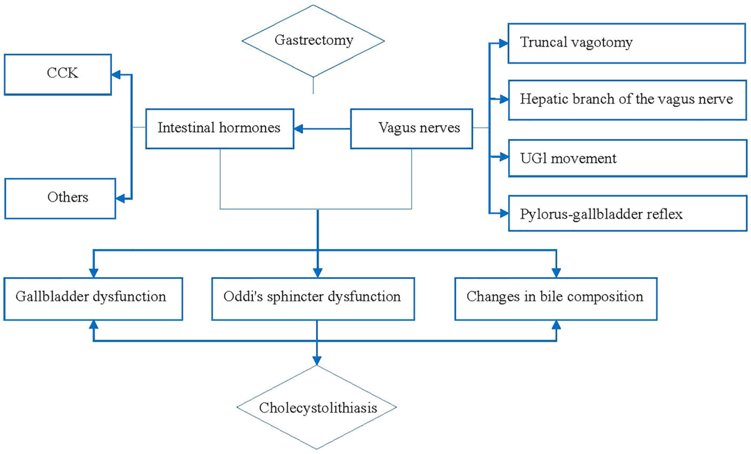

FIGURE 1
Pathophysiological mechanism of gallstone development after gastric cancer surgery.

Risk factors for CL development after gastric cancer surgery

CL development is related to many factors, and we summarized these by consulting multiple studies (see Table 1).

The type of gastrectomy

Studies have shown that the type of gastrectomy is an independent risk factor for CL (3), especially total gastrectomy (5, 25, 26) and distal gastrectomy (13). The incidence of CL after total gastrectomy is significantly higher than that after other surgical methods, ranging from 6% to 71%, and the onset time is early (4, 5, 9, 26). Jun et al. (4) retrospectively studied 2480 patients undergoing gastrectomy, and the results showed that the incidence of CL after total gastrectomy (10%) was significantly higher than that after subtotal gastrectomy (3%) ($P<0.001$). A national retrospective cohort study in Korea found that CL was most common after total gastrectomy (6.6%), followed by proximal gastrectomy (5.4%), distal gastrectomy (4.8%), and pylorus-sparing distal gastrectomy (4.0%) ($P < 0.001$). Multivariate analysis showed that total gastrectomy is an independent risk factor for CL development after gastric cancer (26).

However, Park et al. (8) retrospectively reported that 110 (11.2%) of 979 patients who underwent distal gastrectomy for cancer developed CL after surgery. CL occurred in 32 (13.9%) of

TABLE 1 The risk factors for cholecystolithiasis development after gastric cancer surgery.

Preoperative	Intraoperative	Postoperative
Sex	Type of gastrectomy	Total parenteral nutrition
Age	Digestive tract reconstruction	Weight loss
BMI	Extent of lymph node dissection	Immobilization
Percentage decrease in BMI	Jejunum climbing length	Pathological type
Tumor location	Blood supply	Postoperative complications
Clinical stage	Perioperative blood transfusion	Infectious febrile dehydration
Diabetes	Combined evisceration	Immunity
Triglycerides	Laparotomy	Chemotherapy and radiotherapy
Cirrhosis	Inflammation and Machinery	Analgesic
Hepatitis		Gallbladder volume
Coagulation function		Inflammation and machinery
Liver function		Bacterial translocation
Cardiovascular diseases		
Chemotherapy and radiotherapy		

230 patients who underwent total gastrectomy and in 6 (9.7%) of 62 patients who underwent proximal gastrectomy after gastric surgery. CL occurred in 2 (15.4%) of the 13 patients who received PPG, but the difference was not statistically significant (P=0.634), indicating that the type of gastric cancer surgery was not an influencing factor for the development of postoperative CL.

Although, there are conflicting evidences on the relationship between the type of gastrectomy and CL development after gastric cancer. We analyzed that the most likely reason is that the interference of other risk factors is not completely eliminated in the different studies. We still believe that the type of gastrectomy is one of the important risk factors for CL.

Reconstruction of the digestive tract

The reconstruction of the digestive tract during gastric cancer surgery is closely related to the formation of gallstones. Jun et al. (4) studied 2480 patients undergoing gastric cancer surgery; 128 patients (5.2%) developed CL after surgery, of which Roux-en-Y reconstruction accounted for 60 cases (46.9%), which had a higher risk than Billroth I and Billroth II (P < 0.001). Paik et al. (5) confirmed that the incidence of CL after B2 is higher than that after B1, possibly because the change in the CCK secretion pattern leads to weakened gallbladder systolic function and a high incidence of CL. Studies have shown that nonphysiological reconstruction is an important risk factor for the development of postoperative CL (5, 8) and that this incidence of CL is significantly higher than that after physiologic reconstruction (4), especially with Roux-en-Y (4, 8) and Billroth II (5). The high incidence of CL in the Roux-en-Y procedure can be explained by the extent of gastrectomy and duodenal dissection. Therefore, from above evidences, we believe that Roux-en-Y reconstruction was an independent risk factor for CL development after gastric cancer surgery.

Degree of lymph node dissection

Thorough lymph node dissection (D2 lymph nodes and enlarged lymph nodes dissection), especially the dissection of hepatoduodenal ligament lymph nodes(No.12), is closely related to the occurrence of postoperative CL. Akatsu et al. (27) studied 805 patients with gastric cancer who underwent D1 (n=490) and D2 (n=315) lymph node dissection. During the follow-up, 102 (12.7%) patients developed CL. D2 lymph node dissection was higher than D1 lymph node dissection (17.8% vs. 9.4%, P = 0.001). Fukagawa et al. (2) found that 173 (25.7%) of 672 patients with gastric cancer who underwent lymph node dissection developed CL after surgery and that enlarged lymph node dissection was a significant risk factor for CL development after surgery (P < 0.001: D1+α vs. D2+α; P < 0.01: D2 vs. D2+α). This may be No.12 lymph nodes are adjacent to the gallbladder and pyloric branches of the vagus nerve that innervate the gallbladder and the common bile duct. During the dissection of No. 12 lymph nodes, the hepatoduodenal ligament is completely "skeletal" (4), and lead to the injury of hepatobiliary branch of the vagus nerve (28). The above studies confirmed that hepatoduodenal ligament lymph node dissection is the most important independent risk factor for postoperative CL development.

Weight

Paik et al. (5) reported that BMI decline ≥4% (kg/m^2) was an independent risk factor for CL development after gastric cancer surgery. Park et al. (8) reported that weight cycling (weight loss and weight gain) and large weight fluctuations are risk factors for the development of CL, and concluded from multivariate analysis that obesity is an independent risk factor for the development of CL after gastric cancer surgery. In general, all the proof suggesting a link between a high BMI value and a higher incidence of CL after gastric cancer surgery. Weight loss after gastric cancer surgery leads to the mobilization of cholesterol reserves. Without the activation of gallbladder bile, cholesterol and bile are supersaturated, thus leading to CL. In addition, excessive obesity may increase cholesterol secretion by the liver, which is the key reason for the formation of cholesterol stones.

Liver function

Nakamura et al. (29) analyzed 698 patients with gastric cancer who underwent surgical treatment and found that abnormal liver function after surgery is related to the development of CL. Lee et al. (30) reported that a high preoperative serum total bilirubin value is an important independent risk factor for the development of CL after gastric cancer surgery. The reason may be that a high level of bilirubin easily leads to gallbladder crystallization, especially the formation of brown or melanin stones. Studies have reported a positive correlation between high triglycerides and gallstone disease. Triglyceride synthesis is stimulated by insulin; So it is concluded that the etiology of CL after gastric cancer surgery may be related to two variables, namely, triglycerides and insulin (31).

Sex

Most studies have reported that male sex is a risk factor for the development of CL after gastric cancer surgery (5, 8, 26). In a nationwide study conducted in South Korea, Seo et al. (26)

reported that men had a higher incidence of CL after surgery than women (5.8% vs. 4.1%, P <0.001) and revolved that male sex was an independent risk factor for CL after gastric cancer.

Age

Lai et al. (32) reported that elderly patients (aged over 60) are at high risk for the formation of gallbladder stones after gastric cancer surgery. Similarly, Seo et al. (33) reported that older patients (60~89 years old) have a higher incidence of CL (6.1% vs. 4.3%, P < 0.001) than younger patients (30~59 years old) and that advanced age (60~89 years). This may be due to increased bile secretion and intestinal absorption of cholesterol with age, reduced liver synthesis and secretion of bile salts, and reduced gallbladder contractility, all of which increase the susceptibility to cholesterol stones. In terms of genetics, elderly patients may exhibit an enhanced prevalence of the Lith (gallstone) gene, which would promote the formation of gallstones after gastric cancer (34). It was revolved that age is an independent risk factor for CL development after gastric surgery.

Diabetes

Paik et al. (5) studied 1480 patients who underwent gastrectomy without CL before surgery and concluded that diabetes is an independent risk factor for CL development after gastric cancer surgery. The effect of diabetes on CL is multifactorial, and the mechanism may be that diabetes leads to neuritis and neuromyopathy. In diabetic patients, oxidative stress from low heme oxygenase-1 levels increases, and insulin levels decrease. Insulin-like growth factor-1 signal transduction leads to loss of Cajal interstitial cells, leading to abnormal gallbladder emptying and promoting CL development (35).

Gallbladder volume

Rieu et al. (23) conducted a prospective study to determine the effects of partial gastrectomy without vagus nerve transection on postprandial gallbladder contraction, CCK secretion, and pancreatic polypeptide PP and found that the basal gallbladder volume was larger after surgery than before (P < 0.02). Portincasa et al. (36) divided the study subjects into a gastrectomy group and a control group and concluded that the gastrectomy group had a larger gallbladder volume during fasting than the control group and that the gastrectomy patients' gallbladders emptied faster after a meal. In these patients, the postoperative fasting gallbladder volume increased over time. After eating the experimental meal, the patients' feelings of satiety, abdominal distension and epigastric pain were significantly higher than those in the control group. Therefore, it is believed that the increased gallbladder volume during fasting may lead to cholestasis, which may play an important role in the pathogenesis of CL development after gastrectomy.

Others

Many other factors, such as bacterial translocation (BT), surgical methods(laparoscopic vs open) (8), parenteral nutrition, dietary lifestyle changes, length of the jejunal loop, postoperative complications (29), combined organ resection, blood supply, perioperative drugs, are also thought to be involved in gallstone formation after gastric cancer surgery.

From the above evidences, we found that the formation of gallstone after gastric cancer surgery is the result of the joint action of multiple factors and mechanisms. Single factor can hardly explain the cause and mechanism of CL development. Previous studies have identified many independent risk factors for postoperative CL, but have not elucidated their intrinsic association of them. Mechanistic research is complex and lengthy and do not provide useful therapeutic value. Instead of wasting time and resources on etiology and mechanism research, it is better to work directly on treatments.

Treatment of CL after gastric cancer surgery

Studies have reported that preserving the vagus nerve that innervates the gallbladder during gastric cancer surgery (37), and pyloric-preserving gastrectomy (PPG) (38), and prophylactic use of drugs such as erythromycin (39) and ursodeoxycholic acid (39, 40) can reduce the development of cholecystolithiasis, but the clinical effect is controversial. Which strategies are the most appropriate treatments for CL after gastric cancer surgery?

Watchful waiting

Studies have reported that most postoperative CL cases associated with gastric cancer are asymptomatic (3, 9), so most scholars support watchful waiting as the most reasonable treatment method (41), but there are potentially fatal hazards, such as inducing acute pancreatitis, acute cholangitis and gallbladder cancer, with high mortality.

Vagal-nerve-sparing gastrectomy

Studies have reported that retaining the vagus nerve that innervates the gallbladder during gastric cancer surgery can ensure the normal function of the gallbladder and significantly reduce the incidence of gallbladder stones (13, 19); however, there are also studies showing that some patients (10.1%) still relapse after surgery (19). A prospective case–control study by Wang et al. (42) compared the vagus nerve-sparing group (h-DG, n=85) and the dissected nerve group (s-DG, n=238) under laparoscopic distal gastrectomy and the vagus nerve preserving group (h-PPG, n=123) and dissected nerve group (s-PPG, n=21) under laparoscopic pylori-preserving gastrectomy. The results showed that the 3-year cumulative incidence of CL in the h-DG group was significantly lower than that in the s-DG group (2.7% vs. 14.6%, P=0.017). Similarly, this incidence in the h-PPG group was significantly lower than that in the s-PPG group (1.6%). vs. 12.9%, P=0.004). It suggested that both vagal-nerve-sparing gastrectomy and PPG can significantly reduce the incidence of CL development after gastric cancer surgery (38, 42). However, recent studies have suggested that PPG has no effect on the development of CL (10, 13, 26). In our view, vagal-nerve-sparing gastrectomy is complicated, which is not conducive to promotion and implementation. In addition, the formation of CL after gastric cancer surgery is multi-factor, and the effect of prevention from a certain factor is not certain. So, this approach is not valuable to be recommended.

Medical prevention

Some studies have reported that prophylactic use of drugs such as erythromycin (15), ursodeoxycholic acid (39, 40), exogenous CCK-8, cisapride, motilin, domperidone, cimetidine, opioid antagonists, naloxone, and aspirin can reduce CL development after gastric cancer surgery. A prospective multicenter randomized controlled clinical trial conducted by Lee et al. (40) randomly divided 465 patients who underwent gastric cancer surgery into 151 patients who received 300 mg ursodeoxycholic acid (UDCA), 164 patients who received 600 mg UDCA, and 150 patients who received placebo. The results showed that after 12 months, the incidence of CL was 5.3% (8/151) in the 300 mg group, 4.3% (7/164) in the 600 mg group, and 16.7% (25/150) in the placebo group. Compared with the placebo group, the results indicating that 12 months of UDCA after gastric cancer surgery can significantly reduce the incidence of CL. However, studies have shown that gallstones after gastric cancer are dominated by bile pigment stones (3). Oral stone-dissolving drugs are less effective and require a long treatment period. So, the clinical effect of medical is not satisfactory. Long-term medication will increase the physical, psychological and economic burdens on patients.

Secondary surgery

Cholecystectomy is the "gold standard" for the treatment of CL. With the improvement of minimally invasive surgery concepts and techniques, laparoscopic cholecystectomy (LC) and endoscopic retrograde cholangiopancreatography (ERCP), endoscopic sphincterotomy (EST), endoscopic papillosphincter balloon dilatation (EPBD), percutaneous hepatobiliary drainage, and percutaneous puncture drainage have gradually been applied to patients with a history of gastric cancer surgery. Minimally invasive surgery (represented by LC and ERCP+EST) can significantly shorten the disease course and relieve patients' pain and is considered to be safe and effective (33). However, some studies have shown that cholecystectomy after gastric cancer surgery increases the difficulty of surgery, mortality, and the cost of surgery (9, 16, 43, 44). Application of ERCP is technically difficult due to anatomical changes, such as after physiologic reconstruction (4), especially with Roux-en-Y (4, 8) and Billroth II (5).

At present, there is no unified guideline for the selection of CL treatment strategy after gastric cancer surgery. Due to the shortcomings and deficiencies of various treatment methods, the treatment effect is not satisfactory. As a new treatment strategy, PC is expected to become the most valuable treatment for CL after gastric cancer in the future. Surgeons have been devoted to the study of PC during gastric cancer surgery.

Proposed background of the PC concept

Incidence of CL after gastric cancer surgery

Most studies have reported that the incidence of CL within 5 years after gastric cancer surgery is as high as 15%-25%, with an average of 17%. In previous studies, the rate was as high as 47%-60% (33). Liang et al. (3) and Bernini et al. (45) reported that the incidence of CL after gastric surgery showed an increasing trend over time and had not yet reached an equilibrium level. Bencini et al. (3) reported that for patients with gastric cancer who survived 60 months after surgery, the incidence of postoperative CL increased by 18.5%. However, some studies reported that the incidence of CL after gastric surgery was less than 10% (4, 5, 9, 46, 47), and the incidence of cholangitis or cholecystitis in patients with CL after gastric cancer surgery was 20.3%, which was almost the same as that in the general population (9).

Interval time for CL development after gastric cancer surgery

Liang et al. (9) and Fukagawa et al. (2) both reported that 64.7% of CL cases developed within 1 year after gastric surgery, and Murata A et al. (48) confirmed that the earlier the development of CL after gastric cancer surgery, the greater the threat to the prognosis and quality of life of patients.

Complications related to CL after gastric cancer surgery

Acute postoperative cholecystitis, defined as occurring during the same hospital stay or within 30 days after surgery (49), is a serious complication, especially for patients who have recently undergone gastrectomy (50–52); it is difficult to diagnose and has mortality rates as high as 10-50% (52). Table 2 show all the studies related to the acute postoperative cholecystitis and revolved that PC can minimize the risk of acute postoperative cholecystitis (53) and avoid the formation of gallstones (2, 3, 11).

Stones is also a common complication related to CL. Studies have shown that most CL cases occurring after gastric surgery involve multiple (72.5%) stones that are less than 10 mm in diameter (79.4%) (27); small stones are an independent risk factor for pancreatitis (54), which will increase the incidence of biliary complications. Bencini et al. (3) reported that 12.3% of patients ain the standard gastric surgery (SS) group had abnormal biliary tracts after surgery, while only 1.5% of patients in the PC group had common bile duct dilation (CBD) after surgery, and the difference was statistically significant. (8/65 vs. 1/65, P= 0.033). This suggests that PC can reduce the biliary tract related complications.

Secondary operation related to CL after gastric cancer surgery

Studies have reported a high proportion of secondary surgical intervention due to biliary tract diseases after gastrectomy, and frequent biliary colic and cholecystitis are the main causes of subsequent cholecystectomy (32). Moreover, the upper abdominal inflammatory adhesions caused by previous gastrectomy make the subsequent operation difficult (9, 16, 33), and the incidence of surgical complications, common bile duct injury, mortality(20.0-57.0%) (51), medical expenses, average hospital stay, medical resources, conversion rate to laparotomy (10-50%) (54), and operation time of subsequent cholecystectomy after gastric cancer surgery increases, especially in emergency operations (9, 11, 16, 44). Gillen et al. (33) reported that the surgical risk of subsequent cholecystectomy after gastric cancer surgery is 15 times higher than that of PC during gastrectomy for cancer and the incidence of surgical complications, common bile duct injury, mortality, medical expenses, average hospital stay, medical resources, conversion rate to laparotomy, and operation time of subsequent cholecystectomy after gastric cancer surgery increases significantly, especially in emergency operations (9, 11, 16). Studies have reported mortality rates of subsequent cholecystectomy as high as 20.0-57.0% (51), and the laparoscopic conversion rate is 10-50% (54). The reasons may be related to a patient's advanced age, poor physical condition (44) and difficulty in managing the inflammatory gallbladder in the surgical field due to prior gastrectomy and lymph node dissection (9).

Gastrectomy will result in secondary bile duct stones, and the change in anatomical structure after gastrectomy will increase the difficulty of reaching the duodenal papilla during elective surgery (5), especially when duodenal reconstruction (Billroth II or Roux-en-Y (45)) is applied. Paik et al. (5) reported that only 6 of the 20 patients with choledocholithiasis after gastrectomy successfully underwent ERCP. For patients with a history of gastrectomy, subsequent cholecystectomy is often accompanied by a risk of damage to the bile duct and surrounding tissues (55), among which bile duct injury is the most serious complication and has a high mortality rate.

Gastrectomy combined with cholecystectomy is a mostly laparoscopic surgery, as surgeons have gained experience in laparoscopic surgery and exceeded the "learning curve" (56). The safety and feasibility of surgery have been greatly improved (57). Combined gastric cancer surgery has been greatly improved. Therefore, some scholars believe that if PC does not increase serious surgical complications, it would be better than subsequent cholecystectomy after gastric cancer surgery (43).

Quality of life and laparoscopic techniques

In the surgeon's clinical work, an effective assessment of a patient's quality of life can affect the decision of whether to operate. Fukagawa et al. (2), Bernini et al. (45) and Wu et al. (50) all reported that PC could improve the quality of life of patients who survived. Mentes et al. (58) used the gastrointestinal quality of life score to evaluate the effect after cholecystectomy and concluded that PC during gastric cancer surgery at least does not reduce postoperative quality of life.

Due to the high incidence and short interval time for CL development after gastric cancer surgery, additional, PC can minimize the risk of acute postoperative cholecystitis, it also can avoid the difficulty of secondary surgical intervention after gastrectomy and surgical risk and the high incidence of surgical complications after the gastrectomy, these advantages provide the best opportunity for using PC.

TABLE 2 Acute cholecystitis after gastrectomy for cancer.

Author	Patients(n)	Surgery	AC(n)	Character	FT (day)	Surgical (n)	Mortality
Takahashi (44)	1096	gastrectomy	7(0.6%)	NC	20 (5-70)	7 (0.6%)	4 (0.4%)
Oh (52)	8033	gastrectomy	5 (0.06%)	NC	14 (2-31)	5 (0.06%)	0%
Ito (51)	190	gastrectomy	24(12.6%)	NC	ns	6 (3.2%)	0%
Wu (50)	288	gastrectomy	9 (3.1%)	NC	ns	7 (2.4%)	2 (0.6%)

AC, acute cholecystitis; NC, noncalculous cholecystitis; FT, formation time; ns, not stated.

However, it has been reported that almost all biliary abnormalities after gastrectomy were detected by ultrasound 4.5 years later (2, 3, 11). The 3-year mortality rate after gastrectomy was the highest, which would suggest that PC is not necessary for most people, since for some patients who undergo surgery for gastric cancer, gallstones rarely form before the end of their lives. Studies also have reported that almost 90% of CL cases developing after gastrectomy are asymptomatic (2, 5, 10), and the longer the time from surgery, the less likely patients are to develop symptoms (11). Hence, few patients have symptoms after surgery (0.6% to 4.6%) or require additional treatment (0.4% to 4.6%) (2, 3, 5, 9, 10, 32, 54) (Table 3). Fukagawa et al. (2) studied 173 patients who developed CL after gastric cancer surgery. Among the asymptomatic group (161 cases), 77.0% (124 cases) had no change in the size or number of gallstones. Paik et al. (5) studied 1480 patients who underwent gastric cancer surgery, and the results showed that the incidence of postoperative choledocholithiasis was only 1.4% (20 patients), and its development was only related to CL, suggesting that the effect of secondary choledocholithiasis after gastric cancer surgery was negligible. Additional, with improvements in surgical techniques and medical equipment, some studies have reported that subsequent laparoscopic cholecystectomy is safe and reasonable for patients with a previous gastrectomy history (4, 31, 42, 44, 49, 59–62) (Table 4).

From the above evidences, we can found that most of the evidences support the implementation of PC, although there were some arguments to the contrary. Some scholars believe PC is safe and effective (Table 5) (15, 20, 21, 27, 54), while others disagree (Table 6) (3, 5, 10, 29, 30). Moreover, certain scholars believe that the feasibility of PC should be individualized (9). Should PC be used as a routine treatment? We reviewed lots of studies supporting or against PC.

Studies supporting PC

Some studies have reported that PC during gastric cancer surgery is safe, effective and reasonable when compared with SS or subsequent cholecystectomy after gastrectomy because PC during gastric cancer surgery does not increase postoperative complications, gallbladder-related complications, postoperative pulmonary complications (POPCs), biliary complications, surgical complications, nonsurgical complications, complications related to laparoscopy, overall mortality, mortality within 30 days after surgery, in-hospital mortality, average operation time, postoperative hospital stay, postoperative gastrointestinal function recovery time, parenteral nutrition time, enteral nutrition time, overall morbidity, intraoperative blood loss, risk of anesthesia or hospital costs (16, 20, 21, 25, 26, 43).

Jeong et al. (43) retrospectively studied 400 patients who underwent laparoscopic-assisted gastrectomy for early gastric cancer, and found that PC may extend the average operation time by approximately 15 minutes, but it has no effect on the effect of surgery. In all patients with early gastric cancer and gallbladder disease, combined intraoperative cholecystectomy for gastric cancer seems to be safe and feasible.

Bernini et al. (45) analyzed a multicenter randomized controlled clinical trial of 130 patients with gastric cancer, and found that PC during gastric cancer surgery will not increase morbidity, mortality, or hospitalization costs.

TABLE 3 CL development after gastric cancer surgery is rarely symptomatic and requires surgical intervention.

Author	Gastrectomy(n)	CL	Symptomatic CL	Surgical
Liang (9)	17,325	1280 (7.4%)	ns	560 (3.2%)
Bencini (3)	65	8 (12.3%)	3 (4.6%)	3 (4.6%)
Paik (5)	1480	106 (7.2%)	9 (0.6%)	9 (0.6%)
Fukagawa (2)	672	173 (25.7%)	12 (1.8%)	12 (1.8%)
Lai (32)	197	30 (15.2%)	9 (4.6%)	9 (4.6%)
Kobayashi (10)	749	86 (11.4%)	6 (0.8%)	3 (0.4%)
Akatsu (27)	805	102 (12.7%)	15 (1.9%)	13 (1.6%)

CL, cholecystolithiasis; ns, not stated.

TABLE 4 Subsequent cholecystectomy after gastrectomy is safe and feasible.

Author	Groups	Conclusion
Gillen (33)	PC vs. SC	The complication rate and mortality in the SC group were lower than those in the PC group.
Kimura (47)	Cholecystitis and/or cholangitis	Treatment of postoperative cholecystitis and/or cholangitis is effective and does not increase complications or length of hospital stay.
Kim (63)	OCL vs. LCL	Compared with OC, LC for gallstones after gastric cancer surgery results in earlier recovery of diet, shorter hospitalization times and less incidence of complications.
Kwon (64)	CLPG	LC after gastric cancer surgery does not increase the operative time, length of hospital stay, postoperative complications and time to complete normal activities.
Zhang (65)	CLPG vs. CLNPG	Compared with CLNPG, CLPG does not increase the blood loss, conversion rate, intraoperative bile duct injury rate, diet recovery time, and postoperative hospitalization time.
Lai (32)	SC	The incidence of complications and mortality of SC are zero.
Inoue (49)	SC	Cholecystectomy has the lowest mortality and is the optimal treatment for acute cholecystitis after gastric cancer surgery.
Jun (4)	OCL vs. LCL	The operation time and hospitalization time of LCL are shorter than those of OCL.
Sasaki (66)	CLPG vs. CLNPG	CLPG increases the incidence of choledocholithiasis and operative time but does not increase the blood loss, conversion rate, complication rate, recovery time to diet, or postoperative hospital stay

PC, Prophylactic cholecystectomy; CL, Cholecystolithiasis; OC, Open cholecystectomy; LC, Laparoscopic cholecystectomy; SC, Subsequent cholecystectomy; OCL, Open cholecystectomy after gastric cancer surgery; LCL, Laparoscopic cholecystectomy after gastric cancer surgery; CLPG, Cholecystectomy in patients with a prior history of gastrectomy; CLNPG, Cholecystectomy in patients without a prior history of gastrectomy.

Lai et al. (32) retrospectively analyzed 445 patients who received gastrectomy. Among them, the combined cholecystectomy group (n=58) and the simple gastrectomy group (n=387) were analyzed. There were no significant differences in the mortality rate (3.4% vs. 3.1%), complication rate (24.2% vs. 22%) or 5-year survival rate (61% vs. 63%) ($P > 0.05$). At the same time, there were no significant differences in hospital stay, conversion rate or operation time. Therefore, the authors believe that PC can be considered for patients with asymptomatic CL before surgery. Miftode et al. (16) reported that the mortality rate of patients undergoing cholecystectomy after gastrectomy was 63.63% (7/11) and that the mortality rate of patients undergoing PC was 4.92% (3/61); moreover, patients undergoing PC had fewer postoperative complications. Therefore, the authors believe that PC is safe and feasible for reducing postoperative complications and secondary surgery.

A Japanese study based on the National Administrative Database (70) explored the prognosis of laparoscopic

TABLE 5 Studies supporting PC during gastric cancer surgery.

Author	Patients (n)	Gallbladder	Conclusion
Thompson	56	Any gallbladder	(1) PC adds minimal morbidity. (2) The majority of patients with CL after gastrectomy become symptomatic and require secondary surgery, and secondary surgery increases the morbidity.
Saade	109	Asymptomatic CL	(1) PC adds minimal morbidity. (2) The number of secondary cholecystectomies after gastrectomy is large.
Watemberg (67)	4072	Any gallbladder	Complication and mortality rates increase significantly and dreadfully when the gallbladder is left *in situ* after gastrectomy.
Jeong (43)	400	Any gallbladder	PC is safe and feasible in patients with both early gastric cancer and gallbladder disease.
Bernini (68)	130	Any gallbladder	PC added no extra perioperative morbidity, mortality or costs to the sample included in the study.
Lai (32)	445	Asymptomatic CL	PC is not associated with increased surgical morbidity or mortality, and has no significant effect on overall survival.
Miftode (16)	206	Any gallbladder	PC can be safely performed during gastrectomy and thus prevents complications at a later stage.
Murata (69)	14,006	Any gallbladder	PC does not affect the prognosis of patients undergoing gastric cancer surgery.

PC, Prophylactic cholecystectomy; CL, Cholecystolithiasis.

TABLE 6 Research against PC during gastric cancer surgery.

Author	Patients (n)	Conclusion
Kobayashi (10)	749	(1) Hepatoduodenal ligament lymph node dissection, total gastrectomy and duodenum exclusion are risk factors for the development of CL after gastric cancer surgery. (2) The majority of CL cases are asymptomatic (93%), and less than 0.5% of patients need cholecystectomy.
Gillen (33)	3735	The incidence of CL after gastrectomy is low (6%), and selective cholecystectomy is safe.
Shim (53)	–	(1) PC is not ethical. (2) CL after gastric cancer surgery rarely requires surgery. (3) Minimally invasive surgery can effectively treat CL after gastric cancer surgery. (4) Digestive problems occur after PC.
Paik (5)	1480	(1) Advanced age, diabetes, surgical methods, male sex and decreased body mass index are high risk factors for the development of CL after gastric cancer surgery. (2) PC should not be routinely recommended for use during gastric cancer surgery.
Bencini (3)	130	PC has no significant effect on the natural course of gastric cancer patients.

PC, Prophylactic cholecystectomy; CL, Cholecystolithiasis.

gastrectomy combined with cholecystectomy, including 14,006 patients with gastric cancer from 744 hospitals. The subjects were divided into a combined cholecystectomy group (n=1484) and a simple gastrectomy group (n=12,522). The results showed that PC did not increase laparoscopic-related complications (OR, 1.02; 95% confidence interval [CI], 0.84-1.24; P=0.788), mortality during hospitalization (OR, 1.16; 95% CI, 0.49-2.76; P=0.727) or hospital stay (unstandardized coefficient, 0.37 days; 95% CI, -0.47 to 1.22 days; P = 0.389). However, PC significantly increased the cost of hospitalization (unstandardized coefficient, $1256.0 (95% CI, $806.2-$1705.9; P <0.001). The author believes that although the medical expenses during hospitalization have greatly increased, laparoscopic gastrectomy combined with cholecystectomy will not affect the patient's prognosis.

Tan et al. (46) retrospectively analyzed 1,753 patients with gastric cancer who received subtotal gastrectomy or total gastrectomy and divided them into the combined cholecystectomy group (n=62) and the simple gastrectomy group (n=1,691). The results showed that there was no statistically significant difference in mortality and complication rates between the two groups (8.1% vs. 8.9%). Thus, the authors believe that PC will not increase postoperative mortality and morbidity.

All these studies have proved that PC during gastric cancer surgery is safe, effective and reasonable when compared with SS or subsequent cholecystectomy after gastrectomy because PC during gastric cancer surgery does not increase postoperative complications, gallbladder-related complications, postoperative pulmonary complications (POPCs), biliary complications, surgical complications, nonsurgical complications, complications related to laparoscopy, overall mortality, mortality within 30 days after surgery, in-hospital mortality, average operation time, postoperative hospital stay, postoperative gastrointestinal function recovery time, parenteral nutrition time, enteral nutrition time, overall morbidity, intraoperative blood loss, risk of anesthesia or hospital costs (16, 20, 21, 25,7,27, 46).

Research against PC

Gillen et al. (33) studied 3,735 patients who underwent upper gastrointestinal surgery and showed that the mortality rate in the PC group was 0.95%, compared with 0.45% in the preoperative or postoperative cholecystectomy group, with a significant difference (95% CI, 0.54–1.49%; I^2 = 28%). Moreover, the incidence of complications in the PC group was higher than that following subsequent cholecystectomy. Therefore, it has been proposed that removal of the normal gallbladder during gastric cancer surgery is not recommended.

Bencini et al. (3) evaluated the need for PC during gastrectomy in a multicenter randomized controlled trial. A total of 130 patients with gastric cancer were enrolled and divided into a PC group (n=65) and a simple gastrectomy group (n=65). Eight patients (12.3%) in the control group had biliary tract abnormalities (4 cases gallstones and 4 cases cholestasis), and only three (4.6%) were clinically relevant (2 underwent cholecystectomy and 1 case acute pancreatitis). One patient in the PC group had asymptomatic biliary dilatation. The 5-year survival rate in the control group was 60% (95% CI: 47-71%), while that in the PC group was 59% (95% CI: 44-71%). The difference was not statistically significant (log-rank test: P=0.697). Similarly, for early gastric cancer (AJCC stage I or II), there was no statistically significant difference in 5-year survival between the PC group (76% (95% CI: 57-87%) and the control group (77% (59-88%)). There was no statistically significant

TABLE 7 Research evidence for and against PC.

Reasons supporting PC during gastric cancer surgery
PC is safe and effective.
PC can prevent secondary surgery related to CL.
PC can reduce complications related to CL.
PC can improve postoperative quality of life.
The incidence of CL after gastric cancer surgery is high.
The interval between CL development after gastric cancer surgery is short.
Preserving the gallbladder during gastric cancer surgery delays the diagnosis of gallbladder disease.
The incidence of secondary surgery after gastric cancer surgery is high, the operation is difficult, and the mortality is high.
Cholecystitis, cholangitis, pancreatitis and gallbladder cancer development after gastric cancer surgery.
The mortality rate of acute cholecystitis (within 30 days) after gastric cancer surgery is high.
Conservative treatment of CL after gastric cancer surgery is ineffective.
Reasons not to support PC during gastric cancer surgery
PC increases biliary complications (especially bile duct injury).
PC increases hospitalization costs and length of stay.
PC reduces postoperative quality of life.
PC increases surgical mortality.
PC increases medical litigation and claims.
PC increases the development of secondary choledocholithiasis after surgery.
A variety of digestive system diseases are formed after PC (postcholecystectomy syndrome, PCS)
PC increases the incidence of chronic pain.
The incidence of CL after gastric cancer surgery is low.
Most CL cases developing after gastric cancer surgery are asymptomatic.
CL after gastric cancer surgery rarely requires surgical intervention.
Secondary cholecystectomy after gastric cancer surgery is safe and effective.
Treatment of CL development after gastric cancer surgery does not increase mortality.
The incidence of CL after gastric cancer surgery is low.
Some CL cases disappear naturally after gastric cancer surgery.
The conservative treatment of CL after gastric cancer surgery is effective.
The long-term efficacy of PC is unclear.
PC does not conform to the principles of surgery and ethics.

PC, prophylactic cholecystectomy; CL, Cholecystolithiasis.

difference in CL survival between the two groups (P = 0.267). To prevent secondary CL, 1 in 32.5 patients needed to be treated with PC. The authors believe that although PC is safe and can effectively prevent the occurrence of CL in the long term, PC cannot effectively improve the patients' natural course of disease. Most CLs formed after gastric cancer surgery are asymptomatic and delayed, and the actual proportion of surgical intervention due to symptoms is 1:32.5. Such a low percentage does not allow PC to become a routine procedure.

Paik et al. (5) analyzed 1,480 patients who underwent gastrectomy; the results showed that the incidence of CL was low (7.2%, 106/1480), cholecystitis was only found in 9 patients (0.6%), and the incidence of choledocholithiasis was 1.4% (20/1480) Therefore, the authors did not recommend PC as a routine operation. Kobayashi et al. (10) retrospectively analyzed 749 patients who underwent gastric cancer resection. The results showed that the cumulative incidence of CL at 5 and 10 years after surgery was 13.6% and 22.1%, respectively, and 93% (80/86) of the patients were asymptomatic; only 0.4% of patients underwent cholecystectomy, so the authors believed that PC was unnecessary. Shim et al. (53) believed that CL development after gastric cancer surgery rarely requires surgery, and that minimally invasive surgery can effectively treat postoperative CL. In addition, PC is unethical, and a series of digestive problems can occur after cholecystectomy.

Digestive problems after PC during gastric cancer surgery are worth discussing (53). These include chronic diarrhea syndrome (71), diarrhea syndrome after laparoscopic cholecystectomy (postlaparoscopic cholecystectomy diarrhea, PLCD) (71), bile reflux gastritis and esophagitis (59, 72), Mirizzi syndrome (60), chronic pain (61) and secondary common bile duct cholelithiasis (62). Yueh et al. (71) reported that diarrhea occurred in 25.2% of patients 1 week after laparoscopic cholecystectomy and that 5.7% of patients developed diarrhea after 3 months. The incidence of postcholecystectomy syndrome (PCS) after cholecystectomy is 10 to 40% (3, 60), and approximately 5% of patients have chronic pain without an obvious cause (61). Patients receiving cholecystectomy are at risk for chronic postoperative pain, with an incidence ranging from 10 to 40% (62). At present, there are few reports about digestive system diseases after gastric cancer surgery, but theoretically, the abovementioned digestive system diseases will have a great negative impact on the postoperative quality of life of patients, which should be considered.

To date, most studies have discussed the short-term endpoint of the safety of PC during gastric cancer surgery (incidence of complications, duration of surgery, postoperative hospital stay, etc.) (45). However, it was concluded that while PC during gastrectomy for gastric cancer was safe for approximately 5 years of follow-up, the long-term effect was inconclusive (68).

The incidence of CL after gastrectomy was reported to be transient (40), and some cases of CL disappeared during follow-up (73). Inoue et al. (19) and Takahashi et al. (44) both reported that gallbladder contraction recovered to near the preoperative level within 3 months after gastrectomy, and the cholestasis development rate gradually decreased. Inoue et al. (28) reported that in 64.3% of patients, CL formed within 1 year after surgery, and only 19.3% of patients developed CL in the second year after surgery, which may be related to the recovery of gallbladder contraction function 1 year after gastric cancer surgery.

Some scholars believe that PC performed during gastric cancer surgery is inconsistent with the principles of ethics and surgery (53, 68). Both Liang et al. (9) and Cabarrou et al. (6) reported that PC increased medical costs and workload. In recent years, litigation and malpractice claims have raised issues with the removal of normal organs to avoid any benign disease, such as the removal of normal gallbladders (3, 6, 45).

TABLE 8 Conditions under which PC is recommended or not recommended during gastrectomy for cancer.

PC is recommended during gastric cancer surgery:
Extended lymph node dissection
D2 lymphadenectomy
D3 lymphadenectomy
Hepatoduodenal ligament lymph node dissection
Nonphysiological reconstruction
Roux-en-Y
Billroth II
Total gastrectomy
Liver function impairment
Diabetes
Advanced gastric cancer
Early gastric cancer
Young and middle-aged people with early gastric cancer
High risk (postoperative cholecystolithiasis)
Male patients and patients over 60 years old
PC is not recommended during gastric cancer surgery:
Receive palliative care
Life expectancy is less than six months
Distal gastrectomy with Billroth I reconstruction
D1 lymphadenectomy
Patient retains gallbladder intention

Due to some of the studies reported that the incidence of complications in the PC group was higher than that following subsequent cholecystectomy, the actual postoperative proportion of surgical intervention in a low percentage, ethical issues, and a series of digestive problems can occur after cholecystectomy, all these studies do not recommend PC to become a routine procedure. We summarized the research evidence for and against PC as in Table 7. In fact, with the development of surgical techniques, the adverse outcomes caused by PC will become less and less, and most of them can be avoided.

Indications and contraindications for PC

To facilitate the implementation of PC, we reviewed the relevant evidence as follows and summarized its indications and complications as showing in Table 8. Through a series of clinical studies, Sasaki et al. (66), Fukagawa et al. (2), Wu et al. (50), and Gillen et al. (33) suggested that PC should be considered for patients who need enlarged lymph node dissection because such dissection can increase the development of postoperative CL. On the one hand, PC does not affect the postoperative recovery of patients with gastric cancer; on the other hand, it can significantly reduce the biliary tract injury caused by cholecystectomy after gastric cancer. Some scholars believe that PC can be considered for patients who cannot carry out duodenal access preservation (74), especially Roux-en-Y (9) and Billroth II (46), because the risk of CL development after Roux-en-Y reconstruction is significantly higher than that after other procedures, and when CL develops after surgery, ERCP is very difficult to perform. Hauters et al. (31) believe that PC can be considered for total gastrectomy because the incidence of CL after total gastrectomy is higher than that after other surgical procedures, and the development of CL occurs early (4, 5, 7, 26). Tan et al. (46) found that Billroth II and diabetes were independent risk factors for postoperative CL development and elective secondary cholecystectomy, so PC was recommended. Bencini et al. (3) and Jeong et al. (22) believe that PC can improve the quality of life of middle-aged and young patients with early gastric cancer because they have a high life expectancy. Lai et al. (32) believe that PC can be considered in male patients and patients older than 60 years. In addition, Liang et al. (9) reported that PC may be beneficial in non-Asian countries with a higher incidence of CL after gastric cancer.

On the other hand, Watemberg et al. (67) believed that for patients who receive palliative care or whose life expectancy is less than 6 months, there is no need for PC during gastric cancer surgery. In addition, Gillen et al. (33) reported that PC was not routinely recommended during intraoperative D1 lymph node dissection for gastric cancer.

In general, the evidence and reasons in favor of PC are significantly more preponderance, and combined with our own work experience, we are more in favor of PC as a standard strategy for the treatment of gallstones after gastric cancer surgery.

Conclusions

The formation of CL after gastric cancer surgery is the result of multifactorial and mechanisms. Previous studies have identified many independent risk factors for CL after gastric cancer, but have not elucidated the intrinsic association between them. Due to the shortcomings and deficiencies of various treatment methods, the treatment effect is not satisfactory. As a new treatment strategy, PC has undeniable advantages and is expected to become the standard treatment for CL after gastric cancer in the future. The individualized PC strategy for CL after gastric cancer is the main direction of future research.

