Editorial

The esophagogastric junctional adenocarcinoma an increasing disease

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Identifying and defining the esophagogastric junctional adenocarcinoma (EGJA) as an independent disease apart from gastric cancer (GC) and esophagus cancer (EG) it has always been a difficult issue entailing doubts about the appropriate therapeutic approach. In fact, the EGJA is not entirely comparable with GC and EG in terms of epidemiology, risk factors, etiology and pathophysiology.

The incidence of EGJA has showing an opposite trend compared to GC because the incidence of EGJA has been increasing in the recent years while the GC has been decreasing. Furthermore, the EGJA prognosis is worse than the GC. In fact, EGJA has a lower prevalence of early gastric adenocarcinoma (5.6% *vs.* 22.2%, P<0.001) and R0 (86% *vs.* 92.8%, P<0.001) and a higher frequency of lymph node metastasis (76.3% *vs.* 67.4%, P<0.003) compared to GC (1).

Leers *et al.* (2) showed that the presence of reflux symptoms and peritumoral intestinal metaplasia is greater in the distal esophagus adenocarcinoma than in EGJA, while the location and prevalence of lymph node metastases is similar.

The incidence of EGJA, since the mid-1970s, has increased in Western countries, mostly in the white man and in the United States (3.1 per 100.000) surpassing EC and EG (3).

Messager *et al.* (4) compared five different European countries, noting that EGJA and EG predominate in Europe except in Spain where the GC is prevalent.

Conversely, in Eastern countries there are a few reports by incidence of EGJA. There has been a small increase of EGJA in Japan (5) and in China (6-11) in the recent years.

Since the borderline tumor location of EGJA between esophagus and stomach (stratified squamous epithelium *vs.* gastric simple columnar epithelium), a clear definition and classification of the tumor was necessary to arrive to an optimal therapeutic strategy.

In 1996, Siewert at al. (7) have proposed a different classification and definition of the EGJA. The EGJA is a neoformation growing within 5 cm from anatomical cardia (distally or proximally), dividing into three subtypes:

- Type I: adenocarcinoma of distal esophagus with extension from 1 to 5 cm above the junction (which may infiltrate the esophagogastric junction).
- Type II: adenocarcinoma of the cardia or "junctional carcinoma" with extension from 1 cm above to 2 cm under the junction.
- Type III: subcardial gastric carcinoma with extension from 2 to 5 cm under the junction (which may infiltrate the esophagogastric junction).

Type I is often associated with Barrett dysplasia and a long history of gastro-esophageal reflux disease (GERD).

The incidence of GERD is higher in the United States and in Europe than in Asia and Southern China. Although, in recent years it has been an increase on the frequency of GERD in Asia (8).

In 2007 Siewert *et al.* (9) showed that in 79.5% of Type I

EGJA an area of intestinal metaplasia (Barrett's esophagus) was present, while it was not found in the type III. This is probably due to the higher degree of undifferentiation (G3/G4 grading) of type III compared to the type I (54.4% *vs.* 73.4%). Epidemiologically type II has been considered a middle group between type I and type III.

Over the years, a possible correlation between GERD and EGJA has been discussed. Many authors have highlighted that a long exposure of gastric acid can damage epithelium of the esophagus and of the esophagogastric junction resulting mutation in Barrett's esophagus, dysplasia, and then finally in adenocarcinoma (10-12). Chak *et al.* (11) have shown a strong association between EGJA and GERD related to other risk factors like a positive family story, age (older), gender (male) and obesity. However, not all the three types of EGJA seem to have a correlation with GERD. In fact, there is a positive correlation with the type I and not with the type II and III (12).

Liu *et al.* (6) have showed a recent increase of type I and type III prevalence and a type II decrease in 5,053 patients during 1988–2012. In type I the prevalence of GERD oscillated from 41.3% to 57.1%.

In the literature, many authors have attempted to identify the risk factors most involved on this type of tumors. Multiple studies have shown a strong correlation between smoking (pack-years of smoking) and increased risk of EGJA. Moreover, the use of alcohol appears to have no correlation with EGJA. Other risk factors involved in the onset of the EGJA are obesity and high fat dietary (13).

The choice of a more appropriate therapeutic strategy requires a correct staging of the disease determined by TNM classification. This is possible by using CT scan, endoscopic ultrasound, MRI and PET.

Many studies have shown the importance of radical surgery (radical resection of the tumor and complete lymphadenectomy) for a long-term survival in this type of tumors. However, it remains yet discussed the most appropriate surgical approach.

The possible surgical approaches for the EGJA include transhiatal total or subtotal gastrectomy, abdominothoracic total esophagogastrectomy, distal esophagectomy with resection of the proximal stomach, total gastrectomy with transhiatal resection of distal esophagus, limited resection of the esophagogastric junction or Ivor-Lewis.

Vrouenraets *et al.* (14) have highlighted an advantage in terms of fewer complications and reduced hospital stay performing the transhiatal esophagectomy approach for cardia cancer and EGJA compared to transthoracic approach with a better 5-year survival rate.

