Review Article

Extent of lymphadenectomy for Barrett's cancer

Claudia Ly Wong, Simon Law

Division of Esophageal and Upper Gastrointestinal Surgery, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China

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Correspondence to: Professor Simon Law, MBBChir (Cantab), MS (HK), PhD (HK), FRCSEd, FCSHK, FHKAM, FACS. Cheung Kung-Hai Professor in Gastrointestinal Surgery, Chair and Chief of Esophageal and Upper Gastrointestinal Surgery, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong, China. Email: slaw@hku.hk.

Abstract: Adenocarcinoma of the esophagus and esophagogastric junction (EGJ) has become the predominant histological cell type in western countries due to the prevalence of obesity, gastroesophageal reflux disease and Barrett's esophagus. There is some evidence that this is increasing in the East as well. Surgery aims at achieving an R0 resection with clear margins, together with adequate and appropriate lymphadenectomy. Siewert type I and II cancers are more likely to be associated with Barrett's esophagus (especially in western countries), while type III cancers are mostly proximal gastric cancers that have grown upwards to involve the EGJ. For type I cancers, most surgeons would perform an esophagectomy, with at least an infra-carinal lymphadenectomy. It is more controversial for type II tumors, with some surgeons preferring an esophagectomy, while others may opt for a proximal or total radical gastrectomy via an abdominal approach. All procedures can be performed using open or minimally invasive methods. In addition to oncologic reasons, the chosen surgical approach also depends on expertise available, safety issues, and postoperative quality-of-life considerations. More data are needed in this area. How to integrate knowledge and also multimodality treatment strategies is an active area of research.

Keywords: Barrett esophagus; lymphadenectomy; lymphatic metastasis; esophagogastric junction

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Introduction

Barrett's esophagus is known to be a precursor of adenocarcinoma of the esophagogastric junction (EGJ) and esophagus. The rising esophageal adenocarcinoma incidence in the West can be attributed to the epidemic of obesity, gastroesophageal reflux disease and Barrett's esophagus. In the United States, it is estimated that gastroesophageal reflux affects up to 44% of the general population, of whom 5–8% will develop Barrett's esophagus; the estimated annual rate of neoplastic transformation is around 0.5%. When cancer develops, the mainstay treatment remains surgery; metastatic nodal status and the ability to carry out an R0 resection are the main prognosticators (1-7). In the East, there seems to be also a progressive increase in gastroesophageal reflux disease (8-10); whether there is uniformly a concomitant increase in Barrett's cancer remains uncertain. One controversial aspect of surgical resection is the optimal extent of lymphadenectomy. Increasing use of multimodal therapy with perioperative chemotherapy or chemo-radiotherapy, and the advent of minimally invasive resection techniques add to the discussion. In this review many of these issues are reviewed.

Classification of tumors around the esophagogastric junction

The Siewert classification has been applied to

adenocarcinoma around the lower esophagus and esophagogastric junction since the 1980s (11). It applies to adenocarcinomas that involve the esophagogastric junction, and with their epicenter in a region 5 cm proximal and 5 cm distal to the anatomical esophagogastric junction. Type I cancers are mostly regarded as "esophageal" in origin, and are closely related to gastroesophageal reflux disease and Barrett's esophagus. Type III tumors are more akin to proximal gastric cancers that have infiltrated the esophagogastric junction from below and are related to gastric atrophy and Helicobacter Pylori infection. Type II cancers with their epicentre on the esophagogastric junction are most controversial; whether they are more like esophageal or gastric cancers in biology and behaviour and how they should be treated are continually being questioned. Even tumor staging around this area is controversial. The 8th edition of the AJCC stages a tumor with its epicenter located more than 2 cm distally from the anatomical EGJ as gastric cancer, as opposed to the 7th edition of the AJCC. Knowledge around the EGJ is therefore constantly changing (12).

There are drawbacks of the Siewert classification. First, it is a purely anatomical system based only on the epicenter of the tumor, and does not take into account the proximal and distal extent of the cancer. In clinical decision making, the longitudinal extent is more important as far as surgical approach is concerned. Second, pre-treatment classification may not always be accurate especially in advanced cancer. Because of tumor overgrowth, the presence of Barrett's epithelium and hiatus hernia, accurate location of the esophagogastric junction is difficult, affecting the assignment. At best, preoperative classification is accurate in about 70% of patients (13). Despite this drawback, the system is widely adopted internationally.

