Cancer Management and Research

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ORIGINAL RESEARCH

Short-Term and Long-Term Outcomes Following Transhiatal versus Right Thoracoabdominal Resection of Siewert Type II Adenocarcinoma of the Esophagogastric Junction

This article was published in the following Dove Press journal:
Cancer Management and Research

Jiadi Xing*
Maoxing Liu*
Kai Xu*
Pin Gao
Fei Tan
Zhendan Yao
Nan Zhang
Hong Yang
Chenghai Zhang
Ming Cui
Xiangqian Su

Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Gastrointestinal Surgery IV, Peking University Cancer Hospital and Institute, Beijing 100142, People's Republic of China

*These authors contributed equally to this work

Background: Few studies have evaluated the outcomes of transhiatal and right thoracoabdominal resection of Siewert type II adenocarcinoma of the esophagogastric junction. This study investigated the relative effect of these two methods in the surgical treatment of Siewert type II adenocarcinoma of the esophagogastric junction.

Methods: Clinical data for 211 Siewert type II cancer patients were collected and classified into transhiatal group (n = 181) and right thoracoabdominal group (n = 30) according to surgical approach. Short-term outcomes were compared between these two groups. A 1:1 propensity score matching was performed using a logistic regression model. Recurrence-free survival and overall survival were compared between the matched groups.

Results: The right thoracoabdominal group had significantly greater intraoperative blood loss and longer operative time compared with transhiatal group. Complications corresponding to Clavien–Dindo grade III or higher were 4.4% in transhiatal group and 30% in right thoracoabdominal group ($P < 0.05$). The right thoracoabdominal group exhibited greater blood loss, longer operative time, longer hospitalization, and a smaller number of lymph nodes retrieved than the transhiatal group as evidenced by PSM analysis, and patients in transhiatal group also experienced significantly better survival than patients in right thoracoabdominal group.

Conclusion: In this study, the transhiatal approach was associated with more favorable short-term and oncological outcomes than the right thoracoabdominal group approach for Siewert type II adenocarcinoma of the esophagogastric junction. The transhiatal approach with total gastrectomy appears to be an optional choice for this type of tumor, especially for esophagus invasion ≤2 cm. Well-designed randomized control trials are necessary to validate our findings.

Keywords: adenocarcinoma of the esophagogastric junction, Siewert type II, transhiatal resection, right thoracoabdominal resection

Introduction

The incidence of adenocarcinoma of the esophagogastric junction (AEG) has increased rapidly over recent years and is associated with a higher incidence of local recurrence and distant metastasis.[1–3] Surgery remains the only curable method available for treating AEG, and both thoracoabdominal and transhiatal approaches are considered standard surgical procedures.[4–6] The Siewert classification of AEG has been widely adopted, and a consensus has been reached by most researchers that the surgical treatment of Siewert types I and III of AEG should adhere to the

Correspondence: Xiangqian Su
Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Gastrointestinal Surgery IV, Peking University Cancer Hospital and Institute, NO. 52 Fucheng Road, Haidian District, Beijing 100142, People's Republic of China
Tel +86-13801262916
Email suxiangqian@bjmu.edu.cn

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DovePress
http://doi.org/10.2147/CMAR.S275569

principles of esophageal and gastric cancer, respectively.[7] However, for Siewert type II AEG, which is defined as cases where the epicenter of the tumor is located within the proximal 2 cm and distal 1 cm of the esophagogastric junction,[7] the debate regarding the extent of the resection area and lymph node dissection is ongoing due to its specific biological features.[8–15] Thoracic surgeons speculate that the thoracoabdominal approach will reach a safety margin and enable thorough lymph node (LN) dissection, while abdominal surgeons believe that the transhiatal approach is a safer procedure. A recent high-quality meta-analysis reported that the TH approach may be more appropriate for Siewert type II adenocarcinoma of EGJ.[16]

In China, the medical authorities have decided that surgical treatment of esophageal and gastric cancer should be performed by surgeons from different departments in most of the hospitals. This highlights the importance of reaching a consensus as to which procedure is suitable for the individual types of patients, given our national legislation. This study aims to collect data on Siewert type II AEG patients who received radical surgery in our department and compare the safety and oncological outcomes of the transhiatal (TH) and right thoracoabdominal (RTA) resection approaches.

