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Management of Esophagogastric Junction Cancer

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Abstract

The management of Esophagogastric Junction (EGJ) cancer remains a complex issue due to the difficulty in defining it clearly. For this reason, the 8th edition of the TNM classification, defines EGJ adenocarcinoma as the cancer with epicenter located within 2cm proximal or distal to the EGJ which is now considered as esophageal cancer. The diagnosis of EGJ adenocarcinoma is achieved by endoscopy and biopsy while CT, endoscopic ultrasound, PET CT and laparoscopy are essential for the accurate staging of the disease. Treatment of EGJ adenocarcinoma requires a multimodal approach through which the combination of surgery, chemotherapy, immunotherapy and radiotherapy will offer the patient the best possible choice. As surgery remains the cornerstone of curative treatment, the optimal surgical approach (transthoracic or transhiatal surgery) and the extent of lymphadenectomy play critical role in both patient morbidity and overall survival. This review deals with the current practices in the management of EGJ cancer from diagnosis to definitive treatment.

Key words: esophagogastric junction cancer, definition, management, multimodal approach, surgical treatment

Introduction

The esophagogastric junction (EGJ) is an anatomic area that is defined differently between anatomists, endoscopists and pathologists. Therefore, tumors that develop in this site represent a special group of cancer that has been subject to much debate in the international scientific community.[1] The difference in classification between West and East makes the confusion about the definition and management of adenocarcinoma of EGJ even greater. Siewert classification remains the most common method of classifying EGJ adenocarcinoma in the West, according to which tumors are divided into three categories. On the other hand, the Japanese use the Nishi classification, dividing cancers into two groups regardless of histological type.[2]

In Europe and the USA, the incidence of EGJ adenocarcinoma has been increasing in recent decades, in contrast to cancer in other gastric anatomic sites such as the pylorus and body.[3] Similarly, EGJ adenocarcinoma is also increasing significantly in Japan, accounting for 10% of all gastric cancers.[4] Although the exact reasons remain unclear, the major factors that may be associated with this increase are the gastroesophageal reflux disease and Barrett's esophagus, obesity and other dietary factors.[1]

The management of adenocarcinoma of the esophagogastric junction requires multimodal methods of treatment based on the principles of surgery, chemotherapy and radiotherapy.[5] This review focuses on the current advancements in the management of esophagogastric cancer from definition, diagnosis and staging to definitive treatment.

Definition and Classification of Esophagogastric Junction Cancer

Although the location of esophagogastric junction seems to be easily defined as the point where the tubular esophagus joins the saccular stomach, there is yet a lot of controversy about the precise location due to the different methods used to define it.[6] For example, endoscopically the EGJ is defined as the proximal margin of the longitudinal gastric mucosal folds whereas histologically as the proximal end of the oxyntic mucosa.[1] Despite the fact that there are several criteria to define EGJ, it is very difficult to apply them simultaneously especially in cases where conditions in the area have changed. Thus, the development of a hiatal hernia which changes the anatomy or the presence of gastroesophageal reflux which can alter the histology of the epithelium, make the exact identification of EGJ even more complicated.[6]

Siewert classification has been the most widely used classification of EGJ adenocarcinoma in Western countries according to which tumors are divided into 3 types.[7] This classification has been the basis for choosing the proper surgery procedure based on the pattern of lymphatic spread of the tumor. According to Siewert EGJ cancer is divided as follows:

-Type I: tumors with epicenter or more than two-thirds of their bulk located 1-5 cm above the EGJ.

-Type II: tumors located from 1 cm above to 2 cm below the EGJ, described as "true cardiac adenocarcinoma".

