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WORD COUNT

2779

TIME SUBMITTED

22-FEB-2022 07:08PM

PAPER ID

82865530

**Name of Journal:** *World Journal of Gastrointestinal Surgery*

**Manuscript NO:** 73784

**Manuscript Type:** ORIGINAL ARTICLE

*Retrospective Cohort Study*

**Laparoscopic-assisted *vs* open transhithal gastrectomy for Siewert type II adenocarcinoma of the esophagogastric junction: A retrospective cohort study**

Laparoscopic-assisted transhithal gasyrectomy

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## **Abstract**

### **BACKGROUND**

The studies of laparoscopic-assisted transhial gastrectomy (LTG) in patients with Siewert type II adenocarcinoma of the esophagogastric junction (AEG) are scarce.

### **AIM**

To compare the surgical efficiency of LTG with the open transhial gastrectomy (OTG) for patients with Siewert type II AEG.

### **METHODS**

We retrospectively evaluated a total of 578 patients with Siewert type II AEG who have undergone LTG or OTG at the First Medical Center of the Chinese People's Liberation Army General Hospital from January 2014 to December 2019. The short-term and long-term outcomes were compared between the LTG ( $n = 382$ ) and OTG ( $n = 196$ ) groups.

### **RESULTS**

Compared with the OTG group, the LTG group performed longer operative time, but less blood loss, shorter length of abdominal incision and more number of harvested lymph nodes ( $P < 0.05$ ). Patients in the LTG group were able sooner to eat liquid food, ambulate, expel flatus and discharge ( $P < 0.05$ ). No significant difference were found in postoperative complications and R0-resection. The 3-years overall survival (OS) and disease-free survival (DFS) performed better in the LTG group compared with that in the OTG group (88.2% vs 79.2%,  $P = 0.011$ ; 79.7% vs 73.0%,  $P = 0.002$ , respectively). In the stratified analysis, both OS and DFS were better in the LTG group than those in the OTG group for stage II/III patients ( $P < 0.05$ ), while not for stage I patients.

### **CONCLUSION**

For patients with Siewert type II AEG, LTG is associated with better short-term outcomes and similar oncology safety. Besides, patients with advanced-stage may benefit more from LTG in the long-term outcomes.

**Key Words:** Adenocarcinoma of the esophagogastric junction; Siewert type II; Laparoscopic-assisted transhithal gasyrectomy; Open transhithal gastrectomy

Song QY, Li XG, Zhang LY, Wu D, Li S, Zhang BL, Xu ZY, Wu RLG, Guo X, Wang XX. Laparoscopic-assisted *vs* open transhithal gastrectomy for Siewert type II adenocarcinoma of the esophagogastric junction: A retrospective cohort study. *World J Gastrointest Surg* 2022; In press

**Core Tip:** 1. Our objective was to compare the surgical efficiency of laparoscopic-assisted transhithal gastrectomy (LTG) with the open transhithal gastrectomy (OTG) focus on patients with Siewert type II adenocarcinoma of the esophagogastric junction (AEG). 2. We found that LTG is associated with better short-term outcomes, similar oncology safety. Besides, patients with advanced-stage may benefit more from LTG in 3-years overall survival and disease-free survival.

## INTRODUCTION

In recent decades, the global incidence of gastric cancer has declined annually while the incidence of adenocarcinoma of the esophagogastric junction (AEG) has presented an upward trend, especially in Asian countries [1-5]. Although there are many controversies concerning the optimal treatment for AEG patients, surgery is still the cornerstone of therapeutic strategies [6]. According to the results of the nationwide clinical trial (JCOG 9502) in Japan, the transhithal approach is recommended for Siewert type II/III AEG patients with esophageal invasion within 3cm [7,8]. Since the first report of laparoscopic-assisted transhithal gastrectomy (LTG) by Kitano in 1994, LTG has developed rapidly worldwide [9]. With the improvement of laparoscopic technology and the optimization

of equipment, a large number of countries have successively carried out LTG for gastric cancer because it provides not only better short-term outcomes but also comparable oncologic safety and survival in comparison with open transhita gastrectomy (OTG), especially in early-stage and distal gastric cancer [10-13]. Conversely, due to the lack of scientific evidence, the feasibility of LTG in proximal gastric cancer is still controversial. Moreover, peripheral lymphatic drainage pathways of Siewert type II AEG are more complicated as the particularity of the anatomical location, and LTG surgery with D2 Lymphadenectomy remains more challenging than other sites gastric cancer [14,15].