Extent of lymphadenectomy: Barrett's adenocarcinoma and esophagogastric junction cancer

When surgery is discussed on Barrett's cancer, usually Siewert type I and type II cancers are included, the former arises from Barrett's epithelium, while short-segment Barrett's epithelium may at least be in part responsible for the latter. For type III cancers, they are generally regarded as gastric cancer with upward extension and the presence of Barrett's epithelium is correspondingly uncommon. In a large series of patients with esophagogastric junction tumors, the presence of Barrett's epithelium was identified in 76.9%, 9.8% and 2.0% of type I, II, and III tumors respectively (14). Similarly another study showed the corresponding figures as 80%, 18% and 2% (15). At the authors' institution, the corresponding numbers are 29%, 6.5% and 2.5% (unpublished data). Surgical principles for these cancers aim at achieving an R0 resection with clear proximal, distal and lateral margins, and adequate and appropriate lymphadenectomy. At the same time morbidity and mortality rates should be minimized, and quality-of-life is another issue related both to access as well as to the method of reconstruction. These principles dictate the surgical approach.

Pattern of lymphatic spread

Knowledge of the pattern of lymphatic spread is key to dictate the appropriate extent of nodal dissection. The behaviour of lymphatic spread of Barrett's adenocarcinoma and esophagogastric junction is different from that squamous cell carcinoma. Positive nodes are found in approximately 10% of patients with squamous cell cancers for T1a lesions, while in Barrett's cancer this is only 0–6%. In T1b cancers, the respective figures are 30–50% for squamous cell and 20% for adenocarcinomas. In addition, the pattern of lymphatic spread also differs; more than 85% of all positive nodes in early adenocarcinoma are located in close proximity to the primary tumor in contrast to fewer than 60% in squamous cell cancers (16). Data suggest that nodes are not commonly found in the superior mediastinum and, when present, probably indicates widespread disease (14). Thus lymphadenectomy is generally performed using a standard two-field approach. Parry and associates compared lymph node spread in type I and II cancers. In type I tumors, 10.4% of affected nodes were located in the supracarinal area, 1.5% in the aorto-pulmonary window and 15% subcarinally; whereas in type II cancers, only 0.8% had supracarinal nodes, 1.7% in the subaortic nodes, and 10% subcarinally. Those with supracarinal nodes had a survival rate of less than 10% at 5 years (17). Leers and associates analysed nodal distribution of types I and II tumors separately in a retrospective cohort of transthoracic and transhiatal esophagogastrectomies. The analysis was done exclusively on those with *en bloc* two-field lymphadenectomy. It showed that for type I tumors, lower mediastinal nodal metastasis was found in more than one quarter of patients and the rate was similar to that type II tumors. Lower mediastinum was the only site of metastases in 9% of node-positive type I tumors. While subcarinal metastasis was detected in 8% of all type I tumors, with a reported rate of 18% when only node-positive tumors were

included. It is less prevalent in true cardial tumors (18). Similar findings have been demonstrated in other large western series (19).

Detailed analysis has been performed in Japan for esophagogastric junction tumors, mainly for type II and III cancers since type I cancers are correspondingly rare in Asia. A nation-wide retrospective study was performed to look at the distribution of lymph node metastases for tumors at this region. Inclusion criteria including tumors of 4 cm or less in size and the epicenter locating within 2 cm of the anatomical esophagogastric junction (10). For T2 tumors, nodal spread to lower mediastinum is very rare, for T3/4 tumors, significant percentage of patients (>10%) had lower mediastinal spread for esophageal-predominant cancers (where the extent of esophageal involvement is more than that of the stomach). It was concluded that for esophageal-predominant cancers (especially advanced ones), lower mediastinal nodal incidence and therapeutic index was similar to that of supra-pancreatic nodal dissection. However it was also stated that the extent of esophageal resection and mediastinal nodal dissection was still controversial. For gastric-predominant tumors, it seemed that mediastinal dissection might not be necessary. A nation-wide prospective study on nodal spread has subsequently been carried out, jointly by the Japanese Esophageal Society and the Japanese Gastric Cancer Association. In this study, the extent of nodal dissection was pre-determined, this would capture more reliable and consistent data. The results of the study are eagerly awaited.

Limited number of studies with three-field lymphadenectomy (lymph node dissection around the celiac axis, in the mediastinum as well as bilateral neck) have been reported, and cervical nodes can be involved in up to 30% of patients with esophageal adenocarcinoma (20,21). However these data have not been widely reproduced and few surgeons would advocate cervical lymphadenectomy for such cancers.

