Treatment of esophago-gastric junction adenocarcinoma

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AIM: *The incidence of Adenocarcinoma of the esophagogastric junction (EGJ) is increasing and its treatment is still debated, primarily because of the non-uniform definition of EGJ.*
MATERIALS AND METHODS: *The most used classification of EGJ cancer was proposed by Siewert and it divides the EGJ in three regions: from 5 to 1 cm above the Z line (Siewert type I or esophageal Adenocarcinoma), from 1 over to 2 below the Z line (Siewert type II or real Cardia cancer) and from 2 below to 5 below the Z line (Siewert type III or proximal Gastric cancer diffused to Cardia). The neoplasia is defined type I, II or III depending on where is the center of the cancer.*
DISCUSSION: *This classification did not show to be related to differences in prognosis and survival, but it has been used to guide the surgical strategy based on the site of the tumor. Criticism about this classification focuses mainly on the non-uniform treatment, in the current literature, of Siewert Type II cancer.*
CONCLUSION: *From January 2010, a new definition of EGJ carcinoma has been introduced by TNM. This new definition considers esophageal cancers all the ones whose centers falls inside a line drawn 5 cm below the Z line with invasion of the esophagus. This means that Siewert type I and II are now considered esophageal cancers, while type III can be esophageal or proximal gastric cancer depending if the esophagus is infiltrated or not. Criticism about this new definition rises on the border-line definition of former Siewert type III cancers.*

KEY WORDS: Esophago-gastric adenocarcinoma, EGJ, TNM, Siewert classification, Nodal diffusion

Neoplastic diffusion

The gold standard in the curative treatment of resectable EGJ cancer consists of surgical resection with complete tumor removal (R0 resection) [1,2]. The surgical strategy depends on neoplastic diffusion, which consists of intramural diffusion (T) and nodal status (N) [2,3].

Nodal spread is a main prognostic determinant, both considering site and number of involved nodes, and is also strictly correlated to intramural diffusion of the cancer [2].

NODAL SPREAD BY SITE OF CANCER

In EGJ Adenocarcinoma lymphatic pathways are mainly directed toward the abdomen [2,4,5,6].
Esophageal cancers (ex Siewert type I cancers) tend to diffuse to medium-inferior paraesophageal nodes and paracardiac nodes even if involvement of left gastric artery and celiac trunk nodes are not negligible (respectively 10% and 20% of the cases) [2]. Proximal gastric cancers (ex Siewert type III cancers) often inter-

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est inferior mediastinal nodes, sparing medium and upper mediastinal nodes. Interest of paraaortic nodes is quite common, reaching 30% of the patients with locally advanced tumors [2]. For esophageal cancers corresponding to Siewert type II cancers, it is not easy to foresee the nodal pattern of diffusion: if cancer extends itself toward the esophagus the behavior seems similar to ex type I cancers, vice versa if it extends to the stomach, the nodal diffusion is similar to ex type III cancers (Table I). Virtually all patients with pN+ disease have abdominal nodes involved, as shown in Table I; mediastinal involvement instead differs in various studies [2,4], especially when considering ex Siewert type II, even though involvement of chest alone is rare [2,4].
According to JGCA, in EGJ cancer the nodes of the first level comprised stations 1, 2, 3 and 4s for abdomen associated with station 110 in type I tumors. In pN+ patients, node metastases in non first level are often present[2,4]: 53.8% of the cases for ex Siewert type I, 59.3% for ex Siewert type III and peaking up to 65.9% in ex Siewert type II [2].
Authors that suggest the three-field lymph node dissection have described a non-negligible rate of cervical node involvement for EGJ Adenocarcinoma [7,8], ranging from 18% to 37% of the patients. These studies, even though with low statistical power, raise the problem of a possible pathway of nodal spread upward.

Nodal spread by T status

If nodal spread is strictly dependent from the site of tumor, the incidence of nodal metastases correlates with depth of tumor invasion (pT) [2,4,7-11]. The incidence of nodal metastases, as described in different studies, is shown in Table II. In situ cancers have no possibility of nodal involvement, while pN+ rate for T1m patients ranges from 0% to 12%. This frequency rises rapidly for T1sm patients, with a range of 27-50%. More advanced cancers show a percentage of nodal involvement from 40% to 100%.
Also the number of nodal metastases is directly correlated with depth of tumor invasion: taking 6 lymph nodes as a cutoff, more than 6 nodes where present in 29.0% of pT2 cancers, 44.9% in pT3 and 75.0% in pT4 [2].