Materials and Methods

Patient Selection

From November 2009 to March 2018, we retrospectively reviewed the records of 231 patients with Siewert type II AEG who had undergone gastrectomy at Peking University Cancer Hospital in China. The inclusion criteria were as follows: histologically confirmed Siewert type II AEG, use of either the TH or RTA, and D2 lymphadenectomy with curative R0 resection. The exclusion criteria included preoperative chemotherapy or radiotherapy, stage T4b or combined organ resection, ASA >3, and the existence of concurrent tumors. There were 181 patients included in the TH group and 30 in the RTA group. Written informed consent was obtained from all patients before surgery.

Surgical Procedures

TH: Total gastrectomy with standard D2 lymphadenectomy was performed via laparotomy. The transection line was selected 2 cm above the proximal tumor margin. Frozen biopsy of the transection margin was performed immediately. If a negative margin was obtained, reconstruction was performed according to the Roux-en -Y technique. Dissection of the lower mediastinal LNs was unnecessary.

RTA: If a positive margin was identified by intraoperative frozen biopsy, thoracoabdominal resection (Ivor Lewis) using the right transthoracic approach was performed. Anastomoses were performed under aortic arch with tubular remnant stomach. Dissection of the lower mediastinal LNs was necessary. The intra-abdominal lymphadenectomy consisted of a modified D2 procedure, sparing the peripyloric and perigastric LNs along the greater curvature.

Clinical Parameters and Follow-Up

We reviewed the following clinical and pathological factors available in the medical records: sex, age, clinical depth of invasion, clinical nodal stage, histological type, operative time, blood loss, number of harvested LNs, postoperative hospital stay, reoperation rate, postoperative complication rate, pathological depth of invasion, pathological nodal stage, length of the proximal margin, length of esophageal invasion, and postoperative complications. Postoperative complications were classified using the Clavien–Dindo grading system.[17]

Outpatient follow-up involved physical examinations and blood tests, including tumor marker evaluation. Chest/abdominal computed tomography scans were performed every 6 months for the first 2 years and subsequently every year for patients with pStage I and every 3 months for the first 2 years and subsequently every 6 months for patients with pStage II or higher, until at least 5 years postoperatively, as well as annual endoscopic examination. Postoperative SOX (oxaliplatin + S1) adjuvant chemotherapy for 6–8 months was administered primarily to patients with pStage II/III.

Statistical Analysis

Values are provided as the median (range). The Chi-square and Mann–Whitney tests were used for statistical analyses. For survival analysis, a 1:1 propensity score matching was performed using a logistic regression model and the following covariates: body mass index (BMI), ASA Physical Status Classification System, histopathological grade, and pathological tumor/nodal (pT/N) stage. Survival curves were generated using the Kaplan–Meier method. All statistical tests were two-sided, and probability (P) values <0.05 were considered statistically significant. Statistical analysis was performed using

Table 1 Preoperative Patient Demographic Information

	TH Group (n = 181)	RTA Group (n = 30)	*P* value
Sex (male/female)	151/30	26/4	0.657
Age (years)[a]	61.92 (22–80)	61.80 (44–77)	0.976
BMI (kg/m^2)[a]	23.70 (17.1–33.6)	23.85 (17.7–30.1)	0.732
BMI ≤18.5/>18.5 and <25/≥25	8/118/55	1/22/7	0.565
ASA score 1/2/3	151/29/1	24/6/0	0.712
Clinical depth of invasion T1/T2/T3/T4	0/20/121/40	0/0/23/7	0.258
Clinical nodal stage N0/N1/N2/N3a/N3b	47/57/38/30/9	11/0/13/6/0	0.049
Histological grade G1/G2/G3	18/101/62	20/0/10	0.449
Clinical AJCC stage IB/IIA/IIB/IIIA/IIIB/IIIC	45/16/40/38/33/9	2/0/11/7/8/2	0.024
Tumor size (mm)[a]	42.8 (6–75)	54.2 (25–78)	0.005
Extent of esophageal invasion (mm)[a]	9.1 (0–20)	15.7 (10–20)	<0.001
Lauren type Intestinal/diffuse/mixed	58/102/21	18/9/3	0.701

Note: [a]Median (range).