At present, the studies on the short-term and long-term clinical effects of Siewert type II AEG regarding the LTG and OTG are limited [16-20]. Thus, this study retrospectively analyzed the clinical data of Siewert type II AEG patients in our hospital, compared the short-term and long-term outcomes of LTG and traditional OTG, and aimed to explore the feasibility of LTG treatment of Siewert type II AEG.

## **MATERIALS AND METHODS**

### **Patients**

This work retrospectively reviewed patients with Siewert II AEG who have undergone gastrectomy at the First Medical Center of Chinese PLA General Hospital in China from January 2014 to December 2019. The inclusion criteria contained: 1) Histologically proven Siewert type II AEG; 2) Surgery *via* either OTG or LTG with total or proximal gastrectomy, and curative R0 resection with D2 Lymphadenectomy; 3) Staging T1-4a, N0-3, M0 (According to the 8th edition of the TNM staging system of the American Joint Committee on Cancer (AJCC) [21] and 4) Esophageal invasion <3cm. The exclusion criteria were presented as following: 1) Patients with a secondary malignancy within 5 years; 2) American Society of Anesthesiologists physical status score (ASA) > 3; 3) Only underwent palliative resection or combined organ resection and 4) Received preoperative chemotherapy of radiotherapy. Finally, totally 578 patients were pooled into the study (LTG=382, OTG=196).

This study has been registered on Clinical-Trial.gov (ChiCTR2100053647) and approved by the Ethics Committee of Chinese PLA General Hospital.

### **Surgical procedures**

LTG: The patient was placed in a supine position and given general anesthesia, by employing a 5-hole method. After exploring the relevant positions of various tissues in the abdominal cavity and the location and size of the tumor, a radical total and proximal gastrectomy was performed in this study. Gastrectomy and D2-lymphadenectomy were Completed. Then, a small incision was made in the middle of the abdomen to reconstruct the digestive tract. Gastric tube construction and esophagogastrostomy were often performed after proximal gastrectomy. After total gastrectomy, most patients underwent esophagojejunostomy and jejunojunostomy (Roux-en-Y reconstruction).

OTG: The positioning and anesthesia of the patients remained the same as those of the LTG group. An incision was made in the middle of the abdomen to enter the abdominal cavity. Other operative details such as gastrectomy, lymphadenectomy and reconstruction were the same as those in the LTG group.

### **Clinical parameters and Follow-up**

We retrospectively collected the following clinical and pathological factors available in our clinical database: age, sex, body mass index (BMI), smoking/drinking history, ASA score, tumor size, histopathological grade, TNM stage, operation time, intraoperative blood loss, length of abdominal incision, length of proximal margin, number of harvested lymph nodes (LNs), number of positive LNs, R0-resection, postoperative recovery (the time to liquid diet, ambulation, first flatus or defecation, and discharge) and postoperative complications (anastomotic leakage, anastomotic stenosis, abdominal abscess, pneumonia, arrhythmia and wound infection). All postoperative complications were classified with the application of the Clavien-Dindo grading system [22].

Besides, postoperative patients were periodically followed up with blood tests, physical examinations and Chest/abdominal computed tomography scans through outpatient visits. The follow-up interval was every 3-6 mo for the first two years and

every 6–12 mo for the subsequent 3 years. All surviving patients were followed up annually thereafter until death. Overall survival (OS) calculated the time from surgery to death due to any cause or latest follow-up. Disease-free survival (DFS) calculated the time from surgery to first recurrence or death because of any reason.

### **Statistical Analysis**

Continuous were presented as mean  $\pm$  standard deviation (SD) and assessed by Mann-Whitney U test. Dichotomous variables were compared with the Chi-square test or Fisher test. Survival analysis was performed by the Kaplan-Meier curves based on the log-rank test. Statistical analysis was done by IBM SPSS (version 26.0.0.0). The figures were plotted with RStudio (version 1.4.1717). Bilateral p-value  $<0.05$  was considered to be statistically significant.

## **RESULTS**

### **Clinicopathological characteristics**

As shown in Figure 1, totally 578 patients were eligible (512 male and 66 female) for our study, 382 (66.1%) patients underwent laparoscopic-assist transhial gastrectomy and 196 (33.9%) patients underwent open transhial gastrectomy, respectively. The demographic information of the participants was presented in Table 1. No significant difference could be observed in the distribution of baseline features between the two groups.

