Surgical Oncology 25 (2016) 355–363

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

Recurrence after surgery in esophago-gastric junction adenocarcinoma: Current management and future perspectives

Alessandro Neri [a], Daniele Marrelli [a], Costantino Voglino [a, *], Giulio Di Mare [a], Francesco Ferrara [a], Mario Marini [b], Franco Roviello [a]

[a] Department of Medicine, Surgery and Neurosciences - Unit of General Surgery and Surgical Oncology, University of Siena, Viale Bracci - Policlinico "Le Scotte" 53100, Siena, Italy
[b] Department of Medicine, Surgery and Neurosciences - Unit of Gastroenterology and Digestive Endoscopy, University of Siena, Viale Bracci - Policlinico "Le Scotte" 53100, Siena, Italy

ARTICLE INFO

Article history:
Received 26 April 2016
Received in revised form
10 August 2016
Accepted 12 August 2016

Keywords:
Esophago-gastric junction
Gastric cancer
Esophageal cancer
Recurrence
Adenocarcinoma
Palliation

ABSTRACT

Recurrent esophago-gastric junction adenocarcinoma is not a rare event and its correct management is still debated. Many approaches for the treatment of these patients exist, but only few studies compare the different techniques. Most of the studies are retrospectives series and describe the experiences of single institutions in the treatment of recurrent esophageal and esophago-gastric junction cancers. Nowadays surgery is still the main and only curative treatment. Other alternative palliative therapies could be endoscopic stent placement and balloon dilation, photodynamic therapy, thermal tumor ablation (laser photoablation and Argon plasma coagulation), radiation therapy and brachytherapy, and chemotherapy. The aim of this review is to investigate the different rates, patterns and timings of recurrence of this tumor, and to explain the various approaches used for the treatment of recurrent esophago-gastric junction cancer.

1. Introduction

Esophago-gastric junction (EGJ) adenocarcinoma is the worldwide eighth most common malignancy and the sixth cause of cancer related mortality. Its incidence has increased during the last decades, particularly in western countries [1], in relation to the widespread occurrence of gastroesophageal reflux, Barrett's esophagus (BE), and *Helicobacter pylori* eradication, which are the main risk factors for the development of this tumor [2].

In the past, the definition of EGJ cancer has led to some confusion: this type of tumor has been regarded as gastric cancer, as esophageal cancer or as distinct entity. As a consequence, the real incidence of this pathology and its optimal diagnosis and management resulted controversial and not comparable for a long time [3]. In 1998 the classification of EGJ cancers, originally proposed by Siewert [4], was adopted by the Consensus Conference of the International Society for Disease of the Esophagus and the International Gastric Cancer Association [5], thus constituting the basis for a widespread system of definition and treatment reporting for adenocarcinomas arising at the EGJ. Type I EGJ cancer is defined as an adenocarcinoma of the distal esophagus located 1–5 cm above the anatomical EGJ and is more frequent in women. It arises from an area of intestinal metaplasia (mainly BE) and its preferred spreading pattern is preferentially through the lymphatic stream into the thorax and the abdomen. Patients with BE, defined as epithelial metaplasia of the esophageal mucosa, are at high risk of developing adenocarcinoma of the esophagus and type I EGJ cancer. BE may progress to adenocarcinoma, through low grade dysplasia and high grade dysplasia. For patients with low grade dysplasia and non-dysplastic BE, the annual rate of neoplastic progression to adenocarcinoma is 0.12% [6]. This risk is higher (about 6%) among patients with high grade dysplasia [7]. Siewert II adenocarcinoma is related to BE in a very low percentage; it usually arises from a metaplastic area of the cardial epithelium and is localized within 1 cm proximally and 2 cm distally to the EGJ. Finally, Siewert III is a subcardial carcinoma with the primary tumor focus located within 2–5 cm below the EGJ.

In 2009, the American Joint Committee on Cancer (AJCC) has definitely classified the EGJ adenocarcinomas as esophageal cancers

* Corresponding author. Department of medicine, surgery and neurosciences, Unit of General Surgery and Surgical Oncology, University of Siena, Policlinico "Le Scotte", Viale Bracci, 53100, Siena, Italy.
E-mail address: costantinovoglino@gmail.com (C. Voglino).

http://dx.doi.org/10.1016/j.suronc.2016.08.003
0960-7404/

with the introduction of a more detailed subdivision of the T and N stages. This should enable a more accurate prediction of prognosis together with the newly introduced prognostic histologic grouping (separate for squamous cell carcinoma and adenocarcinoma) [8]. Despite an aggressive surgical treatment, EGJ adenocarcinoma has a poor prognosis, with a 5 year survival less than 20% [9]. Cancer relapse is one of the main causes of death in patients undergoing surgery. In patients with isolated loco-regional relapse a chance of cure has been reported with salvage surgery, even if treatment-related morbidities and mortalities are relevant, as well as subsequent local or distant recurrences. Indeed, the therapeutic approaches in these cases are generally limited to the management of the dysphagia due to lumen obstruction, with the aim to relieve symptoms, allow an adequate nutrition and improve the quality of life. Such relief from dysphagia can be achieved with different strategies: stent placement, percutaneous endoscopic gastrostomy, surgical bypass, chemotherapy, external radiation, brachytherapy, laser ablation (thermal Nd: YAG or photodynamic), or intratumoral injection of absolute alcohol. In this review we analyze the different treatment approaches proposed by several authors in recurrent EGJ adenocarcinomas.

