Editorial

Laparoscopic-assisted total gastrectomy for esophagogastric junctional adenocarcinoma

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Adenocarcinoma of the esophagogastric junction (AEG) is a tumor of which the center is ≤5 cm proximal or distal to the anatomical esophagogastric junction (1). The occurrence of AEG has been rapidly increasing in several decades in association with the decreasing rate of *Helicobacter pylori* infection and increasing trends of obesity and gastroesophageal reflux disease (2-4). In Asian countries, most AEGs are classified as Siewert type II or III, and these cancers are thus mainly treated as proximal gastric cancers (5,6). It is generally acknowledged that Siewert type I AEG should be treated as esophageal cancer (7). However, the operative procedure for Siewert type II AEG remains debated. Subtotal esophagectomy via right thoracotomy and laparotomy, transhiatal (TH) subtotal esophagectomy via laparotomy, and total gastrectomy (TG) via laparotomy have all been performed with comparable outcomes (7).

A Dutch group conducted a clinical trial comparing the right transthoracic (TT) and TH approaches for Siewert type I and II cancers (8). Postoperative complications were higher with the TT approach. Furthermore, Omloo *et al.* (9) reported the 5-year survival data in the above-mentioned Dutch randomized controlled trial (RCT). Although no significant overall survival (OS) benefit was found for either approach, survival tended to improve with the TT approach. According to a subgroup analysis, patients with Siewert type I cancers had a 14% overall 5-year survival benefit if operated via the TT approach. In contrast, patients with Siewert type II cancers had no survival benefit (–4%) when undergoing the TT approach. These results indicate thorough mediastinal lymph node (LN) dissection via right thoracotomy is necessary for Siewert type I but not II cancers. The Japan Clinical Oncology Group (JCOG) conducted a prospective randomized phase 3 study to compare the effects of the left thoracoabdominal (LTA) approach and TH approach for TG in patients with AEG (JCOG 9502 trial) (10). The LTA approach resulted in increased postoperative morbidity. Furthermore, the LTA approach for treatment of Siewert type II cancers conferred no benefit of survival compared with the TH approach (37.5% *vs.* 52.5%, respectively) (10). Kurokawa *et al.* (11) reported the final analysis based on the 10-year follow-up data of the JCOG 9502 trial. The 10-year OS rate was 37% for the TH approach and 24% for the LTA approach (p=0.06). They concluded that TG with the LTA approach should be avoided in the treatment of AEG.

Based on these trials, TG with TH resection of the distal esophagus is recommended for Siewert type II or III cancers. However, the approach for TG by laparotomy or laparoscopy remains controversial. With the development of laparoscopic devices and increasing experience in laparoscopic surgery, several reports have indicated the short-term outcomes of laparoscopic gastrectomy (including TG) in terms of factors such as postoperative complications, blood loss, and the number of dissected LNs are comparable with those of conventional open gastrectomy (12-14). However, laparoscopic-assisted TG (LATG) has not been as widely performed as laparoscopic-assisted distal gastrectomy. Various problems including technical difficulty and oncological safety have prohibited the popularization of LATG. First, the esophagojejunostomy after LATG is the

most technically difficult type of anastomosis in the field of laparoscopic gastrectomy. Lee *et al.* (14) reported that the pattern of complications differed between LATG and open TG (OTG); anastomosis-related complications, including stricture, leakage, and bleeding at the esophagojejunostomy site, were more common in the LATG group, whereas the OTG group tended to have a large number of wound infections. Another problem associated with LATG is the oncological aspect. Lymphatic pathways in esophagogastric junctional cancer are complex because of the particular anatomical location of this tumor. Whether the laparoscopic approach permits complete resection of the primary tumor and surrounding LNs within a limited space is unclear, especially in patients with advanced AEG; therefore, the indications for LATG in such patients must be carefully considered. To solve these problems, Huang *et al.* (15) recently conducted a case-control study focused on the outcomes of LATG for Siewert type II and III cancers. They found that LATG is associated with better postoperative outcomes for Siewert type II and III cancers. Furthermore, LATG achieved better long-term outcomes than OTG, especially for Siewert type II cancers, using propensity score matching (PSM). From January 2007 to June 2014, a total of 989 patients with Siewert type II or III cancer underwent TG at single institution in China. In total, 342 patients (OTG, 171 patients; LATG, 171 patients) were analyzed. There was no significant difference in postoperative complications in both groups. In addition, the blood loss volume, operation time, and duration of hospital stay were significantly lower in the LATG than OTG group. Notably, the operation time for LATG (197.8±53.9 minutes) was significantly shorter than that for OTG (275.0±58.0 minutes) (P<0.001). In some studies, the operation time was longer for laparoscopic gastrectomy than conventional open gastrectomy (12,14). Nevertheless, another study showed that the operative time significantly decreased as surgical experience (number of cases) increased (16). LATG may not require more time than OTG when performed by an experienced surgeon.