Data availability statement

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

Author contributions

HL study design, collation of results, writing original draft, writing-review, and editing. JL, data collection, collation of results, and writing original draft. WX and XC, data collection and collation of results. 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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Laparoscopic and endoscopic cooperative surgery for early gastric cancer: Perspective for actual practice

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Early gastric cancer (EGC) has a desirable prognosis compared with advanced gastric cancer (AGC). The surgical concept of EGC has altered from simply emphasizing radical resection to both radical resection and functional preservation. As the mainstream surgical methods for EGC, both endoscopic resection and laparoscopic resection have certain inherent limitations, while the advent of laparoscopic and endoscopic cooperative surgery (LECS) has overcome these limitations to a considerable extent. LECS not only expands the surgical indications for endoscopic resection, but greatly improves the quality of life (QOL) in EGC patients. This minireview elaborates on the research status of LECS for EGC, from the conception and development of LECS, to the tentative application of LECS in animal experiments, then to case reports and retrospective clinical studies. Finally, the challenges and prospects of LECS in the field of EGC are prospected and expounded, hoping to provide some references for relevant researchers. With the in-depth understanding of minimally invasive technology, LECS remains a promising option in the management of EGC. Carrying out more related multicenter prospective clinical researches is the top priority of promoting the development of this field in the future.

KEYWORDS

early gastric cancer, laparoscopic and endoscopic cooperative surgery, sentinel nodes, endoscopic submucosal dissection, endoscopic resection

Abbreviations: EGC, early gastric cancer; AGC, advanced gastric cancer; LECS, laparoscopic and endoscopic cooperative surgery; QOL, quality of life; Hp, Helicobacter pylori; GIST, gastrointestinal stromal tumors; SMTs, submucosal tumors; LAEFTR, laparoscopy-assisted endoscopic full-thickness resection; NEWS, non-exposure endoscopic wall-inversion surgery; CLEAN-NET, full-layer resection of gastric wall with non-exposure technique; EFTR, endoscopic full-thickness resection; SN, sentinel lymph node; SENORITA, SEntinel Node ORIented Tailored Approach; LSNNS, laparoscopic sentinel node navigation surgery; LSG, laparoscopic standard gastrectomy; 3y-DFS, 3-year disease-free survival; ESD, endoscopic submucosal dissection; SNBD, sentinel node basin dissection; NESS-EFTR, non-exposure endo-laparoscopic full-thickness resection with simple suturing technique; GAFT, gastric cancer of fundic gland type LLND, Laparoscopic lymph node dissection; LNM, Lymph node metastasis; NOTES, Natural orifice transluminal endoscopic surgery; LADG, Laparoscopic distal gastrectomy.

Introduction

With people's increasing attention to healthy diet and the popularization of *Helicobacter pylori (Hp)* eradicating treatment, the incidence and mortality of gastric cancer in European and American countries have been significantly reduced in recent years, ranking after the tenth among all tumors (1). However, gastric cancer is still a heavy burden in East Asian countries such as China, Japan and South Korea (2). Noteworthily, early gastric cancer (EGC) has a desirable prognosis compared with advanced gastric cancer (AGC). Statistics from the Japan Gastric Cancer Association show that the five-year disease-specific survival rates of EGC invading the mucosa and submucosa reach 99.3% and 97.2%, respectively (3). Therefore, diagnosing and managing gastric cancer as early as possible is the most cost-effective mean to improve the prognosis of gastric cancer patients.

Currently, endoscopic resection and laparoscopic resection are the mainstream surgical methods for EGC, but both have certain inherent limitations (4). For example, endoscopic resection of EGC has strict indications, and the size, location of the tumor, and whether it is accompanied by ulcers are critical factors that need to be considered. Although laparoscopic resection is guaranteed in terms of radical resection, the increase in postoperative complications seriously affects the quality of life (QOL) in EGC patients (5). Fortunately, the advent of laparoscopic and endoscopic cooperative surgery (LECS) has overcome these limitations to a considerable extent, which not only expands the surgical indications for endoscopic resection, but greatly improves the QOL in EGC patients (6). LECS refers to a new surgical method that combines the advantages of endoscopy and laparoscopy, which was first proposed by Japanese scholar Hiki and applied to the administration of gastrointestinal stromal tumors (GIST). With the rapid development of surgical instruments and the accumulation of surgical experience of surgeons, LECS is gradually applied in other gastric tumors, even EGC.

Although numerous clinical studies and reviews on LECS in gastrointestinal tumors have been published, to the best of our knowledge, a comprehensive study focusing on the application of LECS in EGC has not yet been reported. This minireview elaborates on the research status of LECS for EGC, from the conception and development of LECS, to the tentative application of LECS in animal experiments, then to case reports, retrospective clinical studies and ongoing prospective clinical trials. Finally, the challenges and prospects of LECS in the field of EGC are prospected and expounded, hoping to provide some reference for relevant researchers.

History of combined endoscopic and laparoscopic surgery

Since the beginning of the 21st century, the rapid development of endoscopic and laparoscopic technology has pushed gastrointestinal surgery into the era of minimally invasive surgery. Meanwhile, the surgical concept of EGC has altered from simply emphasizing radical resection to both radical resection and functional preservation. To solve the thorny issue that laparoscopic technique needs to be appropriately altered according to the location and size of gastric tumors, Hiki et al introduced a novel surgical procedure named LECS, which could be conducted for gastric SMTs resection and unaffected by tumor site and size (6). Nevertheless, the indications of LECS were quite conservative when it was first proposed, and the majority of applicable tumors were benign ones such as gastric submucosal tumors (SMTs) and GIST. In the same year, Japanese scholars Abe et al. successfully performed laparoscopy-assisted endoscopic full-thickness resection (LAEFTR) with lymphadenectomy in a 62-year-old EGC patient (7). This study confirmed that LAEFTR with lymphadenectomy was a minimally invasive and effective option for the treatment of EGC patients, reducing the extent of gastrectomy without compromising curability.

Although the advent of LECS has successfully solved the problem that the location and size of the tumor affect the surgical method, and the applicable indications of LECS have been extended to EGC (8), however, the gastric cavity and the abdominal cavity need be connected during the operation, which will lead to the increasing risk of gastric peritoneal metastases. Facing these challenges, gastroenterologists did not stop innovating and turned their attention to reducing or even avoiding the occurrence of gastric cancer peritoneal metastasis during LECS. In 2011 and 2012, Japanese scholars Goto and Inoue proposed two improved LECS, non-exposed endoscopic wall-inversion surgery (NEWS) (9) and full-layer resection of gastric wall with non-exposure technique (CLEAN-NET) (10), respectively. Unlike LECS, these two surgical operations do not need to open the stomach cavity, thus avoiding the problem of cancer cell metastasis caused by the communication between the stomach cavity and the abdominal cavity.

In the following years, LECS-related research achievements entered a stage of prosperity. NEWS has been gradually applied to clinical patients from initial tentative exploration in pig models (11). Moreover, the application of LECS is no longer limited to gastric tumors, and it has been successfully reported in duodenal tumors and colorectal tumors (12, 13). In 2017, Professor Kikuchi introduced the closed LECS surgical method in English, which was similar to the previous NEWS and CLEAN-NET surgery. In fact, Dr. Nishizaki is the developer of Closed LECS. Closed LECS avoids the opening of the stomach cavity, and the operation is easier and convenient (14). One year later, Takechi et al. successfully applied LECS to advanced gastric cancer for the first time with the informed consent of patient, marking an epoch-making breakthrough in the history of endoscopic laparoscopic combination therapy (15). In 2019, Japanese scholar Kitakata et al. proposed a new improved LECS procedure, sealed full-thickness resection (sealed EFTR), which has been successfully applied in ex vivo and *in vivo* porcine gastric cancer models (16). In conclusion, since the concept of classical LECS was proposed in 2008, surgeons dedicated to the better application of LECS in early gastrointestinal tumors have not stopped the pace of innovation. After more than ten years of development, up to now, there are six kinds of LECS and their improved operation methods, namely, classical LECS, inverted LECS (Crown Method), NEWS, CLEAN-NET, Closed LECS and Sealed EFTR (17). The schemas of these methods can be found in Figure 1.

However, we need to be clear about: although LECS and its modified surgical methods have been tentatively applied in EGC, there is great controversy about LECS as a therapeutic method for radical tumor resection. Therefore, LECS for EGC is only applicable in the following cases: 1. cases in which ESD is indicated but technically difficult to perform; 2. resection as a palliative treatment for cases in which standard gastrectomy is dangerous due to advanced age and severe comorbidities; 3. a clinical trial with sentinel node biopsy.

According to the latest Japanese gastric cancer treatment guidelines (the 6th edition), radical gastrectomy plus D_{1+} lymph node dissection is the first choice for the treatment of EGC with lymph node metastasis, while for those without lymph node metastasis, local resection of gastric cancer can be performed by endoscopic or laparoscopic surgery. To more accurately and quickly identify the lymph node metastasis of EGC, the concept of sentinel lymph node (SN) came into being and showed a good clinical prospect. The overall assessment of lymph node metastases in EGC by sentinel lymph nodes has been supported by evidence from numerous retrospective studies. Encouraged by several favorable single-institution reports, Japanese scholar Kitagawa et al. conducted a multicenter, single-arm, phase II study in 2013 to evaluate the safety and efficacy of SN mapping using a standardized dual tracer endoscopic injection technique in gastric cancer (18). Through the analysis of 397 eligible patients, the study found that the accuracy of SN biopsy in the assessment of gastric node metastasis was as high as 99%, and no severe adverse reactions related to endoscopic tracer injection or SN mapping procedures were observed, demonstrating the safety and efficacy of endoscopic dual tracer method for SN biopsy in superficial, relatively small gastric adenocarcinoma.

Although lymph node drainage in gastric cancer is quite complex, studies have confirmed that the probability of regional lymph node metastasis in EGC is not high. Therefore, some experts believe that standard D_2 radical gastrectomy for patients with EGC is excessive, and lymph node biopsy may improve this embarrassed situation to a certain extent. Noteworthily, LECS combined with SN biopsy has strict indications: clinical $T_1N_0M_0$ or $T_2N_0M_0$ with single primary lesions (≤4 cm) without previous treatment, fine general condition and able to tolerate surgery, without a history of drug-related allergy or active asthma etc. Moreover, some limitations of LECS combined with SN biopsy are still inevitable, for example, SN biopsy has a certain percentage of false-negative, the oncological efficacy and QOL improvement of LECS combined with SN biopsy have not been validated and supported by multicenter prospective studies (19).

In 2016, many experts dedicated to gastric cancer research in Korea led the SEntinel Node ORIented Tailored Approach (SENORITA) trial, a multi-center randomized phase III clinical trial comparing laparoscopic gastric-sparing sentinel lymph node dissection and standard gastrectomy plus lymph node dissection for EGC (20). Encouragingly, this study, which published results in 2022, showed that laparoscopic sentinel node navigation surgery (LSNNS) did not demonstrate noninferiority to laparoscopic standard gastrectomy (LSG) in terms of 3-year disease-free survival (3y-DFS), and LSNNS had better long-term QOL and nutrition than LSG (21). Considering that there remain several ongoing randomized controlled trials (RCTs) in Japan that have not reported results, a comprehensive consideration of a multi-country prospective clinical trials would be more convincing.

Application of LECS for EGC

Animal experimental studies related to LECS for EGC

EFTR is a commonly used surgical procedure for the treatment of early gastric benign and malignant tumors, but its indications are limited due to the inevitable spread of tumor cells into the abdominal space on account of transmural communication. In view of this, Goto et al. invented a new method for EFTR that does not require transmural communication (NEWS) and explored its feasibility in three ex vivo porcine models (9). The surgical operation of NEWS can be summarized into four steps. First, a flexible endoscope is used to make a mark around the model lesion. Second, a circumferential serous-muscular incision is made externally with electrocautery, based on markers and endoscopic gastric navigation. Third, linearly suture the muscle layer and the lesion medially. Finally, a mucosal-submucosal circumferential incision is made with electrocautery under the endoscope. It is worth mentioning that there was no perforation or obvious air leakage during or after the resection. The authors believe that NEWS is an effective minimally invasive endoluminal procedure for gastric SMTs with or without ulcers, or even node-negative EGCs that are difficult to remove by endoluminal submucosal dissection (ESD). Four years later, goto's research team conducted a survival study on a live pig model to explore the safety and feasibility of NEWS with sentinel node basin dissection (SNBD) (22). The lesions were completely resected

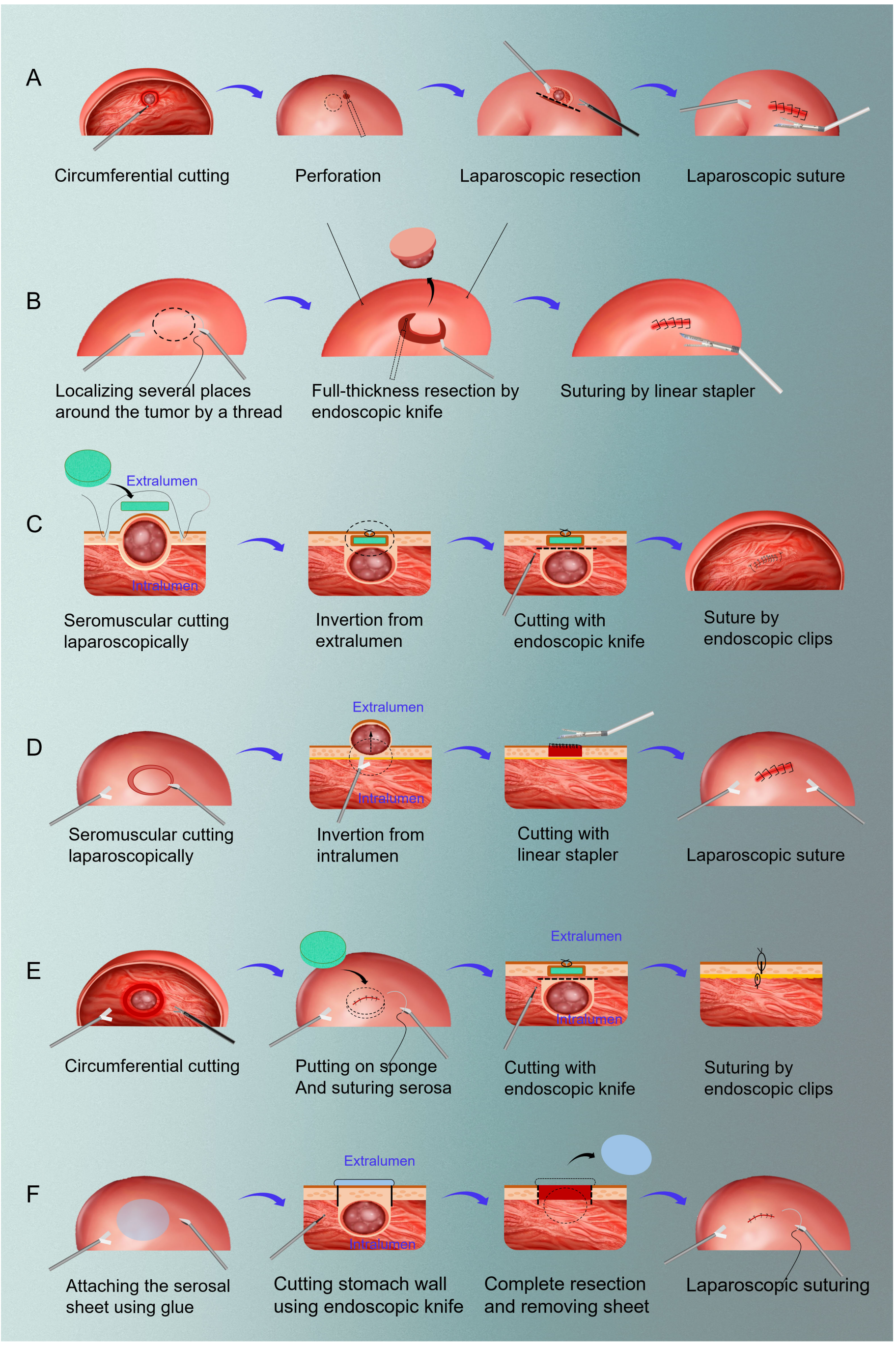

FIGURE 1
The schemas of six resection methods of LECS. **(A)** classical LECS; **(B)** inverted LECS (Crown Method); **(C)** NEWS; **(D)** CLEAN-NET; **(E)** closed LECS; **(F)** sealed EFTR. LECS, laparoscopic and endoscopic cooperative surgery; NEWS, non-exposure endoscopic wall-inversion surgery; CLEAN-NET, full-layer resection of gastric wall with non-exposure technique; EFTR: endoscopic full-thickness resection.

and the mean operative time was 170 minutes (130-253 minutes), and all pigs survived with no undesirable events. All pigs were sacrificed one week later and necropsy showed no signs of serious complications. This animal survival study illustrated that NEWS combined with SNBD was safe and feasible, and may provide minimal local excision for potentially node-positive EGC patients without the risk of tumor spread.

Similarly, Mitsui from Japan and Kim from South Korea have also explored the feasibility of LECS for EGC in animal experimental models, respectively. In the former research, 6 explanted pig stomachs and 6 live pigs were selected and then completed the NEWS operation (23). All 12 lesions were successfully resected without perforation. Three pigs were monitored for 7 days, all survived without adverse events, and necropsy revealed no leaks or abscesses, demonstrating that NEWS is technically feasible and safe in both *in vitro* and *in vivo* pig studies. The latter performed non-exposure endo-laparoscopic full-thickness resection with simple suturing technique (NESS-EFTR) in 4 pigs (24). All pigs underwent complete excision and no adverse events occurred. The mean operation time was 137.0 minutes. Gross and microscopic examination of the excision site showed healing with no evidence of leakage or infection, indicating that NESS-EFTR was feasible in animal models. The summary of animal experimental studies related to EGC and LECS is presented in Supplementary Table S1.

Case reports related to LECS for EGC

After animal experiments demonstrated the feasibility and safety of LECS, surgeons began to try to apply the procedure to clinical patients. Proverbially, compared with endoscopic resection, laparoscopy facilitates intraoperative lymph node dissection and can perform local resection from outside the stomach, thereby ensuring the integrity of lesion resection. In 2008, Japanese professor Abe attempted to utilize LAEFTR to treat a 62-year-old EGC patient. LAEFTR consists of 4 main procedures: first, a circumferential incision deep to the submucosa is made around the lesion by ESD technique; second, an endoscopic incision is made laparoscopically over three-quarters of the circumference of the above submucosal incision; next, complete the remaining quarter-circumferential laparoscopic full-thickness incision in the peritoneal cavity; finally, laparoscopic suturing of the gastric wall defect. The entire laparoscopic procedure was successfully completed with a total of 389 minutes and no adverse events occurred. The entire peripheral tumor of the specimen was negative, 23 lymph nodes were free of cancer cells, and the patient recovered well after surgery and did not affect the postoperative QOL. These results indicate that LAEFTR combined with lymphadenectomy is effective in the treatment of EGC (7).

To achieve proper gastric wall resection, Hiki et al. unveiled the LECS and applied it to the resection of gastric SMTs. In LECS, the site of the tumor is first confirmed by endoscopy, followed by submucosal dissection by endoscopic endoscopy to ascertain the appropriate resection line. Then, the seromuscular layer is laparoscopically dissected, and the incision line is closed with a laparoscopic stapler. Nunobe et al reported a case of laterally diffusing intramucosal gastric cancer with a diameter of 6 cm located in the gastric fornix, and they successfully employed LECS (8). The entire operation time was 152 minutes, and the estimated intraoperative blood loss was 0 ml. Postoperative pathological report confirmed that the tumor was located in the mucosa without lymphatic or venous invasion, and the resection margin was negative. The successful application of LECS in EGC proves that if the EGC meets the criteria for endoscopic resection and there are technical difficulties in performing ESD, it will be a good indication for LECS. The authors also expected that if the concept of sentinel lymph nodes was established, the LECS indications for EGC will be expanded in the future.

As a new minimally invasive surgery that can effectively avoid intraoperative proliferation of gastric cancer cells, NEWS combined with sentinel node navigation surgery can minimize the size of lymph node dissection, whose feasibility has been demonstrated in pig survival studies (9). Goto et al were the first to report a clinical case of NEWS with SNBD for diffuse intramucosal EGC with ulceration in a 55-year-old female patient (11). The operation time was 270 min, and there were no complications. The patient was discharged from the hospital 10 days after the operation and the final pathological diagnosis was consistent with preoperative and intraoperative assessments. This case and Niimi's study (25) re-validate the feasibility and safety of NEWS plus SNBD, which is expected to be a promising, minimally invasive, function-sparing procedure for potentially node-positive EGC.

Coincidentally, Kato et al. reported the successful treatment of intramucosal differentiated gastric cancer with CLEAN-NET (26). The patient was an 80-year-old man who was diagnosed with intramucosal differentiated gastric cancer by gastroscopy and preoperative pathology. The authors used CLEAN-NET to resect the tumor without any complications under the informed consent of the patient. The postoperative pathological diagnosis was basal gland-type gastric cancer (GAFT) without lymphatic involvement, and the surgical margins were all negative. This case demonstrates that CLEAN-NET is an effective regimen for the treatment of gastric cancer patients with low-risk lymph node metastases, preventing not only the removal of excess gastric wall, but also the exposure of cancer cells to the abdominal cavity. The detailed information of case reports related to LECS for EGC can be seen in Supplemental Table 2.

Clinical studies related to LECS for EGC

There are numerous similar clinical studies, and researchers have demonstrated the feasibility of various LECS methods, such as ESD combined with laparoscopic lymph node dissection (LLND), hybrid natural orifice transluminal endoscopic surgery (NOTES), etc. (27, 28)

CLEAN-NET is a non-exposed tumor technology that combines the characteristics of laparoscopy and endoscopy. Full-thickness resection of gastric tumors is maneuverable when endoscopy is combined with laparoscopy. However, a major handicap of this procedure is that stomach contents may flow into the abdominal cavity through the open stomach wall incision, thereby increasing the risk of tumor dissemination. Therefore, it is urgent to develop a non-exposed technology to effectively solve this drawback. CLEAN-NET is developed using a serous muscle incision that preserves the continuity of the mucosa, which acts as a clean net to block the communication between the gastric and abdominal cavities. The mucosa surrounding the tumor specimen is then stretched by using a serous muscle incision and the raised full-thickness gastric wall is finally sutured. At this time, the tumor is completely exposed outside the gastric cavity, which can be easily removed by laparoscopy. This operation can control the area of gastric resection to a minimum on the premise of ensuring radical resection. Inoue et al performed CLEAN-NET in 24 consecutive patients (16 gastric cancer and 8 GIST), and the procedure was successful without complications (10).

Sentinel lymph node navigation is an emerging surgical technique in recent years, but the clinical efficacy of this technique for local gastrectomy and regional lymphadenectomy remains unclear. Therefore, Hur et al constructed a prospective pilot study to evaluate the efficacy of LAEFTR combined with sentinel lymph node navigation in patients with EGC (29). The study finally included 9 patients and successfully implemented LAEFTR with sentinel node navigation. The mean operation time and postoperative mean hospital stay were 183.3 minutes and 5.9 days, respectively. Abdominal and pelvic computed tomography examinations did not reveal any recurrence at 6 months after surgery.

There remains a body of single-center retrospective clinical studies exploring the treatment of EGC with LECS, but based on the epidemiological characteristics of the high incidence of EGC in Japan, South Korea and other East Asian countries, majority of these studies are led and carried out by scholars from these countries (30, 31). However, it is undeniable that these studies have provided clinical evidence for the development of LECS and made a significant contribution to its popularization. Fortunately, in the past five years, LECS has not only been carried out in Germany, Japan, and South Korea, but also gradually introduced in China, the Czech Republic and other countries in the world (32, 33). The detailed information of studies related to LECS for EGC can be seen in Table 1.

Challenges and prospects

Although significant progress has been made in the application of LECS in the management of EGC, there are still the following areas for improvement. First, the indications of LECS are relatively limited, and laparoscopic radical resection is still the first choice for EGC with lymph node metastasis. Second, LECS requires the tacit cooperation of endoscopists and laparoscopists, and has a long learning curve. There is still a long way to go to further popularize the application of LECS in EGC. Moreover, most of the relevant studies have small sample

TABLE 1 Summary of studies related to LECS for EGC.

Ref.	Year	Country	Number of cases	Surgery	Conclusion
Abe et al (27)	2005	Japan	5	ESD and LLND	This combination treatment was a potential, minimally invasive method, and may obviate unnecessary gastrectomy without compromising curability for EGC patients having the potential risk of LNM.
Cho et al (28)	2011	Korea	14	Hybrid NOTES	Hybrid NOTES could be a bridge between endoscopic resection and laparoscopic surgery and may prevent extensive gastrectomy in patients with EGC
Inoue et al (10)	2012	Japan	16	CLEAN-NET	CLEAN-NET potentially avoided tumor dissemination. CLEAN-NET combined with regional lymph node dissection may suggest further application of this procedure to submucosal cancer.
Hur et al (29)	2014	Korea	9	LAEFTR	This technique could be a novel treatment strategy for gastric cancer patients with inconclusive diagnoses, who would typically undergo laparoscopic gastrectomy or endoscopic resection.
Hajer et al (32)	2018	Czech Republic	2	NEWS	NEWS combined laparoscopic and endoscopic techniques, and preserved the full function of the stomach.
Aoki et al (30)	2018	Japan	7	LECS	LECS was likely to be effective for cases involving intra-mucosal gastric carcinoma that are difficult to treat by ESD due to ulcer scars.
Okubo et al (31)	2020	Japan	25	CLEAN-NET and SNNS	CLEAN-NET with SNNS preserved a better QOL and nutrition status than LADG in patients with early gastric cancer.

LECS, Laparoscopic and endoscopic cooperative surgery; EGC, Early gastric cancer; ESD, Endoscopic submucosal dissection; LLND, Laparoscopic lymph node dissection; LNM, Lymph node metastasis; NOTES, Natural orifice transluminal endoscopic surgery; CLEAN-NET, Full-layer resection of gastric wall with non-exposure technique; LAEFTR, Laparoscopy-assisted endoscopic full-thickness resection; NEWS, Non-exposure endoscopic wall-inversion surgery; SNNS, sentinel node navigation surgery; QOL, Quality of life; LADG, Laparoscopic distal gastrectomy.

sizes and are mainly reported in Japan and South Korea, which cannot reflect the global research status. Whether other countries in the world can complete this relatively complex operation remains to be discussed. Finally, most studies related to LECS and EGC are retrospective studies, which may overestimate the real performance of LECS due to selection bias.

Despite the fact that LECS has made major breakthroughs in EGC, we have more expectations for the optimization of LECS. For instance, with the gradual improvement of residents' health awareness and increasing people take health check-ups, the number of EGC patients will undoubtedly grow. How to expand the applicable indications of LECS and provide more choices for EGC and even AGC patients with individual differences is a meaningful research direction. Furthermore, how to simplify the surgical operation of LECS, thereby shortening the learning cycle is also a problem that needs to be considered. Finally, and most importantly, although there are several ongoing clinical trials, this is far from enough. It is urgent to carry out more multicenter and large-sample clinical research on the application of LECS for EGC, so as to provide a solid theoretical basis for the application and popularization of LECS.

Conclusion

This minireview first elaborates on the research status of LECS for EGC, from the conception and development of LECS, to the tentative application of LECS in animal experiments, then to case reports and retrospective clinical studies, which enables us to have a comprehensive and in-depth understanding of this filed. Finally, the challenges and prospects of LECS in EGC are prospected and expounded. Noteworthily, LECS makes a significant contribution to the development of minimally invasive technology. At the same time, LECS still has certain limitations need to be overcome or improved. To sum up, LECS remains a promising option in the management of EGC, and conducting more multicenter prospective clinical research related to LECS and EGC is the top priority in the future.

Author contributions

P-yZ performed the majority of the writing, prepared the figures and tables. Z-fM and Y-nJ prepared the tables and performed the drawing of figures. YY and S-yL edited and revised the manuscript. X-hD designed the study. All authors approved the final version to be published.

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Conflict of interest

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Supplementary material

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Effectiveness and safety of self-pulling and latter transected Roux-en-Y reconstruction in totally laparoscopic distal gastrectomy

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Background: Self-pulling and latter transection (SPLT) reconstruction has been applied in total laparoscopic total gastrectomy and BI reconstruction (known as Delta SPLT) in total laparoscopic distal gastrectomy (TLDG) in some previous studies. This approach can reduce the technical difficulty of the surgery as well as the quantity of cartridges required, with manageable safety. Here, we used SPLT to complete Roux-en-Y reconstruction in TLDG and evaluated the safety and effectiveness of this novel method by comparing it with conventional Roux-en-Y reconstruction in laparoscopy-assisted distal gastrectomy (LADG).

Methods: Patients with gastric cancer who underwent SPLT-TLDG or LADG between June 2019 and September 2021 were retrospectively analyzed. Baseline information and postoperative short-term surgical outcomes of the two groups were compared.

Results: A total of 114 patients with gastric cancer were included in the study. Patients underwent SPLT-TLDG (n = 73, 64.0%) or LADG (n = 41, 36.0%). No patient underwent open surgery. There were no differences in patient demographics or tumor characteristics between the two groups. The mean intraoperative blood loss was 47.1 ± 34.3 ml in the SPLT-TLDG group, which was significantly less than that in the LADG group ($P = 0.022$). There were no significant differences in operation time, harvested lymph nodes, time to first flatus, time to liquid intake, or postoperative hospital stay between the two groups. Nine and five patients had short-term postoperative complications in the SPLT-TLDG and LADG groups, respectively.

Conclusion: We introduced a self-pulling and latter transected Roux-en-Y reconstruction (SPLT-RY) for use in TLDG. We showed that SPLT-RY reconstruction in TLDG is a safe and feasible surgical method in terms of short-term surgical outcomes and has the advantages of simplifying the reconstruction.

KEYWORDS

totally laparoscopic distal gastrectomy, Roux-en-Y reconstruction, gastric cancer, self-pulling and latter transection, laparoscopy-assisted distal gastrectomy

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Introduction

Laparoscopy-assisted gastrectomy (LAG) for gastric cancer was first reported in 1994 (1). LAG is less invasive, and patients recover earlier than with open gastrectomy (2–4). Total laparoscopic gastrectomy (TLG) was first reported with intracorporeal Billroth II (BII) reconstruction using laparoscopic linear staplers (5). TLG was proven to be reliable and feasible in patients with gastric cancer (6–8). Nevertheless, for surgeons, TLG remains a surgical challenge due to the difficulty of intracorporeal reconstruction (9).

The reconstruction method for total laparoscopic distal gastrectomy (TLDG) includes Billroth I (BI) reconstruction (10), BII reconstruction (11), Roux-en-Y (RY) reconstruction (12), and uncut RY reconstruction (13). BI reconstruction has specific requirements in terms of gastric cancer location. BII and RY reconstruction both had wide indications, but RY seemed to be a preferred reconstruction after TLDG in terms of short- and long-term surgical outcomes (14, 15); however, RY is a complex procedure and is markedly more expensive and requires more surgical skills than do BI and BII. Self-pulling and latter transection (SPLT) reconstruction, which can reduce the technical difficulty of the surgery and the quantity of cartridges required, with manageable safety, has been used in total laparoscopic total gastrectomy and with BI reconstruction (known as Delta SPLT) in TLDG in some previous studies (16, 17).

To simplify RY reconstruction, we implemented SPLT to complete RY reconstruction in TLDG. The purpose of this study was to describe the SPLT-RY procedure in TLDG and to evaluate its effectiveness and safety by comparing it with conventional RY reconstruction in laparoscopy-assisted distal gastrectomy (LADG).

Patients and methods

Patients

The patient selection criteria were as follows. Inclusion criteria: Patients had undergone SPLT-TLDG or LADG between June 2019 and September 2021; the procedures were performed by the same surgeon, who had more than 10 years of surgical experience; gastric adenocarcinoma was confirmed by pathological biopsy; the tumor was located in the gastric antrum, lesser curvature of the stomach, or corner of the stomach; preoperative CT suggested T1–3, without detection of any distal metastasis (M0); and patients were informed of the advantages and disadvantages of the two procedures before the operation and chose a surgical method by signing an informed consent form. Exclusion criteria: Patients had a serious dysfunction in the heart, lung, bone marrow, kidney, or liver; patients had other synchronous malignancies; or patients had undergone combined resection of other organs.

Procedures of SPLT-TLDG

After general anesthesia, the patient was placed in a split-leg position. The surgeon was positioned on the right side, the assistant was positioned on the left side of the patient, and the cameraman stood between the legs of the patient.

The port placement process started after establishing pneumoperitoneum, which maintained a pressure of 1.6 kPa. Three trocars were inserted for laparoscopic exploration, and after confirming that there was no metastasis, another two trocars were inserted. The positions of the five trocars were as follows: a 10-mm trocar was inserted 1 cm below the umbilicus, 12- and 5-mm trocars were inserted 2 cm below the lower edge of the costal arch, at the left and right anterior axillary lines; and 12-mm and 5-cm trocars were inserted on both sides of the lower quadrant on the umbilicus line (Figure 1A).

D2 lymph node (LN) dissection was performed according to the Japanese Gastric Cancer Association guidelines (18). The SPLT-RY reconstruction was then conducted according to the following procedures: We punctured the posterior wall of the proximal stomach, at least 5 cm away from the tumor (Figure 2A). We also punctured the antimesenteric border of the jejunum, 15–20 cm away from the Treitz ligament (Figure 2B). We then tailored the mesentery along the jejunum. We made an anastomosis of the proximal stomach and distal jejunum by using a linear cutting stapler from the right 12-mm trocar (Figure 2C). We closed the common opening of the proximal stomach and distal jejunum and cut off the distal stomach and proximal jejunum by linear cutting stapler from the left 12-mm trocar at the same time and then sutured the opening of the distal stomach (Figures 2D, E). Next, we disconnected the distal stomach and duodenum from the right 12-mm trocar (Figure 2F). Subsequently, we punctured the antimesenteric border of the small intestine 40 cm away from the proximal stomach and distal jejunum anastomosis (Figure 2G). We also punctured the antimesenteric border 1 cm away from the margin of the

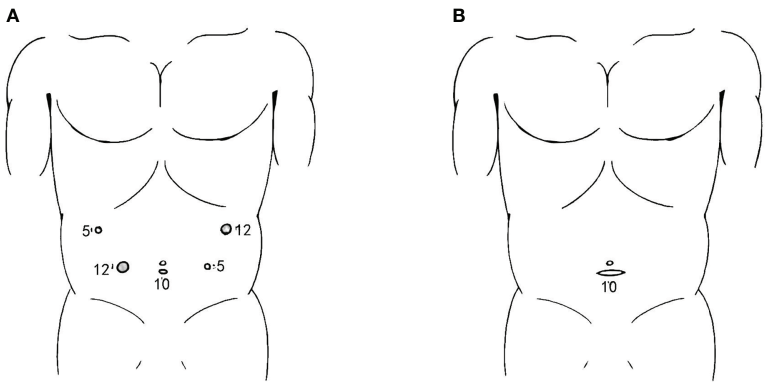

FIGURE 1
Incisions for SPLT-RY in TLDG. **(A)** Placement of the trocars; **(B)** abdominal transverse incision used to remove the resected specimen. SPLT-RY, self-pulling and latter transected Roux-en-Y; TLDG, total laparoscopic distal gastrectomy.

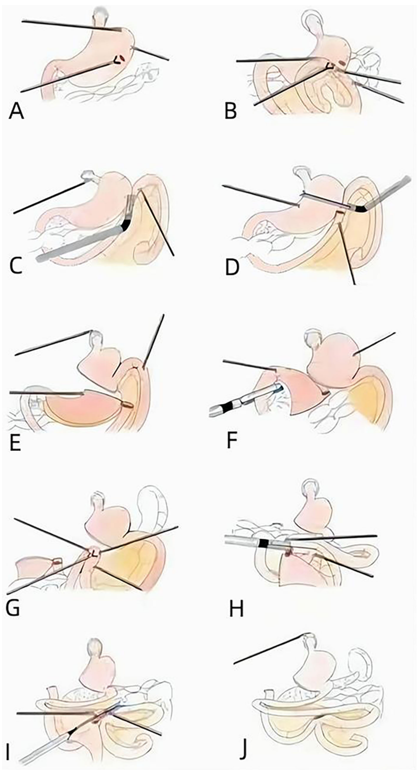

FIGURE 2
Procedure of SPLT-RY in TLDG. **(A)** Puncturing the posterior wall of the proximal stomach. **(B)** Puncturing the antimesenteric border of the jejunum. **(C)** Anastomosis of the proximal stomach and distal jejunum. **(D)** Closing the common opening. **(E)** Cutting off the proximal stomach. **(F)** Disconnecting the distal stomach and duodenum. **(G)** Puncturing the antimesenteric border of the small intestine. **(H)** Anastomosis of the small intestine and proximal jejunum. **(I)** Closing the common opening. **(J)** Removing the distal stomach. SPLT-RY, self-pulling and latter transected Roux-en-Y; TLDG, total laparoscopic distal gastrectomy.

proximal jejunum and made an anastomosis of the common opening of the small intestine and proximal jejunum by linear cutting stapler from the right 12-mm trocar (Figure 2H). The common opening of the proximal jejunum and small intestine was closed by linear closure from the right 12-cm trocar (Figure 2I), and the distal stomach was removed (Figure 2J).

A 3- to 4-cm transverse abdominal incision was made to remove the specimen after reconstruction was completed (Figure 1B). After anastomotic stomas were checked for patency, including bleeding or tension, and bleeding was stopped carefully, the transverse incision was closed, and the operation was completed.

Procedures of LADG

All procedures before reconstruction in LADG were the same as those in SPLT-TLDG. After D2 LN dissection, the pneumoperitoneum was released. A 7- to 8-cm incision was made at the exact center of the epigastrium and was protected using an incision protector. The distal stomach was resected with a linear cutting stapler and was removed from the previously dissected tissues. Side-to-side gastrojejunostomy and jejunojejunostomy were performed using a linear cutting stapler. All anastomotic stomas and stumps were checked carefully to ensure that there was no visible bleeding or tension. Reinforcing with interrupted sutures was used if necessary. The abdominal incision was closed after placing an indwelling drainage tube. The surgery was then completed.

Postoperative management

All the patients underwent standardized postoperative management. Broad-spectrum antibiotics were used for 48 h during their postoperative hospitalization. Routine octreotide was administered until liquid intake was permitted in both the groups. Upper gastrointestinal water-soluble contrast radiography was typically performed for 3 days after gastrectomy. A liquid diet was recommended if the patient's flatus recovered or if no anastomosis leakage was found on upper gastrointestinal water-soluble contrast radiography (Figure 3). Ambulation was encouraged on the first postoperative day. Patients without complications were discharged once their bowel movements recovered, and they showed no discomfort with the liquid diet.

Data collection

The baseline information collected from the two groups included sex, body mass index (BMI), preoperative hemoglobin, preoperative albumin, tumor stage, and important history. Intraoperative data collected included operation time, intraoperative blood loss, and harvested lymph nodes. Postoperative data included time to ambulation postoperatively, time to first flatus, time to first fluid intake, postoperative hospital stay, decrease in hemoglobin and albumin levels, and complications.

Statistical analysis

All statistical analyses were performed using the SPSS software (version 26.0; IBM Inc., Armonk, NY, USA).

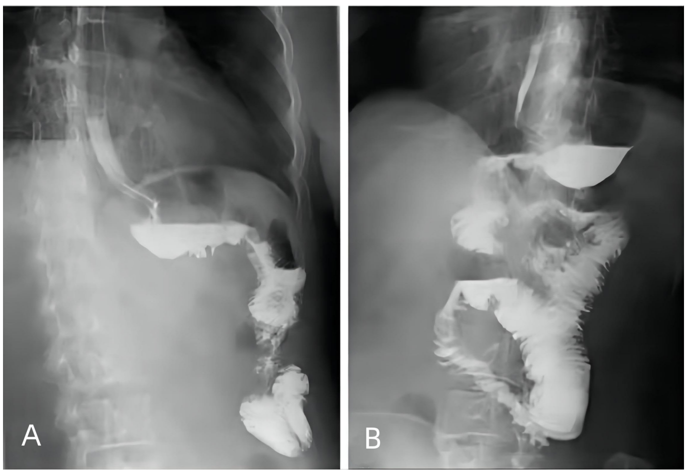

FIGURE 3
Upper gastrointestinal water-soluble contrast radiography performed 3 days after SPLT-RY in TLDG. **(A)** Anastomosis of the proximal stomach and distal jejunum. **(B)** Anastomosis of the small intestine and proximal jejunum. SPLT-RY, self-pulling and latter transected Roux-en-Y; TLDG, total laparoscopic distal gastrectomy.

Differences in continuous variables between the two groups were tested using the Mann–Whitney U test. Differences in ordered categorical variables were compared using chi-square tests. Statistical significance was set at $P < 0.05$.

Results

A total of 114 patients were included in this study, and the baseline information of the two groups was compared (Table 1). No significant between-group differences were found for sex, BMI, ASA scores, preoperative hemoglobin and albumin levels, tumor characteristics, or medical history, such as abdominal surgery history.

