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Review

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Minimally invasive approach for cancer of the esophagogastric junction

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Abstract

The incidence of esophagogastric junction (EGJ) cancer is increasing in the world. EGJ cancer is traditionally classified by the Siewert classification, despite its limitations. The definition and classification of EGJ cancer is a controversial topic. Thus, the best available strategy for the surgical treatment of EGJ cancer remains controversial. This chapter reviews a minimally invasive approaches for EGJ cancer. Most operations for EGJ cancer that are performed by open surgery can be performed minimally invasively. A minimally invasive transthoracic approach (Ivor-Lewis or McKeown esophagectomy) is the optimal surgical approach for Siewert type I cancer. Mediastinoscope-assisted transhiatal esophagectomy, which was recently reported, may be a suitable surgical option, especially for frail patients with Siewert type I cancer. Generally, laparoscopic total or proximal gastrectomy is regarded as the standard for surgerical method for Siewert type III cancer, while both laparoscopic gastrectomy (with lower esophagectomy) or a minimally invasive Ivor-Lewis approach are recommended for Siewert type II cancer. Minimally invasive surgery (MIS) has the potential to shorten the length of hospitalization, reduce the risk of postoperative pulmonary complications, and improve quality of life with a similar margin status, nodal harvest, and survival rate to open techniques. However, as the existing literature is still limited, the choice of surgical method should be judged by the experienced surgeons, especially in MIS. This review reveals that further large clinical stuidies are need to deepen our understanding of MIS for EGJ cancer.

Keywords: Esophagogastric junction cancer, thoraco-abdominal approach, transhiatal approach, minimally invasive esophagectomy

INTRODUCTION

Esophageal cancer and gastric cancer are among the most common malignancies worldwide, and are a main causes of cancer-related mortality[1]. The term "esophagogastric junction (EGJ) tumor" refers to a tumor that arises close to the esophagogastric junction. The incidence of EGJ cancer has dramatically increased in the last decade[2]. In Eastern countries, westernized lifestyle habits, *Helicobacter pylori* infection, obesity, a combination of alcohol and smoking, and the increased incidence of gastroesophageal reflux disease are thought to be possible reasons[3].

EGJ cancers are traditionally classified into one of the three categories of the Siewert system, which is the most commonly used classification system, based on the location of the epicenter of the given tumor.

Type I: Adenocarcinoma of the distal esophagus with the center located within 1 to 5 cm above the anatomic EGJ. Type II: True carcinoma of the cardia infiltrating from 1 cm on the side of the esophagus up to 2 cm below the GEJ in the stomach. Type III: Subcardial gastric carcinoma with the tumor center between 2 and 5 cm below the GEJ.

Meanwhile, in the Japanese Classification of Gastric Carcinoma, EGJ cancer has been defined as cancer with its center located within 2 cm of the EGJ since 1972. In 2012, the Japanese Gastric Cancer Association and Japan Esophageal Society joint force conducted a nationwide surveillance of EGJ cancer of < 4 cm in diameter, which included the retrospective data of 3,177 patients from 273 institutions[4]. The joint force presented an algorithm showing the tentative standard in the extent of lymphadenectomy, based on this surveillance, in Japanese Gastric Cancer Treatment Guidelines, 2014 (ver. 4). Similarly, the American Joint Committee on Cancer (AJCC) has changed the definition of EGJ cancer to a cancer whose epicenter is within the proximal 2 cm of the cardia (Siewert I/II) in the eighth edition of the TNM classification[5]. However, they categorized EGJ cancer as an esophageal cancer and staged it accordingly. Meanwhile, The National Comprehensive Cancer Network, recommends that Siewert type III tumors should be treated as gastric cancers, since their lymph nodal flow and prognosis are different from Siewert type I and type II cancers[6]. Thus, a current concern of surgeons is whether Siewert type II and III cancer should be regarded-and thus surgically approached-as the same tumor. The lack of consensus regarding the definition of EGJ cancer and the classification scheme that could affect the standard of care for this category contribute to this controversy[7].