### **Perioperative outcomes**

Perioperative outcomes are shown in Table 2. The LTG group was experienced a significantly longer operation time (230.14 $\pm$ 58.92 min *vs* 198.4 $\pm$ 56.76 min,  $P<0.001$ ) but significantly fewer blood loos (200.42 $\pm$ 304.34 mL *vs* 275.77 $\pm$ 384.72 mL,  $P = 0.01$ ) and significantly shorter abdominal incision (9.66 $\pm$ 1.73 cm *vs* 18.12 $\pm$ 3.92 cm,  $P<0.001$ ) in comparison with OTG. Patients with LTG were sooner able to take a liquid diet (3.65 $\pm$ 2.56 days *vs* 4.62 $\pm$ 2.59 days,  $P<0.001$ ) and expel flatus or defecation (3.87 $\pm$ 2.17 days *vs* 5.62 $\pm$ 2.35 days,  $P<0.001$ ) after the operation, indicating the restoration of the intestinal function. Additionally, patients in LTG groups were able to ambulate after



2.93±2.04 days, which is fewer days than that in the OTG groups required 4.13±2.55 days ( $P < 0.001$ ). In addition, the duration of postoperative hospitalization of LTG groups was significantly shorter than that in OTG groups (10.82±7.97 days *vs* 11.42±4.46 days,  $P < 0.001$ ).

Postoperative complications occurred in 5.0% after LTG and in 4.6% after OTG ( $P = 0.84$ ). There existed no significant difference between the two groups in terms of anastomotic leakage, anastomotic stenosis, abdominal abscess, pneumonia, arrhythmia or wound infection ( $P > 0.05$ ). Furthermore, the complications of Clavien-Dindo grade III or higher were comparable in both groups ( $P = 0.365$ ). No mortality existed within 30 days postoperatively in either group. Further details are presented in Table 2.

According to the histopathological analysis, the rate of complete tumor resection (R0) could be achieved in 99.5% in the LTG group and 99.0% in the OTG group ( $P = 0.879$ ). The number of the harvested LNs was significantly higher in the LTG groups (28.81±12.16 *vs* 26.20±12.23,  $P = 0.015$ ). Besides, the number of positive LNs was similar in the two groups ( $P > 0.05$ ). Apart from that, the length of the proximal margin was also comparable between the two groups ( $P = 0.597$ ).

### Survival

The Median follow-up time was 38.94 mo (Interquartile range IQR 23.28-59.93) for all patients. In comparison with OTG group, LTG group showed better 3-year OS (88.2% *vs* 79.2%,  $P = 0.011$ ). (Figure 2A). Then, we performed a stratified analysis of survival according to the TNM stage. For patients with stage I, there existed no significant difference in 3-year OS between the two groups, but patients in the LTG group with stage II and stage III observed better 3-year-OS compared with that of the OTG group (Stage II: HR 0.126, 95%CI 0.027-0.584,  $P = 0.008$ ; Stage III: HR 0.361, 95%CI 0.134-0.967,  $P = 0.043$ ) (Figure 2B, C, D).

### Recurrence

The rate of recurrence presented no significant difference in the LTG and OTG groups (12.8% *vs* 10.7%,  $P = 0.547$ ). The patterns of recurrence were listed in Table 3. Distributions of recurrence for LTG were similar to that for OTG, and there existed no



differences in organ metastasis (liver, lung, bone, brain, pancreas), anastomotic recurrence, peritoneal dissemination, lymph node metastasis, or others ( $P>0.05$ ).

<sup>1</sup> The 3-year DFS was significantly better in the LTG group than that in the OTG group (79.7% vs 73.0%,  $P = 0.002$ ) (Figure 3A). After stratification by TNM Stage, the 3-year DFS was similar between the two groups in stage I patients. However, for stage II and stage III patients, the 3-year DFS was better in the LTG group compared with that of OTG group with significant difference (Stage II: HR 0.191, 95%CI 0.052-0.709,  $P = 0.013$ ; Stage III: HR 0.386, 95%CI 0.161-0.924,  $P = 0.033$ ) (Figure 3B, C, D).