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; TH, transhiatal; RTA, right thoracoabdominal; JCC, American Joint Committee on Cancer.

IBM SPSS statistics version 22 (SPSS Inc., Chicago, IL, USA).

Results

Patient Characteristics

Patient demographic information is shown in Table 1. There were no significant differences between the groups with regard to basic background information, such as sex, age, BMI, physical status (ASA), clinical T stage, or histological type (all $P > 0.05$). However, smaller tumors ($P = 0.005$), shorter esophageal invasion ($P < 0.001$), and earlier clinical N stage ($P = 0.049$) were more frequently observed in the TH group than in the RTA group.

Surgical Outcomes

Surgical outcomes, including postoperative complications, are shown in Table 2. RTA patients experienced a significantly larger intraoperative blood loss ($P < 0.001$) and significantly longer operative time ($P < 0.001$). The incidence of early-phase complications of Clavien–Dindo grade III or higher significantly differed between the groups ($P < 0.001$). There was one case of fatality within the first 30 days postoperatively in the TH group. Significant differences were observed between the groups regarding the frequency of anastomotic bleeding, intraperitoneal bleeding, and anastomotic leakage ($P < 0.001$). Postoperative hospitalization was significantly longer in the RTA group than in the TH group ($P = 0.004$). Significantly more cases of reoperation were observed in the RTA group than in the TH group ($P < 0.001$).

Pathological Information

As for the oncological parameters, a significant difference between the groups was observed with regard to the total number of harvested LNs ($P = 0.010$). The lengths of the proximal margin of resected specimens ($P < 0.001$) and the extent of esophageal invasion ($P < 0.001$) differed significantly between the two groups, there were no cases of positive margin in either of the two groups. Tumor size

Table 2 Pathological Information and Surgical Outcomes

	TH Group (n = 181)	RTA Group (n = 30)	*P* value
Length of proximal margin (mm)[a]	19.2 (15–30)	38.8 (30–65)	<0.001
Length of esophagus resected[a]	27.1 (20–40)	57.3 (50–75)	<0.001
Number of metastatic LNs[a]	1.63 (0–30)	3.25 (0–29)	0.163
Total number of harvested LNs[a]	30.85 (13–68)	24 (11–56)	0.010
Pathological depth of invasion T1/T2/T3/T4	 23/0/115/43	 0/0/20/10	 0.053
Pathological nodal stage N0/N1/N2/N3a/N3b	 40/64/34/33/9	 3/11/6/8/2	 0.053
Operative time (min)[a]	258.64 (150–465)	386.67 (200–515)	<0.001
Blood loss (mL)[a]	63.33 (10–1200)	175 (100–800)	<0.001
Postoperative hospitalization (days)[a]	9.7 (6–176)	16.71 (11–44)	0.004
First flatus time (days)[a]	3.32 (2–5)	3.44 (2–5)	0.461
Morbidity grade ≥IIIa[b] Anastomotic bleeding Intraperitoneal bleeding Anastomotic leakage	8 (4.4%) 3 (1.6%) 1 (0.5%) 5 (4.4%)	9 (30%) 2 (6.7%) 0 (0.0%) 7 (23.3%)	0.045
Reoperation	4 (2.7%)	3 (10%)	<0.001

Notes: [a]Median (range), [b]according to the Clavien–Dindo grading system.
Abbreviations: LNs, lymph nodes; TH, transhiatal; RTA, right thoracoabdominal.

(P = 0.005), number of tumors with a size >4 cm (P = 0.003), and the length of esophagus resected (P < 0.001) also differed significantly between the groups. There were more patients with more advanced stages in the RTA group than in the TH group (P = 0.024).