-Type III: tumors located from 2-5 cm below the EGJ.[2]

On the other side, the Japanese use a simpler classification, the Nishi's classification, according to which as EGJ carcinoma is designated any tumor whose epicenter is located between 2 cm above and 2cm below the EGJ, regardless of the histological type. This definition seems to be more in line with Sievert's type II tumors and is referred to as true EGJ adenocarcinoma (Fig.1).[2,8]

In the 8th edition AJCC/UICC staging, the classification of EGJ cancer has been simplified so that EGJ adenocarcinoma is defined as any tumor located between 2 cm above and 2 cm below the EGJ. Tumors with epicenter within this area are staged now as esophageal adenocarcinoma whereas cancers whose epicenter extending 2 cm distal the EGJ are considered gastric cancers.[9,10] The next step in identifying the real cell of origin of EGJ adenocarcinoma is genetic analysis.[11] Subsequently, classification in the 9th edition staging will probably include the genetic identity of tumors.

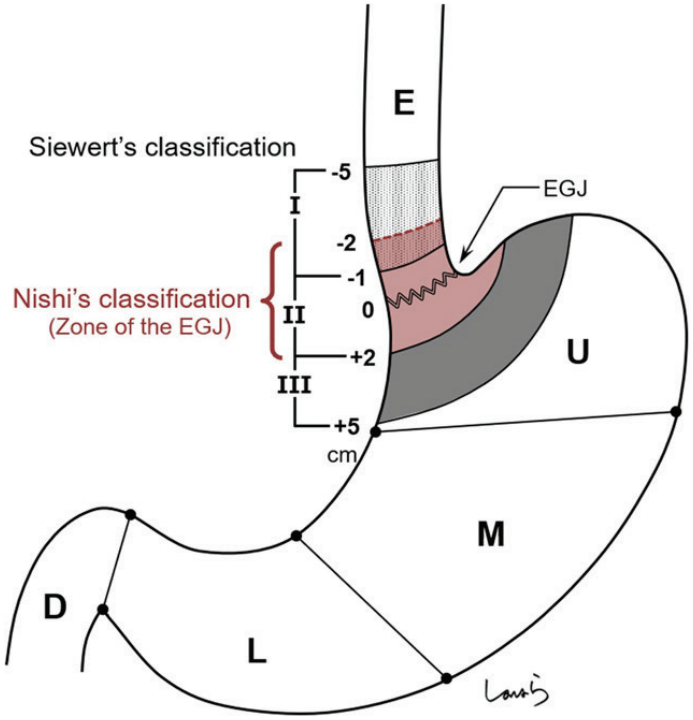


Figure 1: Siewert's and Nishi's classification for esophagogastric junction carcinoma. E: esophagus, U: upper third of stomach, M: middle third of stomach, L: lower third of stomach, D: duodenum.[2]

Diagnosis and Staging

Medical history, physical examination and endoscopy with biopsy are the first steps in the diagnosis of EGJ cancer. The most common symptom for which patients seek medical help is dysphagia. Other manifestations of the disease include bleeding, emesis, weigh loss or loss of appetite.[12,13]

The accurate staging investigation of EGJ adenocarcinoma includes Endoscopic Ultrasound (EUS), CT scan, PET CT scan and laparoscopy.[13,14] Endoscopic ultrasound is the best imaging modality for assessment of T and N stage. As regards the first, EUS can best evaluate the depth of invasion as giving valuable information about the possibility of lymph node or distal metastasis. EUS can also detect suspicious lymph nodes and offers the potential of FNA cytologic sampling.[15] CT scan of thorax, abdomen and pelvis is useful for the evaluation of distal metastasis and regional lymphadenopathy. As CT has a sensitivity of 52% and a specificity of 91% in detecting distal metastasis, 18F-FDG PET/CT can add by increasing sensitivity at rates of up to 90%. PET CT is also helpful in evaluating locoregional lymph node metastases, thus determining the possibility of neoadjuvant therapy.[16] Some limitations of PET CT are the diffuse

and mucinous type adenocarcinomas which show low tracer uptake. In cases of locally advanced (T3, T4) tumors infiltrating the cardia, staging laparoscopy and peritoneal washings for malignant cells is recommended to rule out occult peritoneal metastatic disease. In this way, findings of M1 disease detected in about 15% of patients can prevent them from undergoing a futile surgery.[17,18]