Hulscher *et al.* (15) compared transhiatal esophagectomy with extended transthoracic esophagectomy in patients with adenocarcinoma of the mid-to-distal esophagus or cancer involving the gastric cardia and the distal esophagus at early stage. The transhiatal approach is associated to a lower morbidity, while the 5-year survival was slightly better in the extended transthoracic approach.

Many authors described a different surgical approach according to the classification of Siewert. For the type I no impressive differences were found in the long-term survival rate between the radical transmediastinal esophagectomy and the transthoracic esophagectomy with the resection of proximal stomach. For type II and III a transhiatal total gastrectomy was recommend with the resection of distal esophagus (16-18).

In the early carcinoma (with tumors limited to the mucosa and without lymph node metastases, T1N0) a limited resection of the esophagogastric junction (16) possibly associated to the distal esophagus with interposition of a pedicled jejunal was indicated (17). Whereas, many authors have shown that the subtotal gastrectomy is characterized by an increased post-operative complications rate, such as increased incidence of reflux oesophagitis and anastomotic stenosis, compared to a total gastrectomy (18,19).

In the stage T3/T4 a neoadjuvant therapy was recommended (17).

Duan *et al.* (20) compared the application of the right transthoracic Ivor-Lewis to the left transthoracic and thoracoabdominal approach in Siewert type II, concluding that the Ivor-Lewis approach is a more effective approach concerning the margin free resection, the adequate lymphadenectomy and the long-term patient survival.

The intraoperative digestive tract reconstruction after total gastrectomy plays an important role to reduce post-operative complications. The classic Roux-en-Y reconstruction is considered the optimal choice. Xiao *et al.* (21) compared the Roux-en-Y reconstruction with the antrum-preserving double-tract reconstruction showing that the Roux-en-Y approach is characterized by an increased complications rate such as cholelithiasis, malnutrition, dumping syndrome and esophageal reflux. Furthermore, the antrum-preserving double-tract reconstruction by jejunal interposition offers less hospitalization and reduces the gastroesophageal reflux, the malabsorption syndrome and the dumping syndrome. Moreover, they recommended this approach for the Siewert type I and III.

For the reconstruction of digestive tract in limited

resection (subtotal gastrectomy) a gastric-esophageal anastomosis is normally performed, leading to a severe alkaline reflux and a low quality of life. The interposition of an isoperistaltic jejuan or colon segment can improve the quality of life (22).

The 5-year survival in EGJA is also related to an adequate lymphadenectomy. Lymph node involving is less common in the type I than in the type II and III. In the type I is more common the lymph node dissemination in the mediastinum (in the tracheal bifurcation and above). Type II and III are most affected by the lymph node dissemination in the lower mediastinum and in the area of coeliac trunk (8).

In a German review (23) a D2-lymphadenectomy extended to the lower mediastinum by a transhiatal approach is recommended in type II and III. For type I is recommended a lymphadenectomy of the lower mediastinum and a lymphadenectomy of the perigatric region.

In the esophagus-predominant adenocarcinoma a lower mediastinal lymphadenectomy has a greater therapeutic index value. In the stomach-predominant adenocarcinoma the right and left cardia, the small curvature, along the left gastric artery and the subpancreatic lymphadenectomy has a greater therapeutic index value. In conclusion, the prophylactic distal stomach lymphadenectomy seems to offer an advantage in terms of survival (24).

Finally, Ito *et al.* (25) showed a lack of cervical lymph node invasion in EGJA and a higher incidence of mediastinal lymph node metastasis in the esophageal-predominant cancer, resulting in a lower survival compared to a gastric-predominant cancer.

Liu *et al.* evaluated a sample of 5,053 patients with GERD and EGJA underwent surgical treatment during a period of 25 years (from 1988 to 2012) highlighting the changing of epidemiological characteristics and treatment approaches in recent years. The study is well written, presenting a large number of patients enrolled during 5 homogeneous periods of time. Thus, the study is statistically valid.

The strength of this study is that in different periods of time various aspects were analysed: the changing trend of EGJA subtypes (Siewert classification), the changing trend of the presence of GERD in EGJA, the change of trend of clinical-pathological features and the changing of trend of surgical treatment and post-operative complications.

However, the study retains a retrospective nature, carried out in a single centre of Western China. Only patients who underwent surgical treatment were enrolled while those patients with EGJA who did not have the surgical treatment were excluded.

In conclusion, the recent increase of 5-year survival rate in EGJA may be due to the new EGJA classification (considering the EGJA a different tumor from esophagus or GC) and to the new technologies and surgical techniques. In the future, the advent of newer diagnostic techniques, allowing an earlier diagnosis, and innovative surgical techniques associated to decreased post-operative complications will probably lead to an improvement of survival and quality of life of patients with EGJA. Furthermore, an effective screening with a primary prevention can reverse the trend in countries with increased incidence of GERD and EGJA.

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Footnote

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

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