Minimally invasive surgery have been gaining popularity in recent years. Cuschieri *et al.*[8] first described the successful performance of thoracoscopic esophagectomy for esophageal cancer in 1992, and several authors have reported their experience with good results[9,10]. The first laparoscopy-assisted distal gastrectomy was reported by Kitano *et al.*[11] Thereafter, many clinical trials have unveiled the benefits of this technique, generally revealing surgical and oncological outcomes that are equal to those of open surgery[12,13]. Minimally invasive surgeries have evolved for the purpose of further reducing postoperative complications and enhanced recovery. Intrducing minimally invasive esophagectomy (MIE) for esophageal cancer has some potential benefits over conventional open esophagectomy (OE)[14]. In this article, we reviewed the existing evidence and rationale for minimally invasive surgeries of EGJ cancer.

SURGICAL APPROACH FOR THE EGJ CANCER

Although, the optimal surgical approach for these tumors remains under debate, three main surgical approaches are applied in the resection of EGJ tumors: transthoracic esophagectomy (the right transthoracic approach and the left transthoracic approach), transhiatal esophagectomy, and total gastrectomy. All three approaches enable a minimally invasive approach to be pursued. Irrespective of the surgical method and tumor stage, complete removal of the primary tumor is most relevant to prognosis[15].

The right transthorathic approach is possible to ensure a sufficient proximal margin even in EGJ cancer with long esophageal invasion. The upper mediastinal LNs can be removed by this approach. However, because of the surgical stress associated with thoracotomy, careful management is required to avoid postoperative pneumonia. There are two types of left transthorathic approaches in open surgery: the left thoracoabdominal approach, with an oblique incision from the left thorax to the abdomen, and left thoracophrenolaparotomy, which includes laparotomy and transdiaphragmatic thoracotomy. The one of the merit of these techniques is no requirement of repositioning during surgery. However, it is not possible to dissect the upper and middle mediastinal LNs with these approach.

The transhiatal approach, consists of transhiatal surgery on the abdomen and lower mediastinum and does not require thoracotomy. The procedures in the lower mediastinum include lower esophagectomy and only peri-esophageal LN dissection. Respiratory damage appears to be less than with the other approaches. Although *en bloc* dissection of the lower mediastinal LNs is possible, the surgical view of the mediastinum of this approach in open surgery is worse compared with the other approaches.

In general, Siewert type I cancer should be treated with *en bloc* transthoracic or transhiatal resection. The transthoracic approach is most beneficial, especially in advanced Siewert type I cancer, and the appropriate extent of lymphadenectomy (two-field Ivor-Lewis esophagectomy or three-field McKeown esophagectomy) remains a focus of discussion[16,17]. Generally, transhiatal esophagectomy has limitations due to the inability of mediastinal lymphadenectomy and should therefore be applied for frail patients.

The standard surgical approach for Siewert type II and type III cancers involves total gastrectomy with D2 lymphadenectomy. In Siewert type II, it involves the transhiatal resection of the distal esophagus with lower mediastinal lymphadenectomy. Splenectomy and pancreatectomy are not essential if the tumor is not located along the greater curvature and harbors metastasis of the no. 4sb lymph nodes[18]. Furthermore, in Siewert type II and III early cancers, recent evidence suggests that proximal gastric resection with D1 + lymphadenectomy may contribute to avoid postgastrectomy syndrome without a detrimental effect on complete oncologic clearance[19].

Finally, minimally invasive approaches have been developed as a safe and feasible alternative to traditional open surgery for the treatment of esophageal cancer[20,21]. Efforts have been made by surgeons to establish all types of minimally invasive surgery (MIS), including minimally invasive Ivor-Lewis, McKeown esophagectomy, and transhiatal esophagectomy. An *en bloc* lymphadenectomy method in the upper and middle mediastinum with a single-port mediastinoscopic cervical approach that was recently developed by a Japanese surgeon is a hot topic in the treatment of EGJ cancer [22]. In combination with lower mediastinal lymph nodes dissection using laparoscopic trans hiatal approach, they perform total mediastinal lymphadenectomy under pneumomediastinum assistance without thoracotomy. This technique achieves minimum invasiveness and has curative potential. Further investigation is needed to evaluate its safety and feasibility.