Esophagogastric junction adenocarcinoma should be staged according to the 8th edition of the American Joint Committee on Cancer AJCC/UICC TNM classification system. In this edition, tumors whose epicenter does not extend beyond 2cm into gastric cardia are classified as esophageal adenocarcinomas.[19] Apart from anatomic staging, all patients should have a medical risk and nutritional assessment prior to surgery or neoadjuvant therapy. It is very important that patients receive nutritional support according to ESPEN guidelines, which will help reduce operative risks and improve their quality of life.[13,20]

Endoscopic Treatment

Endoscopic resection techniques, either Endoscopic Mucosal Resection (EMR) or Endoscopic Submucosal Dissection (ESD), are the treatment of choice for early tumors (Tis, T1a). Histopathological examination of specimen determinates the final staging of the disease and if deep margins are clear and there are no risk factors for lymph node metastases, endoscopic treatment is considered definitive.[21]

Neoadjuvant and Perioperative Therapy

Management of the rest EGJ cancer (≥T1b) is based on a multimodal approach which includes surgery, chemotherapy, radiotherapy and immunotherapy.[22] According to the last NCCN guidelines for esophageal and EGJ cancers, small and low-risk for metastasis tumors (cT1b-T2N0) can be treated directly with surgery. In advanced lesions with positive lymph node metastasis, perioperative chemoradiotherapy or chemotherapy alone has the primary role followed by surgery (Fig.2).