Optimal surgical approaches

Given that detailed knowledge of lymphatic spread is still incomplete, the surgical approach for esophagogastric junction tumors remains controversial. Logan and Skinner *et al.* first introduced the concept of *en bloc* resection for esophageal cancer (22,23). In *en bloc* resection, the thoracic esophagus is resected together with a fascial cylinder enclosing the tumor-bearing zone of the esophagus and the lymphatic drainage system. The structures for resection include the primary tumor, azygos vein, thoracic duct, pericardium, intercostal vessels and bilateral mediastinal pleurae. This approach increases clearance of the lateral margin and is most suitable for adenocarcinoma because of its tumor location. *En bloc* resection is less applicable for squamous cell carcinoma, since most are located adjacent to the tracheobronchial tree where extension of this lateral margin is not possible.

Excellent results are reported for en-bloc resection in appropriately selected patients; a morbidity rate of 40%, mortality rate of less than 5%, and a 5-year survival rate of 37% to 52% has been reported in dedicated centers (24). The local recurrence rate is less than 5% within the field of dissection, and if nodal recurrence developed, they are mostly found outside the dissection field (25,26). En-bloc resection is mainly aimed at true esophageal Siewert type I adenocarcinomas.

Two pivot trials were published to address the issue of whether a transthoracic approach was beneficial, though both studies were dated. The popularization of transhiatal esophagectomy came at a time when esophagectomy was a high-risk operation with high mortality rates, and this less invasive method probably contributed to reducing overall death rates (27,28). This approach however limits the extent of mediastinal lymphadenectomy (especially mid and upper portion of the mediastinum) and remains controversial. The Dutch randomized trial compared 106 patients who underwent transhiatal and 114 with transthoracic resection for mid-lower third/cardia adenocarcinoma. Pulmonary complication rates were 27% for transhiatal *vs.* 57% for transthoracic group. The transthoracic group had longer ventilation time, intensive care unit and hospital stay. In-hospital mortality and overall 5-year survival rates were similar in both groups. Patients who underwent transthoracic resection had more lymph nodes harvested (31 *vs.* 16). In those with 1–8 positive lymph nodes, transthoracic approach had a survival advantage (64% *vs.* 23%, in 5-year). However, survival rates were similar in those patients without nodal metastases or with more than eight nodal metastases. In patients with type I cancers, 5-yr survival was 51% in those with transthoracic resection *vs.* 37% for transhiatal resection, although statistically the comparison was not significant (29,30). It was concluded that transthoracic resection could have survival advantage in type I cancers, especially in those with limited nodal metastases in the expense of increased morbidity. For type II cancers, no differences were found.

With improvement in surgical techniques and perioperative care, it seems that both procedures can be

carried out safely and the margin of benefit in reducing morbidity for most patients with the transhiatal operation is not overwhelming. In addition, more evidences are accumulating to demonstrate the benefits of radical lymphadenectomy.

The Japanese Oncology Group trial 9502 was a randomized trial comparing a transabdominal versus a left thoraco-abdominal approach for Siewert II or III adenocarcinomas (31,32). It was hypothesized that up to 30% of patients with such tumors would have lower mediastinal nodal metastases and that a left thoraco-abdominal approach could result in better mediastinal clearance and therefore better prognosis. Adenocarcinomas of the esophagogastric junction that had infiltrated to the esophagus for 3 cm or less, clinically T2-4, N0-2, M0 were randomly assigned to a transabdominal (n=82) or left thoracoabdominal approach (n=85). Both groups underwent total radical gastrectomy with left upper paraaortic dissection. The left thoracoabdominal group also had formal lower mediastinal dissection. The trial was closed prematurely after the first interim analysis, when the predicted probability of left thoracoabdominal approach having a significantly better overall survival than transabdominal route at the final analysis was only 3.7%. The morbidity rate was worse after the left thoracoabdominal approach (especially pulmonary complication rates). A 10-year follow-up of the trial yielded similar results (32). Thus a transabdominal approach seems adequate, though the surgeon must be prepared to add a thoracotomy when frozen section indicates a positive proximal resection margin. Although JCOG 9502 is very influential, the trial is somewhat limited by the slight imbalance of factors between the two groups, the finding of lower mediastinal nodal involvement being lower than originally projected when the trial was planned, and the premature closure of the study.