2. Risk factors for recurrence

Few studies have analyzed the risk factors for recurrence in EGJ cancer. Indeed, the correct identification of patients at higher risk of post-operative relapse would allow a tailored treatment and may also improve the prognosis of this cancer. Du Rieu analyzed the risk factors for recurrence after Ivor-Lewis esophagectomy for EGJ or esophageal cancer in a series of 120 cases, with 53 patients (44%) relapsing at a median follow-up of 58 months. At univariate analysis, an increased risk of recurrence resulted associated to age above 60 years, loss of weight greater than 10%, preoperative tumor stenosis, metastatic lymphnodes at endoscopic ultrasound (EUS), poor tumor differentiation, pT stage > 2, R+ surgery, infiltration of circumferential margins, angiolymphatic and neural invasion, positive nodal status, node capsular penetration, higher number of positive lymph nodes and lymph node ratio > 0.2. At multivariate analysis pT stage >2, positive lymph node status and lymph node ratio >0.2 were independent predictors of poorer prognosis and relapse risk and the combination of these factors was proposed as an indication to adjuvant post-surgical therapy [10]. Even though the risk factors of early recurrence after radical resection for EGJ cancer remain controversial, it is accepted that the most important prognostic is R0 surgery [11]. Wang et al., in a retrospective analysis of 147 EGJ cancer patients who underwent R0 surgery, analyzed the prognostic factor for early recurrence, within one year after surgery [12]. The recurrence rate at 1 year was 48.3% and a logistic regression analysis showed that tumor grade and vascular tumor thrombi were the only independent risk factors for early relapse. In esophageal-EGJ cancer patients treated with neoadjuvant therapy plus surgery, vascular, lymphatic and perineural invasion have been identified as independent prognostic factors and their combination may identify patients at increased risk of relapse who would benefit from further adjuvant treatments [13].

Some original reports suggest other potential risk factor of recurrence, such as the preoperative neutrophil–lymphocyte ratio and the anastomotic leakages [14,15]. In summary, even if many factors for increased risk of recurrence have been proposed, there is no consensus yet on what type of patients may benefit from an intensified follow-up or adjuvant therapies.

3. Rates and patterns of recurrence

The particular anatomic features of these borderline cancers between thorax and abdomen determine the intricate patterns of recurrence in EGJ carcinomas. Local recurrence could be caused by the infiltration of tumoral masses directly to surrounding structures. Lymph-nodal and distant metastases could be related to the invasion of lymphatic and/or vascular structures located in the submucosal layer. Finally, the transcoelomic spread could justify the peritoneal recurrences.

At present, only few authors have studied the rates and patterns of recurrence in EGJ cancer (Table 1). Comparable data are not often available in literature, because patients groups are usually not homogeneous in terms of surgical radicality, tumor location based on Siewert classification, histology and pre-operative chemo or radiotherapy.

According to the available data in literature, the recurrence pattern of EGJ cancer seems to be related to its anatomical location. In particular, haematogenous spreading and locoregional recurrence are more frequent in type I and type II EGJ cancers, making them more similar to esophageal adenocarcinomas. Indeed, as extensively reported in literature, most of patients with esophageal cancer present haematogenous failure and locoregional relapse [16,17]. The peritoneal spreading is more common in Siewert III cancers, whose recurrence pattern is comparable to gastric cancer, which has a high percentage of peritoneal relapse after radical resection [18].

One of the first study published in the early '90s investigated the rate and the pattern of recurrence in 93 patients surgically treated for adenocarcinoma of gastric cardia: 57% of these patients experienced a recurrence, even though 12 patients had positive resection margins. The 5-year rates for loco-regional and distant recurrences were 36% and 64%, respectively. Distant metastases occurred more frequently in the liver, peritoneum and lung [19]. A retrospective analysis of 126 patients operated for cardial adenocarcinoma by Mattioli et al. [20] reported similar results. With a median follow-up of 33 months, the recurrence rate was 48,3%; local relapses were observed in 26% (15 patients) and distant relapses in 74% of cases (44 patients). A ten-year retrospective study at a single institution was performed by Stassen et al. [21] analyzing the recurrence rate after resection of adenocarcinoma of gastric cardia. Recurrence of disease, after a mean follow-up of 26 months, was found in 102 of 184 patients (55,4%) and it was significantly related to lymphnodal metastases in a multivariate analysis. Another study analyzed the pattern of spread and recurrence in patients with Siewert I and Siewert II adenocarcinomas. In a cohort of 169 surgically treated patients, 103 patients (61%) had developed recurrent disease (59% Siewert I and 64% Siewert II). The pattern of recurrence was similar in Siewert I e Siewert II cases: haematogenous spread was the most common, followed by local and lymphnodal relapses, while the transcoelomatic diffusion was uncommon [22]. The distribution of the pattern of recurrence according to Siewert classification has been specifically studied in two studies [23,24]. These studies included patients submitted to R0 surgery (macroscopic and microscopic examination of resection margins is negative) who had not been previously treated with neoadjuvant therapy (chemo and/or radiotherapy).

The different Siewert types showed distinct patterns of recurrence. The most frequent pattern of spreading in Siewert II adenocarcinomas was haematogenous; Siewert I cancers showed a similar high rate of distant relapses in the series of de Manzoni, while the four cases of Hosokawa study had a predominant lymphnodal relapse. On the other hand, type III tumors presented a high incidence of peritoneal dissemination, very similar to gastric cancer.

The impact of neoadjuvant treatments, either chemotherapy and/or radiotherapy, on the patterns of recurrence has been investigated in different randomized trials, with contrasting results.