EVIDENCE FOR VARIOUS SURGICAL STRATEGIES IN THE MINIMALLY INVASIVE APPROACH FOR CANCER OF THE EGJ

Table 1 summarized the cited results in this manuscript. Schoppmann *et al*.[23] described a case controlled study (n = 31) that demonstrated higher rates of morbidity, transfusion rate, and postoperative respiratory complications in MIE comparing to OE. Briez *et al*.[24] evaluated the impact of a hybrid MIE (HMIE, laparoscopic gastric mobilization and open thoracotomy, n = 140) to OE (n = 140) on respiratory complications. They found that the incidence of respiratory complications at 30 days after HMIE was significantly lower in comparison to OE. Moreover, the in-hospital mortality and overall morbidity rates were significantly

Table 1. Summary of the cited results

author	reference#	case	location	procedure	methods	conclusions
Schoppmann	23	62	esophagus or EGJ	MIE, HMIE (I, M)	RS	higher rates of morbidity, transfusion, and respiratory complications in MIE
Briez	24	280	mid- or distal esophagus	HMIE (I)	RS	lower rates of respiratory complications, in-hospital mortality, and overall morbidity rates after HMIE
Luketich	9	1,011	esophagus or EGJ	MIE (I, M)	RS	reduced blood loss and post-operative complications, and a shorter LOS in MIE
Seeing	25	866	esophagus or EGJ	MIE (I, M)	PMA	shorter LOS, but higer rates of anastomotic leakage and reintervention in MIE.
Maas	28	100	distal esophagus or EGJ	MIE (T)	RS	shorter hospital and intensive care unit stay with a similar operation time in MIE
Dantoc	34	1,598	esophagus or EGJ	MIE, HMIE (I, M)	SR	higher number of dissected lymph nodes in MIE with no difference in 5-year survival rates
Mamidanna	35	7,502	esophagus or EGJ	MIE, HMIE (I, M)	RS	higher reintervention rate in MIE, but no difference in 30-day mortality and overall medical morbidity
Zhou	36	14,311	esophagus or EGJ	MIE, HMIE (I, M)	MA	lower rate of in-hospital mortality, pulmonary complications, and arrhythmia in MIE
Luketich	14	95	mid- or distal esophagus	MIE (I, M)	PS	low peri-operative morbidity and mortality in MIE
Biere	37	115	esophagus or EGJ	MIE (I, M)	RCT	lower rates of respiratory complications, a shorter LOS and better QOL scores in MIE
Mariette	38	207	mid- or distal esophagus	HMIE (I)	RCT	reduced the rate of postoperative complications and improved morbidity with better global health in MIE
Sihag	40	3,780	esophagus	MIE (I, T)	PMA	longer operation times, higher rates of reoperation, but a shorter LOS in MIE
Yerokun	41	4,574	mid- or distal esophagus	MIE (I, M)	RS	higher number of exracted lymph nodes and shorter LOS in MIE
Shanmugasundaram	42	573	esophagus or EGJ	MIE (M)	MA	reduced incidence of respiratory complication, bleeding, LOS, but a longer operating time in MIE