The operative and postoperative data of the study patients are shown in Table 2. All 114 patients successfully underwent SPLT-TLDG (73, 64.0%) or LADG (41, 36.0%). None of the patients underwent open surgery. Intracorporeal anastomosis was successfully performed in all the patients in the SPLT-TLDG group. The mean operation time was similar in the SPLT-TLDG and LADG groups. In contrast, the mean intraoperative blood loss in the SPLT-TLDG group was significantly lower than that in the LADG group ($P = 0.022$). No significant differences were found in the number of LNs harvested, time to ambulation, time to first flatus, time to first liquid intake, length of postoperative hospital stay, and decreases in hemoglobin and albumin levels between the two groups. Nine patients (12.3%) in the SPLT-TLDG group had postoperative complications, which was not significantly different from the six patients (14.6%) in the LADG group ($P = 0.777$). One duodenal stump fistula, one anastomotic leakage, and two abdominal cavity infections occurred in the TLDG group, which recovered after treatment with peritoneal drainage and antibiotics. One patient in the TLDG group experienced an intra-abdominal hernia 17 days after the operation, which was cured by emergency surgery without intestinal resection. One gastrojejunal anastomotic stenosis occurred 1 month after surgery and was completely relieved after two endoscopic dilations. One patient in the LADG group experienced postoperative bleeding and recovered after treatment with hemostatic treatment and blood transfusion. In addition, anastomotic leakage, pancreatic fistula, and abdominal cavity infection occurred in some patients in the LADG group and were cured with peritoneal drainage and antibiotics. Other complications, including pulmonary infection, were also cured after a period of appropriate therapy.

During the follow-up period of 6 months at least, none of the patients complained of reflux symptoms or experienced tumor recurrence or metastasis.

Discussion

BI reconstruction, also called delta-shaped anastomosis, was first reported in 2002 (10) and was modified by Huang et al. to improve its safety and reliability (19). Although widely accepted, however, BI reconstruction could not be conducted if the remnant stomach was small or if the duodenal stump was short. RY reconstruction had a reduced risk and lower degree of residual gastritis and bile reflex than encountered with BI and BII reconstructions (14, 15, 20). Furthermore, RY reconstruction

TABLE 1 Patient demographics and tumor characteristics of both groups.

Characteristics	SPLT-TLDG(n = 73)	LADG(n = 41)	P value
Age (years)[a]	61 (35-84)	62 (34-84)	0.545
Sex (male/female) [b]	41/32	28/13	0.204
BMI (kg/m^2) [c]	22.8 ± 2.8	22.5 ± 3.1	0.816
Smoking [b]	28	23	0.068
Drinking [b]	22	18	0.139
Abdominal surgery history [b]	13	9	0.591
Main comorbidity			0.327
Hypertension/T2DM/COPD [b]	8/6/3	10/1/2	
ASA score (1/2/3/4) [b]	27/42/4/0	13/24/4/0	0.643
Preoperative hemoglobin (g/L) [c]	121.9 ± 23.7	116.1 ± 18.4	0.125
Preoperative albumin (g/L) [c]	39.9 ± 4.2	39.3 ± 4.5	0.116
Neoadjuvant chemotherapy [b]	18	13	0.417
Tumor size (cm)[c]	3.1 ± 2.0	2.8 ± 1.6	0.535
T stage (T1/T2/T3/T4) [b]	36/10/22/5	16/9/9/7	0.187
Node stage (N0/N1/N2/N3) [b]	46/9/9/9	23/4/8/6	0.705
TNM stage (I/II/III/IV) [b]	38/16/19/0	19/9/13/0	0.789

Data are shown as medians, with ranges in parentheses. [b]Data are given as n of corresponding groups. [c]Data are shown as mean ± standard deviation.
T2DM, type 2 diabetes mellitus; COPD, chronic obstructive pulmonary disease; BMI, body mass index; ASA, American Society of Anesthesiologists; SPLT, self-pulling and latter transected; TLDG, total laparoscopic distal gastrectomy; LADG, laparoscopy-assisted distal gastrectomy.

TABLE 2 Comparison of surgical outcomes between SPLT-TLDG and LADG.

Characteristics	SPLT-TLDG(n = 73)	LADG(n = 41)	P value
Operation time (min)	176.2 ± 40.8	182.0 ± 40.7	0.467
Intraoperative blood loss (mL)	47.1 ± 34.3	77.1 ± 93.4	0.022
Harvested lymph nodes	23.7 ± 9.2	21.1 ± 8.6	0.075
Incision size (cm)	3.6 ± 0.6	7.1 ± 1.1	<0.001
Time to ambulation (days)	1.6 ± 0.8	2.2 ± 0.8	0.123
Time to first flatus (days)	2.5 ± 1.1	1.8 ± 0.9	0.265
Time to first liquid intake (days)	4.0 ± 1.8	4.2 ± 1.8	0.325
Postoperative hospital stay (days)	8.9 ± 4.4	9.5 ± 4.3	0.144
Decrease in hemoglobin (g/L)	11.5 ± 13.3	10.2 ± 6.7	0.876
Decrease in albumin (g/L)	8.0 ± 4.7	6.8 ± 3.8	0.122
Second operation	1	0	>0.999
Postoperative complications	9 (12.3%)	6 (14.6%)	0.777
Duodenal stump fistula	1	0	
Anastomotic leakage	1	1	
Anastomotic stenosis	1	0	
Pancreatic fistula	0	1	
Abdominal cavity infection	2	1	
Intra-abdominal hernia	1	0	
Pulmonary infection	1	1	
Pleural effusion	2	1	
Postoperative bleeding	0	1	
Wound infection	0	0	
Death	0	0	

Variables are expressed as mean ± standard deviation or as n (%).
SPLT, self-pulling and latter transected; TLDG, total laparoscopic distal gastrectomy; LADG, laparoscopy-assisted distal gastrectomy.

could expand the indications of TLDG, irrespective of whether the remnant stomach was small. However, RY is a complex process and has therefore not gained widespread acceptance in TLDG (14, 15). To simplify RY, we first used SPLT to complete RY reconstruction in TLDG and then evaluated the safety and feasibility of this novel method by comparing it with conventional RY in LADG. Compared with LADG, SPLT-RY in TLDG involved less intraoperative blood loss and had a similar operation time. This result was similar to that in other studies (21, 22). During the LADG, the remnant stomach was pulled out *via* a small invasion and anastomosis was performed in a relatively narrow operative field, which may cause more tissue trauma. However, in TLDG, we had a better visual field, and more accurate operation could be performed, especially on patients with obesity; this explains the decreased intraoperative blood loss in TLDG. The overall complication rate in SPLT-TLDG was as controllable as that in LADG, and no conversion to open surgery or death occurred in SPLT-TLDG; therefore, we believe that SPLT-RY is a safe and feasible reconstruction method in terms of short-term surgical outcomes.

In contrast to conventional RY-TLDG, when performing RY reconstruction in TLDG, we used later transection techniques (16), and it required fewer staplers to close the common opening of the proximal stomach and distal jejunum. We cut off the stomach and jejunum by using a linear cutting stapler. Thus, SPLT-TLDG may reduce cost and simplify the reconstruction procedure. Furthermore, the stumps of the stomach and jejunum were in a straight line in SPLT-RY (Figure 4), which reduced the size of the cutting edge intersection, as compared with conventional RY, which might improve anastomosis security and diminished the tough hand suturing required to close the common opening. Moreover, when applying SPLT, the distal stomach was initially retained uncut so it could be used to draw the stomach to a proper position for reconstruction, which can reduce the difficulty of the procedure. However, when frozen sections during surgery are indispensable for determining the proximal margin, SPLT is not recommended, because the specimen cannot be obtained until the anastomosis is complete.

Gastrectomy is an onco-metabolic surgery, and diabetes and hypertension could be resolved after gastrectomy (23, 24). RY reconstruction and the extent of gastrectomy might contribute to the remission of diabetes and hypertension (23, 25, 26). In this study, SPLT-RY reconstruction was performed, and the extent of gastrectomy could be controlled using SPLT-TLDG. SPLT-

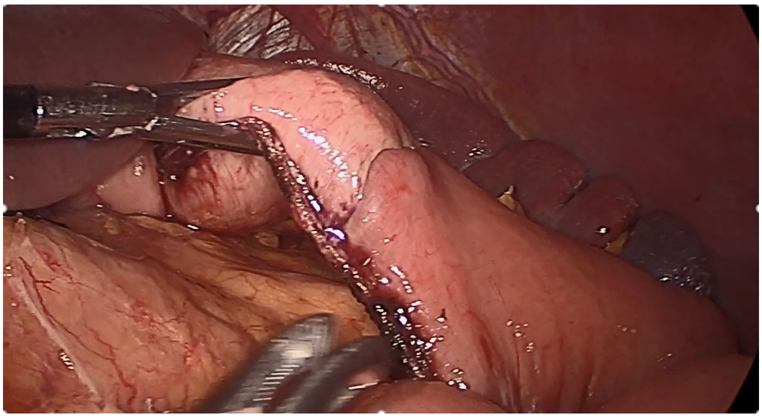

FIGURE 4
In SPLT-RY, we closed the common opening of the stomach and jejunum and cut off the stomach and jejunum in the same step, so that the stumps of the stomach and jejunum were in a completely straight line. SPLT-RY, self-pulling, and later transected Roux-en-Y.

TLDG might provide promising benefits to patients with concurrent gastric cancer and metabolic diseases.

There are several tips for applying SPLT-RY to TLDG. First, we performed SPLT-TLDG on the patient's right side. During the SPLT-RY reconstruction procedure, all anastomoses were performed by the surgeon, except for closing the common opening of the proximal stomach and distal jejunum and cutting off the proximal stomach by means of a linear cutting stapler by the assistant through the left 12-mm trocar hole. The surgeon and assistant did not exchange their positions, thereby reducing anastomosis time. However, this requires more experienced skills in the assistant. We have also attempted to complete all anastomoses by the surgeon on the right side, but when closing the common opening of the proximal stomach and distal jejunum, and when cutting off the proximal stomach by means of a linear cutting stapler, the anastomosis was clearly twisted. Thus, having the assistant perform this procedure could resolve the problem. Second, punching a small hole in the small intestine through which the linear cutting stapler can enter minimizes damage to the small intestine. Furthermore, the common opening should be carefully checked to prevent bleeding from the intestinal cavity after anastomosis. Third, the transverse incision is made above the pubic symphysis so that it may be better concealed, particularly in patients with high esthetic demands.

This study had some limitations. First, this was a retrospective study, with limited data included. Second, this study aimed to evaluate the effectiveness and safety of SPLT-RY in TLDG. However, the follow-up time was relatively short, and its long-term outcomes were uncertain. A longer follow-up would be needed in future. Third, given the aim of this study, it could be better to compare it with conventional RY in TLDG; however, because there were only approximately 20 patients who underwent conventional RY-TLDG in our center and as all these procedures were performed before implementation of SPLT-TLDG at our institution, considering the experience level according to the period, we did not have enough comparable conventional RY-TLDG samples in our center. Fourth, although the data from our center showed that SPLT-TLDG was feasible, it does not address the learning curve for surgeons elsewhere.

Conclusion

We introduced the SPLT-RY method in TLDG. Our study showed that SPLT-RY reconstruction in TLDG is a safe and feasible surgical method in terms of short-term surgical outcomes and that it can simplify reconstruction after gastric cancer surgery. A well-designed prospective study should be conducted in the future to validate the clinical efficacy of this reconstruction method.

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 Medical Ethics Committee of Chongqing Medical University. Written informed consent for participation was not

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required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

DC contributed to the conception and design of the study. KQ provided study materials and patients. FY and CT collected and assembled data. DC wrote the first draft of the manuscript. SW contributed to manuscript modification. All authors contributed to manuscript revision and read 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 potential a conflict of interest.

Publisher's note

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Survival benefit of surgical resection for stage IV gastric cancer: A SEER-based propensity score-matched analysis

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Background: Gastric cancer (GC) is a major malignancy worldwide, and its incidence and mortality rate are increasing year by year. Clinical guidelines mainly use palliative drug combination therapy for stage IV gastric cancer. In accordance with some small sample studies, surgery can prolong survival. There is no uniform treatment plan for stage IV gastric cancer. This study focused on collecting evidence of the survival benefit of cancer-directed surgery (CDS) for patients with stage IV gastric cancer by analyzing data from a large sample.
Methods: Data on patients with stage IV gastric cancer diagnosed between 2010 and 2015 was extracted and divided into CDS and no-CDS groups using the large dataset in the Surveillance, Epidemiology, and End Results (SEER) database. With bias between the two groups minimized by propensity score matching (PSM), the prognostic role of CDS was studied by the Cox proportional risk model and Kaplan-Meier.
Results: A total of 6,284 patients with stage IV gastric cancer were included, including 514 patients with CDS who were matched with no-CDS patients according to propensity score (1:1), resulting in the inclusion of 432 patients each in the CDS and no-CDS groups. The results showed that CDS appeared to prolong the median survival time for stage IV gastric cancer (from 6 months to 10 months). Multifactorial analysis showed that poorly differentiated tumors (grades III-IV) significantly affected patient survival, and chemotherapy was a protective prognostic factor.
Conclusion: The findings support that CDS can provide a survival benefit for stage IV gastric cancer. However, a combination of age, underlying physical status, tumor histology, and metastatic status should be considered when making decisions about CDS, which will aid in clinical decision-making.

KEYWORDS
gastric cancer, stage IV, cancer-directed surgery, overall survival rate, SEER

Introduction

Gastric cancer (GC) is a major malignancy worldwide, ranking fifth in terms of incidence and fourth in terms of mortality (1). In China, gastric cancer has the second-highest incidence and fatality rates of all malignant tumors (2). According to the bulk of gastric cancer cases, progressive gastric cancer accounts for more than

90%, of which unresectable gastric cancer accounts for about 10% (3). By combining surgery, radiotherapy, and adjuvant chemotherapy, the 5-year survival rate for early stomach cancer can reach 95%. However, according to statistics, the 5-year survival rate for progressive gastric cancer is still less than 50%, and between 80% and 90% of gastric cancers develop into advanced stages and become incurable or recur within 5 years following surgery (4). Due to the insidious nature of gastric cancer and the invasive biological properties of cancer, the majority of patients have distant metastasis by the time they are detected. According to the AJCC cancer staging criteria, stage IV gastric cancer is classified as locally progressive gastric cancer that invades adjacent organs or gastric cancer with distant metastases (5). Traditionally, this category of patients was believed to be incurable, and therapy consisted primarily of a combination of palliative medications. The National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) guidelines for the treatment of advanced gastric cancer both advocate chemotherapy or combination therapy for advanced gastric cancer (6, 7). Additionally, the Japanese guidelines encourage the use of chemotherapy or combination therapy. Also in the Japanese guidelines, surgery is specifically mentioned as a palliative treatment aimed at managing symptoms such as obstruction and bleeding (8). In addition, stenting, radiotherapy, and symptomatic treatment should also be considered (9). Surgical resection for the benefit of patients is becoming achievable with the advancement of surgical procedures and mastery of laparoscopic techniques. Several studies have demonstrated that surgery can be conducted more safely, with a lower surgical risk, and may result in an increase in survival (10–13). Nevertheless, the decision to undergo cancer-directed surgery (CDS) for patients with advanced tumors is sometimes based on the surgeon's own choice (14). Although standard recommendations do not support the surgical excision of stage IV gastric cancer, in patients with advanced gastric cancer who underwent combined gastrectomy and hepatectomy, the median overall survival (OS) for the liver was 21 months, as reported in a systematic review, suggesting that surgical resection is beneficial in these patients (15). Eight studies compared surgical resection with other palliative treatments. Subgroup analysis found that patients who underwent liver resection had improved survival and a 20% lower risk of overtime death. To some extent, this also clarifies the potential beneficial role of surgery in the treatment of patients with metastatic gastric cancer (16). In the case of liver metastases from gastric cancer, C-GCLM staging type I and some type II are feasible for comprehensive surgery-centered treatment, and it is noted that resection of the primary site and metastases can increase the overall 5-year survival rate of patients with liver metastases from gastric cancer to more than 20% under strict screening of the patient population (17). Yu et al. (18) conducted a retrospective analysis of the treatment of 132 patients with concurrent liver metastases. The results showed that R0 resection significantly prolonged survival time (33.6 months vs. 12 months). (33.6 months vs. 12.4 months, $P < 0.001$). Yu et al. (19) showed that the prognosis of the group receiving systemic therapy + resection was better than that of the palliative chemotherapy group (21.1 months vs. 10.8 months, $P = 0.002$) in the treatment of peritoneal metastases from gastric cancer with a primary exploration PCI < 20, and found that patients with a secondary laparoscopic exploration PCI < 6 after systemic therapy had a better prognosis. In summary, many studies have indicated that CDS is most advantageous for patients with stage IV gastric cancer who have received translational therapy (systemic chemotherapy and local radiotherapy). The selection of patients for surgery after chemotherapy for stage IV gastric cancer depends largely on the degree of response to chemotherapy, and a good response to chemotherapy and the ability to achieve R0 resection are the most important screening indicators for surgical treatment. Therefore, some advanced gastric cancers still have certain surgical value, and actively choosing the appropriate timing and surgical method can help prolong survival and improve prognosis. As a result, our work was confirmed further by extracting large-sample, multicenter data from the SEER database, which revealed a correlation between CDS and increased overall survival in patients with stage IV gastric cancer. However, due to the fact that CDS is not a guideline-recommended standard of care, surgeons' decisions to perform surgery are highly selective. This potential results in a non-random bias in overall survival for patients who produce CDS compared to those who do not. This raises many critical difficulties. First, there is a dearth of research regarding the longevity of individuals with stage IV gastric cancer following surgical resection. Second, there is a dearth of medical evidence or appropriate criteria to assist surgeons in identifying individuals who are candidates for surgical resection. The ability of surgical resection to provide a survival benefit to patients has not been well studied. To address this uncertainty, based on the SEER database, this study controls for potential confounders by using propensity score matching (PSM) to verify whether there is an improvement in survival in patients with stage IV gastric cancer treated with CDS. PSM was combined with other prognostic factor indicators to provide a more reliable estimate of survival for CDS patients and ultimately guide clinical decision-making.

Patients and methods

Patients

Between 2010 and 2015, data on patients with stage IV gastric cancer were extracted from the SEER database. The following criteria were used to determine inclusion and exclusion: (1) patients with pathological histologically confirmed primary gastric adenocarcinoma and tumor M stage M1; (2) demographic information including age, race, gender, and marital status included; (3) clinicopathological information including primary site, differentiation level, T stage, and N stage included. (4) Patients with incomplete demographic and clinicopathological information were excluded. The final 6,284 patients diagnosed with stage IV gastric cancer were included in this research, and the patients were divided into those with cancer treated with CDS (CDS group) and those not treated with CDS (no-CDS group), including 514 patients with CDS who were propensity score-matched (1:1) to those with no-CDS, and 432 patients each in the CDS and no-CDS groups were finally included. This was ultimately used to gather evidence for the benefit of CDS for stage IV gastric cancer.

Data collection

Parameters such as age, race, gender, marital status, tumor primary site, differentiation grade, T stage, N stage, chemotherapy, and overall survival were selected for this study, and due to the fact that the SEER database no longer contains information on tumor T stage, tumor N stage, or chemotherapy after 2015, we only selected data before 2015.

Statistical analysis

Propensity score matching (PSM)

Subjects were matched by propensity score (1:1), a process that reduces selective bias for specific patients treated with CDS, and then compared survival outcomes for patients in the matched CDS and no-CDS groups. Notably, validation of PSM was achieved by comparing each observed variable in the CDS and no-CDS groups before and after PSM. $\chi 2$ test was used to compare categorical variables, while the unpaired Student's t-test was used to compare continuous variables.

Survival analysis

The study was statistically analyzed using R software (version 4.1.2). A P value of 0.05 was considered statistically significant. The log-rank test was used to compare the median survival rates of CDS groups. The Kaplan-Meier method was used to calculate overall survival. Models were also screened automatically using a stepwise method and AIC (Akaike Information Criterion) was calculated for each generated model, AIC values were used to select the 95% confidence set, which may contain the best approximation model for all the data considered. Moreover, we averaged hazard ratio estimates for CDS and other predictors at 95% confidence intervals, which were used to infer prognostic factors for survival.

Results

Baseline characteristics of study subjects and propensity score matching

A total of 6,284 patients with stage IV gastric cancer were included, of whom 514 received CDS and 5,770 did not. The most common tumor primary sites were cardia and fundus (27.2% in the CDS group and 47.8% in the no-CDS group), the most common differentiation grade was grade III (69.1% in the CDS group and 52.8% in the no-CDS group), the most common T stage was T1 (9.3% in the CDS group and 20.5% in the no-CDS group), and the most common N stage was N1 (27.2% in the CDS group and 37.9% in the no-CDS group), respectively. For the clinical characteristics of stage IV gastric cancer patients such as age, race, gender, and marital status, age was concentrated above 65 years (51.9% in the CDS group and 56.2% in the no-CDS group), males were higher than females (67.9% in the CDS group and 70.1% in the no-CDS group), racial groups were more common in whites (60.9% in the CDS group and 57.6% in the no-CDS group), and marital status was mostly seen in married (66.3% in the CDS group, 75.0% in the no-CDS group). In addition, the CDS group had a considerably longer mean survival duration than the no-CDS group (16 months in the CDS group, 8.64 months in the no-CDS group) (**Table 1**).

After matching patients in the CDS and no-CDS groups 1:1, there were 432 patients in each of the two groups, with $P > 0.05$ for each variable after propensity score matching (**Table 2**, **Figure 1**). Prior to PSM, the data showed significant differences in baseline characteristics between the CDS and no-CDS groups for various variable parameters. After PSM, there were no significant differences between the two groups on multiple variables (**Table 2**).

Survival outcome after propensity score matching

As shown in **Figures 2**, **3A**, comparing the two groups after PSM (432 patients each), the median survival was higher in CDS patients (8–11 months) than in non-CDS patients (5–7 months). In addition, the 12-month predicted survival rate was 1.47 times higher for CDS patients than for non-CDS patients (CDS [95CI]: 0.358–0.451; non-CDS [95CI]: 0.2337–0.3191), and the 24-month predicted survival rate was 2.17 times higher for CDS patients than for non-CDS patients

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TABLE 1 Baseline characteristics before propensity matching scores, showing statistical comparisons between the CDS and no-CDS groups.

	CDS (N = 514)	No-CDS (N = 5770)	Overall (N = 6284)	χ^2	p
Age				3.521	0.172
≤49	61 (11.9%)	644 (11.2%)	705 (11.2%)		
50-64	186 (36.2%)	1,884 (32.7%)	2,070 (32.9%)		
≥65	267 (51.9%)	3,242 (56.2%)	3,509 (55.8%)		
Sex				0.972	0.324
Female	165 (32.1%)	1,726 (29.9%)	1,891 (30.1%)		
Male	349 (67.9%)	4,044 (70.1%)	4,393 (69.9%)		
Race				26.668	<0.001
White	341 (66.3%)	4,326 (75.0%)	4,667 (74.3%)		
Black	71 (13.8%)	739 (12.8%)	810 (12.9%)		
Other	100 (19.5%)	687 (11.9%)	787 (12.5%)		
Unknown	2 (0.4%)	18 (0.3%)	20 (0.3%)		
Marital status				6.569	0.161
Divorced	41 (8.0%)	503 (8.7%)	544 (8.7%)		
Married	313 (60.9%)	3,322 (57.6%)	3,635 (57.8%)		
Single	61 (11.9%)	893 (15.5%)	954 (15.2%)		
Widowed	59 (11.5%)	680 (11.8%)	739 (11.8%)		
Unknown	40 (7.8%)	372 (6.4%)	412 (6.6%)		
Primary Site				148.950	<0.001
Body of stomach	40 (7.8%)	488 (8.5%)	528 (8.4%)		
Overlapping lesion of stomach	48 (9.3%)	378 (6.6%)	426 (6.8%)		
Stomach	75 (14.6%)	953 (16.5%)	1,028 (16.4%)		
Cardia and fundus of stomach	140 (27.2%)	2,756 (47.8%)	2,896 (46.1%)		
Gastric antrum and pylorus	149 (29.0%)	730 (12.7%)	879 (14.0%)		
Greater and lesser curvature	62 (12.1%)	465 (8.1%)	527 (8.4%)		
Grade				69.774	<0.001
Grade I	4 (0.8%)	125 (2.2%)	129 (2.1%)		
Grade II	128 (24.9%)	1,342 (23.3%)	1,470 (23.4%)		
Grade III	318 (61.9%)	3,046 (52.8%)	3,364 (53.5%)		
Grade IV	17 (3.3%)	52 (0.9%)	69 (1.1%)		
Unknown	47 (9.1%)	1,205 (20.9%)	1,252 (19.9%)		
T				543.500	<0.001
T0	0 (0%)	33 (0.6%)	33 (0.5%)		
T1	48 (9.3%)	1,185 (20.5%)	1,233 (19.6%)		
T2	28 (5.4%)	174 (3.0%)	202 (3.2%)		
T3	173 (33.7%)	730 (12.7%)	903 (14.4%)		
T4	216 (42.0%)	866 (15.0%)	1,082 (17.2%)		
Tx	49 (9.5%)	2,782 (48.2%)	2,831 (45.1%)		
N				849.840	<0.001
N0	101 (19.6%)	2,036 (35.3%)	2,137 (34.0%)		
N1	140 (27.2%)	2,189 (37.9%)	2,329 (37.1%)		
N2	110 (21.4%)	258 (4.5%)	368 (5.9%)		
N3	134 (26.1%)	170 (2.9%)	304 (4.8%)		
Nx	29 (5.6%)	1,117 (19.4%)	1,146 (18.2%)		
Chemotherapy				0.429	0.512
No	221 (43.0%)	2,389 (41.4%)	2,610 (41.5%)		

(*continued*)

TABLE 1 Continued

	CDS ($N = 514$)	No-CDS ($N = 5770$)	Overall ($N = 6284$)	χ^2	p
Yes	293 (57.0%)	3,381 (58.6%)	3,674 (58.5%)		
Survival months					
Mean (SD)	16.0 (19.4)	8.64 (12.6)	-	329.13	<0.001
Median [Min, Max]	9.00 [0, 103]	4.00 [0, 107]	-		

(CDS [95CI]: 0.189–0.269 CDS [95CI]: 0. 0786–0.1381), and the 36-month predicted survival rate for CDS patients was 2.44 times that of non-CDS patients (CDS [95CI]: 0.124–0.193; non-CDS [95CI]: 0.0437–0.0923) (**Figure 3A**). there was a significant improvement in survival for CDS patients (mean survival in the CDS group survival was 16.7 months in the CDS group and 10.6 months in the non-CDS group) (**Table 2**). A relatively close model (AIC = 9147.59) was finally identified using a stepwise method to automatically screen the model. This model suggested that factors that could predict survival included (1) age, (2) race, (3) grade of differentiation, (4) tumor T stage, (5) chemotherapy, and (6) CDS (**Table 3**).

In addition, we finally obtained risk ratio estimates for each factor in the model by calculating the estimates for each model that was in the mean confidence set. The results showed that CDS was a factor of significant value in the model (**Table 3**). Additionally, our findings indicated that patients with CDS had a greater survival rate than those without (**Figure 4**), and among the other factors analyzed, receiving chemotherapy also significantly improved the survival rate of patients with advanced gastric cancer, and tumor hypofractionation (grade III-IV) similarly affected the survival rate of patients (**Table 3**, **Figures 3B–E**, **4**). It is worth mentioning that race, age, and tumor T-stage were also included in this model, but did not seem to be more significant in terms of predictive accuracy than CDS, chemotherapy, and differentiation grade.

Discussion

This study could show by comparing matched cohorts in the SEER database that overall survival was significantly longer in patients with stage IV gastric cancer treated with CDS than in those not treated with CDS. The analysis also showed that chemotherapy and the degree of tumor differentiation were meaningful prognostic indicators. These results suggest that CDS is most effective in treating patients with stage IV gastric cancer who have received chemotherapy and have a good degree of tumor differentiation. However, CDS may also provide meaningful survival improvement for patients with a poor prognosis. Therefore, age, underlying physical condition, tumor histology, and metastatic status, all of these conditions should be taken into consideration in clinical practice.

GC has a high incidence, insidious onset, and lacks obvious or characteristic clinical manifestations in early stages. In China, the detection rate of early gastric cancer is much lower than that of Japan and Korea due to the lack of popularity of gastroscopy, which results in most patients being diagnosed with gastric cancer at progressive or advanced stages (stage IV). Early or progressive gastric cancer can be treated surgically with R0 resection and associated site lymph node dissection to achieve a relatively good prognosis. However, for patients with stage IV gastric cancer, the 5-year survival rate is only 4% (5). According to a Japanese survey, the 5-year survival rate of stage IV gastric cancer can be increased to 16.4% by surgical resection or chemotherapy interventions (20). Therefore, it is critical to study how surgical resection affects the survival and prognosis of patients with stage IV gastric cancer and to develop a more systematic and beneficial treatment plan.

In conventional wisdom, numerous researchers feel that surgical excision of stage IV gastric cancer does not improve overall survival. Because advanced gastric cancer is inherently more difficult to resect surgically than early or progressive gastric cancer, and because surgery is more time-consuming and cancer patients are in long-term negative nitrogen balance, the benefit of surgery in the treatment of stage IV gastric cancer is not clear. Based on the MAGIC and FNCLCC/FFCD9703 studies, in the majority of European countries, chemotherapy is the conventional treatment technique for progressive gastric cancer (21). The REGATTA study further rejected the use of palliative surgery in the initial treatment of advanced gastric cancer (22). AL-BATRAN et al. (23) advocated that chemotherapy before considering surgery might benefit patient survival. The three major guidelines of NCCN, ESMO, and JGCA also recommend unless serious complications such as bleeding and obstruction occur, which seriously threaten patients' lives. Because the probability of intraoperative and postoperative complications is higher than that of conventional surgery in general, and resection does not significantly prolong patient survival, but rather affects the subsequent quality of life, Fujitani et al. concluded that non-radical surgery decreases chemotherapy adherence without any prognostic benefit (22).

TABLE 2 Baseline characteristics after propensity matching scores, showing statistical comparisons between the CDS and no-CDS groups.

	CDS ($N = 432$)	No-CDS ($N = 432$)	Overall ($N = 864$)	χ^2	p
Age				3.119	0.210
≤49	50 (11.6%)	35 (8.1%)	85 (9.8%)		
50–64	153 (35.4%)	165 (38.2%)	318 (36.8%)		
≥65	229 (53.0%)	232 (53.7%)	461 (53.4%)		
Sex				0.551	0.458
Female	135 (31.3%)	124 (28.7%)	259 (30.0%)		
Male	297 (68.8%)	308 (71.3%)	605 (70.0%)		
Race				1.443	0.696
White	295 (68.3%)	311 (72.0%)	606 (70.1%)		
Black	59 (13.7%)	51 (11.8%)	110 (12.7%)		
Other	77 (17.8%)	69 (16.0%)	146 (16.9%)		
Unknown	1 (0.2%)	1 (0.2%)	2 (0.2%)		
Marital status				2.566	0.633
Divorced	31 (7.2%)	31 (7.2%)	62 (7.2%)		
Married	262 (60.6%)	266 (61.6%)	528 (61.1%)		
Single	57 (13.2%)	43 (10.0%)	100 (11.6%)		
Widowed	48 (11.1%)	54 (12.5%)	102 (11.8%)		
Unknown	34 (7.9%)	38 (8.8%)	72 (8.3%)		
Primary Site				2.975	0.704
Body of stomach	36 (8.3%)	28 (6.5%)	64 (7.4%)		
Overlapping lesion of stomach	39 (9.0%)	36 (8.3%)	75 (8.7%)		
Stomach, NOS	65 (15.0%)	72 (16.7%)	137 (15.9%)		
Cardia and fundus of stomach	139 (32.2%)	151 (35.0%)	290 (33.6%)		
Gastric antrum and pylorus	97 (22.5%)	99 (22.9%)	196 (22.7%)		
Greater and lesser curvature	56 (13.0%)	46 (10.6%)	102 (11.8%)		
Grade				2.969	0.563
Grade I	4 (0.9%)	2 (0.5%)	6 (0.7%)		
Grade II	116 (26.9%)	105 (24.3%)	221 (25.6%)		
Grade III	259 (60.0%)	258 (59.7%)	517 (59.8%)		
Grade IV	6 (1.4%)	9 (2.1%)	15 (1.7%)		
Unknown	47 (10.9%)	58 (13.4%)	105 (12.2%)		
T				4.818	0.307
T1	48 (11.1%)	50 (11.6%)	98 (11.3%)		
T2	28 (6.5%)	24 (5.6%)	52 (6.0%)		
T3	144 (33.3%)	165 (38.2%)	309 (35.8%)		
T4	163 (37.7%)	136 (31.5%)	299 (34.6%)		
Tx	49 (11.3%)	57 (13.2%)	106 (12.3%)		
N				4.524	0.340
N0	101 (23.4%)	78 (18.1%)	179 (20.7%)		
N1	140 (32.4%)	155 (35.9%)	295 (34.1%)		
N2	88 (20.4%)	84 (19.4%)	172 (19.9%)		
N3	74 (17.1%)	81 (18.8%)	155 (17.9%)		
Nx	29 (6.7%)	34 (7.9%)	63 (7.3%)		
Chemotherapy				3.351	0.067
No	174 (40.3%)	147 (34.0%)	321 (37.2%)		
Yes	258 (59.7%)	285 (66.0%)	543 (62.8%)		

(*continued*)

TABLE 2 Continued

	CDS ($N = 432$)	No-CDS ($N = 432$)	Overall ($N = 864$)	χ^2	p
Survival months					
Mean (SD)	16.7 (19.7)	10.6 (15.2)		102.65	<0.001
Median [Min, Max]	10.0 [0, 103]	5.00 [0, 103]			

On the contrary, in recent years, palliative primary resection for stage IV gastric cancer has gradually become a consensus, especially for younger patients with more differentiated tumor cells and lower tumor grade. Patients with stage IV gastric cancer benefit from palliative surgical resection (24–27). Min et al. (28) concluded that in patients with stage IV gastric cancer, radical gastrectomy may be an option. In certain patients with stage IV gastric cancer, laparoscopic gastrectomy is safe and viable. Sun et al. (13) conducted a Meta-analysis of 14 publications containing 3,003 cases and found that palliative resection in patients with stage IV gastric cancer where radical resection was not possible improved long-term survival, especially in stage M1 gastric cancer. A multi-institutional analysis in China suggested that patients with progressing gastric cancer may benefit from radical surgical resection (29). In addition, surgical resection may reduce some acute complications during chemotherapy, such as bleeding, obstruction, and carcinoid syndrome. These acute complications also require urgent surgical treatment when they occur. However, without adequate preoperative preparation, the incidence of postoperative complications will increase, which in turn will reduce the quality of patients' survival after surgery and even accelerate their death. For early-stage gastric cancer and progressive gastric cancer, R0 resection can often be achieved through surgical resection, i.e., "no evidence of disease (NED")," is the principle of GC surgical treatment. However, whether the patient can be safely transitioned and whether the primary tumor can meet the criteria of R0 resection at the time of surgical resection is an issue that should be carefully considered by the surgeons before surgery (30). Seo et al. showed the benefit of surgery, with median survival times of 41.3 months and 21.2 months in patients undergoing translational surgery after chemotherapy for R0 and R1–2 resections, respectively (31). These data imply that R status may have an effect on the prognosis of stage IV gastric cancer patients undergoing conversion surgery. Overall survival was considerably longer in the CDS group than in the no-CDS group for patients with stage IV gastric cancer, which was also better validated in the matched cohort in the SEER database. In addition, differentiation grade and chemotherapy were meaningful prognostic factors. In this study, the findings showed that CDS was most effective when patients received chemotherapy and had well-differentiated tumors.

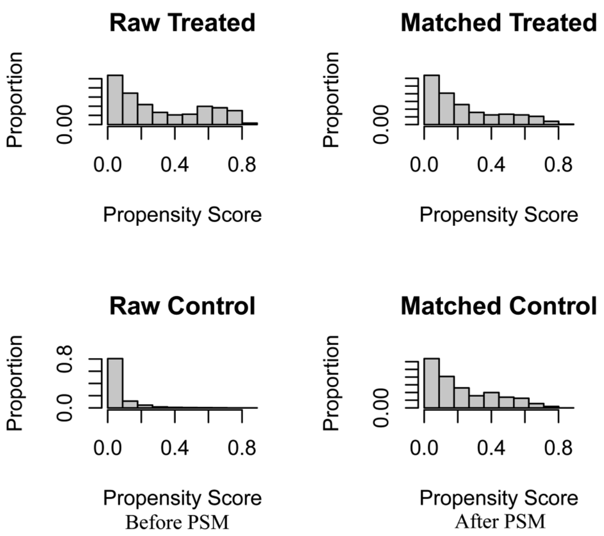

FIGURE 1
Before and after changes in propensity score matching between the CDS and No-CDS groups. CDS: cancer-directed surgery, PSM: propensity score matching.

We believe that the improvement in overall survival of patients with stage IV gastric cancer following surgical resection is due to several factors: first, surgical resection reduces the tumor burden and restores some immune capacity to the patient, even in metastatic lesions (32). Second, after tumor resection, chemotherapy is more effective in people with stage IV gastric cancer following surgery, resulting in improved survival rates. Finally, in patients with stage IV gastric cancer, surgical resection decreases the probability of acute complications such as bleeding, blockage, and perforation. It is worth mentioning that an inappropriate surgical approach may accelerate the medical spread of tumors and postoperative recurrence and metastasis (33).

In recent years, an increasing number of scholars have provided new insights. For example, based on the successful practice of conversion therapy in liver metastases from colorectal cancer, conversion therapy has been attempted in stage IV GC (34, 35). The study by Cascinu et al. (36) included 82 patients with stage IV GC, 37 of whom

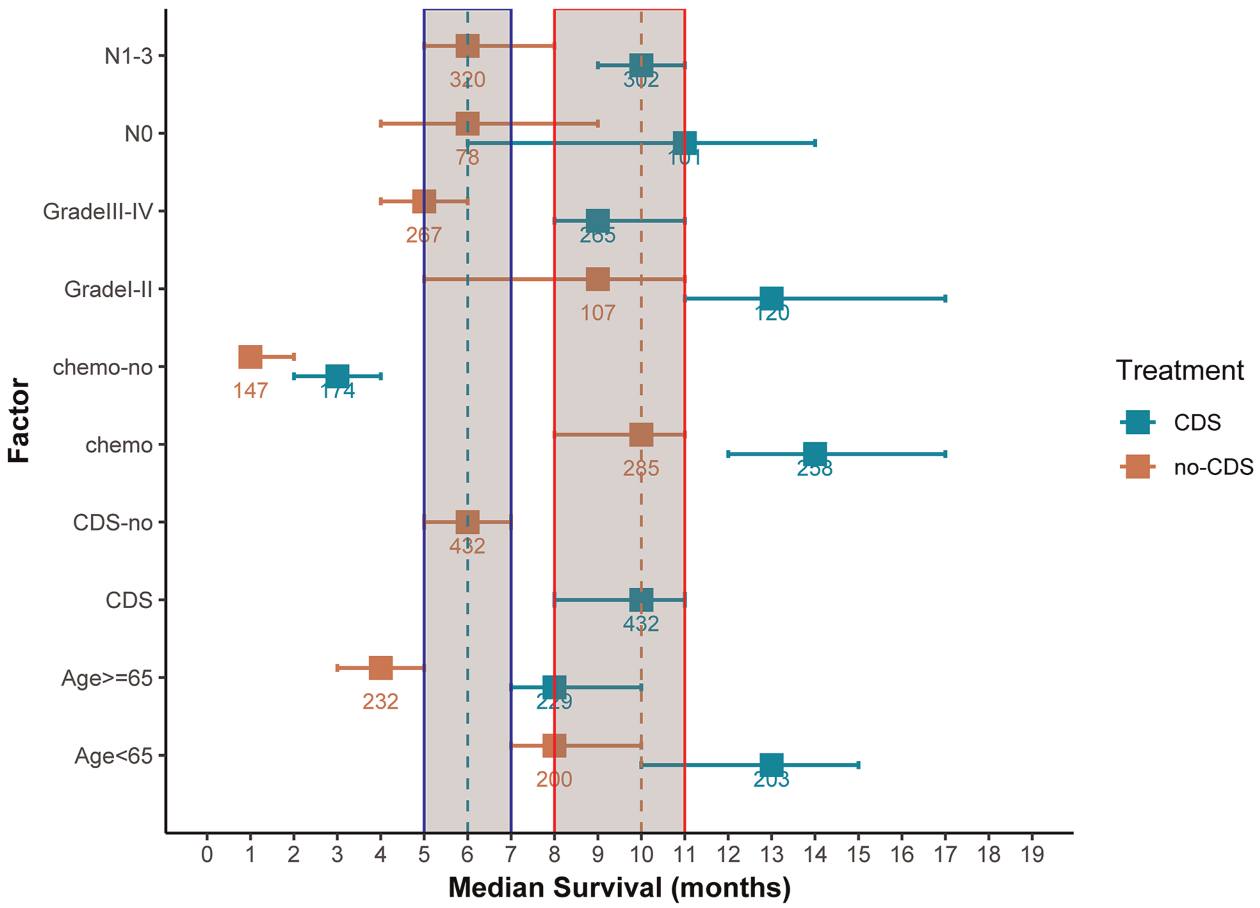

FIGURE 2
Median overall survival (months) ± 95% confidence interval for patients in the CDS and No-CDS groups. The dashed and shaded areas cover the median and confidence intervals for the total sample. Numbers are sample sizes. For ease of reading and understanding, certain factor levels have been removed and results are given for the total sample and for meaningful prognostic factors. CDS: cancer-guided surgery, Grade: tumor differentiation grade, N: tumor stage N, chemo: chemotherapy.

underwent post-transformation surgery, and at the end of the 48-month interim follow-up, the survival rate of the operated patients was 68%, and the median survival was significantly better than that of the non-operated patients. While Yoshida et al. (37) proposed a new idea of Yoshida staging of advanced gastric cancer based on the biological behavior of gastric cancer, scholars tried to explore individualized treatment of gastric cancer patients in terms of molecular staging, multi-omics, and artificial intelligence big data analysis. We believe that surgeons or clinicians should fully consider the complementary nature of surgery and systemic therapy, as well as the combination of surgery and novel adjuvant chemotherapy before making a decision. In addition, the clinical characteristics of patients, tumor biology, and whether or not they receive chemotherapy can affect the overall survival rate.