Propensity Score Matching (PSM) Analysis

After PSM, 28 patients in each group were selected. Baseline characteristics and surgical outcomes of the matched patients were compared as shown in Table 3. Adjuvant chemotherapy was administered to 64.2% and 85.7% of patients in the RTA and TH groups, respectively (P = 0.024). The rate of completed planned adjuvant chemotherapy was much higher in the TH group than in the RTA group (64.2% vs 25%, P = 0.003). Recurrence was recognized in 54% and 25% of the patients in the RTA and TH groups, respectively (P = 0.029). The patterns of recurrence are shown in Table 4. The distributions of recurrences were similar in both groups, and there were no differences in peritoneal dissemination, liver, lung, or adrenal metastasis and anastomotic recurrence; however, there were two cases of abdominal LN metastasis recurrence in the TH group vs eight cases in the RTA group (P = 0.037). The median follow-up time was 40 months (6–62) in the RTA group and 41 months (12–86) in the TH group. The 3-year RFS was significantly better in the TH group than that in the RTA group (P = 0.019) (Figure 1). The 3-year OS rates also differed significantly between the RTA and TH groups (57% vs 83%, P = 0.014) (Figure 2).

Discussion

Adenocarcinomas of the esophagogastric junction (AEG) generally have a poor prognosis due to a high incidence of recurrence and metastasis.[18,19] Although efforts have been made to improve the treatment outcomes, surgery remains the only curable approach for AEG.[20] The optimal approach of surgery for AEG, particularly Siewert type II tumor, is still being debated. Thoracic surgeons usually treat this cancer according to esophagus carcinoma guidelines and consider thoracic surgery the preferred method.[6] Abdominal surgeons, on the other hand, consider the abdominal transhiatal approach the better choice.[4,5,21] The right thoracoabdominal approach (RTA) with

Table 3 Clinicopathological Characteristics and Perioperative Outcomes After PSM

	TH Group (n = 28)	RTA Group (n = 28)	*P* value
Sex (male/female)	23/5	24/4	0.722
Age (years)[a]	62.33 (42–80)	62.33 (46–77)	0.972
Body mass index (kg/m^2)[a]	23.47 (18.3–30.1)	23.85 (17.7–30.1)	0.520
BMI ≤18.5/>18.5 and <25/≥25	 1/21/6	 1/21/6	 1.000
Physical status (ASA) 1/2/3	 22/6/0	 22/6/0	 1.000
pT stage T1/T2/T3/T4	 0/0/18/10	 0/0/18/10	 1.000
pN stage N0/N1/N2/N3a/N3b	 3/10/6/7/2	 3/10/6/7/2	 1.000
Histological grade G1/G2/G3	 0/19/9	 0/19/9	 1.000
Operative time (min)[a]	264 (150–360)	386.67 (200–515)	<0.001
Blood loss (mL)[a]	73.81 (20–600)	170 (100–800)	0.004
Postoperative hospitalization (days)[a]	10.29 (7–61)	16.71 (11–39)	0.014
First flatus time (days)[a]	3.25 (2–5)	3.5 (2–5)	0.286
Tumor size (mm)[a]	40.8 (16–75)	52.5 (25–70)	0.083
Length of esophageal invasion (mm)[a]	10.3 (0–20)	16.0 (10–20)	<0.001
Length of proximal margin (mm)[a]	18.9 (15–25)	38.8 (30–65)	<0.001
Length of esophagus resected (mm)[a]	27.6 (20–40)	57.3 (50–75)	<0.001
Number of metastatic LNs[a]	28.3 (0–20)	32.5 (0–29)	0.983
Total number of harvested LNs[a]	30.5 (16–62)	24.5 (11–56)	0.018
Morbidity grade≥ IIIa Anastomotic bleeding Anastomotic leakage	2 (7.1%) 1 (3.5%) 1 (3.5%)	8 (28.5%) 2 (7%) 6 (21.4%)	0.037
Reoperation	1 (3.5%)	3 (10.7%)	0.267
Adjuvant chemotherapy	26 (85.7%)	19 (64.2%)	0.024
Initiation of adjuvant chemotherapy[a]	4(4–5)	7(4–15)	0.045
Completion of adjuvant chemotherapy	18 (64.2%)	7 (25%)	0.003

Note: [a]Median (range).
Abbreviations: PSM, propensity score matching analysis; LNs, lymph nodes; TH, transhiatal; RTA, right thoracoabdominal.

proximal gastrectomy plus gastric tube reconstruction and the abdominal transhiatal (TH) approach with total gastrectomy are the two most frequently used methods for Siewert type II AEG. To the best of our knowledge, studies evaluating the differences in outcomes between RTA and TH for Siewert type II AEG are far from sufficient. In this study, we compared the short-term clinical and oncological outcomes of patients with Siewert type II AEG who received surgery using the TH and RTA approach.