E esophageal cancer, EGJ Esophagogastoric junctional cancer, I Ivor-Lewis, M McKeown, T Transhiatal, LOS length of hospital stay RCT randomized controlled trial, RS retrospective study, PS prospective study, PMA Propensity-matched analysis, SR systematic review, MA meta-analysis

lower in the HMIE group. Luketich *et al.*[9] reviewed 1,033 consecutive patients undergoing MIE and revealed reduced blood loss, reduced post-operative complications and a shorter hospital stay, with same oncological outcomes. Seeing *et al.*[25] compared the short-term surgical results of OE (n = 433) with MIE (n = 433) after propensity score matching. Although OE and MIE showed similar rates of mortality and pulmonary complications, anastomotic leakage and reintervention was more frequently observed after MIE. However, MIE was associated with a shorter length of hospitalization . The problem of their study was that the complication rates in both groups (62.6% after OE and 60.2% after MIE) were relatively high in comparison to historical studies[25,26,27]. Maas *et al.*[28] also demonstrated that minimally invasive transhiatal esophagectomy by a laparoscopic approach (n = 50) is feasible and has the comparable oncologic outcome as open transhiatal esophagectomy (n = 50), and a shorter hospital and intensive care unit stay with a similar operation time (300 *vs.* 280 min, P = 0.110). Other retrospective reviews have also revealed that MIE is safe without compromising oncologic outcomes in comparison to the OE[29-33].

Dantoc *et al.*[34] reported a systematic review of 17 case-control studies that compared total minimally invasive (thoracoscopy "and" laparoscopy, n = 494) or hybrid MIE (thoracoscopy "or" laparoscopy, n = 386) to OE (n = 718) for esophageal or EGJ cancer. In comparison to OE, MIE and HMIE had a higher number

of dissected lymph nodes, while the overall 5-year survival rates of the OE and MIE/HMIE groups did not differ to a statistically significant extent. Mamidanna *et al*.[35] investigated a population-based national study evaluating the short-term outcomes following OE (n = 6347) *vs*. MIE (n = 1155) for cancer in England. No differences were observed between the OE and MIE groups with regard to 30-day mortality and overall medical morbidity. The reintervention rate of the MIE group was higher than that of the OE group. Zhou *et al*.[36] reported a meta-analysis of 48 studies involving 14,311 cases of resectable esophageal or EGJ cancer. In comparison to patients undergoing OE (n = 9,973), those undergoing MIE/HMIE (n = 4,509) had a significantly lower rate of in-hospital mortality. Patients undergoing MIE also had significantly lower rates of pulmonary complications and arrhythmia. The limitation of this study was that almost all of the included studies were non-randomized case-control studies (RCTs, n = 1; observational studies, n = 47), with a diversity of study designs and surgical interventions. They concluded that MIE should be the first-choice surgery for esophageal cancer patients. However, these findings must be interpreted cautiously due to the selection bias, as the patients selected for MIE had early-stage cancer with better physical status.

Luketich *et al*.[14] conducted a multi-center, phase II, prospective study that revealed that MIE (n = 95) is feasible with low peri-operative morbidity (49.5%) and mortality (2.1%), and a 3-year overall survival rate of 58.4% Biere *et al*.[37] conducted a randomized trials of MIE *vs*. OE for patients with esophageal or EGJ cancer. In this study, 59 patients were randomized to the MIE group and 56 patients were randomized to the OE group. They revealed the advantages of MIE over OE, including a reduced incidence of postoperative pulmonary infections, a shorter length of hospitalization and better quality of life scores, indicating improved patient recovery. Mariette *et al*.[38] conducted a multicenter, randomized controlled trial that included 207 patients (MIRO trial). They investigated a HMIE using thoracotoic chest access with laparoscopy for abdominal access. In comparison to Ivor-Lewis resection, HMIE reduced the rate of postoperative complications and improved morbidity with an equivalent number of dissected lymph nodes, and no difference in resectability and curability. In the OE group, 64.4% of the patients had major postoperative morbidity in comparison to 35.9% in the HMIE group ($P < 0.01$). The incidence of pulmonary complications was 30.1% in the OE group and 17.7% in the HMIE group ($P < 0.05$). The 30-day mortality rate was 4.9% in both arms. They also reported a one-year follow-up results of the quality of life with their RCT participants and demonstrated that the MIE group had a better physical component, global health, and postoperative pain[39]. A propensity score matched analysis of 3,780 patients who underwent OE or MIE for esophageal cancer by both transhiatal and Ivor-Lewis approaches demonstrated that OE and MIE had similar rates of morbidity and mortality. MIE was associated with longer operation times, higher rates of reoperation, and empyema, but a shorter median length of hospitalization. OE was associated with higher rates of wound infection, postoperative transfusion, and ileus[40].

