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EDITORIAL

Treatment of esophagogastric junction carcinoma: An unsolved debate

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Abstract

The incidence of esophagogastric junction adenocarcinoma (AEG) is increasing worldwide. Barrett's esophagus (BE) associated with dysplasia is the main risk factor for the development of cancer. Currently, screening programs to individuate and eradicate BE represent the best way to reduce AEG cancer. Several endoscopic approaches are here discussed. Surgical strategies for different types of AEG cancer are now fairly standardized, and multidisciplinary strategies using chemotherapy or chemoradiotherapy may improve the outcome of these patients. Here we briefly discuss the keypoints, main topics, and critical issues, according to accumulating evidence and taking into account our own experience.

Key words: Barrett's esophagus; Esophagogastric junction adenocarcinoma; Endoscopic resection; Surgery; Chemotherapy; Chemoradiotherapy

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Core tip: Barrett's esophagus (BE) associated with dysplasia is the main risk factor for the development of esophagogastric junction adenocarcinoma (AEG). Currently, screening programs to individuate and eradicate BE represent the best way to reduce AEG cancer. We aim to discuss several endoscopic approaches, surgical strategies for different types of AEG cancer, and multidisciplinary strategies using chemotherapy or chemoradiotherapy may improve the outcome of AEG patients.

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INTRODUCTION

The incidence of esophagogastric junction carcinoma has dramatically increased worldwide, partly due to widespread occurrence of gastroesophageal reflux,

Barrett's esophagus (BE), and *Helicobacter pilory* eradication[1]. Despite a more tailored approach and innovative multimodality treatments, prognosis remains unsatisfactory[2].

In 1998, Siewert classified for the first time three different cancers originating from 5 cm proximal to 5 cm distal of the anatomic cardia[3]. This classification has been adopted by the International Gastric Cancer Society and by the International Society for Disease of the Esophagus, and helped clarify that different approaches are needed for the different types of cancer.

Adenocarcinoma of the esophagogastric junction (AEG) type Ⅰ is esophageal cancer located 1-5 cm above the EGJ, and is prevalent in women. It arises from an area with specialized intestinal metaplasia (mainly Barrett's cancer) and spreads above and below the diaphragm by the lymphatic route.

Barrett's esophagus, defined as metaplasia of the esophagus epithelium, is the main risk factor for the development of esophageal cancer, along with the presence and degree of dysplasia. The annual rate of neoplastic progression to adenocarcinoma for patients with low grade dysplasia (LGD) and non-dysplastic BE was 0.12% in the most recently published study[4], and this risk increased up to 6% in patients with high grade dysplasia (HGD)[5].

In contrast, AEG type Ⅱ (so called true carcinoma of the cardia) is associated with BE in very few cases; it arises from a metaplasic area of the cardial epithelium and is localized within 1 cm proximal and 2 cm distal to the esophagogastric junction. Finally, AEG type Ⅲ is a subcardial gastric carcinoma infiltrating the EGJ or the distal esophagus from below, and lies 2-5 cm distal to the EGJ. Overall, advanced type Ⅱ and, particularly, type Ⅲ cancer display worse prognosis than type Ⅰ.

ERADICATION OF BARRETT'S ESOPHAGUS

High rates of disease eradication may be obtained with endoscopic mucosal resection (EMR), although methacronous lesions may become apparent in one-third of patients during follow-up after focal resection; in addition, the rate of stenosis requiring dilation exceeds 50%, particularly in patients treated with consecutive endoscopies[6,7], the so-called stepwise radical endoscopic resection (SRER). Endoscopic resection associated with radiofrequency ablation (RFA) may be preferred over SRER in patients with BE and HGD and/or early cancer[8]. Endoscopic submucosal dissection is mainly undertaken in Asian countries, may result in high curative resection rates and low rates of recurrence, but requires an adequate learning curve. However, following EMR, the remaining Barrett segment should be eradicated regardless of whether or not it includes the presence or absence of dysplasia[9].