In conclusion, the treatment of stage IV gastric cancer is a difficult clinical problem. Gastric cancer has multiple metastases, and there are more adjacent organs around the stomach with abundant blood vessels, which undoubtedly adds a higher degree of difficulty to surgical resection. Secondly, there is no unanimous consensus on whether surgical treatment has a clear improvement on the overall survival, survival rate, and quality of life of patients. Thirdly, the tension between doctors and patients makes it necessary for surgeons to be more cautious when choosing surgical treatment. Ultimately, only a fraction of patients were treated with CDS due to subjective or objective factors, while chemotherapy remains the mainstay of stage IV GC for a significant proportion of patients, especially for those with a poor physical foundation, multiple underlying diseases, and advanced age. More randomized controlled studies are still needed to verify which surgeries will be beneficial in the future for patients with stage IV GC.

There are also some obvious limitations and shortcomings in this study: (1) The data analyzed in this study were all derived from the SEER database, i.e., the

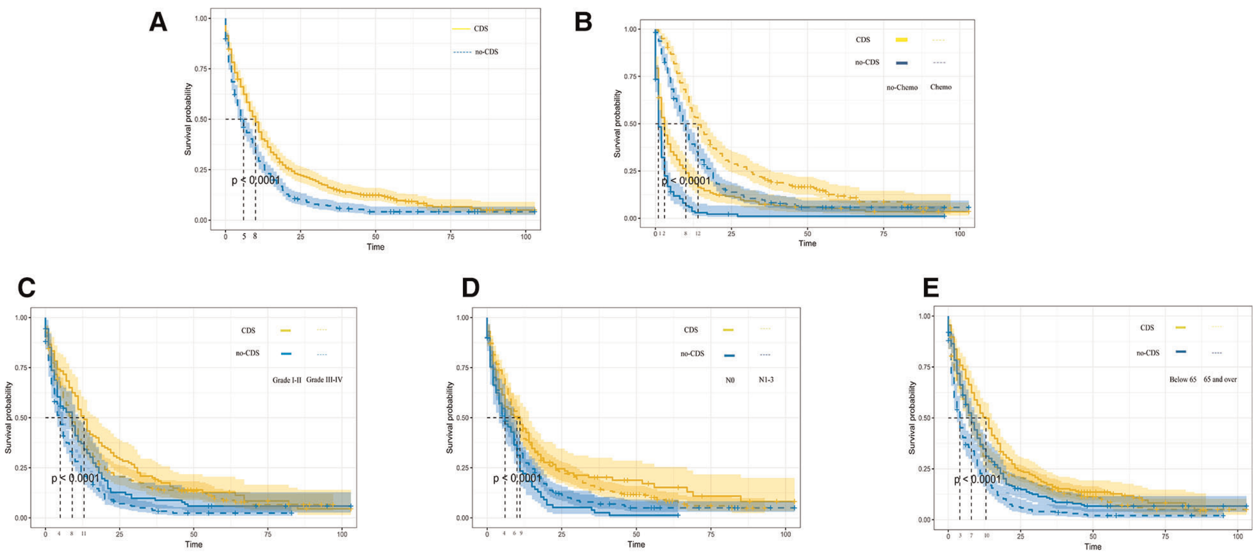

FIGURE 3
Kaplan-Meier overall survival (OS) estimates and 95% confidence intervals for patients in the CDS and no-CDS groups. (A) In the total sample, (B) Chemotherapy, (C) Grade, (D) N-stage, and (E) age. CDS: cancer-guided surgery.

TABLE 3 Stepwise regression analysis method for automated model screening.

	HR	95%CI	*P*
Age			
<65	Reference		
≥65	1.14534	1.01315876–1.2947705	0.069
Race			
Black	Reference		
White	1.15323	0.96327929–1.3806284	0.193
Other	1.06197	0.85117918–1.3249732	0.655
Unknown	0.15777	0.02983461–0.8343466	0.068
Grade			
Grade I-II	Reference		
Grade III-IV	1.42907	1.24228609–1.6439408	<0.001
Unknown	1.21551	0.98108638–1.5059437	0.134
T			
T1	Reference		
T2	0.84571	0.62794846–1.1389890	0.356
T3	0.86839	0.70968537–1.0625911	0.250
T4	1.13828	0.92875278–1.3950809	0.295
Tx/NA	1.34726	1.05125127–1.7266097	0.048
Chemotherapy			
No	Reference		
Yes	0.33161	0.29021219–0.3789054	< 0.001
Surgery			
CDS	Reference		
no-CDS	1.78204	1.57616003–2.0148153	< 0.001

HR, Hazard ratio; CI, Confidence interval.

data resolution was low for clinically significant variables that may be critical to the overall survival of patients with stage IV GC treated with CDS. Moreover, we cannot obtain detailed information about patients from them, such as their underlying disease status, whether they have a family history of tumors, their preoperative or postoperative chemotherapy regimen and chemotherapy cycles, specific surgical procedures, and postoperative quality of life. (2) Usually, in clinical work, patients who choose surgical resection are mostly with less underlying disease and better health status, so there is some selective bias in this study. However, these limitations can only be addressed by the randomized controlled trial method. (3) The SEER database included mainly Americans, while malignant tumors often have racial differences in metastasis and survival in different organs, and whether the study results are applicable to other countries or ethnic groups remains to be studied in depth. (4) This study screened data from 2010 to 2015, but the current international guidelines for stage IV GC are still dominated by chemotherapy, and more in-depth studies are needed in the future to determine whether surgery is appropriate and the survival benefit brought by surgical treatment to patients. Therefore, the results of this study are not representative of survival in all stage IV gastric cancers, and caution is still needed in interpreting these results. However, the SEER database includes a broad population of 30% of the US population, and the results of clinical studies will become increasingly convincing in the future as the included population continues to expand.

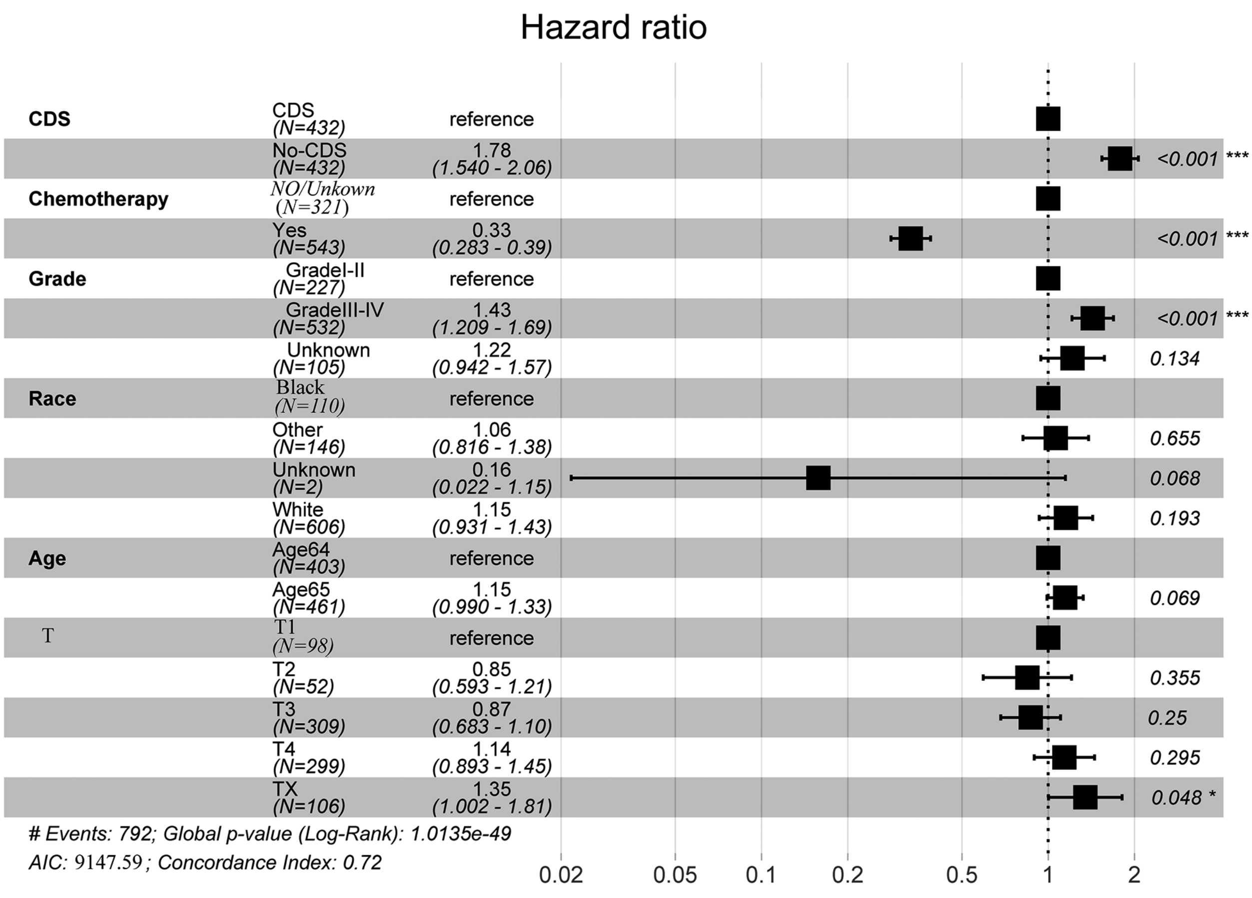

FIGURE 4
Full model average Cox proportional hazard ratios with 95% confidence intervals. There is a dashed line indicating the equivalent hazard ratio (HR = 1) (Table 3).

Conclusion

Although the benefits of CDS in malignancies are well recognized, the value of CDS in stage IV gastric cancer remains highly controversial. Different scholars also hold different attitudes regarding the survival benefit of CDS in patients with stage IV gastric cancer. Our study provides evidence for the possible survival benefit of CDS for patients with stage IV gastric cancer. However, given the aforementioned shortcomings and certain limitations of this paper, it is important to explore the multidisciplinary and multimodal approach of CDS in patients with stage IV gastric cancer and to combine it with radiotherapy, chemotherapy, targeted drugs, and immunotherapy to develop a personalized treatment plan based on precise classification in order to possibly help patients with advanced gastric cancer to obtain the maximum survival and quality of life. In the future, large sample, multicenter randomized controlled trials and evidence-based medical studies are still needed to validate and ultimately help clinical decision making.

Data availability statement

The SEER Dataset Repository (https://seer.cancer.gov/) contains datasets from the SEER database that were created and/or processed for this study currently available.

Ethics statement

The data for this research was obtained from public databases and no ethical approval was required.

Author contributions

JS: study protocol design, data compilation, statistical analysis, and paper writing. QN: research supervision, thesis revision. 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/fsurg.2022.927030/full#supplementary-material.

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Development and validation of a nomogram for patients with stage II/III gastric adenocarcinoma after radical surgery

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Background: We aimed to construct nomograms based on clinicopathological features and routine preoperative hematological indices to predict cancer-specific survival (CSS) and disease-free survival (DFS) in patients with stage II/III gastric adenocarcinoma (GA) after radical resection.

Methods: We retrospectively analyzed 468 patients with stage II/III GA after curative gastrectomy between 2012 and 2018; 70% of the patients were randomly assigned to the training set ($n = 327$) and the rest were assigned to the validation set ($n = 141$). The nomogram was constructed from independent predictors derived from the Cox regression in the training set. Using the consistency index, the calibration and the time-dependent receiver operating characteristic curves were used to evaluate the accuracy of the nomogram. Decision curve analysis was used to assess the value of the model in clinical applications. Patients were further divided into low- and high-risk groups based on the nomogram risk score.

Results: Multivariate Cox model identified depth of invasion, lymph node invasion, tumor differentiation, adjuvant chemotherapy, CA724, and platelet-albumin ratio as covariates associated with CSS and DFS. CA199 is a risk factor unique to CSS. The nomogram constructed using the results of the multivariate analysis showed high accuracy with a consistency index of 0.771 (CSS) and 0.771 (DFS). Moreover, the area under the curve values for the 3- and 5-year CSS were 0.868 and 0.918, and the corresponding values for DFS were 0.872 and 0.919, respectively. The nomogram had a greater clinical benefit than the TNM staging system. High-risk patients based on the nomogram had a worse prognosis than low-risk patients.

Conclusion: The prognostic nomogram for patients with stage II/III GA after radical gastrectomy established in this study has a good predictive ability, which is helpful for doctors to accurately evaluate the prognosis of patients to make more reasonable treatment plans.

KEYWORDS

nomogram, gastric adenocarcinoma, decision curve analysis, prognosis, survival, plateletalbumin ratio

Introduction

Gastric adenocarcinoma (GA), which accounts for 95% of gastric malignancies, is the fifth most common cancer and a major global health challenge (1). GA usually originates from the lining of the stomach, and its early symptoms are not obvious; therefore, many patients with GA are not diagnosed until the metastatic or advanced stage (2). Radical surgery with subsequent adjuvant chemotherapy is the main treatment for early stage GA; however, the overall survival rate remains poor due to the high frequency of metastasis and recurrence (3). Therefore, there is an urgent need to individually analyze independent risk factors and establish novel predictive models that can accurately identify high-risk patients with GA.

Multiple studies have shown that nutritional factors, inflammation, and coagulation are associated with cancer patient outcomes, including GA (4–6). Systemic inflammation and immune evasion are the cardinal features of malignancy, and various inflammatory factors contribute to tumor progression. Interestingly, in addition to neutrophils and lymphocytes, recent studies have revealed that platelets are potent immune modulators and effectors, including direct identification and elimination of pathogens or enhancement of leukocyte immunity, in addition to their central role in hemostasis (7). Additionally, nutritional status is also a critical part of cancer management, especially in gastrointestinal tumors with high prevalence of malnutrition (8). Feng et al. reported that lower preoperative serum albumin levels are associated with unfavorable prognosis in patients with gastric cancer (9). Furthermore, patients with cancer often have abnormal coagulation, which is closely related to tumor progression (10). Several peripheral blood markers have been shown to correlate with cancer prognosis, including the platelet-albumin ratio (PAR), platelet-lymphocyte ratio (PLR), albumin-fibrinogen ratio (AFR), lymphocyte-monocyte ratio (LMR), neutrophil-lymphocyte ratio (NLR), aspartate aminotransferase-alanine aminotransferase ratio (SLR), and D-dimer (9, 11). These indicators can directly reflect inflammation, nutritional level, liver function, and coagulation in patients with cancer. In addition, some classic tumor markers, including carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and CA72-4, are widely used for prognostication of cancer patients (12). The hematological indicators mentioned above from routine testing are economical and readily available; therefore, we selected these indicators for evaluation as potential predictive factors.

The nomogram can visualize and integrate independent predictors, realize individualized prognostic assessment, and improve accuracy, and has been studied and applied to multiple cancer types (13, 14). In this study, we attempted to combine clinicopathological characteristics and preoperative routine laboratory indicators to construct and verify a nomogram for patients with stage II/III GA after radical surgery. This personalized prediction system can facilitate clinicians in identifying high-risk patients to develop more personalized treatments.

Materials and methods

Patients and data collection

We retrospectively collected the data of 468 patients with stage II/III GA who underwent radical gastrectomy at the First Affiliated Hospital of Zhengzhou University between May 2012 and May 2018. Seventy percent of the patients were randomly selected as the training set ($n = 327$), and the rest were assigned to the validation set ($n = 141$). The inclusion criteria were as follows: (1) histologically confirmed stage II/III GA; (2) R0 resection; (3) no antitumor therapy before surgery; (4) complete clinicopathological and follow-up data, and all hematological parameters to be assessed should be measured within 1 week before surgery; (5) no other malignancies; (6) no parenteral nutrition, acute inflammation, or significant organ damage within 1 week before surgery; and (7) no cause of death other than GA.

Widely accepted thresholds for grouping continuous variables: D-Dimer (0.3 mg/L), CA199 (35 U/ml), CA724 (6.9 U/ml), and CEA (5 U/ml). The optimal cutoff values for age (68), tumor size (3.5 cm), PAR (6.4), AFR (9.7), NLR (2.3), LMR (3.1), SLR (1.8), and PLR (202.9) were determined using X-tile (15) analysis because of the lack of a defined threshold. Studies involving human participants were reviewed and approved by the Medical Ethics Committee of the First Affiliated Hospital of Zhengzhou University. According to the Declaration of Helsinki, patient data were anonymized and kept confidential. Due to the retrospective nature of this study, informed consent was not obtained.

Follow-up and outcome

Follow-up was done *via* different methods such as medical records and telephone surveys. Patients were observed after curative gastrectomy every 3 months during the first year, every 6 months for 2–3 years, and annually thereafter for up to 5 years post-surgery. Each follow-up included physical examination, laboratory testing, electronic gastroscopy, as clinically indicated, and chest/abdomen/pelvic enhanced computed tomography. The primary endpoint of this study was cancer-specific survival (CSS), which was defined as the time from the date of surgery to cancer-related death. Disease-free survival (DFS) was defined as the time from curative surgery to death, recurrence, or the final follow-up.

TABLE 1 Baseline characteristics of patients in the training and validation cohorts.

Variables	NO. (%) Training Cohort ($n = 327$)	NO. (%) Validation Cohort ($n = 141$)	X^2	*P*
Sex			0.5	0.480
Male	240 (73.4)	99 (70.2)		
Female	87 (26.6)	42 (29.8)		
Age, years			3.754	0.053
≤68	263 (80.4)	102 (72.3%)		
>68	64 (19.6)	39 (27.7)		
Family history			0.41	0.522
No	268 (82.0)	119 (84.5)		
Yes	59 (18.0)	22 (15.5)		
Diabetes			0.653	0.419
No	312 (95.4)	132 (93.6)		
Yes	15 (4.6)	9 (6.4)		
Hypertension			0.044	0.843
No	264 (80.7)	115 (81.6)		
Yes	63 (19.3)	26 (18.4)		
Tobacco			0.076	0.783
No	236 (72.2)	100 (70.9)		
Yes	91 (27.8)	41 (29.1)		
Alcohol			0.217	0.641
No	263 (80.4)	116 (82.3)		
Yes	64 (19.6)	25 (17.7)		
Depth of invasion			2.041	0.153
T1-2	80 (24.5)	26 (18.4)		
T3-4	247 (75.5)	115 (81.6)		
Lymph node invasion			0.126	0.722
N0	83 (25.4)	38 (27.0)		
N1-3	244 (74.6)	103 (73.0)		
TNM stage			0.066	0.798
II	113 (34.6)	47 (33.3)		
III	214 (65.4)	94 (66.7)		
Tumor differentiation			0.661	0.416
Middle or high	70 (21.4)	35 (24.8)		
low	257 (78.6)	106 (75.2)		
Size, cm			0.247	0.619
≤3.5	105 (32.1)	42 (29.8)		
>3.5	222 (67.9)	99 (70.2)		
Tumor location			4.5	0.104
Upper 1/3	166 (50.8)	75 (53.2)		
Middle 1/3	73 (22.3)	20 (14.2)		
Lower 1/3	88 (26.9)	46 (32.6)		

(*continued*)

TABLE 1 Continued

Variables	NO. (%) Training Cohort ($n = 327$)	NO. (%) Validation Cohort ($n = 141$)	X^2	*P*
Adjuvant chemotherapy			0.002	0.962
No	143 (43.7)	62 (44.0)		
Yes	184 (56.3)	79 (56.0)		
CA199, U/ml			0.306	0.580
≤35	257 (78.6)	114 (80.9)		
>35	70 (21.4)	27 (19.1)		
CA724, U/ml			0.017	0.898
≤6.9	251 (76.8)	109 (77.3)		
>6.9	76 (23.2)	32 (22.7)		
CEA, U/ml			0.229	0.632
≤5	257 (78.6)	108 (76.6)		
>5	70 (21.4)	33 (23.4)		
D-Dimer, mg/l			0.065	0.798
≤0.3	238 (74.3)	101 (71.6)		
>0.3	89 (27.2)	40 (28.4)		
PLR			0.514	0.473
≤202.9	245 (74.9)	110 (78.0)		
>202.9	82 (25.1)	31 (22.0)		
PAR			1.515	0.218
≤6.4	177 (54.1)	85 (60.3)		
>6.4	150 (45.9)	56 (39.7)		
AFR			0.181	0.671
<9.7	49 (15.0)	19 (13.5)		
≥9.7	278 (85.0)	122 (86.5)		
NLR			0.224	0.636
≤2.3	184 (56.3)	76 (53.9)		
>2.3	143 (43.7)	65 (46.1)		
LMR			0.061	0.805
<3.1	119 (36.4)	53 (37.6)		
≥3.1	208 (63.6)	88 (62.4)		
SLR			0.119	0.731
≤1.8	280 (85.6)	119 (84.4)		
>1.8	47 (14.4)	22 (15.6)		

Statistical analysis

Statistical analysis was performed using SPSS Statistics (version 26.0, IBM, USA) and R software (version 4.1.2). The optimal cut-off value was determined using X-tile software. The continuous variables were transformed into categorical variables. The chi-square test was used to compare categorical data. Statistical significance was set at $P < 0.05$. For continuous variables, the Kolmogorov–Smirnov test was first performed. If an approximately normal distribution was displayed, the data were described using the mean and standard deviation. Otherwise, the median with the interquartile range (IQR) was used. First, the proportional hazards hypothesis test was performed using the Cox regression model. If the hypothesis was not satisfied, a Cox regression model with time-dependent covariates was used (16). Significant factors in the univariate analysis will be included in the Cox regression equation to identify independent factors that will be used to construct nomograms. Nomograms for CSS and DFS were constructed using the rms and survival packages in the R software. Internal validation was performed to demonstrate the reliability and repeatability of the nomograms. The consistency index (C-index), calibration curve, and time-dependent receiver operating characteristic curve were used to evaluate the accuracy and discriminative ability of the prediction map in the training and validation sets, respectively. The ggDCA package in the R software was used to construct the decision curve analysis (DCA) to further evaluate the clinical benefit of the nomogram. Each patient was scored using the survival package in R software and divided into high- and low-risk groups based on the median risk score. The Kaplan–Meier method was used to draw the CSS and DFS survival curves, and the log-rank test was used for statistical analysis.

Results

Clinicopathological characteristics

Table 1 shows the clinicopathological characteristics of the 468 patients with GA, including 327 patients in the training set and 141 patients in the validation set. In the training set, the age of the patients at diagnosis ranged from 25 to 88 years, with a median age of 61 years (IQR, 52–66 years). Most patients were male ($n = 240$, 73.4%), and the rest were female ($n = 87$,

TABLE 2 Univariate and multivariate cox regression analyses of prognostic factors for cancer-specific survival.

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Sex (male)	0.929 (0.674–1.283)	0.656		
Age (>68)	1.721 (1.239–2.390)	**0.001**	0.953 (0.660–1.377)	0.797
Family history (yes)	0.959 (0.659–1.398)	0.829		
Diabetes (yes)	1.458 (0.793–2.681)	0.225		
Hypertension (yes)	1.000 (0.695–1.439)	0.999		
Tobacco (yes)	0.750 (0.536–1.049)	0.093		
Alcohol (yes)	0.720 (0.487–1.065)	0.100		
Depth of invasion (T3-4)	4.981 (2.979–8.326)	**<0.001**	6.495 (3.763–11.208)	**<0.001**
Lymph node invasion (N1-3)	3.111 (2.037–4.753)	**<0.001**	4.762 (2.995–7.573)	**<0.001**
Differentiation (low)	1.720 (1.169–2.531)	**0.005**	1.657 (1.102–2.492)	**0.015**
Tumor size (>3.5)	1.852 (1.327–2.585)	**<0.001**	1.042 (0.731–1.486)	0.819
Tumor location				
Upper 1/3	1			
Middle 1/3	1.102 (0.771–1.574)	0.515		
Lower 1/3	0.853 (0.601–1.212)	0.375		
Adjuvant chemotherapy (yes)	0.599 (0.449–0.799)	**<0.001**	0.582 (0.426–0.796)	**0.001**
CA199 (>35)	2.385 (1.740–3.269)	**<0.001**	1.436 (1.019–2.023)	**0.038**
CA724 (>6.9)	2.800 (2.056–3.812)	**<0.001**	1.704 (1.223–2.375)	**0.002**
CEA (>5)	1.362 (0.974–1.906)	0.071		
D-Dimer (>0.3)	1.575 (1.160–2.139)	**0.004**	1.165 (0.843–1.609)	0.355
PLR (>202.9)	1.839 (1.355–2.496)	**<0.001**	0.878 (0.620–1.242)	0.461
PAR (>6.4)	2.660 (1.980–3.575)	**<0.001**	1.822 (1.299–2.556)	**0.001**
AFR (<9.7)	2.469 (1.741–3.500)	**<0.001**	1.081 (0.734–1.592)	0.693
NLR (>2.3)	0.814 (0.608–1.090)	0.168		
LMR (<3.1)	0.745 (0.548–1.014)	0.061		
SLR (>1.8)	1.728 (1.194–2.499)	**0.004**	1.010 (0.682–1.498)	0.959

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26.6%). The median tumor size was 4.5 cm (IQR, 3.5–6.0 cm). According to the 8th edition of the American Joint Committee on Cancer staging system, it is more common in patients with pT3–4 ($n = 247$, 75.5%), and most patients have lymph node invasion ($n = 244$, 74.6%). Most patients with GA were classified as stage III ($n = 214$, 65.4%). Poor differentiation ($n = 257$, 78.6%) was the most common tumor grade. In total, 184 patients (56.3%) received adjuvant chemotherapy. Furthermore, the baseline characteristics did not differ between the training and validation groups ($P >$ 0.05). For all patients, the final follow-up period ranged from 0.5 to 96 months, with a median of 36.0 months. In the training set, the 1-, 3-, and 5-year CSS rates were 82.9, 48.6, and 40.3%, respectively. The 1-, 3-, and 5-year DFS rates were 75.5, 46.8, and 39.5%, respectively. In the validation set, the 1-, 3-, and 5-year CSS rates were 81.6, 51.1, and 44.6%, respectively. The 1-, 3-, and 5-year DFS rates were 75.2, 48.9, and 42.9%, respectively.

Independent predictors

Tables 2, 3 show the results of univariate and multivariate Cox analyses on the training set data, including hazard ratios and 95% confidence intervals (CI). Univariate analysis showed that age, depth of invasion, lymph node invasion, tumor size, differentiation, adjuvant chemotherapy, CA199, CA724, D-dimer, PLR, PAR, SLR, and AFR were related to CSS and DFS, while CEA was only relevant for DFS ($P < 0.05$). Significant factors in the univariate analysis were included in multivariate analysis. Depth of invasion ($P < 0.001$), lymph node invasion ($P < 0.001$), tumor differentiation ($P = 0.015$), adjuvant chemotherapy ($P = 0.001$), CA199 ($P = 0.038$), CA724 ($P = 0.002$), and PAR ($P = 0.001$) were independent predictors of CSS, while depth of invasion ($P < 0.001$), lymph node invasion ($P < 0.001$), tumor differentiation ($P = 0.003$), adjuvant chemotherapy ($P = 0.004$), CA724 ($P = 0.001$), and PAR ($P = 0.002$) were independent predictors of DFS.

TABLE 3 Univariate and multivariate cox regression analyses of prognostic factors for disease-free survival.

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Sex (male)	0.926 (0.675–1.271)	0.636		
Age (>68)	1.631 (1.78–1.2.258)	**0.003**	0.930 (0.648–1.336)	0.695
Family history (yes)	0.952 (0.657–1.379)	0.793		
Diabetes (yes)	1.359 (0.739–2.499)	0.323		
Hypertension (yes)	1.074 (0.755–1.526)	0.692		
Tobacco (yes)	0.719 (0.489–1.056)	0.093		
Alcohol (yes)	0.718 (0.488–1.055)	0.091		
Depth of invasion (T3-4)	4.265 (2.652–6.858)	**<0.001**	5.951 (3.583–9.886)	**<0.001**
Lymph node invasion (N1-3)	3.180 (2.096–4.824)	**<0.001**	4.848 (3.067–7.662)	**<0.001**
Differentiation (low)	1.712 (1.175–2.493)	**0.005**	1.887 (1.241–2.870)	**0.003**
Tumor size (>3.5)	1.908 (1.372–2.654)	**<0.001**	1.091 (0.767–1.551)	0.630
Tumor location				
Upper 1/3	1			
Middle 1/3	1.147 (0.809–1.627)	0.442		
Lower 1/3	0.831 (0.586–1.179)	0.300		
Adjuvant chemotherapy (yes)	0.650 (0.489–0.863)	**0.003**	0.642 (0.473–0.870)	**0.004**
CA199 (>35)	2.426 (1.776–3.315)	**<0.001**	1.315 (0.924–1.871)	0.128
CA724 (>6.9)	2.905 (2.138–3.948)	**<0.001**	1.735 (1.235–2.438)	**0.001**
CEA (>5)	1.424 (1.024–1.979)	**0.036**	1.390 (0.953–2.029)	0.087
D-Dimer (>0.3)	1.473 (1.086–1.996)	**0.013**	1.065 (0.768–1.476)	0.706
PLR (>202.9)	1.863 (1.378–2.519)	**<0.001**	0.964 (0.684–1.359	0.834
PAR (>6.4)	2.542 (1.899–3.401)	**<0.001**	1.718 (1.226–2.407)	**0.002**
AFR (<9.7)	2.356 (1.6663–3.338)	**<0.001**	1.097 (0.753–1.599)	0.628
NLR (>2.3)	0.808 (0.605–1.078)	0.147		
LMR (<3.1)	0.764 (0.564–1.035)	0.082		
SLR (>1.8)	1.750 (1.216–2.518)	**0.003**	1.041 (0.708–1.529)	0.839

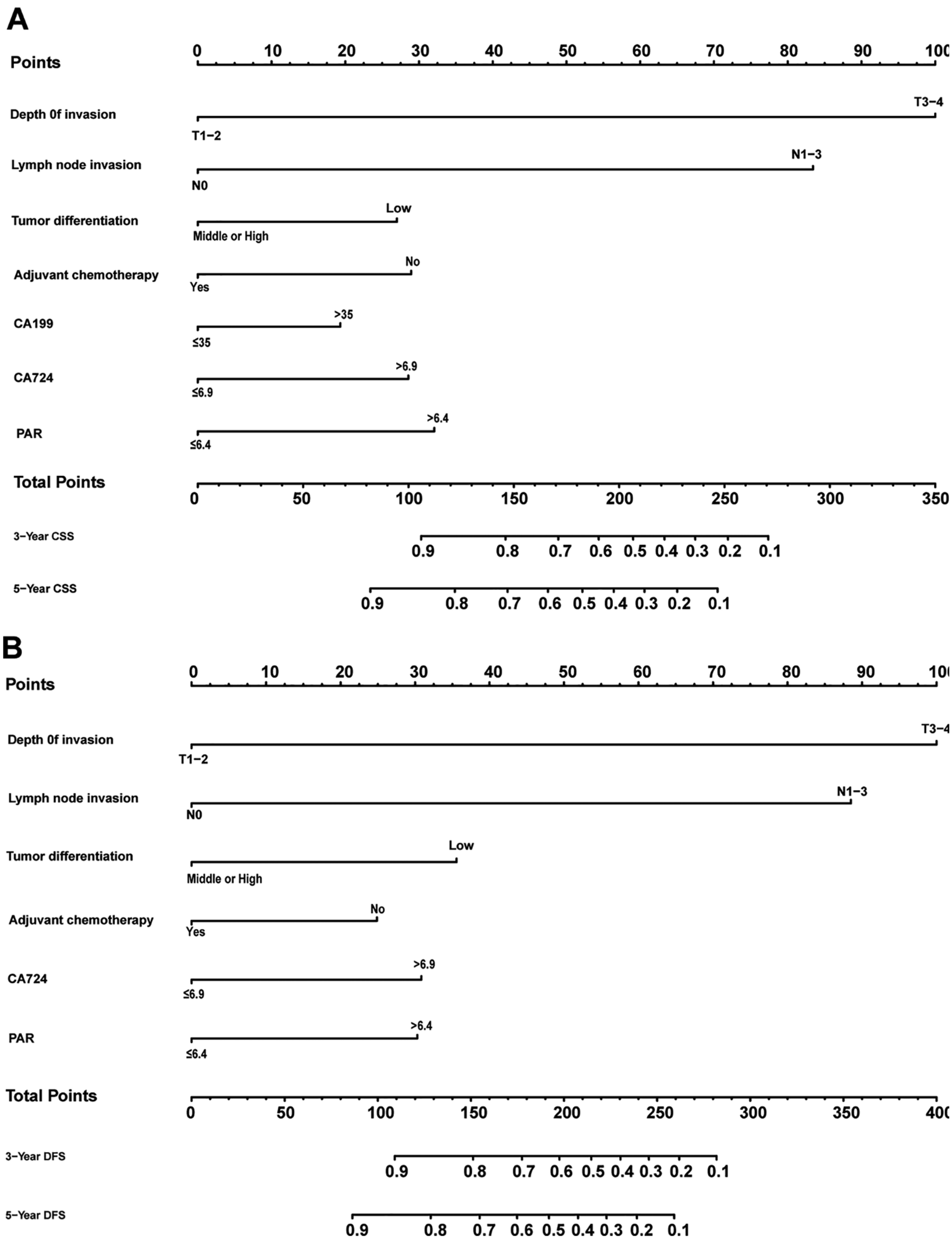

FIGURE 1
Nomogram predicting cancer-specific survival (A) and disease-free survival (B) of patients with stage II/III gastric adenocarcinoma who underwent gastrectomy.

Construction and verification of nomogram models

Figure 1 shows the nomogram predicting CSS and DFS that was constructed based on the results of the multivariate analysis with hazard ratios. The models can score each patient, and the higher the score, the worse is the prognosis. The C-index for predicting CSS and DFS was 0.771 (95%CI, 0.738–0.804) and 0.771 (95%CI, 0.740–0.802), suggesting that the constructed nomogram had an accurate predictive ability. In addition, as shown in Figure 2, the calibration curve is close to the diagonal line, suggesting that the nomogram predicts the

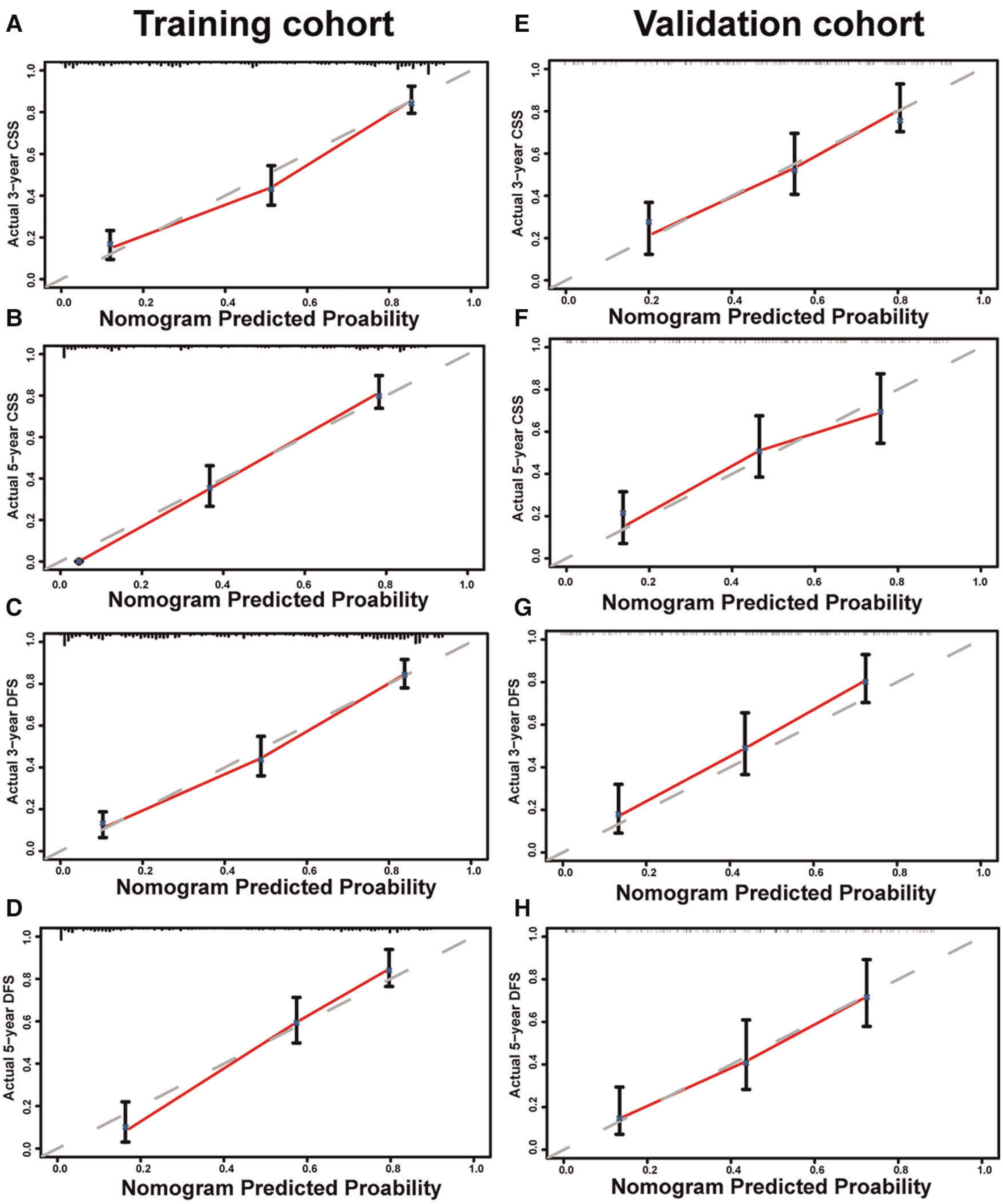

FIGURE 2
Calibration curves of nomogram for predicting 3-year cancer-specific survival (CSS) (A), 5-year CSS (B), 3-year disease-free survival (DFS) (C), and 5-year DFS (D) in the training set. Calibration curves of nomogram for predicting 3-year CSS (E), 5-year CSS (F), 3-year DFS (G), and 5-year DFS (H) in the validation set.

patients' 3- and 5-year CSS and DFS to be similar to the actual situation, further illustrating the predictive accuracy of the model. In the nomogram model, the area under the curve (AUC) for the 3- and 5-year CSS were 0.868 (95%CI, 0.829–0.907) and 0.918 (95%CI, 0.884–0.953), respectively, and the AUC for the 3- and 5-year DFS was 0.872 (95%CI, 0.834–0.910) and 0.919 (95%CI, 0.885–0.952), respectively. In TNM staging, the AUC for 3- and 5-year CSS were 0.696 (95%CI, 0.648–0.743) and 0.749 (95%CI, 0.683–0.816), respectively, and the AUC for 3- and 5-year DFS were 0.712 (95%CI, 0.664–0.760) and 0.747 (95%CI, 0.678–0.816), respectively. These results showed that the nomogram model had a higher accuracy than TNM staging (**Figure 3**). Similarly, in the validation set, the C-indices for CSS and DFS were 0.734 (95%CI, 0.679–0.789) and 0.731 (95%CI, 0.680–0.782), respectively, and the calibration curve predicted survival probability with high agreement, which also proved the reliability of the model.

Decision curve analysis and survival curves based on the nomograms

As shown in **Figure 4**, DCA was used to analyze the net benefit rate of the nomogram and TNM staging at different threshold probabilities. The results showed that the nomogram had a higher clinical benefit than the TNM staging system when the probability threshold was 0.2 to 0.8, whether it was 3-year or 5-year CSS, or 3-year or 5-year DFS. The results of the validation set were consistent with those of the training set. **Figure 5** shows that patients in the high-risk group, based on the median nomogram score, had a worse prognosis than those in the low-rank group ($P < 0.001$).

Discussion

GA is a complex disease and surgical or endoscopic resection remains the only cure. However, the current survival rate of patients with GA remains low, even with the combined efforts of multidisciplinary teams. Over the years, tumor microenvironment has been the focus of our research (17, 18), and chronic inflammation and immune dysfunction are its most important features (19). The release of various pro-inflammatory cytokines and inflammatory substances such as interleukin-1β, interleukin-8, and tumor necrosis factor-α promotes GA progression (19). Neutrophils and lymphocytes are the most important immune cells that can intuitively reflect the level of inflammation in the human body, and abnormal changes in these cells are thought to be related to tumor progression. Recently, in addition to their known hemostatic effects, researchers found that platelets are potent immunomodulators that play an important role in regulating systemic inflammation and immunity (20).

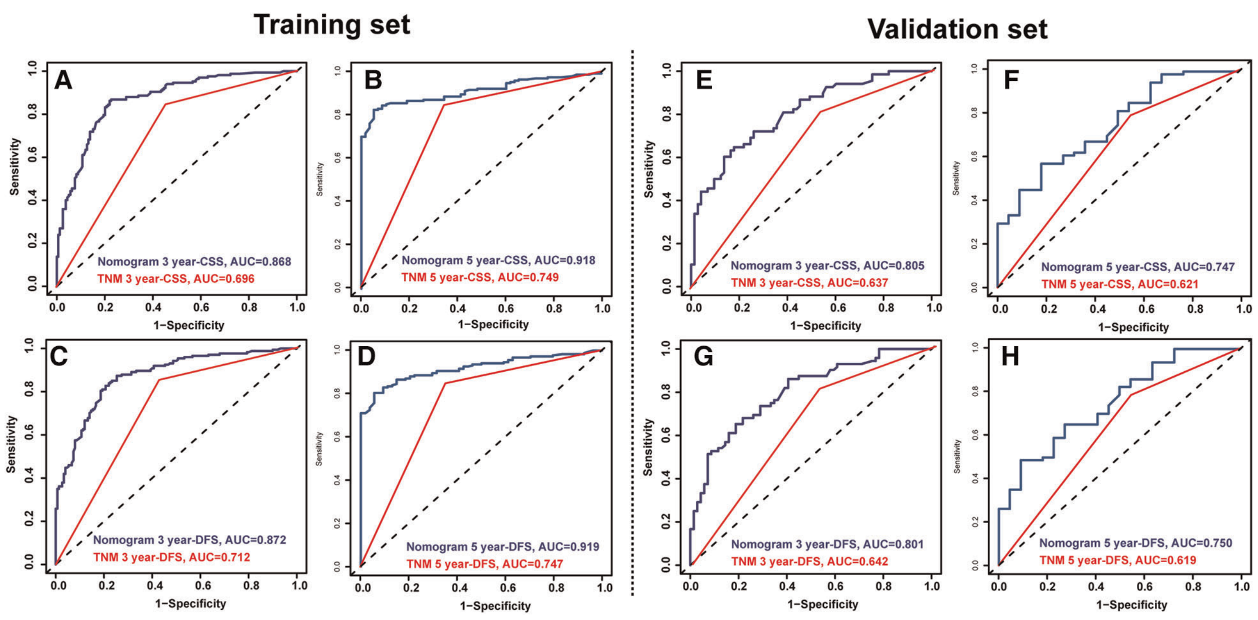

FIGURE 3
Time-dependent reciever operating characteristics (ROC) curves of nomograms and TNM staging were used to test the predictive power of the 3-year cancer-specific survival (CSS) (A) and 5-year CSS (B), 3- year disease-free survival (DFS) (C) and 5-year DFS (D) in the training set. Time-dependent ROC curves of nomograms and TNM staging were used to test the predictive power of the 3-year CSS (E) and 5-year CSS (F), 3- year DFS (G) and 5-year DFS (H) in the validation set.