Surgical strategy

Surgical strategy depends on three main points: site of primary tumor, depth of tumor invasion and nodal invasion.

T1m

T1m cancers of any site have substantially the same approach [2,12], because of the low probability of nodal

Table I - *Percentage of nodal involvement according to site of cancer.*

	ex Siewert I		ex Siewert II		ex Siewert III	
	de Manzoni[2]	Dresner[4]	de Manzoni[2]	Dresner[4]	de Manzoni[2]	Dresner[4]
mediastinal-abdominal	46%	77%	30%	6%	7%	not reported
only mediastinal	/	8%	/	/	2%	not reported
only abdominal	54%	15%	70%	64%	91%	not reported

Table II - *Percentage of nodal involvement according to pT.*

	de Manzoni[2]	Dresner [4]	Altorki [7]	Lerut [8]	Kim [9]	Liu et [10]	Zhang [11]
T1 is	/	0%	0%	0%	0%	0%	
T1 m	/	0-25%	33%	0%	/	12%	22%
T1 sm	/		50%	35%	/	27%	
T2	61%	40%	75%	71%	/	/	33%
T3	88%	100%	83%	78%	/	/	74%
T4	100%		50%	50%	/	/	86%

metastases. In front of a carcinoma in situ or a small (<1cm) well differentiated not ulcerated T1m, an initial endoscopic resection should be performed; if histological examination confirms invasion limited to the mucosa, it is possible to keep the patients in a follow up regimen. If any one of these characteristics is not matched, a surgical approach is compulsory. A limited resection is enough if the tumor is T1m, but a radical surgical intervention is needed in case of T1sm, because the probability of node metastases significantly rises.

T1SM-T2-T3

For T1sm or more advanced cancers, the surgical approach depends on the site of the neoplasm[2,3,12].

For esophageal cancers (ex Siewert type I and Siewert type II cancers) an esophagectomy is warranted and in this case two different approaches could be planned: trans-thoracic (TTE) and trans-hiatal (THE). A TTE approach aims at achieving a radicality both on T and N, performing a complete lymphadenectomy also in the thorax. This approach could be either a Ivor-Lewis procedure, with an intrathoracic anastomosis, or a McKewon procedure, with a cervical anastomosis after a thoracic and abdominal approach [3,12-14]. A third TTE described possibility is a left thoracoabdominal approach [15], however in a recent randomized trial this operation did not show survival advantage compared with a trans-hiatal (THE) approach.

A three field lymphadenectomy, as proposed by some authors[7,8], obviously needs a triple access.

The second option could be a trans-hiatal (THE) approach [13,14,16]. The authors that recommend this second technique emphasize the lower morbidity and mortality rate and minimize the possible effect on survival due to mediastinal lymphadenectomy [16].

An important recent randomized trial comparing TTE and THE did not find statistically detectable differences in terms of morbi-mortality and in terms of overall survival, however there was a trend towards better overall 5-year survival with TTE approach, especially in patients with ex Siewert type I cancers. This gain in survival was statistically significant in the TTE group among patients with less than 8 involved nodes [13,14] suggesting the therapeutic role of lymphadenectomy in locally advanced EGJ cancer.

For all esophageal cancers, but particularly for ex Siewert type II cancers, the presence of safe macroscopic clear margins is of utmost importance. Barbour et al.[17] described that a gross proximal margin length >3.8 cm, recorded by pathologist after fixation in formalin, significantly correlates to improved survival.

An interesting study by Ito et al. [18] demonstrated that a macroscopically clear margin of 2 cm is safe enough for T1sm cancers, permitting to perform a conservative resection with limited lymphadenectomy. For more advanced cancers instead a macroscopically free margin of at least 6 cm can be a good cut off for achieving a microscopically free margin.

To achieve such a free margin a intra-mediastinal approach from the abdomen is rarely possible, making a trans-thoracic approach preferred.

Mentioning the distal margin, Ito and colleagues found that a free distal margin of 4 cm is safe enough and it is possible to use a gastric tube avoiding total gastrectomy. Actually, Orriger et al. [16] describe a 2.5% of R1 resection with a gastric margin of 6 cm.