## DISCUSSION

<sup>6</sup> Recently, the prevalence of Siewert type II AGE has risen rapidly, while most patients are diagnosed as an advanced stage with a poor prognosis at the first visit [23]. Complete removal of the tumor and adequate regional lymph nodes resection remains the only curative treatment for AEG [6]. Since the first report of laparoscopic-assisted gastrectomy, laparoscopic techniques have developed quickly in gastrointestinal tumors [9,24]. However, due to the lack of scientific evidence, the safety and feasibility of LTG in the treatment of Siewert type II AEG still remain controversial [16,17]. In the present study, LTG for Siewert type II AEG showed longer operation time but less blood loss, shorter abdominal incision, and faster recovery compared with OTG. The obtained results were similar to the previous studies [17,18,20]. A large number of studies have demonstrated that LTG performed comparable morbidity and mortality as OTG for gastric cancer while few of them were focused on AEG [25-28]. In this study, no significant difference was observed in postoperative complications between the LTG group and OTG group for Siewert type II AEG. Apart from that, the complications of Clavien-Dindo grade III or higher were comparable in both groups. These results suggested that LTG can be safely performed and provide better short-term outcomes for patients undergoing Siewert type II AEG.

Ensuring the safety of oncology is critical to the choice of surgical strategy. Shi *et al* [17] compared totally 132 patients with LTG and 264 patients with OTG. After propensity

score matching, the number of harvested LNs showed no significant difference for AEG. By contrast, Sugita *et al* suggested an increased number of dissected LNs in LTG groups compared with OTG for Siewert type II AEG [18]. In the current work, there existed higher number of harvested LNs in the LTG group than that in the OTG group. The previous studies reported that the number of harvested LNs is an important prognostic factor for patients with AEG [29,30]. In addition, other oncological parameters in terms of length of proximal margin, R0 resection, and the number of positive LNs were comparable between the two groups. As a result, the oncological safety of LTG is equivalent to OTG.

Regarding the long-term outcomes, we found that the distribution of recurrence patterns was similar in the two groups. Shi *et al* reported that there existed no significant difference for OS between LTG and OTG group [17]. Nevertheless, their study population included not only Siewert type II but also type III AEG. In addition, Huang *et al* and Sugita *et al* suggested that Siewert type II patients in the LTG group performed significantly better OS than that in LTG group [16,19]. The existing limitations included short observation period and small population, respectively. We investigated better 3-year OS and DFS of LTG for Siewert type II AEG patients compared with those of OTG. Moreover, we conducted a stratified analysis based on the TNM stage. Patients with stage I exhibited no survival benefit from LTG while patients with stage II and III also revealed better survival outcomes in the LTG group.

Undoubtedly, our study has some limitations. First, this study was a single-center, retrospective cohort study. Besides, the follow-up compliance of patients is limited, and the specific death and the patterns of recurrence of some patients remain unknown. Thus, prospective randomized controlled studies are still needed.

## **CONCLUSION**

In conclusion, laparoscopic-assist transhiatal gastrectomy is a safe and feasible treatment for Siewert type II AEG. Meanwhile, patients with advanced-stage may benefit more from LTG in the long-term outcomes.

## **ARTICLE HIGHLIGHTS**

### ***Research background***

Due to the lack of scientific evidence, the feasibility of laparoscopic-assist transhiatal gastrectomy (LTG) in patients with Siewert type II adenocarcinoma of the esophagogastric junction (AEG) is still controversial.

### ***Research motivation***

To compare the feasibility of LTG with the traditional open transhiatal gastrectomy (OTG) in patients with Siewert type II AEG.

### ***Research objectives***

We retrospectively evaluated and compared the short-term and long-term outcomes for patients with Siewert type II AEG between LTG and OTG, and aimed to explore the feasibility of LTG treatment of Siewert type II AEG.

### ***Research methods***

We retrospectively evaluated 578 patients with Siewert type II AEG who have undergone LTG or OTG at the First Medical Center of the Chinese People's Liberation Army General Hospital from January 2014 to December 2019. The short-term and long-term outcomes were compared between the LTG ( $n = 382$ ) and OTG ( $n = 196$ ) groups.

### ***Research results***

Compared with the OTG group, the LTG group performed less surgical trauma and faster recovery after surgery. No significant difference between the two groups regarding oncological safety. The 3-years overall survival (OS) and disease-free survival (DFS) performed better in the LTG group than those in the OTG group (88.2% vs 79.2%,  $P = 0.011$ ; 79.7% vs 73.0%,  $P = 0.002$ , respectively). In the stratified analysis, both OS and

DFS were better in the LTG group than those in the OTG group for stage II/III patients ( $P < 0.05$ ), while not for stage I patients.

***Research conclusions***

For patients with Siewert type II AEG, LTG is associated with better short-term outcomes and similar oncology safety. Besides, patients with advanced-stage may benefit more from LTG in the long-term outcomes

***Research perspectives***

The well-designed multicenter prospective randomized controlled studies are still needed

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