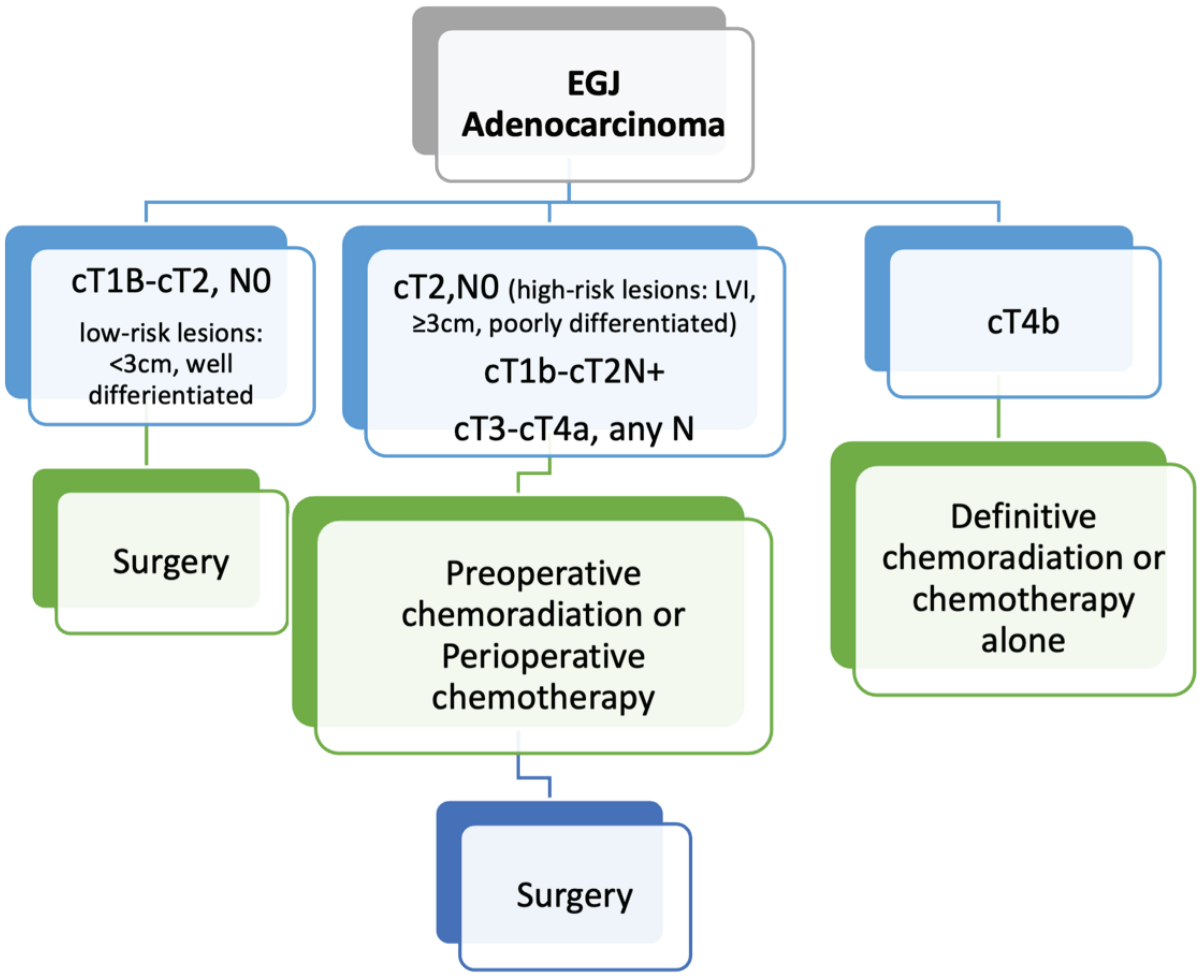


Figure 2: Algorithm of treatment of EGJ cancer (LVI: lymphovascular invasion)[23]

The efficacy of preoperative chemoradiotherapy followed by surgery versus surgery alone, first proven by the CROSS trial, is now well established and is regarded as a standard of care for patients with locally advanced, resectable EGJ adenocarcinoma.[24] After 7 years of follow-up, Shapiro et al found that neoadjuvant chemoradiotherapy offered a median overall survival of 43.2 months compared with 27.1 months in patients who underwent upfront surgery.[25] Regarding the comparison of preoperative chemoradiotherapy with chemotherapy alone, there is no general consensus on the superiority of the former, although some studies suggest that chemoradiotherapy offers higher R0 rates in operable cancers.[26,27] Contrary results have been announced by ESOPEC trial, a prospective randomized multicenter phase III trial, according to which perioperative chemotherapy (FLOT protocol) improves survival compared with neoadjuvant chemoradiation (CROSS protocol).[28]

The evaluation of definitive histopathologic examination and disease risk factors after radical surgery by the multidisciplinary team will determine the decision of adjuvant therapy. If patients did not receive preoperative therapy, adjuvant treatment is indicated in cases of positive lymph nodes and pT3-T4a stage. In R0 pT2N0 stage, adjuvant therapy should be evaluated if there are high-risk histopathological factors such as lymphovascular/perineural invasion, poor differentiation and high-grade disease, or in younger patients (<50 years). Chemoradiation should be evaluated in cases of R1, R2 resections. In the group of patients who underwent neoadjuvant chemoradiation or chemotherapy, it is recommended that they complete the cycles of chemotherapy or undergo chemoradiation if there are positive surgical margins and they did not undergo preoperatively.[29]

Immunotherapy plays also a role in adjuvant therapy of EGJ adenocarcinoma as it was shown in the phase III CheckMate 577 trial. It is recommended in patients who receive preoperative chemoradiation, undergo radical surgical treatment and have evidence of residual disease in the final histopathological specimen (^{3}ypT1 and/or ^{3}ypN1). According to the trial, patients treated with adjuvant nivolumab (anti-PD1 antibody) had a significant improvement in disease-free survival (22,4 months) compared with those who received placebo (11 months).[30]