Hence the Ivor-Lewis procedure with proximal gastrectomy and subtotal esophagectomy, D2 abdominal and standard mediastinal lymphadenectomy is the most used approach to EGJ cancers corresponding to ex Siewert types I and II. This approach avoids a cervical incision, being cervical lymphadenectomy not routinely performed for this kind of cancers in most centers.

The reconstruction of the digestive tract in Ivor-Lewis procedure in our institution is made with a right sovra-azygotic intra-thoracic mechanical termino-terminal esophago-gastro anastomosis.

The normal approach for proximal gastric cancers (ex type III cancers) consists in a total gastrectomy with distal esophagectomy with D2 abdominal and inferior mediastinal lymphadenectomy. A intra-mediastinal approach from the abdomen is possible if esophageal involvement is less than 2 cm, obtaining a clear margin of at least 5 cm. If this could not be obtained, a TTE approach is needed.

T4

The surgical approach to T4 carcinomas depends on the possibility to obtain a R0 resection. Being often difficult to foresee the radicality in clinical T4 cancers, this kind of tumors are often treated with a multimodal treatment: T4a cancers (resectable tumor invading pleura, pericardium, or diaphragm) are usually treated with neoadjuvant treatment followed by surgery, while T4b cancers (unresectable tumors invading other adjacent structures, such as aorta, vertebral body, trachea, etc.) normally requires definitive palliative chemo- or chemoradiotherapy.

Results with surgery alone and multimodal treatment

Surgery is the gold standard for EGJ Adenocarcinoma, but survival with surgery alone remains poor with a overall survival at 5 years ranging from of 17 to 35% [19-22] and a 50% recurrence rate within 12 months [23].

"The low cure rates after locoregional therapy alone prompted the inclusion of multimodality treatment regimens". This sentence by Jemal et al. [24] clearly explains what led to the introduction of multimodality treatment in this type of cancer.

Multimodal treatment can include chemotherapy, radiotherapy or both in combination prior to surgery (neoadjuvant or induction therapy) or after surgery (adjuvant therapy).
Various reviews and meta-analyses on the published trials [20-22,25-27] have been performed to validate the best treatment choice. According to these studies adjuvant therapy is to proscribe [20,25], because it failed to demonstrate any survival benefit and moreover it was difficult to apply to patients already treated with destructive and prostrating surgical operations, such as esophagectomy. A neoadjuvant approach was employed with some success resulting more applicable and safer and achieving better results [20-22,25,26]. Radiotherapy can improve local control of the disease, while chemotherapy can both sterilize hematological metastases and have a radiosensitising effect.
Radiotherapy alone used as neoadjuvant therapy is not supported currently as a viable treatment choice [20,22,25], as no trial demonstrated any advantage in terms of resectability and survival.
The use of a neoadjuvant therapy based on chemotherapy or chemoradiotherapy can currently be considered the standard of care for locally advanced EGJ cancer [28]. Chemotherapy or chemoradiotherapy approaches proved themselves valid options in two recent meta-analyses [20,26]. For chemotherapy approach, this was particularly true considering adenocarcinoma, thus excluding squamous cell carcinoma, which is normally studied together with adenocarcinoma when evaluating multimodal treatments for esophageal cancer.
An important limit of chemotherapy alone consists of the low rate of pathological complete response (pCR)[21,22]. Moreover results in terms of overall survival are less impressive than the ones obtained with chemoradiation[26]. Chemoradiation (CRT) proved to be, in these two meta-analyses, the best treatment choice, especially when concurrent chemoradiation was used, taking advantage of the radiosensitising effect of chemotherapy [20-21,26-27].
A recent meta-analysis by Lv et al. [21] considered 14 randomized trials using either concurrent or sequential neoadjuvant chemoradiation versus surgery alone and demonstrated a statistically significant advantage in terms of 5-year overall survival for concurrent CRT, while sequential CRT did not show a survival benefit. Pathological complete response was obtained in 10%-45% of patients even though there was a trend to increased operative mortality for CRT arm.
Same results were obtained in other two recent meta-analyses [26,27] of randomized trials in the current literature.
A multicenter randomized trials by a Dutch group [29] is still ongoing and definitive results have yet to report, but preliminary results, presented as abstract at ISDE 2010, show a significant benefit in terms of survival for the CRT+surgery arm vs the surgery alone arm (Median Survival 49 vs 26 months; p=0.011).
The current literature then led most centres to adopt neoadjuvant concurrent chemoradiotherapy as standard of care [28,30].
As aforementioned, it is established that patients who show a significant response to neoadjuvant treatment have a better prognosis than non-responders, following surgical resection [20-32]. Pathological response to treatment both on T and N level play a fundamental role in prognosis [31,32].
Neoadjuvant treatment is normally proposed to locally advanced tumors, i.e. T2-4NxM0. Metastatic cancers need only palliation, while T1 cancers normally are operated on d'embleè.
Neoadjuvant therapy have important implications and rises new problems and possibilities: 1. type of protocol to use; 2. inclusion criteria; 3. timing of surgery; 4. definition of the clinical and pathological response.

