Recent management of esophago-gastric adenocarcinoma

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Abstract

At the border between the esophagus and the stomach, gastro-esophageal junction tumors require a specific management that cannot be simplified to either of these two organs. Staging work-up with endoscopy, endosonography and PET-Scan is essential because it will condition the choice of neoadjuvant treatment and of surgical approach. Surgery remains the only curative treatment and should be undergone in specialized centers.

Introduction

Esophagogastric junction adenocarcinomas are tumors, which develop near the anatomic junction between the esophagus and the stomach. It is rather a zone disease than that of an organ. Management is specific, using principles of management of esophagus and stomach cancer. Their incidence is constantly increasing since the last 20 years with an increase of 4 to 10% per year in Europe. In Western world, early stages are rare and the majority of patients are diagnosed in an advanced stage with poor prognosis. In comparison, survival rate are better in Asian countries where national screening programs allow for earlier diagnosis. Risk factors for development of esophagogastric junction tumors are male, obesity, tobacco use and metaplasia of the esophageal epithelium (Barrett esophagus).

Classification

The limit between esophagus and the stomach can be defined in two ways: anatomically with the hiatus diaphragmatic passage or histologically with the transition between the esophagus squamous epithelium to the gastric prismatic cells. Anatomical localization is used during endoscopic evaluation as the histological transition can be altered in case of metaplasia. Ending of the longitudinal symmetrical mucosal folds of the gastric fundus set the transition between the esophagus and the stomach. The classification relying on the anatomical topography proposed by Siewert et al. [1] divide the esophagogastric junction tumors in 3 types according to the localization of the tumor center according to the esophagogastric junction:

Type I: distal esophagus adenocarcinoma. Tumor center is 1 to 5 cm above the esophagogastric junction.

Type II: true cardia tumor. Tumor center is 1 cm above to 2 cm under the junction.

Type III: cardial region tumor. Tumor center is 2 to 5 cm under the junction.

The three types do not behave the same in term of prognostic and lymphatic invasion. Hiatal hernia or deformation by the tumor itself can limit the application of this classification.

Since 2016, TNM classification (10th edition) defines the junction cancer as all tumors which center is found 2 centimeters proximal or distal to the junction (Figure 1). This classification is the application of the Nishi gradation used by the Japanese.

Diagnostic

The main symptoms in patients with esophagogastric junction tumor are dysphagia and weightloss. Eso-gastro-duodenoscopy (OGD) is the first exam in the complementary workup. It allows the classification of the tumor according to Siewert and to collect biopsies. Echo-endoscopy evaluates local invasion and regional lymph node. However in this last case, diagnostic accuracy is limited by the fact that tumor invasion is not well correlated with the size of the lymphadenopathy [2]. Endoscopy can be therapeutic in early tumors (Tis, T1a) by doing endoscopic resection. To evaluate distant lesion, thoraco-abdominal Ct-Scan allow to clarify the number of regional lymph node and eventual metastasis with the most frequent sites being the liver, lungs and retro-peritoneal lymphadenopathy. This modality is not used to localize the tumor as the endoscopy is more accurate and the scanner overestimates the tumor size. The PET-Scan finds in 15 to 20% of cases metastasis non visible on the Ct-Scan [3]. Some histologic subtypes, in particular non cohesive tumor (signet ring cell), pick up less contrast and the staging by PET-Scan will be less precise in these cases [4]. Imaging cannot evaluate reliable presence of peritoneal metastasis and some experts propose explorative laparoscopy as complement workup. Nutritional consultation is part of the evaluation of these patients often malnourished, in bad condition before the start of neoadjuvant treatment or surgery. If classical feeding is not possible, enteral nutrition is the best option with jejunostomy in first intention, better than naso-jejunal tube or percutaneous endoscopic gastrostomy, which is of risk for a potential gastric pull up.

Esophagogastric junction tumor with supraclavicular lymph nodes, distant metastasis or adjacent organs involvement (heart, great vessels, trachea) should not be resected out of clinical trials. A selection of patients with limited metastatic disease would benefit

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The reference study for radio-chemotherapy is a Dutch study (CROSS-Trial) [11] from 2012 comparing surgery alone (188 patients) to surgery with radio chemotherapy (178 patients). Resection rate with negative margin was greater in the group with neo-adjuvant treatment. Global survival was better in the neo adjuvant group (49.4 months vs. 24 months).

Each neoadjuvant treatment has its advantages and disadvantages: radiochemotherapy allow better loco-regional control but lesser than chemotherapy on eventually systemic metastasis. Table 1 resumes the different studies.

The actual recommendation is basing on the Siewert classification. Siewert I or II tumors with a need of neoadjuvant treatment should receive neoadjuvant radiochemotherapy and Siewert III perioperative chemotheraphy [6].