Surgical treatment

Although radical surgery remains the mainstay of curative treatment for EGJ cancer, the optimal surgical approach is still debated. That is due to the complex lymphatic drainage of gastroesophageal junction, which follows a dual route into mediastinum and abdomen.[29] Therefore, the pattern of lymphatic spread of EGJ cancer is the most important factor in determining the optimal lymph node dissection and thus the appropriate surgical procedure. In a retrospective observational study, Siewert e al. found that type II cancer had a rate of 15,6% lymph node metastasis in the lower posterior mediastinum while the predominating metastatic lymph node stations were in abdomen (67,8% in the left and 56,9% in the right paracardial region, 67,8% in lesser curvature).[31] Kurokawa et al reported that the distance of tumor from the EGJ to the proximal edge may be a significant indicator of mediastinal lymph node metastasis in Siewert type II cancers. In particular, when the distance was >2cm, the rate of positive lymph nodes was considerably higher for the lower mediastinal nodes and when >3cm for upper and middle mediastinal nodes.[32] The prospective multicenter study of Kurokawa et al, published in 2019, set the basis for the recommended extent of lymph node dissection based on the incidence of nodal metastasis. It refers to patients with cT2-T4 tumors (adenocarcinoma or squamous cell carcinoma) located within 2cm of the EGJ, treated either with transhiatal or right transthoracic approach. Lymph node stations were classified into 3 categories according to the rate of metastasis and the level of recommendation for dissection (Fig.3). In addition, the frequency of node metastasis was correlated with the extend of tumor invasion in the esophagus.[33] Based on this study results, the 6th edition of the Japanese Gastric Cancer Treatment Guidelines proposed an algorithm for the optimal lymph node dissection and surgical approach for EGJ carcinoma (Fig.4).[34]

Radical resection (R0) is the principal goal of surgical treatment of EGJ cancer as it is one of the most important prognostic factors. While 5-year survival rates after R0 resection range from 32% to 49%, R1 procedures have rates of 5% to 11%.[29,35,36] The optimal proximal resection margin in esophagus is recommended to be at least 2cm on the fresh specimen.[37]

EGJ adenocarcinoma can be treated by either abdominotranshiatal total gastrectomy with distal esophagectomy or by transthoracic subtotal esophagectomy (Ivor Lewis). The choice of the best surgical approach (transhiatal or transthoracic) depends on many factors, the most important of which are the extent of lymph node dissection, the length of esophageal invasion and the physical status of