The number of retrieved LNs is often evaluated as a benchmark of oncological safety. Huang *et al.* (15) found that the number of dissected LNs was significantly higher in the LATG than OTG (34.6±12.7 *vs.* 30.6±11.8, respectively; P=0.003). Furthermore, with respect to oncological outcomes in patients with Siewert type II AEG, a significantly higher 3-year OS rate (81.3% *vs.* 66.4%, P=0.011) and disease-free survival rate (77.5% *vs.* 63.8%, P=0.040) were observed in association with LATG than OTG (15). However, these survival rates were similar for patients with Siewert type III AEG undergoing LATG and OTG (P=0.853 and P=0.844, respectively). These findings are further supported by another PSM analysis by Lin *et al.* (17), who found that LATG for gastric cancer is a safe and reliable procedure with short-term and long-term outcomes similar to those of OTG. Huang *et al.* (15) reported that the laparoscopic approach helps surgeons to identify specific fascial spaces and facilitates LN dissection. LATG can allow for *en bloc* resection of LNs and provide the optimal tissue layers for more sufficient LN dissection compared with OTG. It is generally agreed that LN dissection can be sufficiently accomplished in LATG, but how it affects the difference in prognosis between Siewert type II and III AEG remains unknown.

To the best of our knowledge, Huang *et al.* (15) were the first to report good short-term technical outcomes and good long-term oncologic outcomes of LATG for Siewert type II and III AEG, and their study is considered to very clinically meaningful. However, it seems to have several limitations. First, the selection criteria for LATG and OTG were unclear. According to the treatment guideline for gastric cancer (18), LATG is recommend for early gastric cancer. Basically, laparoscopic gastrectomy is recommended for early lesions and laparotomy for advanced lesions. Therefore, although the clinicopathological factors were adjusted for by PSM, it seems that selection bias was originally present when selecting the operative procedure. Furthermore, the patients' historical backgrounds, such as whether LTG was recently performed, might have influenced the results. Second, they selected only nine covariates to calculate the propensity score, and only three were oncological factors (histopathological grade, Siewert classification, and tumor size). If the number of matched factors is small, some factors affecting the oncological aspect may not be fully matched. For example, although the difference was not statistically significant, the number of LN metastases tended to be higher in the OTG than LATG group (4.8±7.1 *vs.* 3.5±5.1, respectively; P=0.162). Additionally, although not reported in their paper, if the number of patients receiving adjuvant chemotherapy differs between the two groups, there is a possibility that this difference may affect the long-term outcome. Honda *et al.* (12) showed that laparoscopic gastrectomy was comparable with open gastrectomy for clinical stage I gastric cancer by PSM. In the clinical setting, because surgeons choose the most appropriate surgical approach on the basis of much more clinical information, it is important

to incorporate as many preoperative factors as possible to achieve high-quality PSM as close as possible to a RCT. Finally, the authors selected 30 preoperative factors related to surgical decision-making. Thus, because bias may occur even in PSM, it is considered necessary to perform a RCT. Regardless, RCTs are always blocked by a shortage of registered patients, and they tend to require a long term before oncological follow-up can be completed. Therefore, it will be meaningful to find answers to clinical questions using PSM.

A joint study produced novel findings that can affect the surgical procedure for AEG. The Japanese Gastric Cancer Association and Japan Esophageal Society joined forces to conduct a nationwide surveillance of esophagogastric junctional cancer of <40 mm in diameter, and 3,177 patients from 273 institutions who underwent surgery from 2001 to 2010 were retrospectively collected (4). The incidence of LN metastasis at station Nos. 4sa, 4sb, 4d, 5, and 6 was <1% even in patients with high dissection rates. Therefore, the authors concluded that complete nodal dissection along the distal side of the stomach offers only a marginal survival benefit and is not essential for local disease control in this population. These findings indicate that reduction surgery such as proximal gastrectomy might be permitted, avoiding TG for selected patients. Further studies of the treatment strategy for AEG are required.

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Footnote

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