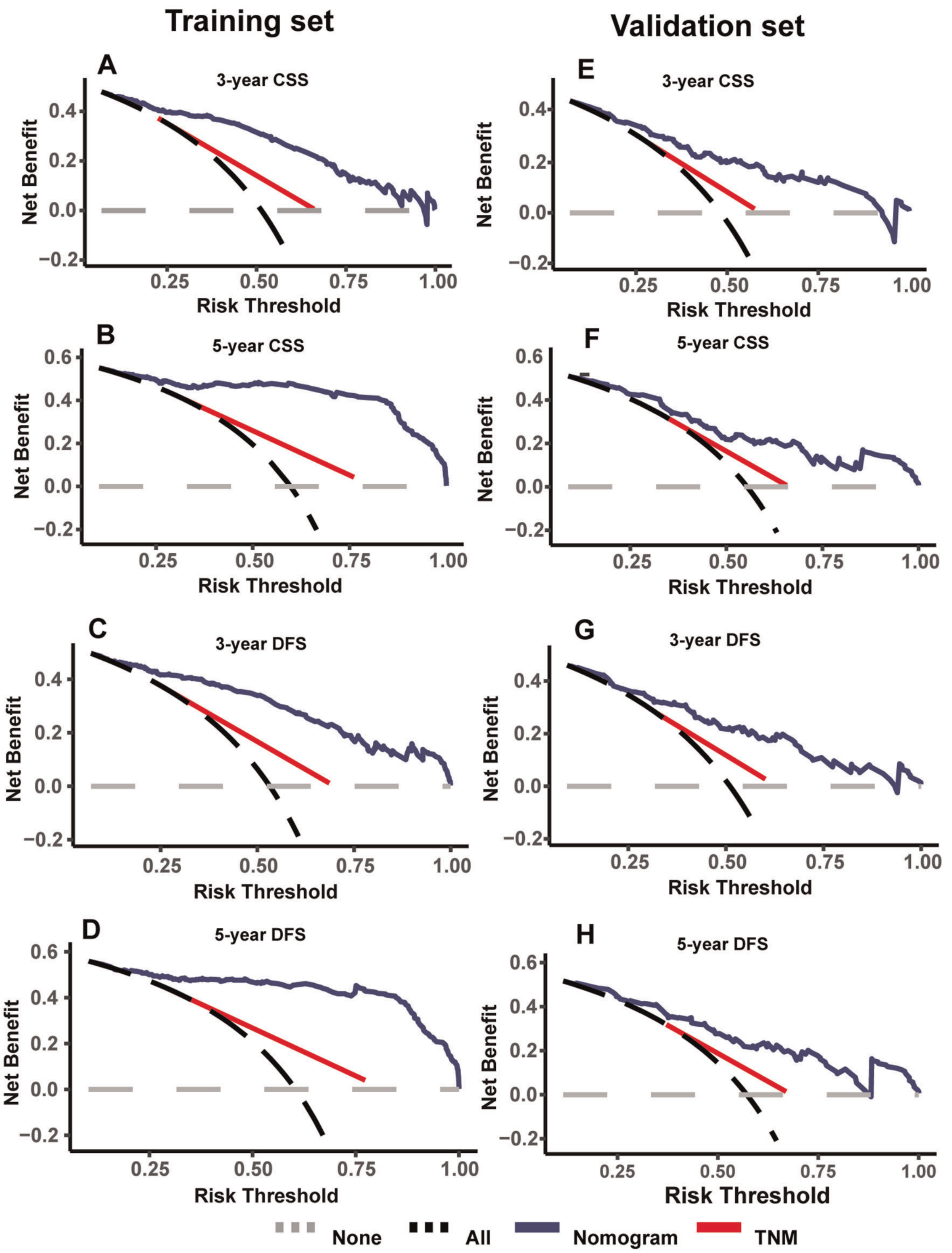

FIGURE 4
Decision curve analysis were used to compare the clinical benefit of nomogram and TNM staging in cancer-specific survival (CSS) (A,B) and disease-free survival (DFS) (C,D) in the training set; decision curve analysis were used to compare the clinical benefit of nomogram and TNM staging in CSS (E,F) and DFS (G,H) in the validation set.

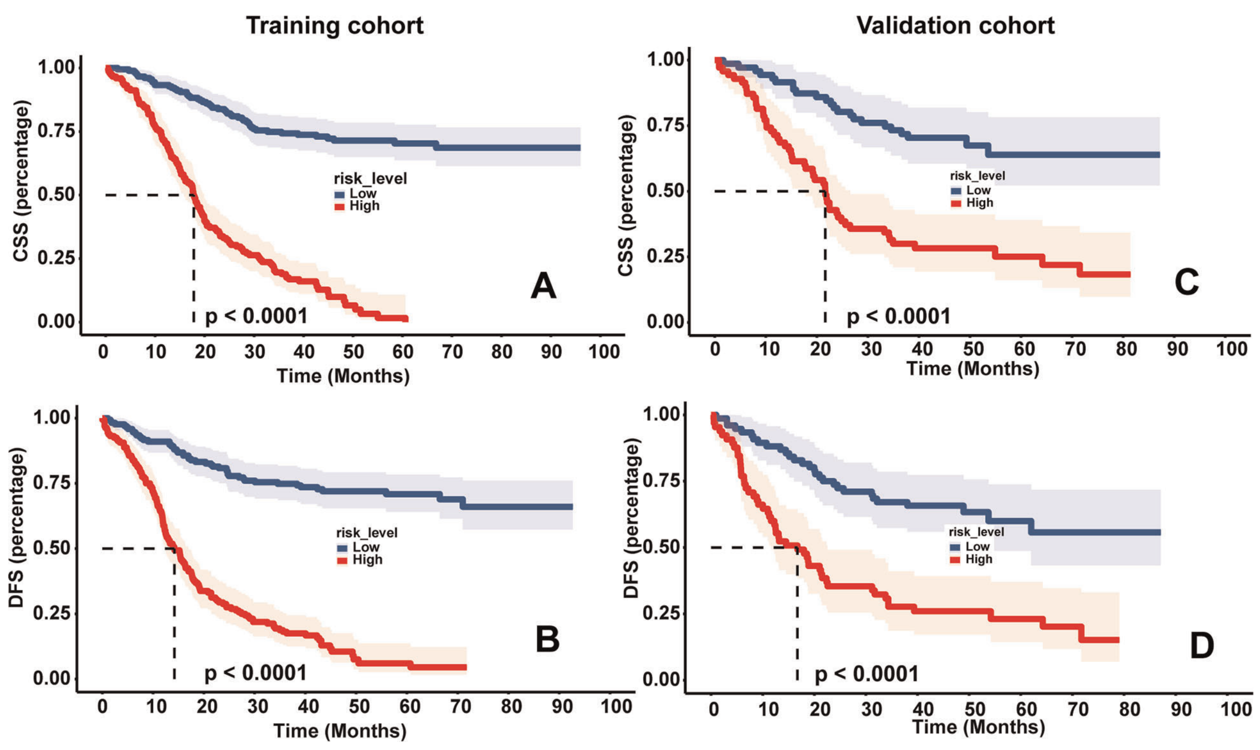

FIGURE 5
Kaplan–meier survival curves of cancer-specific survival (CSS) (A) and disease-free survival (DFS) (B) in the training set based on risk scores; kaplan–meier survival curves of CSS (C) and DFS (D) in the validation set based on risk scores.

Moreover, tumors release a variety of cytokines including vascular endothelial growth factor, platelet-derived growth factor, and transforming growth factor-β1 that can promote platelet production, and the increased platelets can shield tumor cells in peripheral blood and interfere with immune cells to enhance the metastatic potential of tumors (21, 22). However, the nutritional status of cancer patients is an important part of cancer management. The prevalence of malnutrition in patients with cancer is high, particularly in those with gastrointestinal tumors. According to one study, the prevalence of malnutrition in digestive malignancies is approximately 52% (23). Albumin is widely recognized as an indicator of nutritional levels, and the mechanism of hypoalbuminemia is related to the increase in two inflammatory cytokines, tumor necrosis factor-α and interleukin-6, which inhibit the synthesis of albumin (24). A study by Feng et al. indicated that malnutrition is significantly associated with poor prognosis in patients with gastric cancer (9). Hypercoagulability is an important physiological characteristic of patients with malignant tumors. Abnormalities in indicators that can represent coagulation, such as D-dimer and fibrinogen, are often associated with poor prognosis in patients with tumors (25, 26).

In our study, we mainly focused on PLR, PAR, NLR, LMR, STR, AFR, and D-dimer levels, which can reflect inflammation, nutritional status, liver function, and coagulation function in patients. These routine hematological markers are readily available and economical, and previous studies have shown that these indicators are associated with the prognosis of malignancies (11). The NLR and LMR are indicators of systemic inflammation. Previous studies have shown that an increase in NLR or decrease in LMR indicates that the inflammatory response promotes tumor development, indicating a poor prognosis for patients (27, 28). The relationship between PLR and cancer prognosis is unclear, and the underlying mechanism may be related to platelet and lymphocyte functions (28). SLR is an indicator of liver function. Previous studies have indicated that people with an elevated SLR have an increased risk of gastric cancer (29). PAR has also been explored in a variety of other cancers, such as pancreatic, esophageal, and liver cancers; however, its significance in GA has not been explored (30, 31). The study of Huang et al. pointed out that PAR is an independent predictor of esophageal squamous cell carcinoma and can accurately predict the prognosis of patients with this cancer (32). Similar to PAR, AFR also reflects multiple patient metrics, including nutritional levels and coagulation. Feng et al. confirmed its association with gastric cancer prognosis (9). A lower AFR appears to indicate a worse prognosis. In our study, compared to PAR, the other remaining indicators showed no statistical significance as independent prognostic factors in the multivariable Cox regression analysis. This result suggests that we may need to pay more attention to the interaction of platelets with tumor cells and other immune cells. However, preoperative attention to the nutritional status of patients and timely intervention may help prolong patient survival. A study by Bang et al. showed that postoperative platinum-based chemotherapy in patients with gastric cancer can effectively prolong the survival time of patients (33). Our study is consistent with previous findings that timely adjuvant chemotherapy is one of the protective factors for patient outcomes.

A nomogram is an effective predictive tool that quantifies individual risk, and its intuitive and visual features make predictive models more readable and facilitate clinical application (13). In this study, we constructed a nomogram to predict the prognosis of patients with stage II/III GA after curative gastrectomy. The results showed that TNM stage, tumor differentiation, postoperative adjuvant chemotherapy, tumor markers, and PAR were independent patient predictors. In addition, high-risk patients identified using the model had a poorer prognosis. Therefore, timely interventions for high-risk patients, including improved nutrition and inhibition of inflammation, may improve patient outcomes. Compared with the nomogram for stage II/III gastric cancer patients after curative gastrectomy followed by adjuvant chemotherapy constructed by Li-tong Shi (11), our model is different; we only focused on one pathological type, GA; we included adjuvant chemotherapy as a variable and incorporated different hematological indicators while constructing receiver operator characteristic and DCA curves to evaluate the clinical applicability of the model. In our study, the relationship between PAR and GA prognosis was demonstrated, which has not been previously reported. This further confirms that immunity and nutritional status are closely related to GA prognosis. However, we acknowledge that this study has some limitations. First, this was a retrospective single-center study, and the preliminary results need to be further validated in prospective clinical trials. Second, we only performed internal validation of the nomogram, and external validation was required to extend the applicability of the model. Third, we mainly focused on economical and convenient routine laboratory tests; therefore, we did not conduct research on EGFR mutations, Her-2 expression, ERBB2 expression, or microsatellite instability status. Some indicators, such as *Helicobacter pylori* and PG I/II, were not routinely detected; therefore, they were not included in this study. These metrics will be the focus of future research.

Conclusion

In conclusion, the nomogram constructed in this study for patients with stage II/III GA after curative gastrectomy could accurately predict CSS and DFS. In addition, our models are more accurate than traditional TNM staging for predicting GA prognosis and may bring more clinical benefits to patients. For patients with poor outcomes, shortening the follow-up time and timely intervention can be used to prevent the occurrence of adverse events.

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 medical ethics committee of the First Affiliated Hospital of Zhengzhou University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

LW, HQH, and LWF were involved in the study design, data collection, and statistical analysis. LW was responsible for writing the manuscript. YRQ designed the study and revised the manuscript critically. 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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Study protocol for comparing the efficacy of left-open single-flap technique versus double-flap technique after proximal gastrectomy: A multicenter randomized controlled trial

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Background: Proximal gastrectomy has gradually gained more attention due to its superiority in retaining the function of part of the stomach. The inevitable loss of the antireflux barrier and postoperative complications resulting from proximal gastrectomy can severely affect the quality of life. Continuous improvements in digestive tract reconstruction after proximal gastrectomy have yielded the development of a variety of methods with antireflux functions. Recently, our center attempted the left-open single-flap technique and initiated a multicenter, prospective, randomized controlled trial for patients undergoing proximal gastrectomy to reduce the difficulty of surgical anastomosis and the incidence of perioperative complications compared with the double-flap technique. These findings will provide more evidence-based medical research for the development of clinical guidelines.

Methods/design: This study is a prospective, multicenter, randomized controlled clinical trial. We plan to recruit 250 patients who are eligible for proximal gastrectomy. After informed consent is obtained, patients will be randomly assigned to the trial group (left-open single-flap technique) and the control group (double-flap technique) in a 1:1 allocation ratio.

Discussion: Increasingly, clinical studies have focused on the improvement of reconstruction modalities after proximal gastrectomy. Among these methods, the double-flap technique is a clinically effective method. The purpose of this study is to establish a prospective randomized controlled trial to compare the efficacy of the left-open single-flap technique versus the double-flap technique after proximal gastrectomy, aiming to provide more evidence-based medical studies for digestive tract reconstruction in proximal gastrectomy.

Clinical Trial Registration: ClinicalTrials.gov, identifier [NCT05418920].

KEYWORDS

gastric cancer, double-flap technique, left-open single-flap technique, proximal gastrectomy, study protocol

Introduction

Despite the decreasing incidence and mortality of gastric cancer in recent years, the incidence and proportion of proximal early gastric cancer has markedly increased (1). However, the choice of an appropriate surgical procedure, the only radical treatment for this condition, has been controversial (2). Currently, proximal gastrectomy has gradually gained increasing attention due to its superiority in 1) maintaining the distal gastric volume; 2) preserving the fundic gland area and reducing hormonal and nutritional deficiencies; and 3) ensuring the secretion of internal factors and gastric acid, the absorption of iron ions and vitamin B12, and the maintenance of hemoglobin concentration (3–6). However, the inevitable a loss of the antireflux barrier and postoperative complications resulting from proximal gastrectomy can severely affect the quality of life (7).

Recently, continuous improvements in digestive tract reconstruction after proximal gastrectomy have yielded the development of a variety of methods with antireflux functions that contribute to retaining the function of the residual stomach and avoiding serious reflux esophagitis (8–10). Japanese guidelines indicate that popular methods for gastrointestinal reconstruction after proximal gastrectomy include esophagogastrotomy (EG), jejunal interposition (JI), and double-tract reconstruction (DTR) (11–13). In 2016, Kuroda reported a double-flap technique using the anterior gastric wall plasma muscle flap to cover the anastomosis (14). Its unidirectional flap can reconstruct the "sphincter" and reduce the incidence of reflux esophagitis and the risk of anastomotic fistula.

By comparing patients who underwent direct esophagogastrostomy, jejunal interposition, double tract reconstruction, and the double-flap technique, Shoji Y (15) and Saze Z et al. (16) found that patients undergoing double-flap anastomosis had no reflux esophagitis and a lower incidence of postoperative anastomotic stricture, which improved postoperative serum albumin ratio changes and weight maintenance. Consequently, the double-flap technique is considered to be the most effective technique for proximal gastric reconstruction (17, 18).

However, the double-flap technique is associated with shortcomings, such as a more complex suture technique, more difficult operation, longer operation time and higher incidence of postoperative anastomotic stenosis (15, 16, 19). Therefore, our center attempted the left-open single-flap technique to reduce the difficulty of surgical suturing and the incidence of complications. To further evaluate the therapeutic efficacy of this procedure, we initiated a multicenter, prospective, randomized controlled trial for patients undergoing proximal gastrectomy, which will provide more evidence-based medical research for the development of clinical guidelines.

Trial objectives

This study is a prospective, multicenter, randomized controlled clinical trial. We plan to recruit 250 patients who are eligible for proximal gastrectomy. After informed consent is obtained, patients will be randomly assigned to the trial group (left-open single-flap technique) and the control group (double-flap technique) in a 1:1 allocation ratio, with the aim of providing more evidence-based medical outcomes for digestive tract reconstruction in proximal gastrectomy. The surgical methods applied in this study are shown in Table 1.

The objectives of this trial are as follows:

Main objective

The main objective is to investigate the incidence of reflux esophagitis after 2 types of anastomosis (left-open single-flap technique vs. double-flap technique) after proximal gastrectomy.

Abbreviations: GC, gastric cancer; RCT, randomized controlled study; EGC, early gastric cancer; CRF, Case Report Form; EG, esophagogastrotomy; DFT, double-flap technique; LOSF, left-open single-flap.

TABLE 1 Surgical methods applied in this study.

	Proximal gastrectomy	D2 lymphadenectomy	Left-open single-flap technique	Double-flap technique
The trial group	√	√	√	
The control group	√	√		√

Secondary objective

1) to investigate the incidence of anastomotic leakage of 2 types of anastomosis (left-open single-flap technique vs. double-flap technique) after proximal gastrectomy
2) to investigate the incidence of anastomotic stricture of 2 types of anastomosis (left-open single-flap technique vs. double-flap technique) after proximal gastrectomy
3) to investigate the operation time of 2 types of anastomosis (left-open single-flap technique vs. double-flap technique) after proximal gastrectomy
4) to investigate the intraoperative blood loss volume of 2 types of anastomosis (left-open single-flap technique vs. double-flap technique) after proximal gastrectomy

Prospective results

In patients after proximal gastrectomy, the left-open single-flap technique can decrease postoperative complications and increase nutritional status compared with the double-flap technique.

Participant selection

The flow chart of this study is shown in Figure 1. During the routine admission of inpatients, suitable patients will be screened by the study staff according to the inclusion/exclusion criteria. Patients who are successfully selected before formal enrollment will receive study instructions from the investigator with a detailed explanation of the included documents and operations. Participants (or their legally authorized representative) will agree to sign and date the informed consent form after receiving a random serial number. All processes will strictly follow the provisions of the Ethical Review of Biomedical Research Involving Humans (Trial), the Declaration of Helsinki v.08, and the International Ethical Guidelines for Biomedical Research Involving Humans.

Inclusion criteria

1) patients aged 18-80 years, regardless of sex;
2) Siewert III of esophagogastric junction adenocarcinoma: Stage I ($cT_{1-2}N_0M_0$) or adenocarcinoma of the upper part of the stomach: Stage II ($cT_{1-2}N_0M_0$), Stage II ($cT_{1-2}N_{1-3}M_0/cT_{3-4}N_0M_0$), Stage III ($cT_{3-4a}N_{1-3}M_0$). All patients were selected according to the 8th AJCC clinical staging of gastric cancer.
3) primary lesion diagnosed by preoperative endoscopic end pathology: tumor diameter <4 cm and located in the upper part of the stomach (including the esophagogastric junction), histologically confirmed adenocarcinoma;
4) preoperative ASA score: I, II, or III;
5) preoperative Karnofsky physical status score: ≥ 70%; or preoperative ECOG physical status score: ≤ 2;
6) no distant metastases (confirmed by preoperative chest X-ray, abdominal ultrasound, and upper abdominal CT); No peritoneal implant metastases (confirmed by exploration surgery);
7) R0 surgical outcome was expected to be obtained with D2 lymphadenectomy in radical proximal gastrectomy;
8) patients and their families voluntarily participated in this study and signed the informed consent form after understanding the study content.

Exclusion criteria

1) patients who have received any preoperative treatment, such as chemotherapy, radiotherapy, targeted therapy or immunotherapy; preoperative neoadjuvant chemotherapy recipients;
2) patients with clinical stage exceeding Siewert III of the esophagogastric junction adenocarcinoma: Stage I ($cT_{1-2}N_0M_0$) or more than adenocarcinoma of the upper part

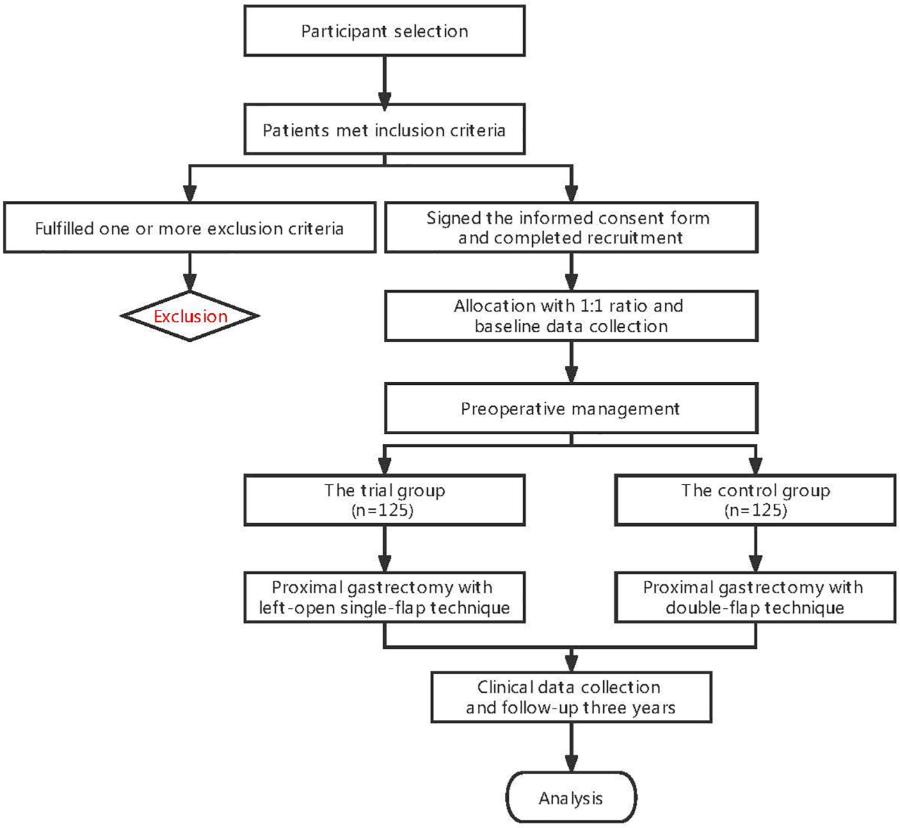

FIGURE 1
Flowchart of the trial.

of the stomach: Stage I ($cT_{1-2}N_0M_0$), Stage II ($cT_{1-2}N_{1-3}M_0$/$cT_{3-4}N_0M_0$), Stage III ($cT_{3-4a}N_{1-3}M_0$);

3) patients with acute infections, especially biliary tract infections;
4) patients with complications of gastric cancer (bleeding, perforation, or obstruction) requiring emergency surgery;
5) patients with uncorrectable coagulation dysfunction;
6) patients with vital organ failure, such as heart, lung, liver, brain, kidney, etc.
7) severe central nervous system disease, mental disorders, or impaired consciousness;
8) pregnant or lactating women;
9) patients with distant metastases;
10) patients with a primary tumor at another site diagnosed within the past 5 years;
11) preoperative ASA score: ≥ IV;
12) preoperative ECOG physical status score: ≥ 2;
13) history of continuous systemic corticosteroid therapy within the past 1 month;
14) history of unstable angina, myocardial infarction, cerebral infarction, or cerebral hemorrhage within the past 6 months;
15) patients with concurrent surgical treatment of other diseases;
16) patients with immunodeficiency, immunosuppression, or autoimmune diseases (organ transplant requiring immunosuppressive therapy within the past 5 years, allogeneic bone marrow transplant patients, taking immunosuppressive drugs, etc.);
17) patients with concurrent participation in other clinical studies;
18) patients refusing to sign an informed consent form to participate in this study;
19) preoperative imaging: regional fusion of enlarged lymph nodes (maximal diameter > 3 cm).

Terminating criteria

1) patients are inoperable for various reasons after recruitment;
2) the investigator considers that the patient should stop this study for safety reasons or the benefit of the patient;
3) serious complications or intolerable adverse reactions of the patient;
4) patients may request to withdraw/terminate from the trial at any time after signing the informed consent form.

Rejecting criteria

1) patients with missing main observation indicators and significantly incomplete study data;
2) incomplete follow-up data;
3) patients who failed to follow the study protocol;
4) the study protocol was discontinued after the patient was judged to be a culled case. Follow-up treatment was determined by the investigator according to clinical guidelines. The excluded cases were still subject to follow-up and were included in the study analysis.

Participating entities

As shown in Table 2, this work is a multicenter, large-sample clinical study with six participating medical institutions (Xi-Jing Hospital, Tang-Du Hospital, First Affiliated Hospital Xi'an Jiaotong University, General Hospital of Ningxia Medical University, Henan Provincial People's Hospital, The First Affiliated Hospital of Shanxi Medical University). The mode of enrollment is competitive. All study institutions and personnel were approved by the ethics committee and possessed extensive clinical experience in the treatment of gastric cancer.

Blinding technique and randomization procedure

The study has an open design.

Before randomization, the oncologic evaluation will be performed based on relevant clinical parameters (vital signs, serum biochemical tests, tumor markers, CT and/or MRI, ultrasound endoscopy, etc.). Eligible participants will be informed by the investigator and required to sign an informed consent form. Patients will be randomly assigned in a 1:1 ratio to the trial group (left-open single-flap technique) and the control group (double-flap technique). The randomization sequence will be generated by a biostatistician using the SPSS 28.0.1 software. The randomization list will be sealed in an opaque envelope and placed in the custody of a dedicated person.

None of the assistants associated with the randomization process are directly involved in this study to avoid bias.

Perioperative management

1) If the patient's condition deteriorates between enrollment and the date of surgery, the investigator will decide whether to perform the surgery as planned. If emergency surgery or cancellation is needed, the case will be excluded according to the exclusion criteria.
2) Perioperative enteral/parenteral nutrition support will be allowed for patients with nutritional risk.
3) For high-risk patients (elderly patients, smokers, diabetic patients, obese patients, or patients with a history of chronic cardiovascular or thromboembolic disease), the perioperative administration of low-molecular heparin, lower extremity antithrombotic compression stockings, aggressive lower extremity massage and respiratory function training are recommended as prophylactic measures. Methods for other potentially high-risk complications will be determined by clinical practice routines and specific needs, but all measures need to be documented in the CRF.

TABLE 2 The perioperative follow-up data were sorted and merged.

Number	Center	Role
1	Xi-Jing hospital	Management
2	Tang-Du Hospital	Participant
3	First Affiliated Hospital Xi'an Jiaotong University	Participant
4	General Hospital of Ningxia Medical University	Participant
5	Henan Provincial People's Hospital	Participant
6	The First Affiliated Hospital of Shanxi Medical University	Participant

4) Regarding the choice of surgical procedure performed in this study, D2 lymphadenectomy in radical proximal gastrectomy will be performed by the investigator according to the 6th edition of the Japanese Guidelines for the Treatment of Gastric Cancer (18);
5) The principles of prophylactic antibiotic use are as follows: the first intravenous drip is started 30 minutes before surgery, and the recommended choice is cephalosporin II antibiotics. The preparation, concentration, and infusion rate will be in accordance with routine clinical methods. Prophylactic use will last no longer than 3 days after surgery, and the frequency of use will be 1 time/8 hours. In cases of allergy to cephalosporins (including a history of allergy or allergy after use), other types of antibiotics will be selected according to clinical specifics, and the duration of prophylactic use will be the same as before.
6) The patient's preoperative fasting, water fasting, and other anesthetic requirements will be implemented according to the routine anesthetic protocol;
7) The investigator will decide to leave a gastric tube or drainage tube in place based on experience and actual needs;
8) Enhanced Recovery After Surgery program: treat preoperatively anemia with intravenous or iron to diminish blood transfusion; malnutrition treatment with hyperproteic nutritional shakes; aerobic exercise daily of 30-45 minutes; anxiety treatment with mindfulness exercise and/or drugs.

Surgical principles

1. Rules for gastric resection:
2. Routine abdominal exploration will be performed to confirm the presence of peritoneal implants, positive abdominal exfoliative cytology, or other distant metastases and to identify those who cannot be resected due to tumor;
3. Proximal gastrectomy should be performed if the tumor is confirmed to be radical;
4. For patients who require total gastrectomy or combined organ resection intraoperatively, whether to proceed to laparoscopic surgery or intermediate open surgery is decided on a case-by-case basis. These cases are not required in this study and need to be recorded in the CRF.
5. Rules for lymph node dissection: D2 lymphadenectomy in radical proximal gastrectomy will be performed according to the tumor infiltration (17, 18).

Treatment protocols and surgical intervention

The mesenterium at the root of the esophagus is fully stripped, and the esophagus is exposed. The location of the tumor is localized according to intraoperative gastroscopy, and the sites of esophageal and gastric body dissection are further clarified (the distances between the cut edges are 5 cm and 3 cm, respectively). The esophagus is dissected, and the stomach is pulled outside the body through an adjuvant incision in the navel or epigastrium. The tumor and remnant stomach are then dissected with linear staplers. Specimens are taken at the cut edge for rapid cytopathological examination.

As shown in Figure 2, patients in the trial group will receive the left-open single-flap technique after proximal gastrectomy, which involves the following (20):

1) Marking an "コ"-shaped mucosal window (A): The mucosal window is located on the anterior wall of the stomach near the lesser curvature, 3-4 cm from the cut edge, and a sideways "コ" shape is marked measuring (2.5-3.5) x 3.5 cm area with methylene blue.
2) Making a left-open single flap (B): an electric knife is used to peel off the plasma membrane and muscle layers, paying attention to the protection of blood vessels and avoiding rupture of the mucosal window.
3) Fixing the esophagus and opening a gastric mucosal window (C): the posterior wall of the esophagus, approximately 5 cm from the severed end, is fixed with four sutures to the top of the anterior wall of the remnant stomach. The gastric mucosal window (upper and lower edges of the anastomosis) is made by opening the mucosal layer under the single muscle flap at the lower left side of the flap. The length of the window is determined by the caliber of the esophagus.
4) Anastomosing by linear staplers (D): the left posterior wall of the esophagus and anterior wall of the gastric mucosal window are anastomosed by linear staplers with an insertion length of 2.5-3 cm.
5) Closing of the common opening (E): the common opening is closed with a full layer of continuous sutures using a barbed wire.
6) Covering the left-open single flap and suturing with barbed wires (F): the anastomosis is covered by a left-open single flap, and the edge of the flap is continuously sutured to the anterior gastric wall with barbed wires. A "コ"-shaped structure is formed.

As shown in Figure 3, patients in the control group will receive the double-flap technique after proximal gastrectomy, which includes the following (21):

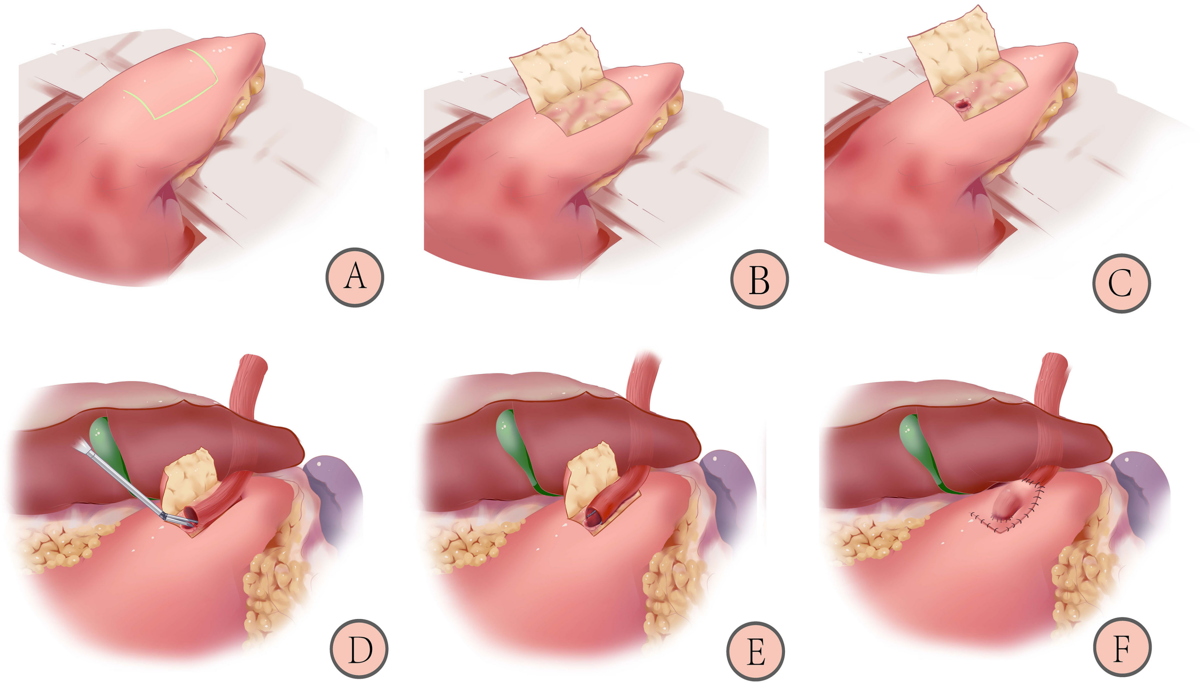

FIGURE 2
Schematic diagram of reconstruction after proximal gastrectomy with left-open single-flap technique: 1) Marking the "コ"-shaped mucosal window **(A)**; 2) Making the left-open single-flap **(B)**; 3) Fixing the esophagus and opening a gastric mucosal window **(C)**; 4) Anastomosing by linear staplers **(D)**; 5) Closing of the common opening with barbed wire **(E)**; 6) Covering the left-open single-flap and suturing with barbed wires **(F)** (20).

1) Marking the "H"-shaped mucosal window (A): the mucosal window is located on the anterior wall of the remnant stomach near the lesser curvature, and the "H"-shaped (2.5~3.5) cm×3.5 cm area is marked with methylene blue.
2) Make a double flap (B): an electric knife is used to peel off the plasma membrane layer and muscle layer, paying attention to the protection of blood vessels and avoiding rupture of the mucosal window.
3) Fixing the esophagus and opening the gastric mucosal window (C): the posterior wall of the esophagus, approximately 5 cm from the severed end, is sutured to the top of the anterior wall of the remnant stomach with 3-4 stitches to keep the anastomosis flat and prevent reflux. The gastric mucosal window is made by opening the mucosal layer below the double flap, and the width is similar to that of the esophagus.
4) Completing continuous hand suture (D and E): the entire esophageal wall is sutured to the gastric mucosa using a barbed wire with a complete continuous inversion. The point of entry is the left side of the upper edge of the gastric mucosa. The direction of entry is entering the gastric mucosal layer and penetrating from the esophageal plasma membrane layer. The direction of the suture is from left to right until the left side of the gastric mucosa upper edge. The direction of the suture at the lower edge is the opposite.
5) Covering the double flap and suturing with barbed wires (F): the anastomosis is covered by a double flap, and the lower edge of the flap is continuously sutured to the anterior gastric wall with barbed wires. The double flap is obliquely reinforced to the esophageal epithelium without mutual sutures, and a "Y"-shaped collar-like structure is formed.

Clinical data collection

According to the privacy policy, only the researcher will know the patient's identity and various information. Clinical information will be recorded by the investigators in the case report form and on the web platform (http://www.medresman.org.cn). The patients' clinical data will include general information, previous medical history, previous surgical history, laboratory findings (preoperative and postoperative blood tests, biochemical indicators, and tumor markers), upper gastrointestinal endoscopy, imaging findings, the incidence of

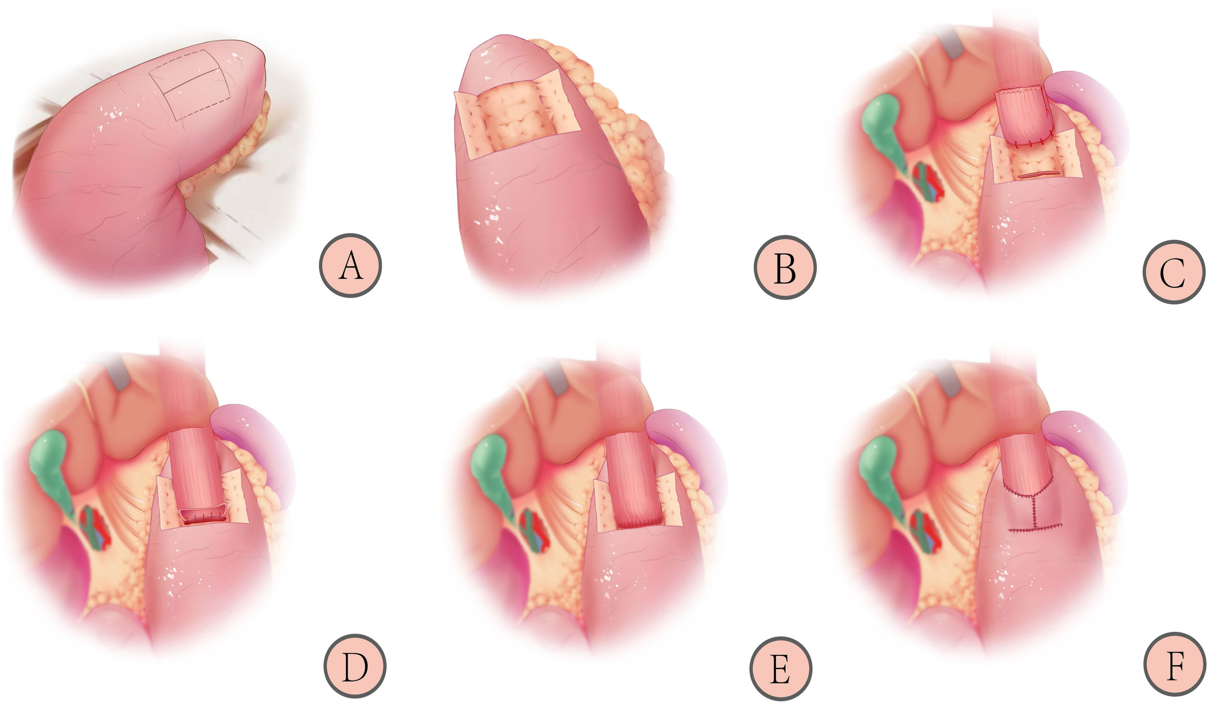

FIGURE 3
Schematic diagram of reconstruction after proximal gastrectomy with the double-flap technique: 1) Marking the "H"-shaped mucosal window **(A)**; 2) Making the double-flap **(B)**; 3) Fixing the esophagus and opening the gastric mucosal window **(C)**; 4) Completing continuous hand suture **(D, E)**; 5) Covering the double-flap and suturing with barbed wires **(F)** (21).

postoperative reflux esophagitis, the incidence of anastomotic leakage, the incidence of anastomotic stricture, operative time and intraoperative blood loss. The schedule of data collection in this study is shown in Table 3.

Collection, preservation, and management of biochemical specimens

In this study, blood samples will be collected from subjects to monitor blood biochemical indicators and tumor markers. After testing, all samples will be destroyed in strict accordance with laboratory regulations.

Sample size estimate and statistical analysis

The left-open single-flap technique after proximal gastrectomy is a new and improved procedure in our center, and national or international studies comparing clinical outcomes after reconstruction with the double-flap technique have not been conducted. Kuroda S et al. (22) showed that the incidence of reflux esophagitis, performed by endoscopy at 1.0 years (median) after the double flap technique, was 10.6% for all grades. This finding was considered more in line with "real-world data".

According to the database of this study, we designed a noninferiority study with a noninferiority margin of 10% (α=0.05, β=0.20, δ =0.10, 80% power, 10% dropout rate). The test statistic used is the one-sided Z test (unpooled) by PASS 15.0.5 software.

The result is N = 250. Therefore, 125 patients will be enrolled in each of the 2 groups.

Study endpoints

The postoperative complications are classified according to the Clavien–Dindo grading system.

Primary study endpoints

1) Incidence of reflux esophagitis (22);

TABLE 3 The 6 medical institutions participating in the clinical trial.

Assessment time point	Preoperation (14-1 days)			Intraoperation	Postoperation							
	Enrollment	Allocation	Baseline		1-14 days	1st month	3rd month	6th month	12th month	18th month	24th month	36th month
Inclusion and exclusion	√											
Written informed consent	√											
Patients allocation		√										
Basic data collection			√									
Preoperative management			√									
Operation information				√								
Frozen-section examination				√								
Questioning			√		√	√	√	√	√	√	√	√
Physical examination			√		√	√	√	√	√	√	√	√
Blood examination items			√		√	√	√	√	√	√	√	√
Gastrointestinal endoscopy			√									
Esophagogram fluoroscopy					√	√	√	√	√	√	√	√
Imaging items			√		√	√	√	√	√	√	√	√
Other assessment tools			√	√	√	√	√	√	√	√	√	√

√Indicates the need to collect clinical data.