However, the comparison between radiochemotherapy and chemotherapy alone would not show any differences in term of oncological results and survival. The choice between the two treatments is still under discussion [12].

**Surgical technique**

During surgery for oncologic indication, the main goal is to choose the best approach, which allow removing en bloc the primary tumor and the lymph nodes involved. Resection in negative margin is the priority (R0 resection) and should dictate the choice of surgical approach. Survival is influenced by this parameter: in a retrospective study of 1602 patients, 5 year survival was 43.2% for negative margin versus 11% for positive margin [13].

The localization between the thorax and the abdomen of junction tumors implies a potential dissemination in these two compartments.

Two surgical approaches for esophagogastric junction tumor are possible, especially in Siewert II tumors:

- Thoraco-abdominal oesophagectomy: It is the oesophagectomy technique from Ivor-Lewis, which consist in a double surgical approach abdominal and thoracic. The intervention begins with a laparotomy or thoracotomy during which esophagus is resected and dissociated from the gastric tube. Intervention continues with right thoracic lymphadenectomy limited. It is the surgical approach for Siewert III junction tumor.
- Total gastrectomy with distal esophagectomy: In this procedure, only abdominal approach is needed. It consists in total gastrectomy with lymph node harvested type D2+ that correspond to perigastric nodes, coeliac trunk, splenic artery, hepatic artery and lower mediastinal nodes. Distal esophagus is resected trans-hiatal (Figure 2). Roux-en-Y reconstruction is generally made with eso-jejunal anastomosis. This procedure doesn’t imply thoracotomy making the thoracic lymphadenectomy limited. It is the surgical approach for Siewert III junction tumor.

In the cases of Siewert II tumors, no oncological benefit between oesophagectomy or gastrectomy has been demonstrated [16]. However, the development of minimally invasive techniques for esophagectomy permits to diminish the morbidity. Most of centers propose laparoscopic abdominal approach with gastric mobilization...
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centers.

is still the only curative treatment and should be done in specialized

the extension staging are the basis for therapeutic decision. Surgery

according to the localization of the tumor (Siewert classification) and

that incidence increases in the Western world. The classification

Prevalence of locally advanced tumors at the time of diagnostic

implies a multimodal management either by radio-chemotherapy or

chemotherapy.

Declaration of conflict of interest

Authors reveal no interest with this article.

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Table 1. Summary articles for multimodal treatment for esophagogastric tumors.

| Studies    | Tumor of JOG proportion | Intervention                     | Survival | R0 resection |
|------------|-------------------------|----------------------------------|----------|--------------|
| MAGIC [8]  | 26%                     | Chemotherapy perioperative       | Survival 5 years | Non available |
|            |                         |                                  | 36% surgery + chemotherapy | 23% surgery alone |
| ACCORD [9] | 75%                     | Chemotherapy perioperative       | Survival 5 years | Non available |
|            |                         |                                  | 38% surgery + chemotherapy | 24% surgery alone |
| CROSS [10] | 75%                     | Radio-chemotherapy (RCT)         | Median survival  | Non available |
|            |                         | neoadjuvant                      | 49.4 month RCT + surgery  | 92% RCT + surgery  |
|            |                         |                                  | 24 month surgery alone    | 69% surgery alone |

Table 2. Tumor characteristic and treatment options according to the Siewert classification.

| Siewert classification | Definition | Multimodal treatment | Surgery |
|------------------------|------------|----------------------|---------|
| Type I                 | 1 to 5 cm above the junction | Radio-chemotherapy or chemotherapy | Thoraco-abdominal esophagectomy (Ivor Lewis) |
| Type II                | 1 cm above to 2 cm under the junction | Radio-chemotherapy or chemotherapy | Thoraco-abdominal esophagectomy or gastrectomy (negative margin resection is mandatory) |
| Type III               | 2 to 5 cm under the junction | Chemotherapy | Total gastrectomy with distal esophagectomy |

Figure 2. Total gastrectomy with distal esophagectomy for Siewert III tumor.

and pull up of the stomach through the diaphragmatic hiatus. Thoracic
time is then performed open (Hybrid technique) [17].

The comparison of laparoscopic approach and open for the

abdominal time is the subject of a French Study (MIRO-Trial), which

shows a clear benefit for this hybrid minimally invasive approach [18].

Table 2 resumes the treatment for junction tumor according to the

Siewert Classification.

Conclusion

Esophagogastric junction tumors represent a subtype of cancer

that incidence increases in the Western world. The classification

according to the localization of the tumor (Siewert classification) and

the extension staging are the basis for therapeutic decision. Surgery

is still the only curative treatment and should be done in specialized

centers.
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