



# Selection of surgical approach for esophageal cancer at esophagogastric junction

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The incidence of gastroesophageal junction adenocarcinoma (GEJAC) in Western countries has increased over the last few decades (1). Some increase in the incidence of GEJAC has been seen in Asia as well (2,3).

There is much controversy in the definition and in the choice of optimal surgical treatment for GEJAC. Even the definition of gastroesophageal junction (GEJ) is not clear. Since the 1996 the Siewert classification system has been used for diagnosis, reporting, and research on these tumors. The Siewert classification defines the GEJ as the most proximal end of the gastric folds, and it identifies 3 types of tumors based on where the lesion's epicenter is located: type I, between 1 and 5 cm above the GEJ; type II, between 1 cm above and 2 cm below the GEJ; type III, between 2 and 5 cm below the GEJ (4). The drawback is that the accuracy of pathologic determination of Siewert classification is confirmed by preoperative endoscopic determination in only 70% of cases, and by preoperative radiographic determination in only 72% (5).

The common agreement is that for locally advanced GEJAC, operative resection is necessary for long-term survival. Although there are several surgical treatment options available for the treatment GEJAC, one principle is universally accepted. That principle, which Siewert *et al.* presented in 2000, is the importance to achieve microscopically clear resection margins (R0 resection). Siewert *et al.* showed the correlation of the long-term survival and R0 resection on 1,002 patients (6). This finding has been confirmed by others (7,8).

## Surgical resection: Siewert class I

Another generally accepted principle is a proper resection

of all regional lymph nodes. Data from previous studies have shown that Siewert type I tumors most commonly spread to the upper abdominal and lower posterior mediastinal nodes (9,10). This leads to the consensus of the need for esophageal resection and mediastinal lymph node dissection for type I tumors—a position supported almost unanimously by experts in a recent international survey (11). The two most popular methods to achieve resection of a distal esophageal cancer are transthoracic and transhiatal esophagectomies. Transthoracic esophagectomy is performed through a right thoracotomy and laparotomy (Ivor Lewis or Tanner-Lewis esophagectomy). In addition, the sharp dissection of lymph nodes is performed both in upper abdomen and mediastinum. Then the gastric conduit is brought through the posterior mediastinum and the anastomosis is performed in the chest, or in case of a very long tumor, in the neck (McKeown approach). The advantage of thoracic anastomosis is lower leak rates, but if a leak occurs, the morbidity is higher in case of the chest anastomosis. Overall, the thoracotomy approach is associated with higher peri-procedural morbidity and mortality than transhiatal approach (11,12). The modern way of decreasing the morbidity is to employ total or partly minimally invasive surgery (13,14).

Transhiatal esophagectomy includes a blunt mobilization of the intrathoracic esophagus from the esophageal hiatus and from a left cervical incision to the thoracic inlet without the need for thoracotomy. The advantage of the transhiatal technique is that it avoids thoracotomy while achieving a complete removal of the esophagus. Potential disadvantages include a limited periesophageal and mediastinal lymphadenectomy especially subcarinal, and the risk of causing tracheobronchial or vascular injury

during blunt dissection of the esophagus (particularly for locally advanced tumors). A cervical anastomosis is associated with a higher rate of anastomotic leakage than an intrathoracic anastomosis (12% *vs.* 5%, respectively), although the cervical anastomotic leak is generally confined to the cervical soft tissue with less risk of intrathoracic or mediastinal extension—and therefore the morbidity of a cervical leak is reported to be significantly lower (15). Disadvantages of cervical anastomosis include association with pharyngeal reflux, nocturnal aspiration, and prolonged swallowing dysfunction and hoarseness after surgery, mainly due to high incidence of recurrent laryngeal nerve palsy (16).

The beneficial extent of lymphadenectomy for Siewert I tumors is under debate. On one hand it has been shown that when less than 8 lymph nodes are involved with cancer, GEJ surgery with more radical lymph node resection results in better survival (17,18). On the other hand in a randomized trial there was no overall survival benefit for extended transthoracic approach for GEJAC compared to transhiatal approach—although in a subgroup analysis they were able to demonstrate a substantial difference in survival in patients with Siewert type I cancer (51% in the RT approach group and 37% in the TH approach group;  $P=0.33$ ). Based on these results, RT approach has been recommended for Siewert type I cancer and TH approach for Siewert type II cancer (19). Therefore, both approaches can be considered acceptable.

There are several retrospective series (20,21) and two prospective studies (13,22) showing that totally minimally invasive resection does not risk the radicality of lymph node dissection in the treatment of these tumors.