In recent years, a number of strategies of endoscopic ablation have been proposed for the treatment of dysplastic BE, including photodynamic therapy (PDT), RFA, argon plasma coagulation, electrocoagulation, and cryoablation, with conflicting results. In a recent head-to-head trial, RFA was more effective than PDT in terms of complete eradication (89% *vs* 54%) and complete reversal of intestinal metaplasia (51% *vs* 39%), with a low rate of complications (4% *vs* 31.2%); in addition, costs roughly halved using RFA when compared to PDT[10]. In contrast, the available data on other endoscopic modalities are less robust.

The optimal treatment of LGD BE is still unclear, as reflected by contrasting recommendations from different professional societies[11,12]. In a recent multicenter phase Ⅲ trial comparing RFA *vs* endoscopic surveillance, a significant benefit was noted in the ablation group[13].

For patients suffering from BE with HGD and very low (T1a) cancer, lymph node involvement is extremely rare[14-16], despite recently conflicting observations[17]. For these patients, either endoscopic treatment or surgery is appropriate, since randomized clinical trials comparing surgery *vs* EMR are still pending. Besides, a remarkable shift from surgery to endoscopic treatment has been observed in the last recent years. Esophageal resection should be reserved for submucosal involvement (guideline-recommended therapy); of note, since a subgroup of patients with T1b cancer (well/moderated grade of differentiation, ⩽ 1.5 cm, no ulcer, invasion of the upper third of the submucosal layer ⩽ 500 μm, no lymph-vascular invasion) has a very low risk of lymph node dissemination, treatment may be as for T1a cancer[18]. Clearly, in such a context, pathologist accuracy is essential[19].

Finally, the goal of endoscopic treatment is complete removal or eradication of early stage disease (Tis/T1a) and preneoplastic tissue (BE), with subsequent ablative therapy of residual BE associated with Tis or T1a following mucosal resection[9].

SURGERY

With regard to surgical strategies, AEG type Ⅰ cancer should be treated with *en bloc* transthoracic or transhiatal resection, depending on the extension of the tumor and associated Barrett's disease. The transthoracic approach is most beneficial especially in any TN3 (ⅢC according to TNM Staging System) AEG type Ⅰ cancer, although the extent of lymphadenectomy (two-field *vs* three-field LAD) is still one of the hotspots under discussion[20,21]. If there is a concern with possibly positive celiac lymph nodes, because randomized trial have demonstrated identical survival curves for esophageal cancer patients with regional or celiac lymph node metastases, surgery should not be denied in any case[22].

The standard surgical approach for type Ⅱ and type Ⅲ AEG cancers contemplates an extended total gastrectomy, with standard D2 lymphadenectomy, and,

in type Ⅱ, transhiatal resection of distal esophagus, and *en bloc* lymphadenectomy of node stations 19, 20, 110, 111, according to the Japanese Gastric Cancer Association guidelines[23]. However, modified D2 lymphadenectomy (so called D1+, excluding splenectomy and pancreasectomy, and dissection along the proper hepatic artery) has been proposed to reduce the postoperative complication rate with no detrimental effects on complete oncologic clearance, however, this is a still an unresolved issue[24]. In our experience, such a modified D2 dissection was demonstrated to be safe and to yield the same oncologic adequacy as formal D2 dissection in gastric cancer patients[25]. Finally, in type Ⅱ and Ⅲ early cancers, recent evidence suggests that more limited operations (*i.e.*, proximal gastric resection with D1+ lymphadenectomy) may be useful to avoid postgastrectomy syndrome, without impairment of oncological adequacy[26]. Finally, a minimally invasive approach may reduce postoperative morbidity and mortality rates, which are indeed still high, particularly in low volume hospitals[27,28].

CHEMOTHERAPY AND CHEMORADIOTHERAPY

The role of multidisciplinary approach for GEJ cancer is still a matter of debate. Although the impact of chemotherapy (CT) on pre- and perioperative treatment of esophageal and gastric cancer has been extensively studied[29,30], two randomized trials have *de facto* changed the daily practice in the US and Western Europe. Furthermore, a recent metanalysis on 14 trials with a total number of 2422 patients evaluated surgery *vs* preoperative CT or chemoradiotherapy (CRT). This study showed a significant survival benefit for preoperative treatment over surgery alone with an hazard ratio (HR) of 0.82 and a 5-year absolute overall survival (OS) gain of 9% (23% *vs* 32%)[31].