Previous studies reported that the postoperative morbidity rates were significantly higher in patients who

Table 4 Patterns of Recurrence

	TH Group (n = 28)	RTA Group (n = 28)	*P* value
Peritoneal dissemination	1/27	1/27	1.000
Liver, lung, and adrenal metastasis	3/25	5/23	0.454
Abdominal lymph node metastasis	2/26	8/20	0.037
Anastomotic recurrence	1/27	1/27	1.000

Abbreviations: TH, transhiatal; RTA, right thoracoabdominal.

received transthoracic operation than in those receiving abdominal surgery.[22,23] With regard to the short-term outcomes, we found that patients in the TH group had a smaller blood loss and shorter postoperative hospital stay than those in the RTA group (both $P < 0.05$). Furthermore, patients in the RTA group experienced more surgery-related complications such as anastomotic leakage and postoperative pneumonia (both $P < 0.05$). Anastomotic leakage is among the complications that GI surgeons are most reluctant to encounter postoperatively. The relatively high frequency of anastomotic leakage in the RTA group in our study may be explained by the fact that thoracoabdominal surgery led to prolonged operative time and it was difficult to add reinforcement sutures for the anastomosis to an adequate extent due to limited operative space in the thoracic cavity. Although other studies have indicated that the transthoracic approach is not associated with an increase in the mortality and morbidity compared with the abdominal approach, our study showed that Siewert type II AEG patients may benefit more from transhiatal than from transthoracic surgery.[24]