Secondary study endpoints

1) Incidence of anastomotic stricture;
2) Overall postoperative complication rate;
3) Incidence of anastomotic fistula;
4) Operation time;
5) Blood loss volume;
6) Postoperative mortality rate;
7) R0 resection rate;
8) Overall resection rate;
9) Intraoperative complication rate;
10) Postoperative severe morbidity rate;
11) Postoperative recovery course;
12) 3-year overall survival rate;
13) 3-year disease-free survival rate;
14) Recurrence pattern;
15) The length of ICU stay;
16) Lengths of admission;
17) Length of post operational stays;
18) Nutritional status.

Follow-up

The start time of this study was August 1, 2022. The preliminary completion time is July 31, 2024. Follow-up will be planned for three years, and the study completion time will be July 31, 2027.

Esophagogram fluoroscopy will be performed 6 days after surgery to evaluate anastomotic complications. Subsequent follow-ups will be performed at 1, 3, 6, 12, 24 and 36 months. The follow-up will include questioning, physical examination, gastrointestinal endoscopy, blood examination items (peripheral blood routine, serum iron, vitamin B12, folic acid, blood biochemistry and serum tumor markers), and imaging items (chest imaging, esophagogram fluoroscopy, and whole abdomen enhanced CT). All examinations will be recorded to evaluate the presence of tumor recurrence or metastasis, the survival status of patients and the occurrence of complications. Other assessment tools will be used according to the specific situation, such as color ultrasound of other sites, whole-body bone scan, PET-CT, etc. The follow-up schedule in this study is shown in Table 3.

The diagnosis of postoperative reflux symptoms is based on a combination of symptom presentation, endoscopic evaluation of esophageal mucosa, reflux monitoring, and response to therapeutic intervention (23–25). Heartburn and regurgitation remain the typical symptoms of postoperative reflux symptoms. The control steps of postoperative reflux symptoms are shown in the Table 4.

In this study, the patients should be reexamined at the hospital where the surgery was performed, but cases of outside hospital examination will not be excluded (outside hospital reexamination should be conducted at a tertiary care hospital). A follow-up specialist will follow up and record the results of each examination.

All patients refuse to be followed up according to the above protocol will be recorded as lost cases and analyzed together with cases meeting the study criteria at the end of the study.

Written informed consent forms

The informed consent process was approved by the internal review board/independent ethics committee. If any changes occur during the study, they will be resubmitted for review.

Informed consent procedures will be implemented in strict compliance with relevant Chinese laws. Original informed consent will be retained in writing by the investigator.

We will rigorously protect patient privacy: The collection, transmission, process and storage of participant data will comply with data security and privacy protection regulations.

Monitoring of the study

The study protocol, which was submitted to the ethical review committee of the health administration department, is in line with the relevant regulations in China and the Measures for Ethical Review of Biomedical Research Involving Human Beings (2007).

We will retain video recordings and unedited image files of all patients throughout the surgery. The organizers will review and monitor the quality of the surgery. The main objectives will be performed for these purposes: 1) to confirm the rationality of the surgical approach, the extent of lymph node dissection and the minimally invasive nature of the incision; 2) to verify the original data of all subjects to confirm consistency with the CRF; and 3) to regularly assess the progress of the study at each center to ensure that it was carried out according to the plan.

Patient and public involvement

Patients and the public will not be involved in our process of design, recruitment, clinical treatment, measurement of outcomes and analysis of the data.

Discussion

For patients diagnosed with Siewert III esophagogastric junction adenocarcinoma and early-stage upper gastric cancer, current clinical guidelines recommend proximal gastrectomy (17, 18). Compared with total gastrectomy, proximal gastrectomy can maintain part of the storage and digestive function of the stomach, which has greater advantages for nutrient absorption and weight maintenance (5–8). Therefore, this approach is more commonly used in East Asia.

Unavoidably, patients' postoperative quality of life is severely affected by postoperative complications (7). Wang S et al. (8) found that proximal gastrectomy is also associated with many complications, most notably reflux esophagitis, which causes heartburn, chest pain, acid reflux, and anorexia. These postoperative complications can severely reduce the quality of life after surgery.

Consequently, the choice of a reasonable approach to reconstruct the digestive tract after proximal gastrectomy and addressing complications, such as reflux esophagitis, remain a challenge for clinicians (10–13). Therefore, an increasing number of clinical studies have focused on improving reconstruction modalities after proximal gastrectomy, such as esophagogastrotomy (EG), jejunostomy (JI), jejunal pouch placement (JPI) and double tract reconstruction (DTR).

Among various gastrointestinal reconstruction methods, the double-flap technique is clinically effective, wrapping around and increasing the pressure of anastomosis through a unidirectional flap. This structure is similar to the "reconstructed cardia" structure, which can improve the antireflux effect. Saze Z et al. (16) found that the double-flap technique did not result in postoperative reflux esophagitis and had the smallest postoperative weight change ratio and the lowest prevalence of gastric residual at 12 months after surgery compared with direct esophagogastrostomy, jejunostomy and double tract reconstruction.

However, double-flap technique is also associated with shortcomings, such as a complicated surgical suture technique, difficult operation, strict surgical indications and high incidence of postoperative anastomotic stenosis (26–28).

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TABLE 4 The control steps of postoperative reflux symptoms.

Management	Nonpharmacologic lifestyle modifications	Weight managemen	1. Weight loss in overweight and obese patients for improvement of postoperative reflux symptoms. 2. For the patients with regurgitation or belch predominant symptoms; but we do not recommend baclofen in the absence of objective evidence of postoperative reflux symptoms.
		Body positioning	1. Elevating the head of the bed. 2. Staying upright during and after meals.
		Diet modification	1. Avoidance of "trigger foods". 2. Avoiding meals within 2–3 hours of bedtime. 3. Tobacco and alcohol cessation. 4. Avoidance of late night meals and bedtime snacks.
	Pharmacologic therapy	Proton pump inhibitors	1. Patients presenting with troublesome heartburn, regurgitation, and/or non-cardiac chest pain without alarm symptoms a 4- to 8-week trial of single-dose PPI therapy. 2. With inadequate response, dosing can be increased to twice a day or switched to a more effective acid suppressive agent once a day. When there is adequate response, PPI should be tapered to the lowest effective dose. 3. If the response to one type of PPI is not sufficient, switching to another type of standard-dose PPIs may be considered (administration 30–60 minutes before a meal and on-demand therapy/ maintenance therapy). 4. For patients with

(Continued)

TABLE 4 Continued

	postoperative reflux symptoms who do not have erosive esophagitis or Barrett's esophagus, and whose symptoms have resolved with PPI therapy, an attempt should be made to discontinue PPIs. 5. We recommend maintenance PPI therapy indefinitely or antireflux surgery for patients with Los Angeles grade C or D esophagitis. 6. Endoscopic evaluation:Objective testing with upper GI endoscopy is warranted in PPI non-response, presence of alarm signs/symptoms, isolated extra-esophageal symptoms, or in patients who meet criteria to undergo screening for Barrett's esophagus. In the absence of confirmed erosive disease or Barrett's esophagus on endoscopy, prolonged wireless pH monitoring off PPI therapy is utilized to assess esophageal acid exposure.
Potassium-competitive acid blockers	The efficacy is comparable to proton pump inhibitors for 4 weeks and 8 weeks, which are recommended as an initial treatment of postoperative reflux symptoms.
H2 receptor antagonists	Patients with nocturnal symptoms.
Alginate antacids	Patients with breakthrough symptoms.
Baclofen	Patients with regurgitation or belch predominant symptoms; Don't recommend in the

(Continued)

TABLE 4 Continued

		absence of objective evidence of postoperative reflux symptoms.
	Prokinetics	Patients with coexistent gastroparesis.
	Behavioral therapist	Patients with functional heartburn or reflux disease associated with esophageal hypervigilance, reflux hypersensitivity, and/or behavioral disorders (hypnotherapy, cognitive behavioral therapy, diaphragmatic breathing, and relaxation strategies).
Surgery		Patients with Los Angeles grade C or D esophagitis.

To address the shortcomings of the above procedure, we established a multicenter, prospective, randomized controlled trial to modify the flap-making procedure for the double-flap technique: a left-open single flap will be used instead of a double flap to cover the anastomosis, acting as a "sphincter" and providing a tunneling effect. Preliminary data from our center showed that patients have excellent postoperative results. We will explore and summarize our initial clinical experience and apply it to the development of the treatment protocol. If this study meets the expected results of the trial protocol, it will bridge the gap between the complicated operative procedure and longer operative time of the double-flap reconstruction style and further improve the postoperative quality of life of patients. These outcomes will be landmark improvements in patient prognosis and provide additional high-level research evidence for the standardization of gastrointestinal reconstruction protocols after proximal gastrectomy.Strengths and limitations of this study

Strengths: This was a prospective, large sample, multicenter randomized controlled trial that systematically compared the efficacy of 2 methods of gastrointestinal reconstruction after proximal gastrectomy. In previous studies, the left-open single-flap technique had not been reported.

Limitations: Japanese guidelines recommended that the common methods of gastrointestinal reconstruction after proximal gastrectomy include esophagogastrotomy (EG), jejunostomy placement (JI), jejunal pouch placement (JPI) and double-tract reconstruction (DTR). Nevertheless, we compared only 2 of these reconstruction methods in our study.

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 authors.

Ethics statement

The studies involving human participants were reviewed and approved by Chinese Ethics Committee of Registering Clinical Trials. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Concept Proposal: XL; Survey and Data Summary: QY, WW, RG, CY, JY, and DD; Data Collection, analysis and statistics: QY, WW, ZM, CY, HZ, and JW; Specific scheme implementation: GJ, XL, QY, WW, ZM, CY, RG, DD, HZ, JW, JL, and XY;Research Regulatory: GJ and XL; Writing – Draft:

QY and WW; Writing-Proofreading and Editing: XL and QY. All authors approved the final version of this manuscript.

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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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Near-infrared-dye labeled tumor vascular-targeted dimer GEBP11 peptide for image-guided surgery in gastric cancer

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Introduction: Positive resection margins occur in about 2.8%-8.2% gastric cancer surgeries and is associated with poor prognosis. Intraoperative guidance using Nearinfrared (NIR) fluorescence imaging is a promising technique for tumor detection and margin assessment. The goal of this study was to develop a tumor-specific probe for real-time intraoperative NIR fluorescence imaging guidance.

Methods: The tumor vascular homing peptide specific for gastric cancer, GEBP11, was conjugated with a near-infrared fluorophore, Cy5.5. The binding specificity of the GEBP11 probes to tumor vascular endothelial cells were confirmed by immunofluorescent staining. The ability of the probe to detect tumor lesions was evaluated in two xenograft models. An orthotopic gastric cancer xenograft model was used to evaluate the efficacy of the GEBP11 NIR probes in real-time surgical guidance.

Results: In vitro assay suggested that both mono and dimeric GEBP11 NIR probes could bind specifically to tumor vascular epithelial cells, with dimeric peptides showed better affinity. In tumor xenograft mice, live imaging suggested that comparing with free Cy5.5 probe, significantly stronger NIR signals could be detected at the tumor site at 24-48h after injection of mono or dimeric GEBP11 probes. Dimeric GEBP11 probe showed prolonged and stronger NIR signals than mono GEBP11 probe. Biodistribution assay suggested that GEBP11 NIR probes were enriched in gastric cancer xenografts. Using dimeric GEBP11 NIR probes in real-time surgery, the tumor margins and peritoneal metastases could be clearly visualized. Histological examination confirmed the complete resection of the tumor.

Conclusion: (GEBP11)2-ACP-Cy5.5 could be a potential useful probe for intraoperative florescence guidance in gastric cancer surgery.

KEYWORDS
fluorescence imaging, image-guided surgery, gastric cancer, GEBP11 peptide, near-infrared

Introduction

Gastric cancer is the third leading cause of cancer-related deaths worldwide with over 1 million estimated new cases detected annually (1). Curative surgery constitutes the mainstay for gastric cancers, even though targeted therapies and immunotherapy are widely used (2–4). Surgery for gastric cancer aims at R0 resection with negative margins and adequate lymphadenectomy. Following guidelines on margin length, R0 resection could be achieved in the majority of gastric cancer patients. However, positive resection margin is reported in about 2.8%-8.2% gastric cancer patients who underwent gastrectomy and is associated with poor clinical outcomes (5, 6). Intraoperative fluorescence or endoscopic guidance have been used to assist the gastrectomy procedures (7, 8). However, surgeons still primarily rely on white light to determine the margins in gastric cancer surgery. Powerful intraoperative image guidance will be helpful for fast and accurate visualization of tumors during surgery and minimize R1 resection.

Near-infrared (NIR) fluorescence imaging holds great promise for image-guided surgery due to relatively low autofluorescence and deep photon penetration as well as high sensitivity without risk of radiation exposure (9). With the assistance of NIR fluorescence imaging, surgical field can be color coded and margins between the tumor and normal tissues can be well visualized (10). When combined with appropriate contrast agents, NIR fluorescence imaging can provide real-time image guidance to ensure successful removal of all the cancerous tissue and decrease complications. NIR fluorescence probes have been successful used in intraoperative tumor imaging and sentinel lymph node (SLN) mapping of various types of cancers such as ovary cancer, prostate cancer, colon and rectum cancer and gastric cancer (11–13). Currently, indocyanine green (ICG)-based fluorescence imaging has been used for real-time anatomy assessment and intraoperative lymphography (7, 14). Though promising, ICG is not cancer-specific, and could yield false positive or false negative results (15, 16). Human epidermal receptor 2 (HER2) and folate receptor have also been targeted for real-time intraoperative molecular imaging of gastric cancer (17). But their expression in the cancer tissue significantly affects the performance of these methods.

Using *in vivo* phage display, we have identified a peptide, GEBP11, which specifically binds to the tumor vasculature of human gastric cancer (18). In our previous studies, I131 or FITC labeled GEBP11 probes showed high affinity and specificity to the vasculature of gastric cancer, which could be used for *in vivo* imaging and targeted therapy (19, 20). In the present study, mono and dimeric GEBP11 peptides were labeled with NIR fluorophore dye, Cy5.5. These probes were verified *in vitro* and *in vivo* for their specificity and affinity. Then dimeric GEBP11 NIR probe was used for intraoperative NIR fluorescence imaging guidance in gastric cancer xenograft mouse models. Margins of the surgical specimens was examined to confirm complete resection.

Materials and methods

Synthesis and fluorescence labeling of $(GEBP11)_2$-ACP and GEBP11

Both mono and dimeric GEBP11 peptide were biochemically synthesized by Qiangyao biotechnology company (Shanghai, China). Dimeric GEBP11 peptide was prepared by covalently crosslinking single peptides with an artificial peptide (ACP) linker, to form $(GEBP11)_2$-ACP. For labeling, GEBP11 peptide (2.12 mg, 2 mmol) or $(GEBP11)_2$-ACP (4.43 mg, 2 mmol) and TEA (12 µL, 0.08 mmol) were dissolved in 1ml DMSO, with a 2-fold molar excess of Cy5.5-NHS (2 mg, 4 mmol) separately. The mixture was further protected from light and rotated at room temperature overnight. After completion of reaction, the mixture was lyophilized using a freeze-dryer to remove DMSO. Next, the product was dissolved in 2 mL PBS in dialysis bag and dialyzed (1L PBS × 3) to remove the unconjugated Cy5.5. Finally, the solution was lyophilized to obtain Cy5.5 labeled probes. The probes were characterized by high resolution mass spectrometer to confirm their purities (HRMS, ESI, positive mode; Cy5.5-GEBP11: calculated M_r=1999.7, found m/z =1997.6405 ([M_r]). Cy5.5-$(GEBP11)_2$: calculated M_r = 3210.4, found m/z = 1605.3002 [(M_r+H^+)/2]).

Cell lines

Human umbilical vein endothelial cells (HUVECs) and human gastric adenocarcinoma cell line SGC7901 used for *in vitro* targeting test were preserved in our laboratory. SGC7901 cells constitutively expressing luciferase or GFP (SGC7901-Luc or SGC7901-GFP) were established as previously reported (21), dual transfected cell lines were prepared for establishing tumor xenograft models. All mentioned cells were cultured in RPMI 1640 medium, supplemented with 10% fetal calf serum (Gibco, USA), 100 µg/mL streptomycin and 100 units/mL penicillin.

In vitro specificity and affinity assay

Previous studies have demonstrated that co-culture of the cancer cells with vascular endothelial cells could create a similar microenvironment with the situation in the solid tumor mass (22, 23). SGC7901 cells and HUVECs were cocultured as previously described (18). Co- HUVECs (co-cultured HUVECs), HUVECs and SGC7901 cells were harvested at log-growth phase and characterized by bench top fluorescent microscopy. Cells were incubated with 1μM GEBP11-Cy5.5 or $(GEBP11)_2$-ACP-Cy5.5 for 6h at 37°C in a humidified atmosphere with 5% CO_2. Binding affinity of the probes to cultured cells were detected by laser scanning confocal microscope (FV3000, Olympus, Japan). Nucleus were re-stained with ProLong^{TM} Gold Antifade Mountant with DAPI (Invitrogen, USA) at room temperature. For binding specificity assessment, cells were pretreated with 25μM unlabeled GEBP11 for 30min at 37°C before incubating with the labeled probes.

Animal tumor xenograft models

All animal experiments were conducted in compliance with protocols approved by the Institute of Animal Use Committee of Air Force Medical University. All gastric cancer xenograft models were established in 6–8 week old female athymic nude mice. The SGC7901-Luc or SGC7901-GFP cell suspension at a concentration of 2×10^6 cells/mL was prepared. For subcutaneous xenograft model, SGC7901-GFP cells suspension (100μL/mouse) were injected subcutaneously into the right upper limb (for *in vivo* binding affinity test) or lower flank of mouse (for *in vivo* biodistribution assay). The orthotopic gastric cancer xenograft models were established as described previously (21), In brief, open abdominal surgery was performed on the mice under general anesthesia, SGC7901-Luc cells suspension (100μL/mouse) were injected into the subserosa layer of the stomach.

Tumor growth was monitored by Caliper IVIS Lumina II (PerkinElmer, MA, USA). GFP fluorescence imaging was performed in subcutaneous xenograft model. Bioluminescence imaging (BLI) was performed to monitor tumor growth in the orthotopic xenograft models. Because of its higher penetrability and sensitivity, peritoneal metastasis can be visualized clearly as well. Before BLI was acquired, mice were injected with D-luciferin (150 mg/kg) by intraperitoneal injection and anesthetized with 2% isoflurane. Living Image software 4.7.3 (IVIS) was used to quantify bioluminescence signals.

All mice were fed irradiated alfalfa-free rodent diet (Envigo Teklad, Madison, WI) to reduce background in stomach and gut for one week prior to the imaging experiments. The mice models were used for *in vivo* imaging and surgical procedures when xenograft diameter reached 5 to 10 mm.

Live imaging and biodistribution assays

Xenograft mice were injected with 200 ul GEBP11-Cy5.5, $(GEBP11)_2$-ACP-Cy5.5 or free Cy5.5 (5 μM in PBS) *via* tail veins. Live NIR fluorescence imaging was performed at different time points. NIR Fluorescence intensity was quantified by region-of-interest (ROI) measurement using Living Image software 4.7.3 (IVIS).

Subcutaneous tumor xenograft models were used to detect the biodistribution of NIR signals. Mice were euthanized at 24h after injection of the labeled probes or free Cy5.5. All assays were done in triplicates. Then tumor xenografts and main organs (heart, lung, kidney, bone, muscle, brain, spleen, liver, skin and intestines) were harvested. Living Image version 4.7.3 Software (IVIS) was used to quantify the NIR fluorescence intensity at selected ROIs. All ROI data were collected after subtracting background autofluorescence. Differences in the fluorescence intensities of the ROIs between different probes were statistically analyzed.

Real-time NIR fluorescence imaging-guided resection and histological analysis

Orthotopic gastric cancer xenograft mice were anesthetized with a ketamine/xylazine mixture *via* intraperitoneal injection 24h after injection of $(GEBP11)_2$-ACP-Cy5.5 probe. Real-time NIR fluorescence imaging was used to guide the removal of the primary cancer lesion and potential metastatic lesions. After resection, all surgical specimens and surgical beds were examined by NIR fluorescence imaging to confirm complete resection. To compare the efficacy of the dimer GEBP11 NIR imaging, BLI imaging pictures were taken before and after resection, the findings of BLI imaging were kept blind to the researcher who performed the surgery.

Resected samples were embedded in optimum cutting temperature (OCT) compound (Leica, Germany), and 10μm-thick frozen tissue sections were cut on a cryostat microtome (Leica, Germany). The sections were fixed immediately with precooled isoacetone for 30min and stored at −20 °C. Hematoxylin and Eosin (H&E) staining was used for histological analysis. Tumor margins defined by H&E staining and NIR fluorescence were compared. All slides were scanned by using Pannoramic-250 Flash II slide-scanner (3D-Histech, Budapest, Hungary) and analyzed by Case viewer software (3D-Histech, Budapest, Hungary). Mouse tumor vascular endothelial cells were stained by FITC-labeled rat anti-mouse CD31 (89C2) antibody (CST, Boston, USA). Fluorescence microscopy was used to validate the colocalization of $(GEBP11)_2$-ACP-Cy5.5 probe and tumor microvessel. Fluorescence microscopic images were acquired at 100x magnification by using Echo Revolve upside-down integrated fluorescence microscope (ECHO, USA).

Statistical analysis

Quantitative data were expressed as means± standard error. Student t-test was used to compare mean values. Statistical analyses were performed using the Graphpad Prism 8.0.2(263). All the statistical analyses were two-tailed. *P*-value<0.05 were considered statistical significance (*p<0.05, **p<0.01, ***p<0.005, ****p<0.001.)

Results

Preparation of GEBP11 NIR probes and *in vitro* binding assays

The structures and mass spectroscopy analysis results were shown in Figure S1. The purities of synthesized peptides were 99.2% for GEBP11 and 95.8% for (GEBP11)$_2$-ACP-Cy5.5. The labelling efficiency of Cy5.5-GEBP11 and (GEBP11)$_2$-ACP-Cy5.5 were 90% and 75%, respectively.

After incubation with GEBP11-Cy5.5 or (GEBP11)2-ACP-Cy5.5 probes, Co-HUVECs showed strong fluorescence signal, while only scarce signal could be detected on HUVECs or SGC7901. (GEBP11)$_2$-ACP-Cy5.5 showed much higher signal intensity than GEBP11-Cy5.5. Blocking with unlabeled GEBP11 significantly inhibited the binding of labeled probes to the Co-HUVECs (Figure 1). These findings suggested that both GEBP11-Cy5.5 and (GEBP11)$_2$-ACP-Cy5.5 had high affinity and specificity for tumor vascular epithelial cells.

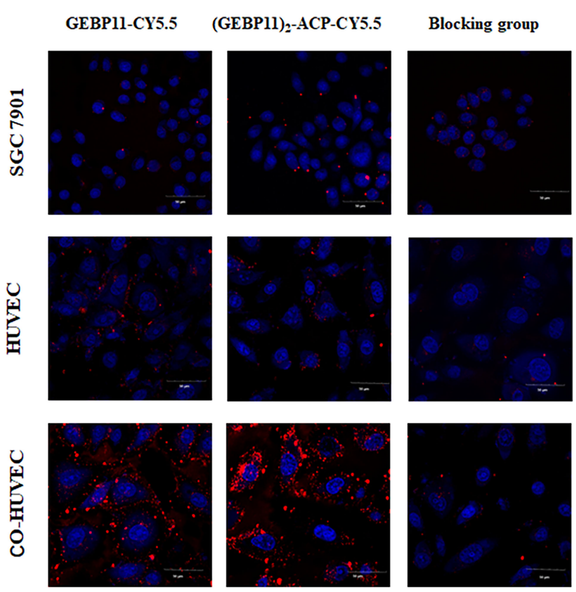

FIGURE 1
In vitro binding affinity of (GEBP11)$_2$-ACP-Cy5.5 or GEBP11-Cy5.5. Confocal immunofluorescence of Cy5.5 labeled GEBP11 probes showed that a high level of (GEBP11)$_2$-ACP-Cy5.5 accumulated in the Co-HUVECs. The competitive inhibition assay demonstrated the suppressive effect of GEBP11-Cy5.5 binding to Co-HUVECs by GEBP11. Cells were stained with DAPI in blue, and Cy5.5 labeled probes colored in red. Scale bar, 50µm.

In vivo NIR fluorescent imaging in subcutaneous gastric cancer xenograft models and biodistribution assays

The subcutaneous gastric cancer xenograft mice were used to test efficacy of the GEBP11 probes for live fluorescence imaging. NIR fluorescence signal could be detected at the tumor sites after injection with GEBP11-Cy5.5 or (GEBP11)$_2$-ACP-Cy5.5. Free Cy5.5 accumulated mainly in the kidneys, and no significant signal was detected at the tumor sites (Figure 2A). At the tumor sites, the NIR fluorescence signal of (GEBP11)$_2$-ACP-Cy5.5 peaked at 24h, gradually declined at 30h and 48h, then dropped markedly at 96h (Figure 2B). GEBP11-Cy5.5 fluorescence signal increased rapidly at 24h, peaked at 30h and decreased sharply at 48h (Figure 2B). To assess the relative signal intensity, tumor to muscle ratio (TMR) of the signal intensity was calculated. Both probes had the highest TMR value at 24h (Figure 2C). Overall, (GEBP11)$_2$-ACP-Cy5.5 showed stronger and prolonged fluorescence signal than GEBP11-Cy5.5, suggesting that (GEBP11)$_2$-ACP-Cy5.5 was more efficient and durable for live imaging (Figure 2C).

To further validate the distribution of the NIR probes *in vivo*, tumors xenografts and major organs were harvested at 24h after the injection and underwent ex vivo fluorescence imaging. As shown in Figure 3, majority of free Cy5.5 was found in the kidney, without enrichment in the tumor. GEBP11-Cy5.5 was enriched in the tumor, with kidney showing moderate enrichment. Significant enrichment of the (GEBP11)$_2$-ACP-Cy5.5 was found in the tumor, comparing with other normal organs. Tumor-to-muscle ratios of (GEBP11)$_2$-ACP-Cy5.5 was 9.76, significantly higher than GEBP11-Cy5.5 (5.65). All these findings suggested that (GEBP11)$_2$-ACP-Cy5.5 had higher specificity and better tumor-to-background contrast for *in vivo* imaging.

In vivo NIR fluorescence imaging in orthotopic gastric cancer xenograft models

To simulate the "natural" scenario, the GEBP11 probes were further evaluated for *in vivo* NIR fluorescence imaging in orthotopic gastric cancer xenograft mice. BLI was used to locate the tumor xenografts. As shown in Figures 4A, B stronger NIR fluorescence signal was detected at the tumor sites in mice injected with (GEBP11)$_2$-ACP-Cy5.5 at 6h comparing with mice injected with GEBP11-Cy5.5 or free Cy5.5. Signal intensity for both (GEBP11)$_2$-ACP-Cy5.5 and GEBP11-Cy5.5 probes peaked at 24h and then declined significantly at 48h, while signal intensity for free Cy5.5 dropped rapidly after 6h. Calculated tumor to muscle ratios (TMR) of the NIR signal intensity showed similar patterns (Figure 4C). The NIR fluorescence intensity curve of the (GEBP11)$_2$-ACP-Cy5.5 NIR probe was smoother than GEBP11-Cy5.5, suggesting that binding of the (GEBP11)$_2$-ACP-Cy5.5 was more rapid and stable from 6h to 24h after injection.

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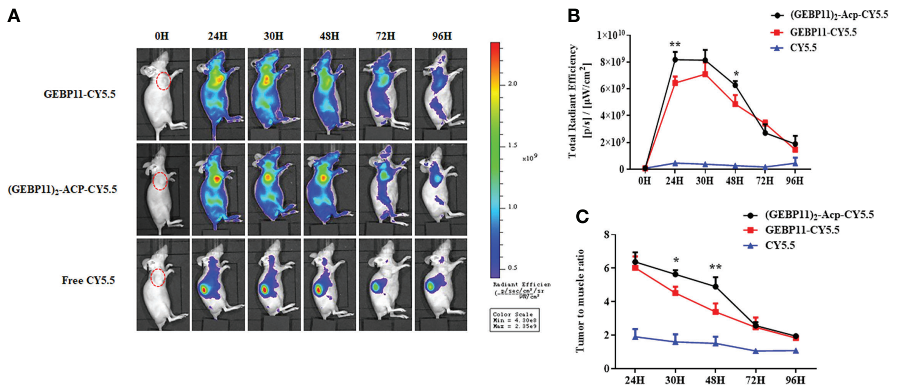

FIGURE 2
NIR fluorescent imaging of GEBP11 series probes in subcutaneous tumor models. **(A)** *In vivo* continuous observations (0-96 h) of SGC7901 bearing xenografts after intravenous administration of series probes by IVIS imaging system. $(GEBP11)_2$-ACP-Cy5.5 probe exhibited more specific tumor targeting and longer retention, while the fluorescence signal mainly focused on kidney in the negative control (Free Cy5.5) group. **(B)** Dynamic changes of total fluorescence signal in the tumor site. **(C)** Comparison of tumor-to-muscle ratio of different probes. All data were expressed as mean ± SD. **p* < 0.05; ***p* < 0.01.

Intraoperative fluorescence imaging guidance for gastric cancer resection

To assess the potential utility of $(GEBP11)_2$-ACP-Cy5.5 to aid tumor resection, real-time intraoperative fluorescence was used to guide surgical resection of gastric cancer in orthotopic gastric cancer xenograft model. Under white light, xenograft tumors seemed to be deeply invasive and the margins between tumor and surrounding normal tissues were hard to identify. Under NIR fluorescence imaging, the tumor margins were located, and tumors were removed (Figure 5A). Interestingly, $(GEBP11)_2$-ACP-Cy5.5 also detected peritoneal metastatic lesions indistinguishable under white light (Figure 5B). Metastatic lesions were also removed. After resection, the

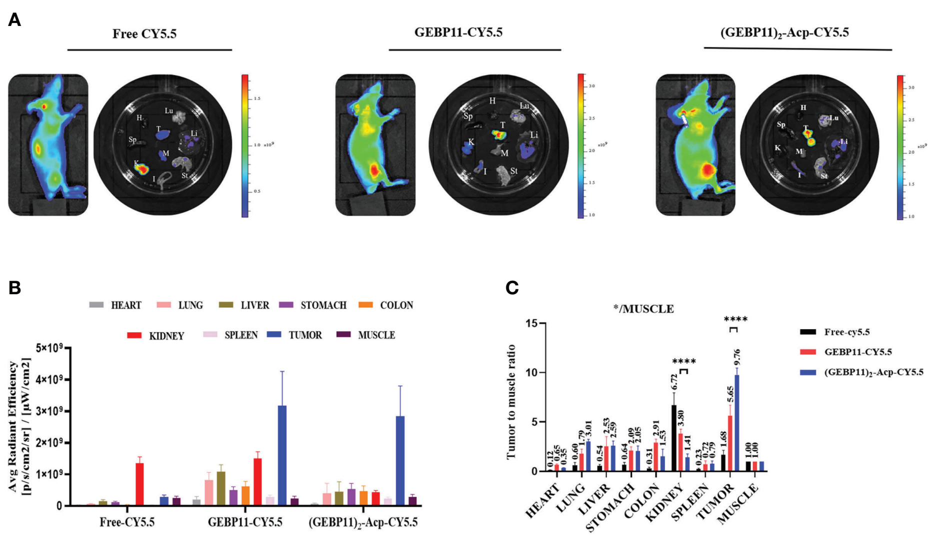

FIGURE 3
Biodistribution study of free Cy5.5, GEBP11-Cy5.5 and $(GEBP11)_2$-Acp-Cy5.5 group *in vivo*. **(A)** Representative fluorescence images of the subcutaneous tumor-bearing mice and excised organs at 24 h post-injection, Color bar Units: $[p/s/cm^2/sr]/[\mu W/cm^2]$. **(B)** Average signal intensity of main organs in each group of mice. **(C)** Quantification of SBR profiles (tumor to muscle) of nude mice administered GEBP11 series probes at 24h. *****P* < 0.001, n=3. *Abbreviation label of main organs: H, Heart, Lu, Lung, K, Kidney, Mu, Muscle; Sp, Spleen; Li, Liver; In, Intesinal; G, Gastric; T, Tumor.

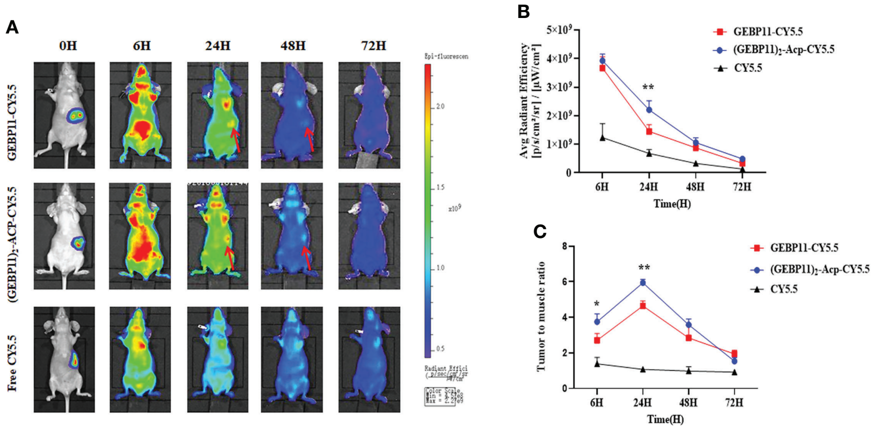

FIGURE 4
Targeting specificity of free Cy5.5, GEBP11-Cy5.5 and $(GEBP11)_2$-Acp-Cy5.5. **(A)** fluorescence imaging of orthotopic tumor-bearing nude mice after injection with probes. **(B)** Total fluorescence signal emitted from the tumor site over time. **(C)** tumor-to-muscle ratio of the series probes over time. *$p < 0.05$; **$p < 0.01$.

surgical beds and resected specimens were examined by NIR fluorescence imaging to ensure complete resection. There was a significant consistence between NIR findings and BLI imaging. No residual cancer lesion could be detected by BLI after NIR-guided resection.

After surgery, the margins between tumor and normal tissue were determined by NIR and BLI, and then histological examination was used to confirm the margins. Macroscopically, the margin defined by NIR fluorescence on macroscopic specimen correlated well with the H&E staining; Microscopic examination also confirmed the demarcation by NIR probe (Figure 6). By confocal fluorescence microscopic examination, fluorescence signals of $(GEBP11)_2$-ACP-Cy5.5 was found to co-localize with CD31 on the tumor vascular epithelial cells that delineated the tumor margins (Figure 7). Taken together, all these findings suggested that NIR-dye-labeled $(GEBP11)_2$-ACP could serve as an optical imaging probe for real-time intraoperative NIR guidance in gastric cancer resection.

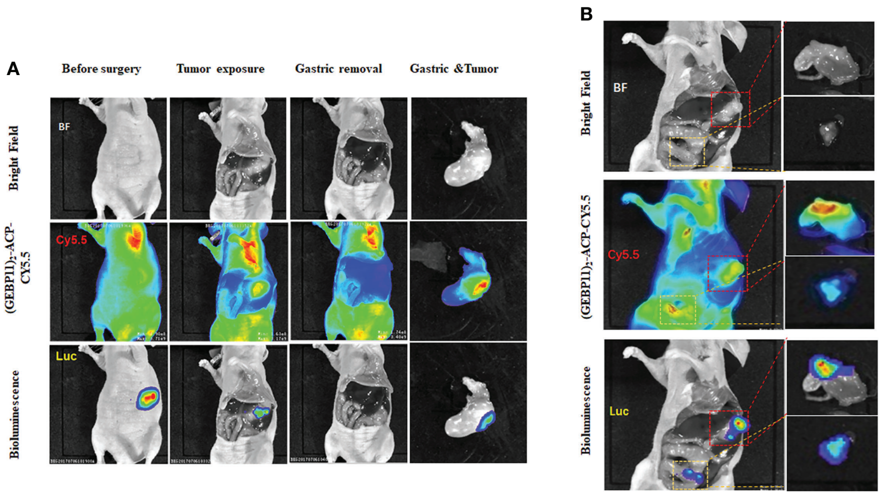

FIGURE 5
Intraoperative detection and resection of gastric cancer by $(GEBP11)_2$-Acp-Cy5.5 probe. **(A)** Representative bioluminescence imaging (BLI) and fluorescence images of mice before and after surgery in orthotopic xenografts models under fluorescence guidance; **(B)** Intraoperative detection of peritoneal metastasis detected by white light imaging, BLI and molecular fluorescence-guided surgery (The red box represents gastric cancer in situ, the white box represents peritoneal metastasis location).

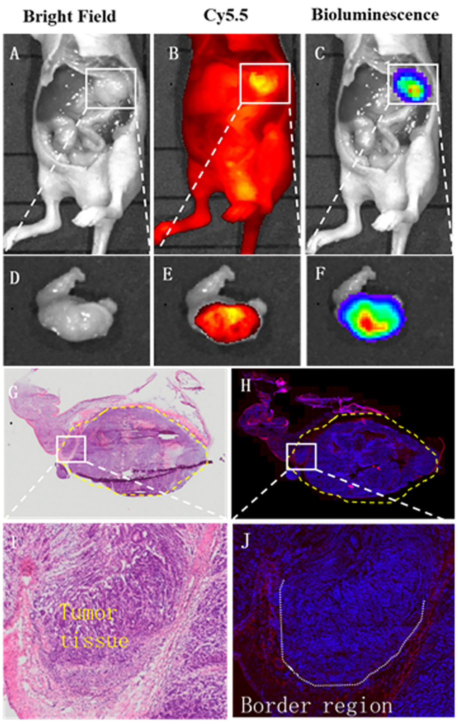

FIGURE 6
Intraoperative tumor margin assessment by $(GEBP11)_2$-Acp-Cy5.5 probe. Compared with bright light imaging **(A, D)**, $(GEBP11)_2$-Acp-Cy5.5 probe enhanced tumor to normal tissue contrast under fluorescence imaging *in vivo* and *vitro* **(B, E)**, which was confirmed by bioluminescence imaging **(C, F)**. **(G, H)** Immunohistochemical staining and fluorescence imaging showed a clear tumor positive circumferential resection margin (yellow dotted line). **(I)** Further microscopic histological analysis of the resected tissue clearly visualized border regions between tumor and surrounding healthy tissues, which was consistent with fluorescence signals of $(GEBP11)_2$-ACP-Cy5.5 **(J)**.

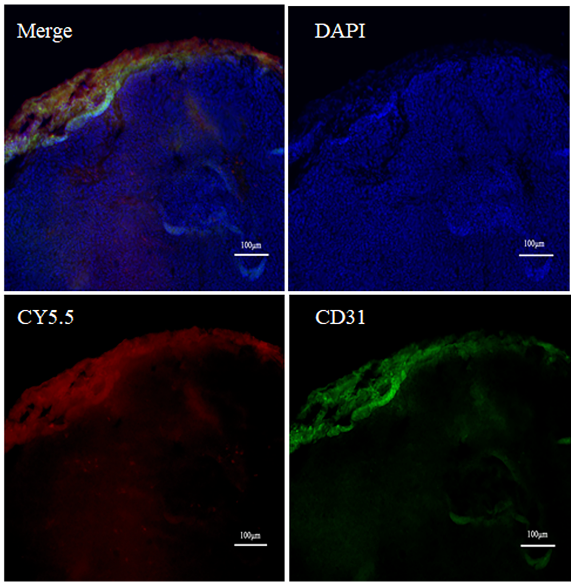

FIGURE 7
Vascular targeted co-location fluorescence probe imaging. Double labeling fluorescence using CD31 (green) and $(GEBP11)_2$-Acp-Cy5.5 (red) probe showed tumor vessels in the peripheral area near the tumor edge.

Discussion

Molecular imaging is playing increasingly important roles in cancer diagnosis and treatment, especially in cancer surgery. Compared with traditional imaging techniques, intraoperative fluorescence imaging shows new possibilities and promising potential in cancer care. Currently, diverse biological imaging agents such as radionuclide, iron nanoparticles, and NIR agents have been designed for tumor imaging and/or therapy of gastric cancer (24, 25). A nanocolloid radiopharmaceutical reagent has been tested for intraoperative visualization of SLN in gastric cancer patients (26). The radionuclide detected SLN with high sensitivity and specificity but could not distinguish metastatic from nonmetastatic lymph nodes. The need for radiometry also complicated the procedure. Moreover, it is hard for the nanoparticles to permeate and transfer to the tumor sites due to increased interstitial fluid pressure in gastric cancer. Several NIR imaging reagents have also been reported. Among them, ICG fluorescence imaging (ICG-FI) is a well-established modality in the SLN mapping and image-guided surgery of gastric cancer (27). Nevertheless, ICG-FI suffers from several intrinsic drawbacks such as its non-specificity, instability and limited quantum yield (27, 28). Specific tumor antigens such as HER2 and carcinoembryonic antigen (CEA) have been targeted for live imaging during gastric cancer surgery (29–32). However, only a small portion of gastric cancer express HER2 and CEA, which limited their use.

Tumor stromal cells serve as potential better targets for fluorescence guided oncologic surgery. Aggressive cancers usually have high stromal content, which often primarily locate at the periphery/invasive front of the tumor. Unlike tumor antigens, tumor stromal markers do not rely on specific genetic variation and seem to be more “universal”. Neo-angiogenic endothelial cells is the first tumor stromal cell to be exploited for imaging (33). Antibodies, peptides, and small molecules targeting tumor vascular endothelial cells have been developed. IRDye800CW labeled with bevacizumab has been used in various fluorescence molecular imaging trial targeting tumors and peritoneal carcinomatosis that overexpress vascular endothelial growth factor (12, 34, 35). Antibodies have large mass and complexed structure, making them unsuitable for the targeting of solid tumors. The properties of peptide, such as small size, high specificity, and easier tissue clearance make them more preferrable for tumor imaging. The stability and half-life of the targeting peptides could be further improved by multivalent modification while preserving the correct conformations (36, 37).