In the FNCLCC and FFCD trial, 224 resectable esophageal, GEJ, and gastric cancer patients (more than 60% of patients were GEJ) were randomized to either upfront surgery or perioperative CT (two or three cycles of cisplatin and 5-fluorouracil) and surgery to assess the benefits in terms of OS and disease-free survival (DFS) yielded by CT. Unfortunately, the study was closed earlier due to difficulties in patient enrollment, although it clearly demonstrated a better 5-year OS and DFS in the CT-treated arm (38% *vs* 24%, and 34% *vs* 19%, respectively). It should be noted, however, that 20% of patients receiving CT experienced grade 3-4 hematological toxicity, and about half of the patients randomized to perioperative treatment did not receive post-surgical therapy[32].

The other high impact study was the MAGIC trial, in which 503 patients (26% of them were GEJ cancer) were randomized to receive 3 cycles of ECF (epirubicin, cisplatin, and 5-fluorouracil) before and after surgery or surgery alone. CT significantly prolonged the 5-year OS and PFS, with an estimated 25% reduction in the risk of death. However, only 42% of patients enrolled in the perioperative group completed the pre-planned treatment protocol[33].

Finally, the results of a large clinical trial carried out in the United Kingdom have been made available a few months ago. Four hundred consecutive patients (approximately 70% were GEJ type Ⅰ or Ⅱ) were treated with preoperative CT (cisplatin and 5-fluorouracil, or ECF, or ECX). OS was shown to be significantly prolonged in patients with downstaged tumors[34].

The potential advantage deriving from preoperative CRT is suggested by several phase Ⅱ studies and by subgroup analysis of four randomized trials, in which patients with all types of esophageal cancer received CRT followed by surgery or surgery alone. However, the statistical power of these trials was weak because of the low numbers of true GEJ cancers[35-38].

In the German study, 119 patients with GEJ cancer (uT3-T4 NxM0) were randomly assigned to receive either CRT (cisplatin, 5-fluorouracil, and leucovorin - PFL - followed by cisplatin and etoposide, plus a total dose of 30 Gy of radiation) and surgery or CT plus surgery. Although the study was closed earlier than planned without reaching a statistically significant survival benefit, outcomes were better in the CRT and surgery arm in terms of 3-year survival (47.4% *vs* 27.7%) and rates of pathologic complete response (pCR: 15.6% *vs* 2%) and tumor-free lymph nodes (64% *vs* 37.7%)[39].

Another milestone phase Ⅲ study was the CROSS trial, in which 366 esophageal or GEJ cancer patients received CRT (weekly carboplatin and paclitaxel, plus 41.4 Gy of radiation) followed by surgery or surgery alone. Median OS was significantly longer in the CRT and surgery arm than in the surgery alone group (49.4 mo *vs* 24.0 mo, respectively); in addition, the rate of pCR was 29% following multimodal therapy. Of note, only 20% of the patients had a true GEJ cancer[40]. In our recently published experience, preoperative CRT (with FOLFOX regimen and 45 Gy of radiation) was shown to be safe in 41 GEJ patients, albeit efficacy was mild[41].

Finally, a recent metanalysis shows that in patients with adenocarcinoma of the esophagus and GEJ, preoperative CT improves OS (HR = 0.83; P = 0.01) when compared to surgery alone. The greater effectiveness of the treatment was, however, observed with CRT with an HR of 0.75[42].

CONCLUSION

Barrett's esophagus is a preneoplastic lesion and can progress to EGJ cancer when HGD is present. Significant disagreement exists in the management of Barrett's disease. Endoscopic treatment, with or without the aid of ablative techniques, has gained broad consensus so as to be considered as effective as surgery for the cure

of BE with LGD and HGD in professional guidelines.

Although surgical procedures of initial and locally advanced EGJ cancer are fairly standardized, the same cannot be said for the role of pre- and perioperative CT and CRT. Few clinical trials with few true EGJ cancer patients have been carried out thus far; therefore, definitive conclusions on the role of radiation and on the best implementable CT protocol cannot be drawn. Currently, we can only affirm that survival of patients with CT-downstaged disease may be prolonged.

Design of large trials with homogeneous series and homogeneous therapies, focusing on predictive factors of response to better select resectable GEJ cancer patients, may definitively answer currently unsolved questions.

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