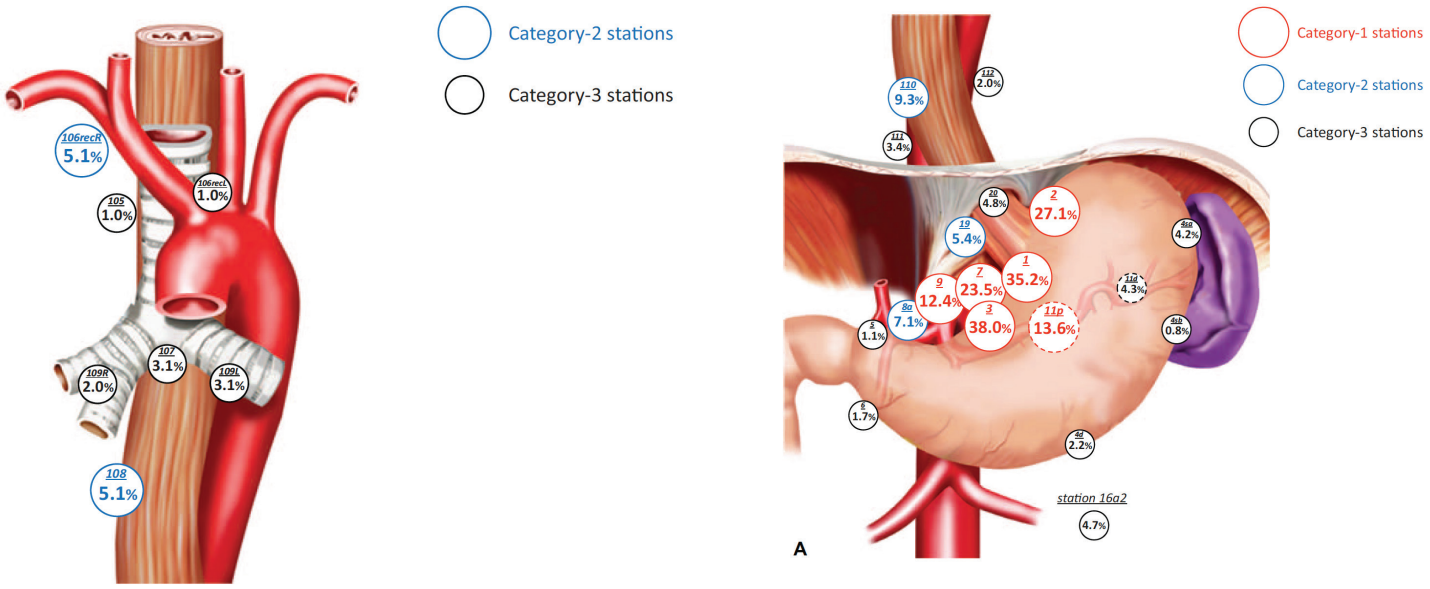


Figure 3: A. Metastasis rates in the abdominal and lower mediastinal nodes. B. Metastasis rates in the upper and middle mediastinal nodes of either adenocarcinoma with esophageal involvement of more than 3.0cm or squamous cell carcinoma.
Category-1: stations with metastasis rates >10% (strongly recommended for dissection).
Category-2: stations with rates 5%-10% (weakly recommended for dissection).
Category-3: stations with rates < 5% (not recommended for dissection).[33]

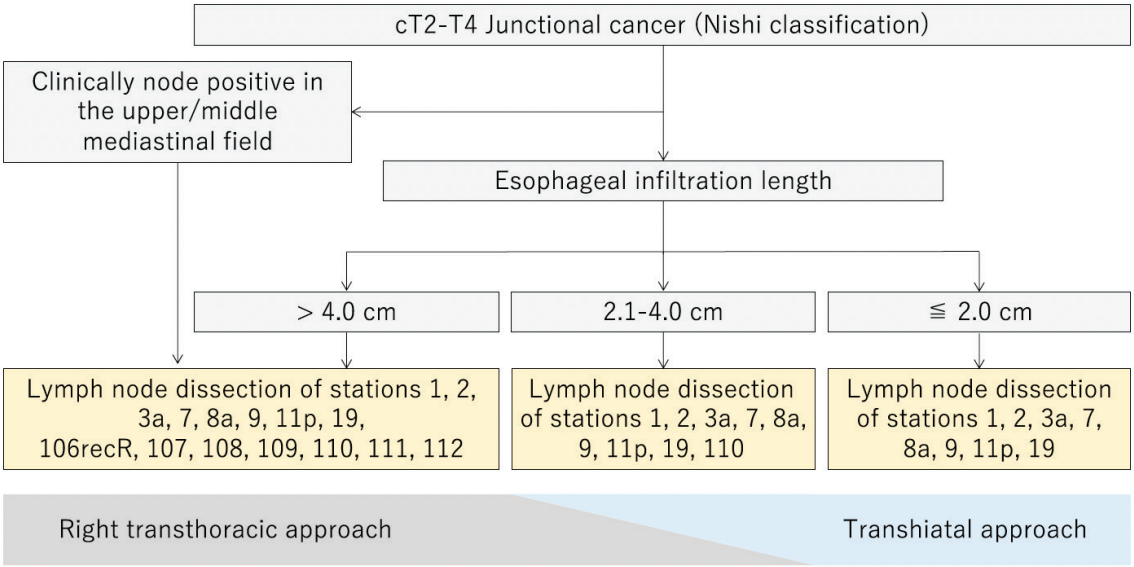


Figure 4: Algorithm of the surgical approach and lymph node dissection for esophagogastric junctional carcinoma.[34]

the patient.[37] The comparison of two procedures showed no significant differences concerning R0 rate, number of dissected lymph nodes, perioperative mortality and morbidity rate, duration of surgery or anastomotic leak. The transhiatal approach was superior to shorter hospital stay and lower incidence of pulmonary complications.[38,39] Regarding the overall survival, some studies showed a potential benefit from transthoracic surgery[39], while others failed to show any difference.[40] More reliable information is expected to come from prospective, randomized trials.[41,42]

Conclusion

As EGJ cancer is a complicated disease with increasing incidence, its management requires a dedicated multidisciplinary team. Good knowledge of the biology of

EGJ tumors and multimodal approach are the two key elements in the treatment of patients with EGJ cancer. Advancements in perioperative therapies combined with radical surgical treatment will offer new perspectives to patients and improve their survival.

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