Yerokun *et al*.[41] investigated the predictive factors associated with the use of minimally invasive approaches (n = 1,308) for patients in the National Cancer Database who underwent resection of middle and distal esophageal cancers (n = 4,266). In the MIE group, the number of lymph nodes examined was significantly higher (15 *vs*. 13; P = 0.016) and the hospital stay was significantly shorter (10 days *vs*. 11 days; P = 0.046), however the rates of resection margin positivity, readmission, postoperative mortality, and, 3-year survival were comparable. With regard to oncological safety, no differences were found in OS or disease-free survival after 1 and 3 years of follow-up, with a better quality of life of physical components at 1 and 3 years of follow-up[33,39]. Thus, they concluded that MIE is considered to be a safe surgical approach and the majority of patients with a resectable cancer of esophagus or EGJ should be treated with MIE.

Shanmugasundaram *et al*.[42] reported a meta-analysis of 4 studies involving 573 cases of resectable esophageal or EGJ cancer. In comparison to patients undergoing OE (n = 9,973), those undergoing McKeown's-MIE (n = 4,509) had a significantly lower rates of pulmonary complications, less blood loss, and a shorter duration of hospital stay but a longer operating time.

However, since the current literatures are still limited, further large scale RCTs are needed. Thus, at present, the surgical method should be decided is at the surgeon's discretion.

ROBOTIC APPROACHES FOR EGJ CANCER

The introduction of surgical robots has shown the potential to expand the capabilities of performing complex operations through improved visualization and maneuverability. Recently, many surgeons have found robot-assisted thoracoscopic and transhiatal esophagectomy to be safe and acceptable for the treatment of esophageal and gastric cancer[43]. Future randomized trials are expected to establish this procedure as one of the best approaches for esophageal and gastric cancer. Robotic surgery will be described in greater detail in another chapter.

CONCLUSION

The incidence of cancer of EGJ has increased in worldwide. This article reviews MIE for cancer of EGJ. All major approaches for the resection of EGJ cancer can be pursued by MIS. EGJ adenocarcinoma is traditionally classified by the Siewert classification system, although which has some limitations. The definition and classification of EGJ cancer remains controversial. MIE has emerged as a promising approach that might reduce the postoperative complications in comparison to open techniques. The advantages of MIE as a treatment for EGJ cancer in comparison to OE included a reduced hospitalization, and rate of pulmonary complications, and an improved quality of life with a similar nodal harvest, margin status, and 1- and 3-year survival rates. However, since the current literature is still limited, the selection of surgical method should be judged by the experienced surgeons. In any type of EGJ cancer, R0 radical resection is mandatory for improving the patient's prognosis. Minimally invasive Ivor-Lewis or McKeown esophagectomy are the treatments of choice for Siewert type I cancer. Transhiatal esophagectomy is a surgical option for frail patients, which is limited because the operator cannot perform mediastinal lymphadenectomy. Single-port mediastinoscope-assisted transhiatal esophagectomy with mediastinal lymphadenectomy is an emerging minimally invasive approach that also has curative potential. Laparoscopic total (or proximal) gastrectomy is the optimal surgery for Siewert type III cancer, whereas both laparoscopic gastrectomy (with lower esophagectomy) and a minimally invasive Ivor-Lewis approach are the optimal minimally invasive choices for Siewert type II cancer. With the introduction of robotic surgery, esophagectomy is expected to evolve even further.

In conclusion, since the current literature is still limited, further well-desined RCTs are needed to clarify the optimal minimally invasive surgery for EGJ cancer.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Shibao K, Hirata K

Performed data acquisition, as well as provided administrative, technical, and material support: Mitsuyoshi M, Matayoshi N, Inoue Y, Katsuki T, Sato N

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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