In our study, we used a peptide specific for gastric cancer vasculature for tumor imaging. Both mono and dimeric GEBP11 polypeptides showed good affinity and specificity for gastric cancer vascular endothelial cells. Previous studies indicated that multivalent modification could increase circulation time and lower renal clearance of the probes (19, 38). In the present study, dimeric GEBP11 peptide showed better accumulation in tumors, prolonged signals and reduced renal accumulation *in vivo*. Therefore, $(GEBP11)_2$-ACP-Cy5.5 was further tested for intraoperative fluorescence imaging. Under NIR, tumor margins and peritoneal metastases could be clearly visualized during surgery. Complete resection was achieved in all animals. By examining the surgical specimens, NIR signals correspond well with the histological findings, which clearly delineated tumor margins and metastatic lesions. The specificity of the probes for tumor vascular endothelial cells was confirmed by CD31 co-staining. Taken together, we developed a specific NIR probe for gastric cancer imaging, which showed promising potential for fluorescence guided oncologic surgery.

Although the findings of this study are encouraging, there are some limitations. First, GEBP11 peptide receptor on vascular endothelial cell is still unclear, but several candidate receptor molecules have been acquired. Further work needs to be conducted to understand the interaction between GEBP11 peptide and its ligand. Second, we used Cy5.5 to label the probes. Currently the use of cyanine dyes is still mostly restricted in the laboratory. IRDye800CW has low auto-fluorescence, high spatial resolution and has been used to label drugs and probes in clinical trials (39). To facilitate clinical translation, labeling $(GEBP11)_2$-ACP with IRDye800CW for intraoperative imaging should be investigated. Third, though specificity and binding affinity of GEBP11 for human gastric cancer vasculature have been confirmed *in vitro* (20). *In vivo* distribution of the probes in human should be invested before clinical application. Besides, the usefulness of the probes for metastatic gastric cancer should also be further studied. Other models of gastric cancer with distal metastasis to lung, liver or other organs should be used.

Conclusion

In summary, the present study demonstrates the potential of a specific targeting probe, $(GEBP11)_2$-ACP-Cy5.5, for highlighting tumor lesions with high contrast during fluorescence-guided surgery, which may be used for the real-time image-guided oncologic surgery of gastric cancer.

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 authors.

Ethics statement

The animal study was reviewed and approved by Institute of Animal Use Committee of Air Force Medical University. Written informed consent was obtained from the owners for the participation of their animals in this study.

Author contributions

All of authors have contributed the work. Contributing to conception and design: JZ, CG, XinZ, ZT. Carrying out experiments: JZ, ZT, MT, XiaZ. Analysis and interpretation of the data: JZ, ZT, CG. Drafting the manuscript: JZ, ZT, CG. Critical revision of the article for important intellectual content: JZ, CG, SL. Final approval of the article: XinZ, JZ, CG. Scientific advisors: JZ, CG, XinZ. Financial support: JZ, SL. They have seen and approvaled the content of the manuscript submitted for publication.

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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.2022.885036/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Chemical structure and MS identification of Cy 5.5 labeled GEBP11 probes.

SUPPLEMENTARY FIGURE 2
Stability of GEBP11-Cy5.5 and $(GEBP11)_2$-Acp-Cy5.5. *In vivo* binding affinity and targeting properties of probes with different storage duration (**A, D:** 7day, **B, E:** 2month, **C, F:** 6month) were tested in subcutaneous tumor models. Fluorescence images of mice and excised organs were collected 24h after tail vein injection (H, Heart, Lu, Lung, K, Kidney, Mu, Muscle; Sp, Spleen; Li, Liver; In, Intestinal; G, Gastric; T, Tumor).

SUPPLEMENTARY FIGURE 3
NIR fluorescent imaging of GEBP11 probes injection within 24 hours in subcutaneous tumor models. (A) *In vivo* continuous observations (24 h) of SGC7901 bearing xenografts after intravenous administration of series probes by IVIS imaging system. (B) Quantification of average fluorescent efficiency changes with time dependent in the tumor site. (C) Comparison of tumor-to-muscle profiles between $(GEBP11)_2$-ACP-Cy5.5 & GEBP11-Cy5.5 probe. ****$p < 0.001$.

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Left versus right approach for middle and lower esophageal squamous cell carcinoma: A propensity score-matched study

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Background: Despite superior short-term outcomes, there is considerable debate about the oncological efficacy of the left approach esophagectomy for middle and lower squamous esophageal carcinoma (ESCC). A propensity score-matched retrospective study was conducted to evaluate the left approach's short- and long-term effects.

Methods: We recorded data from patients with ESCC who underwent curative resection *via* the left or right approach between January 2010 and December 2015. Propensity score matching (PSM) was performed, and maximally selected rank statistics (MSRS) were utilized to determine the appropriate number of lymph nodes to resect during esophagectomy.

Results: One hundred and forty-eight ESCC patients underwent esophagectomy *via* the right approach, and 108 underwent the left approach esophagectomy. After PSM, the left approach esophagectomy showed statistically significant superiority in operative time and time to oral intake, and there was a trend toward a shorter length of hospital stay. Fewer cervical, upper thoracic, and recurrent laryngeal nerve lymph nodes were harvested *via* the left approach than the right approach; the total number of lymph nodes harvested *via* the left and right approaches was similar. Similar long-term survival outcomes were achieved. MSRS suggested that at least 25 lymph nodes are needed to be resected during esophagectomy to improve survival in N0 patients.

Conclusions: The left approach esophagectomy might facilitate postoperative recovery in patients with middle and lower ESCC. With adequate lymphadenectomy, the left approach esophagectomy might achieve similar long-term outcomes for middle and lower ESCC patients.

KEYWORDS

esophageal squamous cell carcinoma, Sweet procedure, Ivor-Lewis procedure, McKeown procedure, lymphadenectomy

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1 Introduction

Esophageal carcinoma is a common malignancy in China, ranked sixth in incidence (285,000) and fourth in mortality (193,000) in 2014 (1). Unlike esophageal adenocarcinoma (the predominant pathological type in the western world), ESCC predominates in East Asia (2). For resectable ESCC, radical resection is the procedure of choice in this era of multi-disciplinary treatment. However, controversies remain regarding the optimal approach for middle and lower ESCC.

The left approach, i.e., a left thoracotomy with or without cervical incision, is common in China, owing (at least in part) to the labor-saving positioning and convenient hilar structure exposure (3, 4). Nevertheless, despite the similar long-term survival outcomes suggested by several studies (3–6), the effectiveness of upper mediastinal lymphadenectomy is debated (7). It appears that this debate between the advocates of left and right approaches was not resolved by a randomized controlled trial (8); there was a critique of the methodology of preoperative evaluation and assignment of adjuvant therapy (9), and there is evidence to suggest the non-inferiority of the Sweet procedure in middle and lower ESCC treatment (10, 11). Therefore, we performed a propensity score matched study to evaluate the effectiveness of the left approach esophagectomy compared to the right approach for middle and lower ESCC.

2 Article types

Original research.

3 Manuscript

3.1 Materials and methods

3.1.1 Study population and groups assignment

Records of patients undergoing curative surgery at Peking University First Hospital between 1 January 2010 and 31 December 2015 were analyzed retrospectively. The ethics committee of Peking University First Hospital approved this study, and consent was acquired for each participant.

Eligibility criteria: 1) age 18 or older; 2) primary squamous cell pathology confirmed; 3) curative surgery undergone; 4) location in the middle or lower esophagus; 5) no distant metastasis suggested before surgery. Exclusion criteria: 1) other histological types; 2) location in the upper esophagus; 3) radical resection not completed, i.e., either the resection was aborted because of intraoperative findings or gross tumor mass remained unresected.

To compare the approaches for middle and lower squamous cell esophageal cancer, we assigned patients into left or right groups based on the procedure; right procedures included Ivor-Lewis and McKeown esophagectomy, and left procedures included thoracic-cervical dual-incision and left thoracic esophagectomy. Because there is evidence suggesting that the greater length of tumor-free esophagus removed with a cervical anastomosis does not result in improved long-term survival (12) (the primary endpoint of our study), the different locations of anastomoses (intrathoracic or cervical) of the same side were included in one group.

3.1.2 Staging and treatment

The preoperative examination included computed tomography (CT) of the chest and upper abdomen, ultrasonography of superficial lymph nodes, cranial magnetic resonance imaging, ultrasonic cardiogram, electrocardiogram, and pulmonary function tests. Positron emission tomography-CT and transesophageal ultrasonography were performed at the surgeon's discretion. The staging was carried out according to the TNM staging system of the AJCC eighth edition.

Surgery was conducted *via* either the left (Sweet procedure or left cervicothoracic dual-incision esophagectomy) or right (McKeown or Ivor-Lewis procedure). The left procedure was performed through a left lower intercostal thoracotomy, usually the sixth intercostal space at the mid-axillary line. After the resectability was confirmed by exploration, the middle and lower esophagus was freed, while lymphadenectomy of adjacent lymph nodes was performed in an en bloc fashion. The 4L station lymph node was routinely resected. Then, the abdominal cavity was entered *via* a radial diaphragmatic incision. A series of linear staplers shaped the gastric conduit after adequate length was acquired, and adjacent abdominal lymph nodes were resected in the process. A resection margin more significant than 5 cm was considered safe, and a frozen biopsy was routinely performed to confirm a clear margin. An additional cervical incision would be made if cervical anastomosis was required, and relevant cervical and recurrent laryngeal nerve lymph nodes would be examined and resected in the process if needed. It was worth noting that, as a center that has conducted thoracoscopy-assisted surgery since the early 90s (13), we routinely conduct lymphadenectomy using thoracoscopy, which could greatly facilitate the proper exposure and resection of lymph nodes that lie in the vicinity of the esophagus and the proximal stomach (Figure 1). However, although the thoracoscope could greatly facilitate the process, one should acknowledge that the exposure of upper mediastinum lymph nodes would be more readily achieved *via* the right approach. We will address this issue in greater detail in the discussion section. Upon the completion of the anastomosis, a gastric tube was placed with the tip around the diaphragmatic level for decompression and later enteral nutrition.

For the right approach (i.e., the McKeown or the Ivor-Lewis procedure), the esophagus resection and anastomosis placement followed the same principle as the left procedure. Regarding

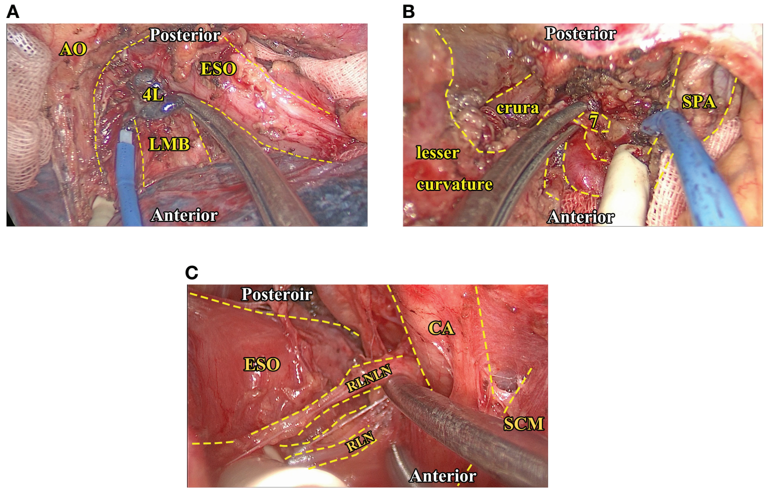

FIGURE 1
Intraoperative images of critical lymph node exposure and dissection. **(A)**, The exposure and dissection of 4L station (thoracic) lymph nodes. Note that the proper traction of adjacent hilar structures could facilitate exposure of 4L station nodes. **(B)**, The exposure and dissection of seven station (abdominal) lymph nodes after the left gastric vessels are dissected *via* the transhiatal approach. In this region, keeping the stomach empty and anterior traction of it could help expose the celiac structure. **(C)**, The exposure and dissection of recurrent laryngeal nerve lymph nodes (left side), the SCM muscle, and the carotid artery could be gently tracked so the exposure of the peri-esophageal region could be more readily exposed. AO, Aortic artery. CA, Carotid artery. ESO, Esophagus. LMB, Left main bronchus. RLN, Recurrent laryngeal nerve. RLNLN, Recurrent laryngeal nerve lymph nodes. SCM, Sternocleidomastoid muscle. SPA, Splenic artery.

lymphadenectomy, however, the upper mediastinal lymph nodes could be more readily harvested through the right approach; therefore, the major difference between the two approaches lies in the patterns of lymph node resection.

After the procedure, the patients received postoperative care, including prophylactic antibiotics, intravenous patient-controlled anesthesia, and mucolytic treatments. Complete blood counts and biochemistry tests were drawn every other day. Individualized total parenteral nutrition was started on the first postoperative day, and an upper gastrointestinal barium contrast meal was usually conducted on the seventh postoperative day to ensure event-free anastomosis. Following a normal barium meal and blood test results, oral nutrition was immediately given. The patient would be considered eligible for discharge if oral nutrition could be administered without complications and the patient could return to a relatively normal life.

3.1.3 Follow-up and outcome

After discharge, the patient would undergo follow-up every three months for the first two years, then every six months in the third to fifth years. Chest CT, esophageal endoscopy, abdomen and superficial lymph nodes ultrasonography, head magnetic resonance imaging, and serum tumor marker tests were performed at each follow-up. The primary outcomes were overall survival (OS) and recurrence-free survival (RFS). OS was calculated from the date of the surgery to the date of death from any cause, and RFS was calculated from the date of the surgery to the date of disease recurrence. The event-free patient at the final available follow-up date was right-censored at this date in the survival analysis.

3.1.4 PSM, MSRS, and competing risks survival analysis

PSM, a method that limits the bias caused by an existing dataset for nonrandom assignment analysis (14), is used to minimize the inherent bias in a retrospective study. Propensity scores were calculated using logistic regression based on preoperative characteristics, including age, sex, body mass index (BMI), smoking and drinking habits, serum carcinoembryonic antigen and squamous cell carcinoma antigen levels, neoadjuvant therapy, and tumor location. A 1:1 matched cohort was generated by matching patients who underwent the right and left approaches using a caliper width equal to 20% of the standard deviation of propensity scores without replacement. The post-matching balance was tested using the Student's t-test or Wilcoxon rank-sum test for continuous variables and the chi-square test or Fisher's exact test for categorical variables.

For the cut-point evaluation, choosing a cut-point that minimizes the p-value of a two-sample test between two groups leads to an increased false error rate. It is necessary to determine whether there is a difference between groups before estimating the cut-point (15). For this purpose, MSRS was used to estimate the cutoff of the number of lymph nodes yielded by radical esophagectomy.

A competing risk is an alternative outcome of equal or more significant clinical importance than the primary outcome that alters the probability of the outcome of interest (16). Competing risk analyses were performed to determine whether the left approach esophagectomy (while offering faster recovery and similar long-term survival) leads to more cervical and mediastinal lymph node recurrence. The sub-hazards of recurrence in the cervical and thoracic lymph nodes and the other regions were calculated using the model developed by Fine and Gray (17), and cumulative incidence functions were plotted.

3.1.5 Statistical analysis

The OS and RFS of patients who underwent the left and right approach esophagectomy were compared using the Kaplan-Meier method in the overall study population and the PSM cohort. A variable would be included in a multivariable Cox regression if the univariable Cox regression suggested significance.

The normality of continuous variables was tested using the Shapiro-Wilk test. Student's t-test and Wilcoxon rank-sum test were used to compare the normal and skewed distributed continuous variables between groups, respectively. The chi-square test or Fisher's exact test was performed for categorical variables. For all analyses, $p < 0.05$ in a two-tailed test was considered statistically significant. All analyses were performed using STATA/MP 15.1 software (StataCorp LLC, College Station, TX, USA), the R Project for Statistical Computing (18), and the R studio.

3.2 Results

3.2.1 Characteristics

We identified 256 esophageal squamous cell carcinoma patients who underwent either the left or right approach, including 108 patients with the left approach (13 Sweet procedures and 95 left cervicothoracic dual-incision esophagectomies) and 148 patients with the right approach (40 Ivor-Lewis procedures and 108 McKeown procedures). There were 20 operations in which a radical resection was aborted due to intraoperative findings (e.g., thoracic or abdominal tumor seeding or tumor invasion to vital structures), 8 of those were through the left approach and 12 through the right approach. More patients received neoadjuvant therapy in the right approach group. PSM generated 81 pairs of patients (seven Sweet procedures and 74 left cervicothoracic dual-incision esophagectomies versus 28 Ivor-Lewis procedures and 53 McKeown procedures) whose preoperative characteristics were well balanced (Table 1).

3.2.2 Perioperative outcomes

Perioperative outcomes of the whole cohort and the PS-matched cohort are displayed in Table 2. The operative time of the left group was significantly shorter than the right approach group in the unmatched and matched groups. After matching, the left group showed a significantly shorter time to oral intake and a trend toward a shorter length of hospital stay. No difference was observed in the severity and incidence of postoperative complications between the groups (Table 2). The number of recurrent laryngeal nerves and upper thoracic lymph nodes harvested were less in the left group, and the total lymph node count was similar between the groups in unmatched and matched cohorts (Table 3).

We further investigated the lymph node yield in a stratified fashion. The number of lymph nodes harvested by the left approach was less than that of the right approach in upper fields (cervical lymph nodes in stage II $p = 0.039$, recurrent laryngeal nerve lymph nodes in stage I $p < 0.001$, stage II $p < 0.001$, upper thoracic lymph nodes in stage I $p = 0.025$, stage II $p = 0.033$, stage III-Iva $p < 0.001$), the number of lymph nodes harvested *via* the left approach was not significantly less than the right approach in the lower fields (i.e., middle and lower thoracic and abdominal) in any stage (Figure 2).

We also investigated the minimal number of lymph node resections for a significant survival benefit using MSRS. The minimum number of lymph nodes harvested during the curative procedure was 25 and 27 for N-negative and N-positive patients. However, no significance was detected between the number of lymph nodes harvested and survival in N-positive patients (Figure 3).

3.2.3 Survival outcomes

The median follow-up period was 47.5 months (range 3–139 months), the 5-year OS was 55.02%, and the 5-year RFS was 50.01%. In the whole cohort, the 5-year OS of the left group was 58.37%, and that of the right approach group was 52.41% ($p = 0.546$) (Figure 4A). The 5-year RFSs of the left and right approach groups were 53.93% and 45.00%, respectively ($p = 0.354$) (Figure 4B). After PS matching, the 5-year OSs of the left and right approach groups were 57.20% and 59.31%, respectively ($p = 0.669$) (Figure 4C), and the 5-year RFSs were 52.11% and 50.46%, respectively ($p = 0.922$) (Figure 4D). We also investigated OS and RFS in both groups in unmatched and matched cohorts in a staged manner; no statistically significant difference was found in any stratum (Figure 5). In the matched cohort, for patients receiving neoadjuvant therapies, there was no significant difference between the left and the right approaches in terms of 5-year OSs (50.00% vs. 50.00%, $p = 0.852$) and 5-year RFSs (50.0% vs. 33.3% $p = 0.748$).

For competing risks, cumulative incidence functions showed no significant difference between the left and right groups in regional (i.e., cervical and mediastinal lymph node) recurrence and recurrence of other regions (Figure 6). In the multivariate competing risks analysis, the left approach esophagectomy showed non-inferiority in the cervical and mediastinal region recurrence rate in the matched cohort (Table 4).

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TABLE 1 The characteristics of the whole and the propensity score matched cohort.

	Full cohort (N = 256)			Matched cohort (81 pairs)		
	Left approach N (108)	Right approach N (148)	p-value	Left approach N (81)	Right approach N (81)	p-value
Preoperative characteristics						
Age	64.08 ± 9.71	62.41 ± 9.44	0.168	63.11 ± 9.9	65.57 ± 9.56	0.110
Gender			0.161			0.678
Male	94 (87%)	119 (80%)		68 (84%)	66 (81%)	
Female	14 (13%)	29 (20%)		13 (16%)	15 (19%)	
Body mass index	22.45 (20.31-25.71)	23.1 (20.70-25.35)	0.646	21.97 (20.20-24.80)	23.31 (20.82-25.60)	0.135
Smoking habit			0.133			0.423
Yes	57 (53%)	92 (62%)		30 (37%)	35 (43%)	
No	51 (47%)	56 (38%)		51 (63%)	46 (57%)	
Drinking habit			0.871			1.000
Yes	58 (54%)	81 (55%)		31 (38%)	31 (38%)	
No	50 (46%)	67 (45%)		50 (62%)	50 (62%)	
CEA	2.58 (1.53-3.57)	2.56 (1.69-3.82)	0.534	2.63 (1.75-3.60)	1.89 (1.44-3.34)	0.075
SCC	1.1 (0.90-1.78)	1.2 (0.80-1.70)	0.422	1.1 (0.8-1.5)	1.2 (0.9-2.2)	0.113
Neoadjuvant therapy			**0.006**			0.576
No	102 (94%)	123 (83%)		75 (93%)	73 (90%)	
Yes	6 (6%)	25 (17%)		6 (7%)	8 (10%)	
Adjuvant Chemotherapy			0.180			1.000
No	98 (91%)	126 (85%)		74 (91%)	74 (91%)	
Yes	10 (9%)	22 (15%)		7 (9%)	7 (9%)	
Adjuvant Radiotherapy			0.557			0.633
No	92 (85%)	122 (82%)		70 (86%)	72 (89%)	
Yes	16 (15%)	26 (18%)		11 (14%)	9 (11%)	
Pathological results						
Resection margin			1.000			1.000
R0 resection	106 (98%)	144 (97%)		79 (98%)	80 (99%)	
R1 resection	2 (2%)	4 (3%)		2 (2%)	1 (1%)	
Positive lymph node	0 (0-2)	1 (0-2)	0.327	0 (0-2)	0 (0-2)	0.629
Location			**0.000**			1.000
Middle	49 (45%)	110 (74%)		45 (56%)	45 (56%)	
Lower	59 (55%)	38 (26%)		36 (44%)	36 (44%)	
Tumor diameter	3.7 (2.5-4.8)	3.5 (2.5-4.7)	0.778	3.5 (2.3-4.5)	3.5 (2.5-4.9)	0.503
T stage			0.242			0.476
T1	21 (19%)	25 (17%)		16 (20%)	13 (16%)	
T2	28 (26%)	26 (18%)		21 (26%)	17 (21%)	
T3	58 (54%)	96 (65%)		43 (53%)	51 (63%)	
T4a	1 (1%)	1 (1%)		1 (1%)	0 (0%)	
N stage			0.496			0.540
N0	58 (54%)	69 (47%)		44 (54%)	41 (51%)	
N1	30 (28%)	43 (29%)		24 (30%)	23 (28%)	
N2	14 (13%)	29 (20%)		9 (11%)	15 (19%)	
N3	6 (6%)	7 (5%)		4 (5%)	2 (2%)	
TNM Stage			0.475			0.677
I	20 (19%)	18 (12%)		15 (19%)	12 (15%)	
II	41 (38%)	55 (37%)		32 (40%)	31 (38%)	
III	41 (38%)	67 (45%)		30 (37%)	36 (44%)	

(Continued)

TABLE 1 Continued

	Full cohort (N = 256)			Matched cohort (81 pairs)		
	Left approach N (108)	Right approach N (148)	p-value	Left approach N (81)	Right approach N (81)	p-value
IVA	6 (6%)	8 (5%)		4 (5%)	2 (2%)	
Vascular tumor thrombus			0.180			1.000
No	98 (91%)	126 (85%)		72 (89%)	72 (89%)	
Yes	10 (9%)	22 (15%)		9 (11%)	9 (11%)	
Nerve invasion			0.679			0.593
No	86 (80%)	109 (74%)		61 (75%)	58 (72%)	
Yes	26 (24%)	39 (26%)		20 (25%)	23 (28%)	
Differentiation			0.877			0.453
High	12 (11%)	19 (13%)		8 (10%)	13 (16%)	
Moderate	76 (70%)	100 (68%)		59 (73%)	57 (70%)	
Low	20 (19%)	29 (20%)		14 (17%)	11 (14%)	

Variables are presented as mean ± standard deviation, median (first quartile – third quartile) or n (%). CEA, carcinoembryonic antigen; SCC, Squamous cell carcinoma antigen. Bold values denote statistical significance.

TABLE 2 The perioperative outcomes of the whole and the propensity score matched cohort.

	Full cohort (N = 256)			Matched cohort (81 pairs)		
	Left approach N (108)	Right approach N (148)	p-value	Left approach N (81)	Right approach N (81)	p-value
Operation time	417.7 ± 128.28)	499.47 ± 127.36	**0.000**	414.63 ± 130.1	488.59 ± 125.93	**0.000**
Operation bleeding	200 (150-400)	225 (150-400)	0.810	200 (150-350)	300 (175-400)	0.471
Length of hospital stay	11 (10-13.75)	11 (10–14)	0.142	10 (9–13)	12 (10–15)	**0.055**
Time to oral intake	8 (7–10)	9 (7–11)	0.108	8 (7–9)	9 (8-11.5)	**0.019**
Length of ICU stay	0 (0-0)	0 (0-0)	0.972	0 (0-0)	0 (0-0)	0.550
Complication (severity)			0.605			0.719
0	77 (71%)	99 (67%)		58 (72%)	52 (64%)	
1	8 (7%)	19 (13%)		8 (10%)	14 (17%)	
2	14 (13%)	18 (12%)		9 (11%)	8 (10%)	
3	7 (6%)	7 (5%)		4 (5%)	4 (5%)	
4	2 (2%)	5 (3%)		2 (2%)	3 (4%)	
Complication (specific)						
Pulmonary infection	2 (2%)	2 (1%)	1.000	2 (2%)	0 (0%)	0.497
Supraventricular tachycardia	4 (4%)	3 (2%)	0.460	2 (2%)	2 (2%)	1.000
Respiratory failure	1 (1%)	1 (1%)	1.000	1 (1%)	1 (1%)	1.000
CCVI	2 (2%)	3 (2%)	1.000	2 (2%)	2 (2%)	1.000
Chylothorax	4 (4%)	2 (1%)	0.244	3 (4%)	0 (0%)	0.245
Anastomosis leak	6 (6%)	7 (5%)	0.780	2 (2%)	5 (6%)	0.495
Gastroparesis	1 (1%)	2 (1%)	1.000	1 (1%)	1 (1%)	1.000
Wound infection	1 (1%)	1 (1%)	1.000	0 (0%)	1 (1%)	1.000
Recurrent nerve injury	1 (1%)	8 (5%)	0.083	1 (1%)	3 (4%)	0.367
Post-op hemorrhage	1 (1%)	1 (1%)	1.000	1 (1%)	0 (0%)	1.000

Variables are presented as mean ± standard deviation, median (first quartile – third quartile) or n (%). Complications were presented by the Clavien-Dindo classification of surgical complications. ICU, intensive care unit; CCVI, Cerebral-cardiovascular incident. Bold values denote statistical significance.

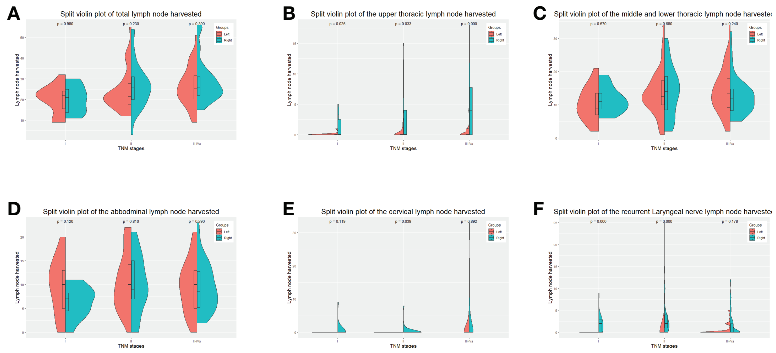

FIGURE 2
Split-violin plots of amount of lymph nodes resected by the Sweet and the right approaches in the PS-matched cohort. **(A)**, the total amount of lymph nodes resected. **(B)**, the amount of the upper thoracic lymph nodes resected. **(C)**, the amount of the middle and lower thoracic lymph nodes resected. **(D)**, the number of abdominal lymph nodes resected. **(E)**, the number of cervical lymph nodes resected. **(F)**, the amount of recurrent laryngeal nerve lymph nodes resected. PS, propensity score.

In the multivariate Cox regression analysis, postoperative chemotherapy, pathologic nerve invasion, and a lower BMI were associated with a worse OS. Elevated serum carcinoembryonic antigen, postoperative chemotherapy, pathologic nerve invasion, and a lower BMI with a worse RFS. Neither the extent of lymphadenectomy nor the laterality of the approach had a significant impact on OS and RFS (Table 5).

3.3 Discussion

In this retrospective study, we confirmed the safety and effectiveness of the left approach esophagectomy in the perioperative period. Survival analysis suggested the non-inferiority of the left approach regarding OS and RFS despite fewer recurrent laryngeal nerve and thoracic lymph nodes.

Long since the Sweet procedure and its variant (the left cervicothoracic esophagectomy) were invented for esophageal carcinoma (19), there has been debate regarding whether the right or left approach was superior to the maturation of surgical technique and whether an accepted staging system is needed to evaluate procedures systematically. Intriguingly, almost all relevant studies involved Eastern Asian patients (20). On the one hand, the predominant pathological type (ESCC) allows for a diverse approach to radical esophageal resection. On the other hand, the left approach has been an effective technique in the history of thoracic surgery in China. Nevertheless, the debate became heated when a prospective randomized controlled trial was published (8). As Peng et al. suggested, we believe it is too early to conclude the optimal approach for middle and lower ESCC (9). With our experience using both approaches, we believe we can contribute to the debate with the present retrospective PSM study results.

Minimizing the surgical disturbance of the normal physiology process for a procedure that affects up to three body compartments is significant. The left approach, which does not require a change of positioning and re-draping, could minimize the traumatic effect of esophagectomy. Our study

TABLE 3 The number of lymph nodes harvested of the whole and the propensity score matched cohort.

	Full cohort (N = 256)			Matched cohort (81 pairs)		
	Left approach N (108)	Right approach N (148)	p-value	Left approach N (81)	Right approach N (81)	p-value
Lymph node harvested (total)	23 (19-30)	25 (20-33)	0.173	22 (18.5-29.5)	25 (21-30.5)	0.095
Lymph node harvested (neck)	0 (0-0)	0 (0-0)	0.089	0 (0-0)	0 (0-0)	0.118
Lymph node harvested (RLN)	0 (0-0)	0 (0-3)	**0.000**	0 (0-0)	2 (0-3)	**0.000**
Lymph node harvested (thorax)	13 (9–18)	15 (10-19.8)	**0.034**	13 (9-17.5)	15 (10–20)	**0.029**
Upper thorax	0 (0-0)	1.5 (0-5.8)	**0.000**	0 (0-0)	1 (0-5)	**0.000**
Middle and lower thorax	13 (9-17.8)	12 (8-16)	0.208	13 (9-17)	13 (8-16)	0.741
Lymph node harvested (abdomen)	10 (5–14)	9 (5-13.8)	0.372	10 (5–14)	8 (5–13)	0.396

RLN, recurrent laryngeal nerve. Bold values denote statistical significance.

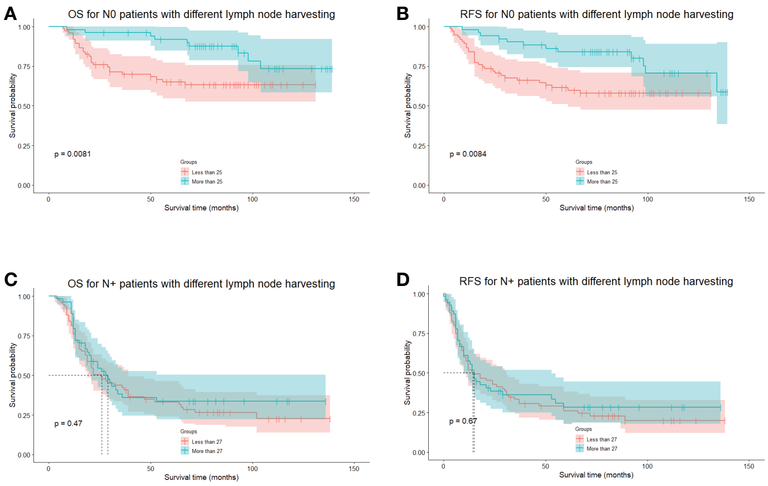

FIGURE 3
The long-term survival of N-negative and N-positive patients grouped by cutoff points calculated using the MSRS. **(A)**, The OS of N-negative patients divided by the cutoff points of 25 lymph nodes. **(B)**, The RFS of N-negative patients divided by the cutoff points of 25 lymph nodes. **(C)**, The OS of N-positive patients divided by the cutoff points of 27 lymph nodes. **(D)**, The RFS of N-positive patients, divided by the cutoff points of 27 lymph nodes. MSRS, maximally selected rank statistics. OS, overall survival. RFS, recurrence-free survival.

showed that, compared to the right approach, the operative time of the left approach was significantly shorter (414.63 ± 130.1 min vs. 488.59 ± 125.93 min, $p < 0.001$), as was the time to oral intake. For the length of hospital stay, patients who underwent the left approach esophagectomy demonstrated a trend toward superiority. These results agree with current literature (6, 11, 20), confirming the left approach's potential to limit the invasiveness of esophagectomy.

Nevertheless, criticism was directed at the lymphadenectomy associated with the left approach, not its feasibility or minimal invasiveness. A contemporaneous randomized controlled trial (RCT) suggested that the lymph node yield of the Sweet procedure was inferior to that of the Ivor-Lewis procedure (7); similar results were reached by several retrospective studies (6, 11, 20, 21). Undeniably, the role of lymph node dissection is fundamental in radical resection for ESCC, and there is

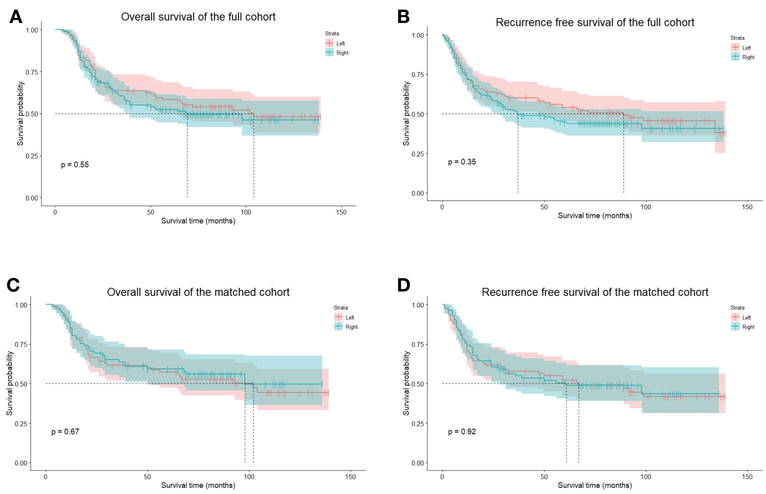

FIGURE 4
The long-term survival of unmatched and PS-matched cohorts. **(A)**, The OS of unmatched patients in the left and right groups. **(B)**, the RFS of unmatched patients in the left and the right groups. **(C)**, The OS of matched patients in the left and right groups. **(D)**, the RFS of matched patients in the left and the right groups. PS, propensity score. OS, overall survival. RFS, recurrence-free survival.

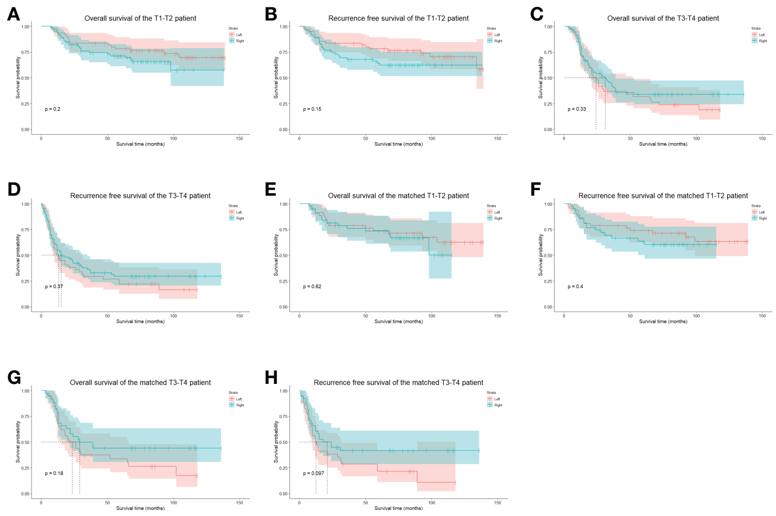

FIGURE 5
The stratified long-term survival of unmatched and PS-matched cohorts. **(A)**, The OS of unmatched stage T1-2 patients. **(B)**, The RFS of unmatched stage T1-2 patients. **(C)**, The OS of unmatched stage T3-4 patients. **(D)**, The RFS of unmatched stage T3-4 patients. **(E)**, The OS of matched stage T1-2 patients. **(F)**, The RFS of matched stage T1-2 patients. **(G)**, The OS of matched stage T3-4 patients. **(H)**, The RFS of matched stage T3-4 patients. OS, overall survival. RFS, recurrence-free survival.

abundant evidence suggesting that a more extensive lymphadenectomy would, if not promote tumor eradication, at least facilitate accurate staging (22, 23). Some aspects remain worth mentioning before concluding whether the left approach is suitable for middle and lower ESCC resection.

First, the question of whether sufficient lymph nodes could be harvested *via* the left approach is not answered. There is evidence validating the capacity of the lymphadenectomy of the Sweet procedure (3, 24, 25) (and the 4L station lymph nodes), which are clinically significant in ESCC procedures (26). Moreover, the evidence suggests that the modified Sweet procedure can achieve satisfactory upper mediastinal and cervical lymph node dissection (27). The upper mediastinum and base of the neck (which were usually considered the blind spots in the left approach esophagectomy) could be readily exposed; therefore, the yield from these regions is not negligible, though less than from the right approach. As the thoracoscopy could also expose the lymph nodes in the lower mediastinal and abdominal region, an adequate lymphadenectomy could be performed with the left approach. Thus, our study showed no significant difference in the number of lymph nodes harvested between the groups. This finding suggests that the left approach using thoracoscope-assisted surgery and careful handling of the resection margin and the anastomosis achieves a local control rate similar to that of the right approach (3). Similarly, we observed no significant difference in the recurrence rate of the cervical and mediastinal region between the groups in the competing risk analysis. Also, as Xing et al. observed, the performance of lymphadenectomy depended heavily on the surgeon's operative skill and familiarity with the procedure. Thus, the narrow, "unacceptable" 30 minutes of the Sweet procedure in the RCT of Chen et al. probably indicated relatively insufficient experience, undermining the validity of their results (8, 10). The efficacy of lymphadenectomy of the upper mediastinum region of the right approach deserves recognition; however, the comparison of the capacity of lymphadenectomy of the two approaches awaits more meticulously and systematically designed RCTs.

Although it is clear that better exposure of upper mediastinum is acquired during the right approach procedure,

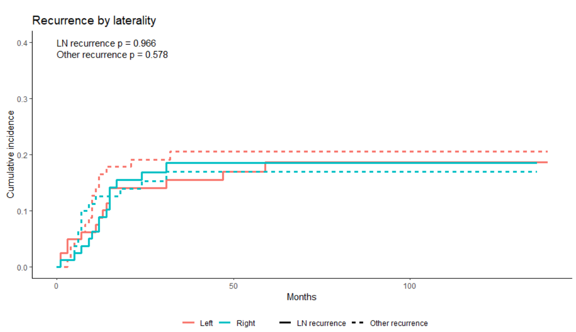

FIGURE 6
The cumulative incidence functions of the PS-matched left and right groups; neither the recurrence rate of the cervical and mediastinal lymph nodes region nor the other region showed a statistically significant difference. LN, lymph nodes. PS, propensity score.

TABLE 4 The sub-hazards of the cervical and mediastinal recurrence, competing with recurrence of other sites.

Variables	Sub-Hazards	p-value	95% Confidence interval	
Left or right approach	1.015	0.971	0.444	2.322
Neoadjuvant therapy	3.115	0.125	0.728	13.322
Operative bleeding	1.001	0.282	0.999	1.004
Length of Stay	1.111	0.108	0.977	1.262
Operative time	0.750	**0.006**	0.612	0.919
Adjuvant radiotherapy	11.391	**0.000**	5.120	25.344
Amount of metastasized LN	0.984	0.898	0.765	1.265
Amount of resected cervical LN	1.015	0.712	0.937	1.100
TNM stage	2.099	0.169	0.730	6.037
Carcinothrombosis	2.419	0.260	0.521	11.235
Nerve invasion	2.468	0.072	0.922	6.609

LN, lymph node. Bold values denote statistical significance.

the causal relationship between a more extended lymph node dissection and better outcomes has yet to be established. Akiyama et al. reported that extensive (i.e., three-field lymph node dissection) significantly improved long-term survival compared to less extensive lymphadenectomy (22). Chen et al. also showed that the extended lymphadenectomy benefited lymph node-positive ESCC patients (28). By contrast, there is evidence from an RCT suggesting that the three-field lymphadenectomy (compared to the two-field lymphadenectomy) did not improve the OS or the RFS in esophagectomy for middle and lower esophageal cancer (29). Lagergren et al. investigated the Sweden esophageal cancer population who underwent curative surgery and found that compared to the limited lymphadenectomy (fewer than ten nodes), a more extended lymph node resection (21–52 nodes) did not improve overall and RFS (30). Our study also indicated that a more extensive lymphadenectomy (more than 27 nodes) for node-positive patients improved neither the OS nor RFS. These findings suggest that it is at least reasonable to assume that lymphadenectomy in the radical resection of middle and lower ESCC might control stage migration more than eradicate tumor cells in curative resections of breast cancer, pancreatic cancer malignancies, and tumors of gastric origin. Thus, it is possible that retrieving representative nodes in the upper mediastinal and cervical region is sufficient for the patient without apparently clinically-positive lymph nodes instead of complete dissection.