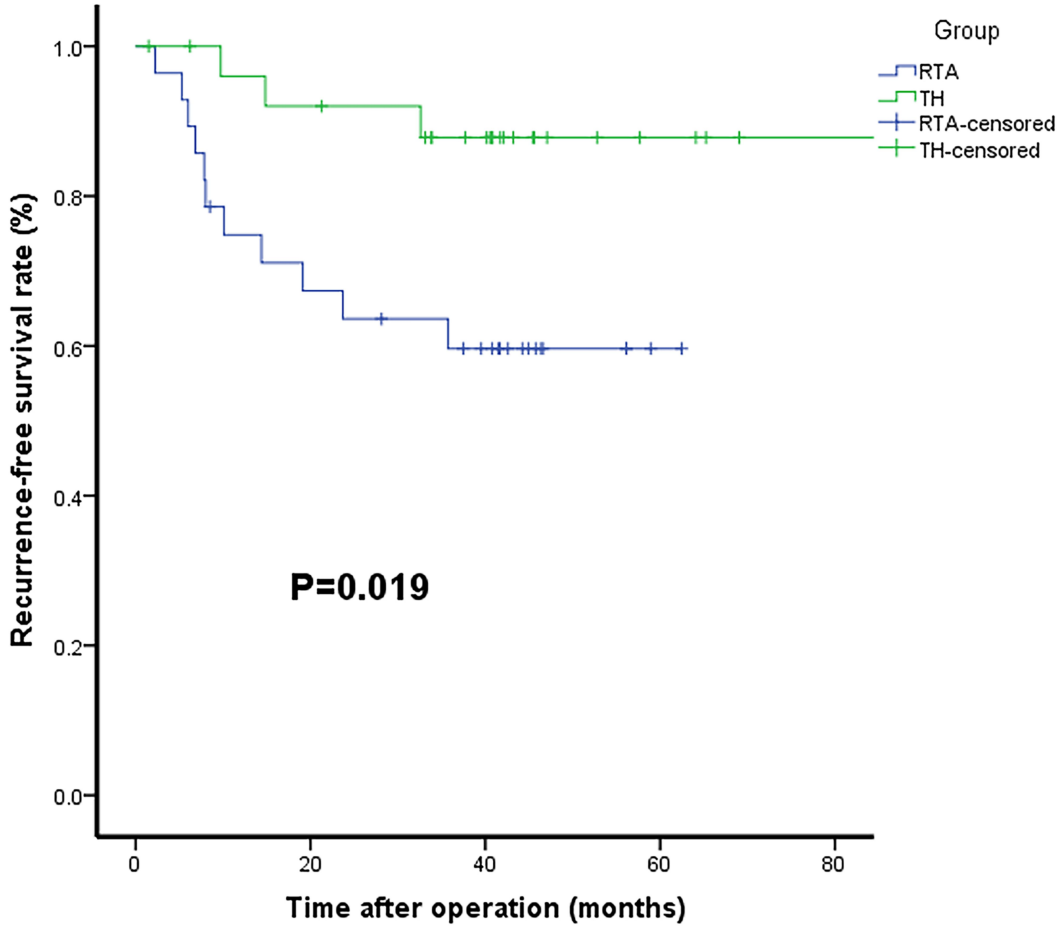

Figure 1 Recurrence-free survival after propensity score matching (PSM) analysis.

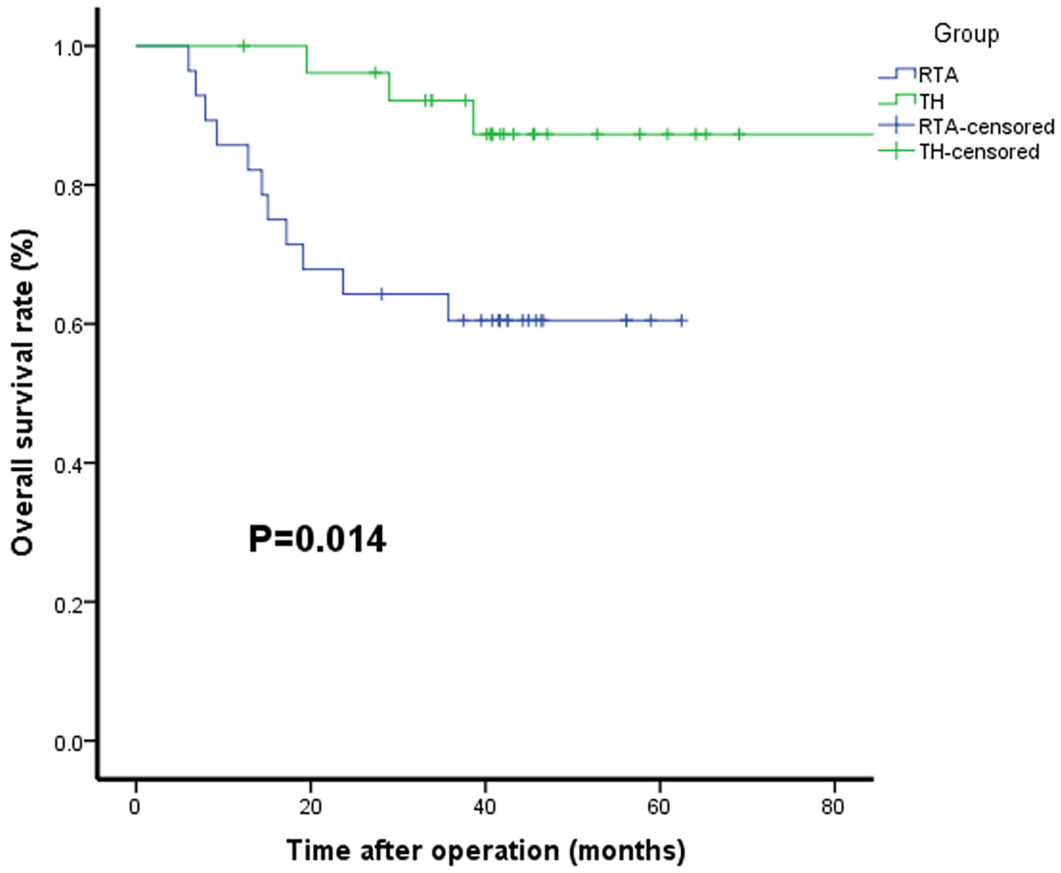

Figure 2 Overall survival after propensity score matching (PSM) analysis.