In summary therefore, for truly Barrett's lower esophageal adenocarcinoma, there seems not much controversy; most surgeons would opt for a transthoracic approach, with at least a infra-carinal two-field lymphadenectomy, the anastomosis being performed high in the intrathoracic cavity or in the neck. Minimally invasive methods, thoracoscopic/laparoscopic or combined approaches have their advocates. One published randomized trial showing its superiority over open esophagectomy especially in reducing pulmonary complications. The study recruited 59 patients who underwent combined thoracoscopic (prone position) and laparoscopic approach and 55 with open esophagectomy. An almost three-fold pulmonary complication rate was found with the open group with no difference in mortality rate. Post-operative quality-of-life was also superior in minimally invasive group (33). Oncologically, the number of retrieved lymph nodes and survival were similar between minimally invasive and open methods (34-36). Another recently published trial demonstrated that performing the abdominal part of the procedure laparoscopically was also beneficial compared to open laparotomy, despite in both groups open thoracotomy was performed (37). Major complications were 36% in the hybrid group compared to 64% in the open esophagectomy group, the respective figures for pulmonary complications were 18% *vs.* 30%. Survival was not different. Both trials included also squamous cell cancers, though most patients had adenocarcinomas.

For Siewert III cancers, most would regard them as gastric cancers, and therefore deem it sufficient to perform an abdominal approach, with a radical total gastrectomy and excision of the distal esophagus; reconstruction being done with Roux-en-Y jejunal loop. An upper abdominal compartment nodal dissection around the celiac axis seems routine for all.

For Siewert type II cancers, whether a gastrectomy via an abdominal approach or thoracic component should be added is most controversial and there is no ready consensus. An international survey was conducted to assess surgeons' preference in surgical approach. Most surgeons opted for esophagectomy for type I cancers and gastrectomy for type III tumors, for type II tumors, only around 65% chose extended gastrectomy, while substantial number opted for esophagectomy. Also interestingly, when East and West was compared, extended gastrectomy was predominantly chosen in the East, while esophagectomy and extended gastrectomy were almost equally chosen in the West (38).

Technical considerations are also important in deciding whether a thoracic phase is needed for tumors around this region; the aims are still to perform a safe operation (especially the anastomosis) with negative margins with adequate lymph node dissection. Factors that may favor a thoracic phase include (I) a bulky tumor, which may make achieving a negative proximal margin difficult, (II) an unhealthy esophageal remnant, which may be a result of high grade obstruction by the tumor (dilated and edematous) or neoadjuvant chemoradiation therapy. Extending resection proximally will have a healthier esophagus for anastomosis (III) poor exposure at the hiatus in an obese patient with a deep abdomen (more prevalent in western patients), (IV)

younger good risk patient, when a thoracic phase adds less morbidity, (V) when a good length of jejunum is available (or when the distal stomach is used for reconstruction). Training and surgeon's preference is also an important consideration. In many countries, esophagogastric junctions are operated on by gastric surgeons who may not have adequate training in thoracic approaches, and thus are limited in their choice of approach unless a thoracic surgeon is available. While in some countries, upper gastrointestinal surgeons deal with both esophageal and gastric cancers and are thus more versatile in their choice of procedure.

Quality-of-life issues

Increasingly quality-of-life issues are important considerations and may be related to surgical approach. Minimally invasive surgery has already been shown to result in better quality-of-life postoperatively. The Japanese detailed study on nodal spread also suggested that nodal dissection around the distal stomach may not be necessary for carefully defined group of tumors around the esophagogastric junction (less than 4 cm, centering on an area 2 cm proximal and distal to the anatomical junction) (10). By convention, a total gastrectomy is performed for a gastric cardia tumor, in part because of presumed better clearance of nodal metastasis, but also because a esophago-gastrostomy will inevitably result in gastroesophageal acid reflux. Given that nodal clearance may not be necessary, proximal gastrectomy is an acceptable procedure. Various novel reconstructive methods are being studied, such as double-tract reconstruction (39), or anti-reflux esophago-gastrostomy including a double-flap technique (40), or creating a pseudo-fornix (angle of His) (41). Some of these techniques are technically demanding and more data is required to prove their worth.

The optimal lymphadenectomy and surgical approach to esophago-gastric junction tumors is still controversial. The widespread use of neoadjuvant and adjuvant therapies adds further considerations; even less data is available to define what is most appropriate after such treatments. More work is required to address many of these issues.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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