From a practical point of view, we believe that the Sweet procedure and its cervicothoracic dual-incision variant possess the capacity to achieve adequate lymphadenectomy for middle and lower ECSS, comparable to the right approaches. However, in the clinical scenario where a thorough exposure and dissection of the upper mediastinal lymph node is mandatory (e.g., possible upper mediastinal lymphadenopathy suggested by the preoperative evaluation or when the tumor is expected to be more closely related to the carina or the right main bronchus), the right approach is preferred at our center. This is because the upper mediastinum and other related structures can be reached more efficiently using the right approach. When these mandatory factors are absent, deciding whether to perform the left and right approaches depends on the patient's status and the surgeon's preference. With better field exposure and more precise performance, the minimally invasive approach to

TABLE 5 Multivariate Cox-regression analysis.

Variables	Hazard ratio	p	95% Confidence interval	
Overall survival				
Body mass index	0.923	**0.006**	0.871	0.977
Adjuvant radiotherapy	2.259	**0.001**	1.416	3.603
Tumor diameter	1.126	0.052	0.999	1.268
Nerve invasion	1.687	**0.018**	1.096	2.596
Recurrence-free survival				
Body mass index	0.935	**0.015**	0.886	0.987
Carcinoembryonic antigen	1.125	**0.006**	1.035	1.223
Adjuvant radiotherapy	4.157	**0.000**	2.668	6.477
Nerve invasion	1.866	**0.002**	1.253	2.779

Bold values denote statistical significance.

upper mediastinal and recurrent laryngeal nerve lymph nodes would contribute to adequate lymph node evaluation in the left approach esophagectomy. Therefore, we believe the left approach is valuable for middle and lower ESCC.

This study has several limitations. First, it is better to utilize clinical rather than pathological status to perform stratified analysis. However, without the routinely performed trans-esophageal ultrasound, the degree of precision of preoperative T and N staging is questionable. Hopefully, the issue will be addressed in future studies. Second, although PSM would theoretically minimize the controllable bias of a retrospective designed study, this balance comes at the expense of sample size, and there are confounding factors due to the nonrandomized nature of our research. For example, there is surgeon's discretion regarding whether to choose the left approach esophagectomy; the decision might derive from preoperative data that are not included in our dataset; finally, PSM cannot control for individual experience. Third, according to current guidelines, the proportion of higher-staged patients who received the neoadjuvant and adjuvant therapies was unsatisfactory. This phenomenon was partially because the survival benefit of neoadjuvant therapy was controversial at the time (31). The non-R0 resection rate (2.34%) was relatively low at our center and was partially derived from the patient's eagerness to undergo surgery as soon as possible and the fear that chemoradiotherapy would have adverse effects that were once common in mainland China. Before surgery, we routinely explain the pros and cons of neoadjuvant and adjuvant therapies and document the decision-making process. The rate of patient acceptance of neoadjuvant and adjuvant therapy has been rising since then, and we are eager to continue recommending treatment plans that could benefit patients, according to current evidence. Fourth, due to the limits of our database, 38 patients (12.9%) were lost to follow-up. Fortunately, the distribution of follow-up loss was relatively even between the groups (24 in the right group and 14 in the left group). The details of the neoadjuvant and the adjuvant therapy were not included in our database, which could mask underlying discrepancies among patients in different groups and influence the results.

In conclusion, esophagectomy using a qualified lymphadenectomy could be conducted *via* the left approach with similar outcomes to the right approach. The left approach was associated with non-inferior long-term OS and RFS. A minimum number of lymph nodes needed to be resected to ensure better survival in surgically-resected N0 middle and lower ESCC. A well-designed multi-center RCT should be conducted to compare the oncological effects of the two approaches.

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 Peking University First Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JL and GL conceived and designed the study. JWL, WH, KQ, and XZ performed data collection and processing and analysis of the data. XZ wrote 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.

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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.2022.858660/full#supplementary-material

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Effects of perioperative blood transfusion in gastric cancer patients undergoing gastrectomy: A systematic review and meta-analysis

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Background: The short-term and long-term effects of perioperative blood transfusion (PBT) on patients with gastric cancer are still intriguing. This systematic review and meta-analysis aimed to investigate the effects of blood transfusion on clinical outcomes in patients with gastric cancer undergoing gastrectomy.

Methods: We searched PubMed, Web of Science, Embase, and The Cochrane Library on December 31th 2021. The main outcomes were overall survival (OS), disease-free survival (DFS), disease-specific survival (DFS), and postoperative complications. A fixed or random-effects model was used to calculate the hazard ratio (HR) with 95% confidence intervals (CIs).

Results: Fifty-one studies with a total of 41,864 patients were included for this review and meta-analysis. Compared with patients who did not receive blood transfusions (NPBT), PBT was associated with worse 5-year OS (HR = 2.39 [95% CI: 2.00, 2.84]; $p < 0.001$; Multivariate HR = 1.43 [95%CI: 1.24, 1.63]; $p < 0.001$), worse 5-year DFS (HR = 2.26 [95%CI: 1.68, 3.05]; $p < 0.001$; Multivariate HR = 1.45 [95%CI: 1.16, 1.82]; $p < 0.001$), and worse 5-year DSS (HR = 2.23 [95%CI: 1.35, 3.70]; $p < 0.001$; Multivariate HR = 1.24 [95%CI: 0.96, 1.60]; $p < 0.001$). Moreover, The PBT group showed a higher incidence of postoperative complications [OR = 2.30 (95%CI:1.78, 2.97); $p < 0.001$] than that in the NPBT group, especially grade III-V complications, according to the Clavien-Dindo classification. [OR = 2.50 (95%CI:1.71, 3.63); $p < 0.001$].

Conclusion: In patients who underwent gastrectomy, PBT was associated with negative survival effects (OS, DFS, DSS) and a higher incidence of perioperative complications. However, more research was expected to further explore the impact of PBT. Meanwhile, strict blood transfusion management should be implemented to minimize the use of PBT.

KEYWORDS

gastric cancer, perioperative blood transfusions, overall survival, disease-free survival, disease-special survival, postoperative complications

1. Introduction

Gastric cancer is an important cause of cancer-related death, ranking fifth for incidence and fourth for mortality worldwide (1). Radical surgery remains the only opportunity to cure gastric cancer (2). Surgical trauma and perioperative anemia often induce blood transfusions in gastric cancer patients but some studies had shown that there were potential risks that can be attributed to immunosuppression (3, 4). Although blood transfusion is widely used by surgeons, the appropriate transfusion strategy of perioperative blood transfusion (PBT) in gastric cancer patients undergoing gastrectomy is not clear.

Previous studies had shown that PBT had adverse effects on patients in different cancers, like prostate cancer (5), lung cancer (6), and hepatocellular cancer (7). But conclusions about the effect of blood transfusion on the prognosis of gastric cancer were contradictory. Some studies had reported a negative association between PBT and prognosis of gastric cancer (8–34), whereas others found no association (35–58). A previous meta-analysis (59) had reported a worse prognosis of gastric cancer patients with PBT but was limited by the small sample size and low credibility of the evidence. Results concentrated on PBT in gastric cancer patients needed to be further confirmed.

Therefore, the study conducted this systematic review and meta-analysis to identify and summarize existing evidence and attempted to define the relationships between PBT and short- or long-term prognosis in patients undergoing gastrectomy. The aim of this study is to provide guidance for clinical decision-making and further optimize the perioperative transfusion management of gastric cancer patients.

2. Methods

This meta-analysis was performed according to the PRISMA Checklist (60). The protocol has been registered in the International prospective register of systematic reviews database (Prospro number: CRD42022314772, https://www.crd.york.ac.uk/PROSPERO/).

2.1. Literature search and study selection

Two authors independently search the databases. The literature was systematically searched using Pubmed, Embase, The Cochrane Library, and Web of Science database on 31st December 2021 for studies published until December 2021. The search strategy was as follows: [(“Stomach Neoplasms” OR “neoplasm stomach” OR “Stomach Neoplasm” OR “neoplasms stomach” OR “Gastric Neoplasms” OR “Gastric Neoplasm” OR “neoplasm gastric” OR “neoplasms gastric” OR “Cancer of Stomach” OR “Stomach Cancers OR Gastric Cancer” OR “cancer gastric” OR “cancers gastric” OR “cancers gastric” OR “Stomach Cancer” OR “cancer stomach” OR “cancers stomach” OR “Cancer of the Stomach”) AND (“Blood Transfusion” OR “Blood Transfusions” OR “Transfusion, Blood” OR “Transfusions, Blood”)]. We also searched the reference lists of relevant studies and previous meta-analyses. Duplicates were excluded. After a preliminary review of the title and abstract, some articles investigating related to blood transfusion were included. The full text of including articles were screened for eligibility for data extraction.

2.2. Inclusion and exclusion criteria

Inclusion criteria were described as follows: (1) Studies evaluating the association between perioperative blood transfusion and prognosis of gastric cancer patients after gastrectomy; (2) At least including one of the outcomes: overall survival (OS), disease-free survival (DFS), disease-specific survival (DSS) and postoperative complications; (3) Human studies.

Exclusion criteria were described as follows: (1) Studies about benign gastric diseases, patients with double primary cancers, without surgical treatment or underwent palliative resection; (2) Studies not in English; (3) Data cannot be extracted; (4) Sample size less than 100; (5) Conference abstract or review was excluded.

Studies based on duplicate authors or centers were excluded and we chose the latest one for inclusion.

2.3. Data extraction

Two authors independently extracted the data from the included studies. For each article included in the meta-analysis, the following information was extracted: (1) Study information: name of the first author; year of publication; data collection method; location of the research; sample size; group selection; median follow-up and time of the last follow-up; (2) Characteristics of patients: age, gender, body mass index (BMI), hemoglobin (Hb), albumin (Alb), comorbidity, tumor size, depth of invasion, lymph node metastasis, stage, tumor location, histologic grade; (3) Surgery information: operation time, American Society of Anesthesiologists(ASA) score, gastrectomy type (total/subtotal, open/laparoscopic), splenectomy, estimated blood loss (EBL), PBT trigger, the quantity of PBT, time of PBT, chemotherapy. (4) Outcomes: OS, DFS, DSS, postoperative complications.

The multivariable HRs with 95% CI for OS, DFS, DSS, and survival data under different stages of patients were extracted if available. The assessment of stage and lymph-node metastasis were based on the American Joint Committee on Cancer (AJCC) staging system (61–64).

2.4. Quality assessment

The quality of included studies was assessed by two dependent reviewers using Newcastle-Ottawa Scale (NOS) (65). The literature quality was evaluated from three dimensions: group selection, comparability, and outcomes for cohort studies. The NOS contained eight items and ranged from zero up to nine stars.

2.5. Statistical analysis

Effects were expressed as weighted mean difference (WMD) with a corresponding 95% confidence interval (CI) for continuous variables and odds ratio (OR) with a corresponding 95% CI for categorical variables (66).

Heterogeneity was tested using the Chi-square test based on the Cochran Q statistic and I^2 metric, and subgroup analyses and a meta-regression model were used to explore sources of heterogeneity.

Heterogeneity between studies was assessed by the Chi-square test and I^2 tests. I^2 values greater than 50% indicated significant heterogeneity (67). In the case of $I^2 > 50\%$, the summary HR and the accompanying 95% CI were calculated with a random-effects model, otherwise, a fixed-effects model was used.

We used forest plots to aggregate the HRs of outcomes from individual studies and funnel plots to examine the bias. We stratified OS data by G. location, average age, publication year, gender, estimated blood loss, transfusion rate, preoperative Hb, stage, transfusion trigger or transfusion quantity. Sensitivity analyses were conducted by removing individual studies in turns. Subgroup analyses and sensitivity analyses were used to analyze sources of significant heterogeneity.

The meta-analysis was performed by Review Manager (RevMan v.5.4) and R (v.4.1.0 x64) software. P value < 0. 05 was considered significant statistically.

3. Results

3.1. Selected studies

A total of 1,769 articles were retrieved by searching electronic databases (Pubmed, Web of Science, Embase, and Cochrane). After the duplicates were differentiated and excluded, there were 1,109 articles remaining. We excluded the studies which were conference abstracts, non-English articles, duplicate databases, or centers by screening the title and abstract and excluded the studies that could not be extracted valid information. Finally, 51 studies (8–58) published from 1987 to 2021 that fulfilled the inclusion criteria were included. **Figure 1** showed the flow chart of the search results. The reasons for excluding studies in the screening stage were shown in **Table S3**.

3.2. Characteristics of the patients and studies

A total of 41,864 patients were included in this meta-analysis, which involved 10,475 patients (25%) with PBT and 31,389 patients (75%) who did not receive perioperative blood transfusion (NPBT). The follow-up period ranged from 12 to 180 months, and the median was 56.2 months. The PBT rate of studies ranged from 3% to 74%. Definition of PBT was reported in 27 studies. The characteristics of these studies and patients were presented in **Supplementary Tables S1, S2**.

15 studies compared the age of patients and compared with the NPBT group, PBT group was older [OR: 3.36, 95%CI: (2.14, 4.57)]. 17 studies presented the preoperative Hb or anemia data, and we found patients with transfusion had a lower preoperative Hb level [OR: −2.19, 95%CI: (−3.02, −1.36)] or higher prevalence of preoperative anemia [OR: 10.83, 95%CI: (7.23, 16.21)]. Besides, PBT group have higher rate of comorbidity [OR: 1.25, 95%CI: (1.02, 1.53)] and lower preoperative albumin level [OR: −0.36, 95%CI: (−0.42, −0.30)]. There were no significant differences in different gender and BMI.

According to the TNM stage system (61–64), data from eligible studies showed that pathological stages of PBT group were more likely to be stage III[OR: 1.89, 95%CI: (1.65, 2.18)] and stage IV [OR: 2.57, 95%CI: (1.44,4.60)]. 17 studies reported the depth of invasion of tumor and 14 studies reported the lymph node metastasis. PBT group had a higher ratio of T3 [OR: 1.43, 95%CI: (1.09, 1.87)], T4 [OR: 2.57, 95% CI: (1.44, 4.60)], N2[OR: 1.49, 95%CI: (1.20, 1.86)], and N3 [OR: 1.75, 95%CI: (1.41, 2.18)]. Differences of tumor location (upper location: OR: 1.54, 95%CI: [1.16, 2.04]; all stomach: OR: 2.27, 95%CI: [1.53, 3.36]) and tumor size (larger tumor size: OR: 1.32, 95%CI: [0.90, 1.75]; tumor size > 5 cm: OR:3.00, 95%CI: [2.54, 3.55]) were also found. However, as for histological differentiation, there was no significant difference between the two groups.

More than two thirds of studies presented the operation data. PBT group had a higher rate of conversion to open surgery [OR: 2.46, 95%CI: (1.65, 3.67)], total gastrectomy [OR: 1.59, 95%CI: (1.24, 2.04)] and multi-organ resection [OR: 2.33, 95%CI: (1.55, 3.52)], especially splenectomy [OR: 2.38, 95%CI: (1.56, 3.64)]. Besides, patients with PBT had higher ASA scores [ASA > 2: OR: 1.91, 95%CI: (1.58, 2.32)], greater EBL [OR: 216.1, 95%CI: (136.24, 295.96)] and longer hospital stay time [OR: 1.26, 95%CI: (0.63,1.89)] when compared with patients without PBT (**Table 1**).

3.3. Postoperative complications

16 studies with 9,942 patients showed postoperative complications after gastrectomy. The OR of postoperative complications was 2.30 [95%CI: (1.78, 2.97)]. According to

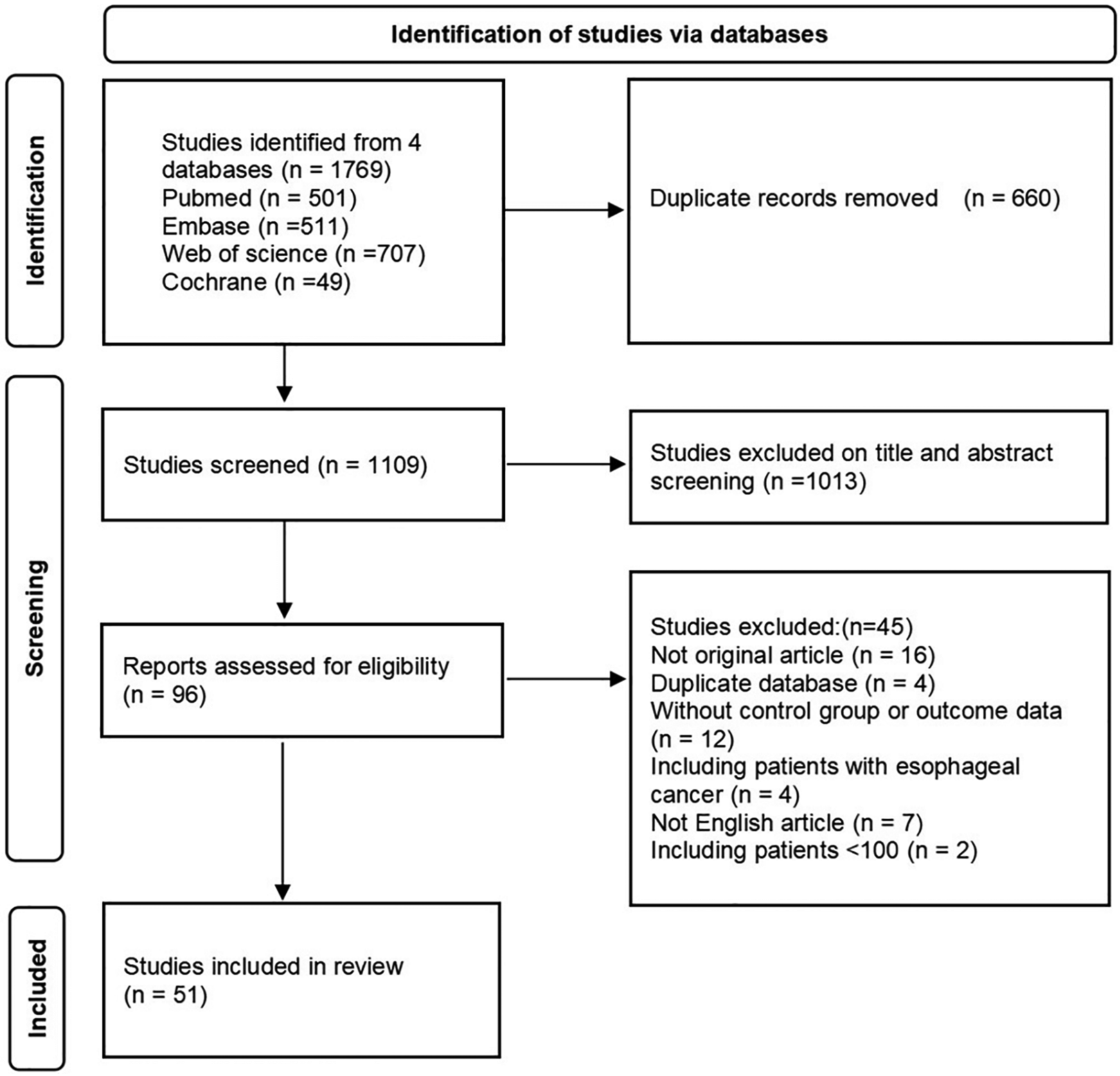

FIGURE 1
Flow chart of the study screening for this analysis.

the Clavien-Dindo grade (68), the PBT group had a higher incidence rate of grade III-V complications [OR: 2.50, 95%CI: (1.71, 3.63); $p < 0.01$], whereas no significant difference was seen in grade I-II [OR: 1.12, 95%CI: (0.63, 2.00); $p = 0.69$]. (Table 2) The forest plot and funnel plot were shown in Figure 2G, Supplementary Figure S1G.

3.4. Long-term outcomes

3.4.1. Overall survival

36 studies reported data on OS. Data on 5-year OS was available from 28 studies and HRs after multivariable analyses were extracted from 24 studies. The total number of enrolled patients was 25,122, with individual samples ranging from 103 to 2,884 (median 699). The HR of 5-year OS was 2.39 [95% CI: (2.00, 2.84), $P < 0.01$] and the summary of the multivariable HR was 1.43 [95% CI: (1.24, 1.63)]. Measure of heterogeneity indicates a high degree of variability about 5-year OS (HR: $I^2 = 83\%$, $P < 0.01$; multivariable HR: $I^2 = 74\%$, $P < 0.01$). The random-effects model was used to obtain estimates. The forest plots of OS were shown in Figures 2A,B.

A stratified analysis of OS was performed and the results were shown in Table 3. Publication years (before or after 2010), NOS score (≤7 stars or >7 stars), geographical location (west or east), average age (≤60 or >60), EBL (≤500 ml or >500 ml), PBT trigger (Hb < 7 g/L or Hb < 8 g/L), PBT rate (≤40% or >40%) and quantity (4U ≤ 50% or 4U > 50%) did not change the outcome significantly, which showed the result was robust.

TABLE 1 Analysis of clinicopathological characteristics between the PBT group and NPBT group.

Group	Included studies	Included patients	I^2	Effect Model	OR/WMD	95%CI	P
Female	26	19,011	46%	Fixed	1.02	[0.95, 1.10]	0.51
Age	15	9,942	86%	Random	3.36	[2.14, 4.57]	<0.001
BMI	7	5,056	1%	Fixed	−0.14	[−0.43, 0.14]	0.33
Pre Alb	5	5,474	70%	Random	−0.36	[−0.42, −0.30]	<0.001
Comorbidity	5	3,237	0%	Fixed	1.25	[1.02, 1.53]	0.03
Preoperative anemia	3	626	0%	Fixed	10.83	[7.23, 16.21]	<0.001
Preoperative Hb	14	8,626	98%	Random	−2.19	[−3.02, −1.36]	<0.001
Depth of invasion							
Tis	3	998	0%	Fixed	0.81	[0.44, 1.51]	0.51
T1	16	10,710	74%	Random	0.41	[0.31, 0.53]	<0.001
T2	17	11,177	75%	Random	0.70	[0.54, 0.90]	0.005
T3	17	11,177	83%	Random	1.43	[1.09, 1.87]	0.009
T4	15	10,547	94%	Random	2.57	[1.44, 4.60]	0.001
Lymph-node metastasis				Random			
N0	14	10,162	68%	Random	0.62	[0.52, 0.74]	<0.001
N1	13	9,486	74%	Random	1.03	[0.82, 1.30]	0.80
N2	13	9,486	64%	Random	1.49	[1.20, 1.86]	<0.001
N3	10	8,631	55%	Random	1.75	[1.41, 2.18]	<0.001
pTNM stage							
I	21	13,010	90%	Random	0.35	[0.25, 0.49]	<0.001
II	23	13,727	58%	Random	1.05	[0.90, 1.23]	0.55
III	24	14,926	61%	Random	1.89	[1.65, 2.18]	<0.001
IV	11	6,945	83%	Random	2.96	[1.78, 4.92]	<0.001
Tumor size	5	3,695	77%	Random	1.32	[0.90, 1.75]	<0.001
Tumor size > 5 cm	5	3,218	20%	Fixed	3.00	[2.54, 3.55]	<0.001
Tumor location							
Upper	15	10,407	80%	Random	1.54	[1.16, 2.04]	0.003
Middle	16	10,570	73%	Random	1.02	[0.84, 1.24]	0.84
Low	16	10,570	52%	Random	0.72	[0.63, 0.82]	<0.001
All stomach	8	5,841	41%	Fixed	2.27	[1.53, 3.36]	<0.001
Histologic grading							
Well/moderate	17	9,913	75%	Random	0.97	[0.80, 1.18]	0.74
Poor/undifferentiate	17	9,913	75%	Random	1.02	[0.93, 1.12]	0.67
Adjuvant chemotherapy	14	11,287	89%	Random	1.01	[0.73, 1.41]	0.93
ASA score > 2	4	4,061	30%	Fixed	1.91	[1.58, 2.32]	<0.001
EBL	9	5,180	98%	Random	216.1	[136.24, 295.96]	<0.001
Operation time	8	4,335	89%	Random	31.51	[17.64, 45.38]	<0.001

(*continued*)

TABLE 1 Continued

Group	Included studies	Included patients	I^2	Effect Model	OR/WMD	95%CI	*P*
Type of gastrectomy							
Total	19	14,989	87%	Random	1.59	[1.24, 2.04]	<0.001
Subtotal	19	15,006	88%	Random	0.64	[0.50, 0.83]	<0.001
Open-gastrectomy	6	3,801	51%	Random	2.46	[1.65, 3.67]	<0.001
Lap-gastrectomy	6	3,801	51%	Random	0.41	[0.27, 0.61]	<0.001
Extended surgery							
Splenectomy	11	9,324	89%	Random	2.38	[1.56, 3.64]	<0.001
Multiple organ resection	14	11,993	92%	Random	2.33	[1.55, 3.52]	<0.001
Hospital stay time	4	3,971	36%	Fixed	1.26	[0.63, 1.89]	<0.001

BMI, body mass index; Pre, preoperative; Alb, albumin; Hb, hemoglobin; ASA, American society of anesthesiologists; EBL, estimated blood loss.

TABLE 2 Analysis of postoperative complications between the PBT group and not-PBT group.

Outcome	Included studies	Included patients	I^2	Effect Model	OR	95%CI	*P*
Postoperative complications	16	9,942	75%	Random	2.30	[1.78, 2.97]	<0.001
Clavien-Dindo grade							
Grade I–II	10	7,918	90%	Random	1.12	[0.63, 2.00]	0.69
Grade III–V	6	5,371	79%	Random	2.5	[1.71, 3.63]	<0.001

Sensitivity analysis, which explored the effect on overall results by sequentially omitting individual studies, and a baujat plot was conducted to explore the source of heterogeneity between studies. (**Supplementary Figure S2**). 6 studies (9, 13, 21, 32, 42, 50) might be the main reason for the high heterogeneity. The funnel plot showed obvious asymmetry and publication bias was detected (**Supplementary Figures S1A,B**).

Moreover, further survival analyses were performed under different tumor stages according to the pTNM stage system. There were 7 studies, 8 studies, and 6 studies that showed survival rates between different groups at stages I, II, and III respectively. Compared to the NPBT patients, the PBT group was associated with lower 1-, 2-, 3-year OS at stages I, II, and III and lower 5-year OS at stage I [HR:2.54, 95%CI: (1.46, 4.44); $p < 0.001$;], III [HR:1.62, 95%CI: (1.38, 1.92); $p < 0.001$] whereas there was no significant difference in 5-year OS among stage II patients [HR:1.46, 95%CI: (0.92, 2.32); $p = 0.11$]. (**Table 4**).

3.4.2. Disease-free survival

17 studies reported data on DFS. Data on 5-year DFS were available from 16 studies and HRs after multivariable analyses were extracted from 9 studies. The 5-year DFS was lower in patients with PBT than NPBT patients. (HR = 2.26, 95% CI: [1.68, 3.05]; multivariable HR = 1.44, 95% CI: [1.18, 1.75]). *I*(2) as shown in **Table 4**. The funnel plot showed obvious asymmetry (**Supplementary Figures S1C,D**). The forest plots of DFS were shown in **Figures 2C,D**.

3.4.3. Disease-specific survival

9 studies reported data on DSS. Data on 5-year DSS were available from 7 studies and HRs after multivariable analyses were extracted from 6 studies. The 5-year DSS was lower in patients with PBT than NPBT patients. (HR = 2.23, 95% CI: [1.35, 3.70]; multivariable HR = 1.35, 95% CI: [1.21, 1.51]). I^2 as shown in **Table 4**. The funnel plot showed obvious asymmetry (**Supplementary Figures S1E,F**). The forest plots of DFS were shown in **Figures 2E,F**.

4. Discussion

To date, the effects of PBT on the prognosis of gastric cancer patients undergoing gastrectomy were still controversial, and consensus had not yet been reached finally. The review and meta-analysis involved 51 studies with 41,864 gastric cancer patients. To our best knowledge, this analysis represented the largest assessment of current research that targeted the impact of PBT on the long- and short-term

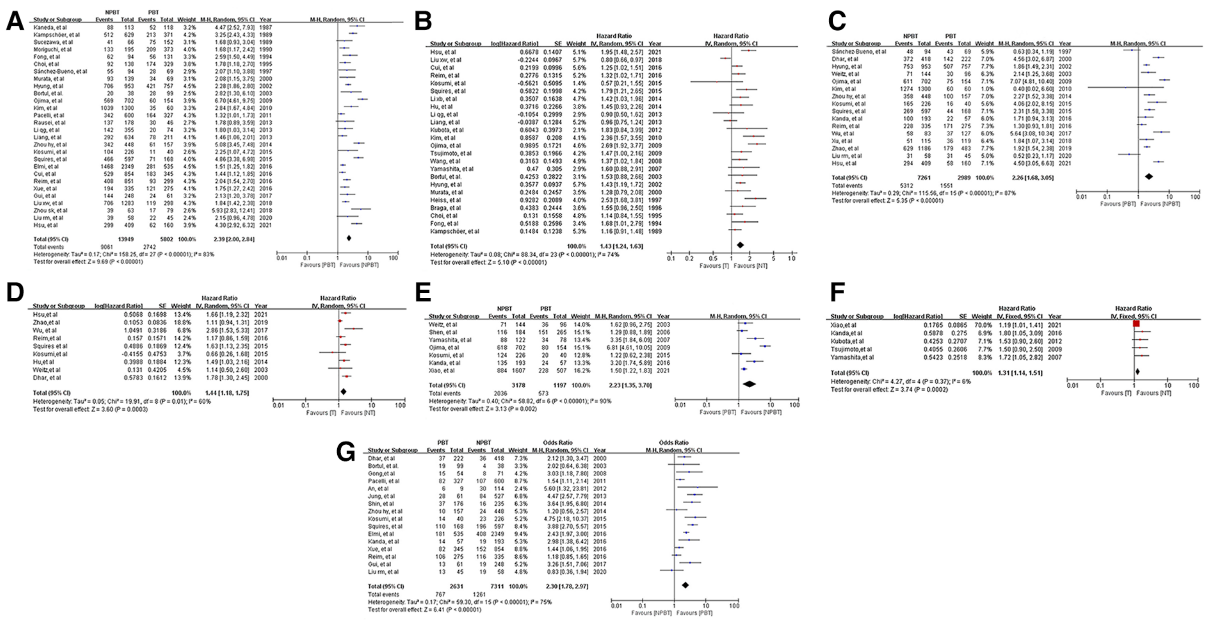

FIGURE 2
Forest plots and results of the meta-analysis of studies. (A) Forest plot of overall survival (OS) based on univariate results of studies. (B) Forest plot of OS based on multivariate results of studies. (C) Forest plot of disease-free survival (DFS) based on univariate results of studies. (D) Forest plot of DFS based on multivariate results of studies. (E) Forest plot of disease-specific survival (DSS) based on univariate results of studies. (F) Forest plot of DSS based on multivariate results of studies. (G) Forest plot of postoperative complications based on results of studies.

outcomes. A primary finding was that PBT was associated with worse prognosis than the NPBT group.

Specifically, the results of the meta-analysis showed that PBT was associated with worse 1-,2-,3- and 5-year OS (82% vs. 91%; 66% vs. 80%; 57% vs. 72%; 47% vs. 65%), DFS (76% vs. 88%; 61% vs. 76%; 53% vs. 74%; 52% vs. 73%), and DSS (86% vs. 89%; 64% vs. 74%; 53% vs. 66%; 48% vs. 64%). The results were similar to the conclusions of previous research (59, 69–72). Similar results were found in other meta-analyses of other solid cancer, including colorectal cancer (73, 74), hepatic cancer (75), esophageal cancer (76, 77), and pancreatic cancer (78). Further, we conducted stratified analysis and sensitivity analysis of OS and the results were consistent and credible. The mechanism could be partially attributed to the suppression of the immune system induced by blood transfusion (79). Firstly, some studies showed that the patients with previous blood transfusions experienced changes in the immune system (80–82) involving inhibition of T cells and alteration in T cell subsets (83). Secondly, transfusion could trigger a series of a cascade of the immune system, including inhibition of the immunoregulatory cytokine IL-2, and the release of immunosuppressive prostaglandins 3. Besides, blood transfusion could induce transfusion-related immunomodulation (TRIM), further inhibits the function of macrophages and monocytes (84), and might lead to the decline of immune surveillance and enhance the potential for tumor growth and cellular metastasis.

Significant differences in the clinicopathological characteristics were found between the PBT group and NPBT group, which were consistent with previous studies 69. Compared with the NPBT group, the PBT group was more likely to be anemic and had lower Hb levels. Previous studies had shown that preoperative anemia was a powerful predictor of the need for blood transfusion and independently associated with an increased risk of mortality in patients undergoing surgery, even to a mild degree (85, 86). Besides, the PBT group had more advanced tumor stages, more open surgery or total gastrectomy, and more EBL. Intraoperative blood transfusion was more likely to result from the complicated operation, especially large EBL (87). In addition, patients with transfusion were older and had more comorbidities, which might also be one of the important reasons for the poor prognosis in the PBT group.

Moreover, our findings showed that the PBT group had a higher postoperative complication rate. After grading the complications according to the Clavien-Dindo grade system, PBT was particularly related to grade III-V complications, but there was no significant difference in grade I-II when compared with the NPBT group. To date, the mechanisms that targeted the association between PBT and postoperative complications were unclear. Previous studies showed that the clinicopathological features of the patients in two groups might independently influence the postoperative complications (44, 47, 88). Compared with the NPBT group, patients with

TABLE 3 Stratified meta-analysis of overall survival comparison between the PBT group and NPBT group.

Subgroup	Included studies	Included patients	I^2	Effect Model	HR	95%CI	P
G.location							
West	8	6,475	83%	Random	2.15	[1.55, 2.97]	<0.001
East	20	13,276	82%	Random	2.49	[2.02, 3.07]	<0.001
Average age							
≤60	4	2,890	0%	Random	2.07	[1.77, 2.41]	<0.001
>60	8	6,163	89%	Random	2.8	[1.84, 4.28]	<0.001
Year							
1987-2010	11	5,783	77%	Random	2.61	[2.00, 3.41]	<0.001
2011-2022	17	13,968	84%	Random	2.26	[1.80, 2.82]	<0.001
NOS score							
>7	12	8,344	74%	Random	2.30	[1.86, 2.84]	<0.001
≤7	16	11,407	95%	Random	2.04	[1.34, 3.12]	<0.001
EBL							
≤500 ml	4	2,216	89%	Random	2.41	[1.21, 4.80]	0.01
>500 ml	4	2,300	92%	Random	2.59	[1.27, 5.27]	0.009
PBT rate							
≤40%	17	14,637	89%	Random	2.39	[1.86, 3.09]	<0.001
>40%	11	5,114	44%	Random	2.29	[1.90, 2.76]	<0.001
Preoperative Hb							
≤11 g/L	6	3,110	85%	Random	2.06	[1.18, 3.63]	<0.001
>11 g/L	5	4,622	69%	Random	1.66	[1.30, 2.12]	0.01
PBT trigger							
Hb < 7 g/L	4	3,259	91%	Random	2.05	[1.22, 3.44]	<0.001
Hb < 8 g/L	3	2,981	70%	Random	4.68	[3.02, 7.27]	0.03
PBT quantity							
4U ≤ 50%	3	3,247	80%	Random	1.75	[1.25, 2.47]	0.001
4U > 50%	4	3,184	93%	Random	4.29	[2.08, 8.85]	<0.001

G. locations, geographical location; NOS, New castle Ottawa scale; EBL, estimated blood loss; PBT, perioperative blood transfusion; Hb, hemoglobin.

PBT were prone to suffer from more surgical trauma and had less tolerance for surgery because of their poor clinical condition. These clinicopathological factors, including old, advanced tumor stage, and complicated type of surgery, might be also associated with postoperative complications (89–91). Relevant mechanisms were expected to be demonstrated further.

Strengths and limitations should be considered when interpreting the study results. In our literature review, we retrieved 3 meta-analysis and systematic reviews related to the effect of perioperative blood transfusion in gastric cancer patients published in 2015 (70, 71) or 2018 (59). These studies were limited by the small number of articles included, univariate analysis or high heterogeneity. In this meta-analysis, the number of studies included was the largest, and adopting the multivariable HR to overcome the potential bias, which made the results more reliable. Besides, we focused on the relationship between the PBT and OS, DFS, DSS, and postoperative complications of gastric cancer patients, and found the relationship between PBT and severe postoperative complications. Nevertheless, there were some limitations to this meta-analysis. For obvious ethical reasons, no

TABLE 4 Survival outcomes of patients between the PBT group and Not-PBT group.

Outcome	Included studies	Included patients	I^2	Effect Model	HR	95%CI	P
OS							
1y-OS	23	15,616	79%	Random	2.28	[1.75, 2.97]	<0.001
2y-OS	23	15,616	85%	Random	2.04	[1.62, 2.57]	<0.001
3y-OS	23	15,616	87%	Random	2.02	[1.61, 2.53]	<0.001
5y-OS	28	19,751	83%	Random	2.39	[2.00, 2.84]	<0.001
10y-OS	5	4,527	91%	Random	1.56	[0.98, 2.46]	0.06
OS-Multivariate HR	24	13,898	74%	Random	1.43	[1.24, 1.63]	<0.001
Stage I-OS							
1-year OS	7	2,781	37%	Fixed	2.38	[1.46, 3.88]	<0.001
2-year OS	7	2,781	56%	Random	2.50	[1.35, 4.63]	0.004
3-year OS	7	2,781	33%	Fixed	2.66	[1.94, 3.64]	<0.001
5-year OS	7	2,781	69%	Random	2.54	[1.46, 4.44]	0.001
Stage II-OS							
1-year OS	6	1,152	0%	Fixed	2.33	[1.42, 3.84]	<0.001
2-year OS	6	1,152	0%	Fixed	2.13	[1.50, 3.01]	<0.001
3-year OS	6	1,152	0%	Fixed	1.83	[1.35, 2.47]	<0.001
5-year OS	6	1,152	55%	Random	1.46	[0.92, 2.32]	0.11
Stage III-OS							
1-year OS	8	2,994	38%	Fixed	1.93	[1.56, 2.39]	<0.001
2-year OS	8	2,994	22%	Fixed	1.71	[1.45, 2.03]	<0.001
3-year OS	8	2,994	40%	Fixed	1.70	[1.45, 2.00]	<0.001
5-year OS	8	2,994	0%	Fixed	1.62	[1.38, 1.92]	<0.001
DFS							
1y-DFS	11	6,178	81%	Random	2.66	[1.79, 3.96]	<0.001
2y-DFS	7	4,313	88%	Random	2.12	[1.43, 3.13]	<0.001
3y-DFS	12	7,195	91%	Random	2.23	[1.44, 3.46]	<0.001
5y-DFS	16	10,250	87%	Random	2.26	[1.68, 3.05]	<0.001
10y-DFS	4	3,088	96%	Random	1.47	[0.59, 3.70]	0.41
DFS-Multivariate HR	9	7,698	60%	Random	1.44	[1.18, 1.75]	<0.001
DSS							
1y-DSS	4	2,804	54%	Random	1.56	[0.94, 2.57]	0.08
2y-DSS	4	2,804	73%	Random	2.16	[1.34, 3.49]	0.002
3y-DSS	4	2,804	81%	Random	2.45	[1.43, 4.19]	0.001
5y-DSS	7	4,375	90%	Random	2.23	[1.35, 3.70]	0.002
DSS- Multivariate HR	6	5,153	0%	Fixed	1.35	[1.21, 1.51]	<0.001

OS, overall suivival; DFS, disease-free survival; DSS, disease-specific survival; HR, hazard ratio.

randomized controlled trial (RCT) was searched and included in this meta-analysis. The heterogeneity of some results was high in this meta-analysis, which might be attributed to the wide span of publication years, different transfusion triggers, and lacking PBT guideline. In addition, few studies presented the data on the amount and components of blood transfusion and the time of PBT, this meta-analysis failed to conduct further research. More research was expected to explore the role of PBT and the appropriate PBT management strategy.

5. Conclusions

In conclusion, PBT was associated with adverse effects on the prognosis of gastric cancer patients undergoing gastrectomy, including OS, DFS, and DSS in this meta-analysis. In addition, PBT had a negative impact on postoperative complications in gastric cancer patients, especially grade III-V complications. The quality of the evidence was not high and bias were detected, which might lead to more significant results. But these results indicated that strict patient blood management strategies aimed at minimizing PBT were necessary. Future studies should be performed to further define the role of PBT and explore the guideline of PBT in gastric cancer patients.

Author contributions

(I) Conception and design: YC, LZ; (II) Administrative support: DZ, YC; (III) Collection and assembly of data: WW, XL; (IV) Data analysis and interpretation: LZ, PN; (V) Manuscript writing: All authors; (VI) Final approval of manuscript: All authors. 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.2022.1011005/full#supplementary-material.

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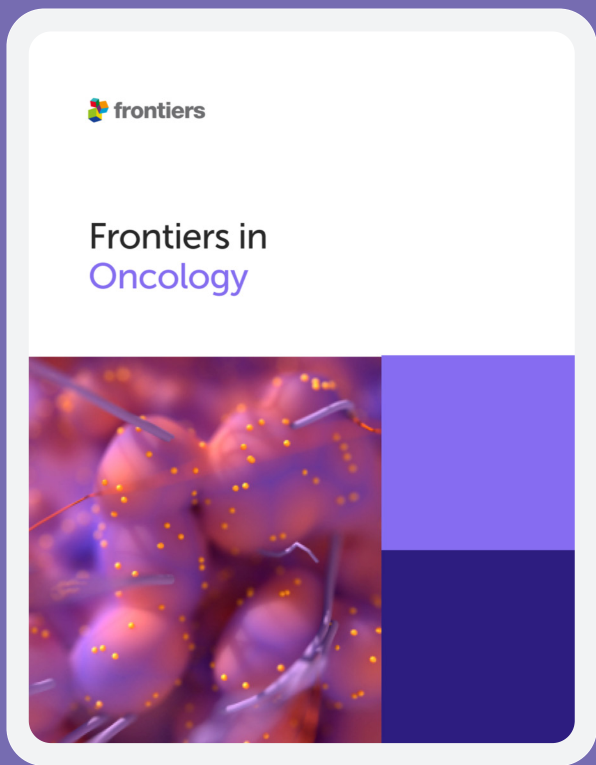

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