With regard to oncological outcomes, patients in the RTA group experienced a significantly worse long-term survival than those in the TH group as evidenced by PSM analysis ($P < 0.05$). One possible explanation is that complications, which were more commonly observed in the RTA group than in the TH group, resulted in a delay of adjuvant chemotherapy initiation, thus adversely affecting the prognosis. Yuan et al found that major complications (III–IV grades in the Clavien–Dindo classification) negatively influenced both OS and RFS of patients following curative gastrectomy.[25] Park et al reported that delayed treatment of adjuvant chemotherapy led to a worse 5-year overall survival than early and intermediate initiation of treatment in patients who underwent radical gastrectomy for gastric cancer.[26] Our study also found that patients in the RTA group had lower adjuvant therapy completion rates than those in the TH group (25% vs.64.2%, $P < 0.05$). It should be noted that the incompletion of adjuvant chemotherapy was identified as an independent risk factor for poor cancer-specific survival in gastric cancer patients in a previous study.[27]

In total gastrectomy for Siewert type II AEG, a sufficient proximal margin should be ensured with curative intent. The proximal margin is crucial for the resection status and therefore associated with the long-term survival of cancer patients.[28] However, the optimal length of the proximal margin remains an issue of controversy.[29,30] Barbour et al reported that a proximal margin >3.8 cm is an independent prognostic factor for AEG patients following radical resection with more than 15 LNs harvested.[10] Mine et al demonstrated that for Siewert type II/III tumors treated with transhiatal total gastrectomy, a gross proximal margin >2cm appears sufficient for acceptable survival outcomes.[11] According to the Japanese gastric cancer treatment guidelines, for tumors with esophagus invasion, a 5cm proximal margin is not mandatory, while frozen-section examination of the resection line is preferable to obtain R0 resection.[31] In our practice, a 2cm gross proximal margin was secured intraoperatively in patients in the TH group. After the removal of the tissue specimen, the proximal margin was regularly sent for frozen-section pathological examination to ensure a negative margin. If

a positive proximal margin was determined intraoperatively, thoracoabdominal surgery was performed. No positive margin was observed in the TH group in the present study (data not shown), and it seems safe and feasible to obtain R0 resection by this method.

LN dissection is considered a major prognostic factor potentially influencing the survival outcome of gastric cancer patients. Regarding lower mediastinal LN dissection, there is no consensus in the indication and extent of this procedure. In this study, we found that the metastasis rate of lower mediastinal LNs in the RTA group was only 6.7% (2/30), which is in accordance with previous studies.[15,32] In a Japanese prospective nationwide multicenter study,[15] LNs were classified into three types based on metastasis rate: category 1 (strongly recommended for dissection), rate more than 10%; category 2 (weakly recommended for dissection), rate from 5% to 10%; and category 3 (not recommended for dissection), rate less than 5%. If the extent of esophagus invasion was less than 2 cm, the lower mediastinal LN metastasis rate was found to be low with only No. 110 metastasis was in category-2. Our results may also suggest that lower mediastinal LN dissection is unnecessary for Siewert type II AEG patients with less than 2 cm of esophagus involvement.

There are several limitations to this study. First, the retrospective design and relatively small sample size may influence the power of the study. Second, the oncological outcome might be affected by the fact that the RTA group received insufficient abdominal LN dissection due to subtotal gastrectomy. Hence, we recommend prospective randomized control trials to be carried out to verify our findings.

Conclusions

For Siewert type II AEG with esophageal invasion ≤2cm, TH surgery led to better results in terms of both surgical and oncological outcomes than RTA surgery. TH surgery may be a better therapeutic approach for Siewert type II AEG with esophageal invasion ≤2cm, than the RTA approach.

Ethics Approval and Consent

The present study was approved by the Medical Ethics Committee of Peking University Cancer Hospital and was conducted following the Helsinki Declaration of the World Medical Association. All participants have given consent for publication.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the National Natural Science Foundation of China (No.81872022, 81672439), Beijing Natural Science Foundation (No.7162039), Capital's Funds for Health Improvement and Research (CFH 2018-2-2153), Beijing Excellent Talent Training Funding (2018000021469G258).

Disclosure

All authors declare that there is no conflict of interest.

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