### **Surgical resection: Siewert class II**

Siewert class II tumors are often considered as true gastroesophageal tumors. There is a lot of controversy in the definition and the treatment of these tumors. They are treated both as esophageal tumors and as gastric tumors with either transthoracic esophagectomy (23), transhiatal esophagectomy (15), a left thoracoabdominal esophagogastrectomy (24), or a total gastrectomy (TG) with extended distal esophageal resection (6). An international survey among the members of both esophageal and gastric societies showed that about two-thirds of surgeons who treat these tumors perform an extended gastrectomy, while the rest prefer an esophagectomy and partial gastrectomy (12).

One recent study showed that the length of the proximal resection margin at least 3.8 cm's *ex vivo* margin length

(about 5 cm *in vivo*) correlates with improved survival regardless of approach (25). In contrast, an earlier study by Ito demonstrated the significance of at least 4 cm of macroscopically free stomach below the tumor (26). In order to achieve a good tumor free margin in the esophagus, the left thoracoabdominal esophagogastrectomy seems to be a bad choice based on a randomized controlled trial from the Japan Clinical Oncology Group. They compared the left thoracoabdominal esophagogastrectomy to transabdominal TG and stopped the study after the first interim analysis due to inferiority of the left thoracoabdominal resection in terms of safety (24).

Siewert's group has been advocating for a TG with extended distal esophageal resection based on their findings that mediastinal nodes are involved in only 11% of patients with type II tumors (27). Their finding can be criticized based on the fact they performed only transhiatal lymph nodes dissection. Similarly, a recent report from seven centers in the USA favored gastrectomy based on the fact that a specific proximal margin did not play any significant role for survival of patients with Siewert type II and type III tumors (28). Another report from two large data sets in the USA concluded the tumor biology and the use of multimodality therapy are determinants of oncologic outcome for cardia cancer, rather than either gastrectomy or esophagectomy (29). On the contrary, Leers *et al.* found that the prevalence and distribution of lymph node metastases in patients with adenocarcinoma of the distal esophagus and gastroesophageal junction were similar and an esophagectomy was similarly effective treatment for both types of tumors (30).

Results of a Dutch trial comparing transhiatal esophagectomy (TH) to transthoracic esophagectomy (RT) showed no overall survival benefit for RT approach compared to TH approach for patient with type II tumors ( $P=0.81$ ). However, the same study suggested significantly better survival for transthoracic approach on patients with at most 8 positive nodes, suggesting the patients with limited regional disease appear to benefit from the transthoracic approach (19). A systematic review of ten cohort studies comparing the gastrectomy and esophagectomy in treatment of GEJ tumors found no statistically significant differences in the 5-year survival rates between esophagectomy (30–42%) and gastrectomy (18–38%) (31).

It is obvious that Siewert classification cannot univocally predict the nodal drainage in GEJAC of Siewert type II. Therefore, better classifications are expected based on tumors' biological properties.

### Surgical resection: Siewert class III

Siewert II type tumors were classified as esophageal cancer in the seventh TNM edition, and then were reclassified as gastric cancer in the eighth edition. Surgical goals are the same as for the other two Siewert type tumors, in other words an R0 resection and appropriate lymph node clearance, while minimizing procedural morbidity. The way of achieving these goals is under debate. Most surgeons, however advocate the need of TG for these patients (11,32).

Some investigators have proposed a proximal gastrectomy (PG) for Siewert III adenocarcinoma of the GEJ as an optimal treatment. Their motivation has been a presumed lower rate of complications such as esophagitis and strictures after PG compared to TG (33), while others have claimed the opposite (34). Two large meta-analyses showed significantly more reflux esophagitis and anastomotic strictures after PG compared with TG (35,36). Also, the patient-reported quality of life outcomes are contradictory. PG may reduce dumping and need for additional meals (37). On the other hand, it may cause higher rates of clinically significant reflux and nausea (38). A recent Swedish population-based register study concluded gastrectomy and oesophagectomy for Siewert II or III GEJAC's seemed comparable regarding tumor-free resection margins, lymph nodes removal, and 5-year survival (39).

Although there are a lot of controversies in the choice of optimal surgical treatment of all types of GEJAC's one common principle is univocally accepted by surgeons: if possible, no residual disease should be left behind after the surgical resection of GEJAC. The patient should achieve the best possible survival and the best possible quality of life after surgery. In practice this means for all 3 types of GEJAC's need for about 4 cm tumor free margin in the stomach, and about 5 cm tumor free margin in the esophagus. Therefore, in most cases, an esophagectomy (either open or minimally invasive transthoracic or transhiatal) is needed for Siewert type I tumors and gastrectomy (or PG) for Siewert type III tumors. On the contrary, the optimal surgical option for tumors of Siewert type II is a matter of debate and no definitive recommendation cannot given based on the evidence available.

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