TYPE OF PROTOCOL. What is clear so far is that 5-Fluorouracile and Cisplatin are normally the basis for most treatments [21,26,27]. Adding Docetaxel led to a significant improvement in response rate and survival [32,33]. Our protocol is fully described in a previous paper [33]. Briefly it consists of 5-Fluorouracil (5-FU) by protracted intra-venous infusion (PVI) with weekly administration of i.v. Cisplatin and Docetaxel The first cycle consists of chemotherapy alone, and is followed by a second cycle of concurrent chemoradiotherapy (50 Gy in total). The aforementioned Dutch trial [29] used a protocol based on 5 cycles of Paclitaxel and Carboplatin along with 40 Gy of radiotherapy, without an induction period of chemotherapy alone.

INCLUSION CRITERIA. It is still debated. We include in our protocol all patients that met the following criteria: locally advanced carcinoma (cT2-4 Nx M0), no other cancer or chemotherapy/radiotherapy in the previous 5 years, age 75 years and good performance status (ECOG 0-2).

TIMING FOR SURGICAL RESECTION. The main point is that radiotherapy continues its effect for an undetermined period after the conclusion of administration. It seems that the highest effect is reached at 5-8 weeks after completion of treatment. For this reason, in our institution, we re-stage patients at 5-6 weeks and proceed to intervention between the 6th and the 8th week after completion of treatment.

DEFINITION OF CLINICAL AND PATHOLOGICAL RESPONSE TO TREATMENT. This problem opens a new wide chapter. Briefly, complete responders to treatment (pCR), i.e. patients with ypT0N0M0, have an important advantage in survival compared at non-responders. Range of response comprises partial responders and non-responders. Normally non-responders are considered patients with huge residual cancer at primary site before treat-

ment or progression disease. More difficult is the definition of partial response and its role in terms of survival. The most widely used response classification was proposed by Mandard et al. [34] in 1994, named Tumor Regression Grade (TRG).
This consists of five grades: TRG 1 - complete response at the primary site, with no residual cancer, TRG 2 - rare residual cancer cells at the primary site, TRG 3 - a larger number of residual cells, with fibrosis outgrowing residual cancer, TRG 4 - residual cancer outgrowing fibrosis and TRG 5 - absence of regression. In a recently published study, we validated the use of this classification[32], on condition that the N status is also considered. In fact, in our series, Disease-related survival decreased with increasing TRG in node-negative patients (log-rank test for trend: P<0.001) while in node positive (N+) patients it was poor, irrespective of TRG (P=0.241).
We also proposed a new method named Size-based Pathological Response Classification (SPR Classification), in which we introduced the concept of Minimal Residual Disease (MRD). MRD is defined as residual cancer at primary site)10 mm.
SPR comprised four grades: SPR1) pathological complete responders at both the primary site and nodal level, ypT0 ypN0 (pCR); SPR2) patients with MRD at the primary site (residual tumor)10 mm) without nodal metastases (MRD N0); SPR3) non-responders at the primary site (residual tumor > 10 mm) without nodal metastases (NR N0); and SPR4) patients with nodal metastases, irrespective of ypT (N+).
SPR1 reached 85% disease related survival at 3 years, while SPR3 and SPR4 respectively 28 and 21%. SPR2 disease related survival was intermediate, reaching 58% at 3 years.
This classification has the advantage of being easily reproducible as been a quantitative method, and probably deserves further studies for validation.

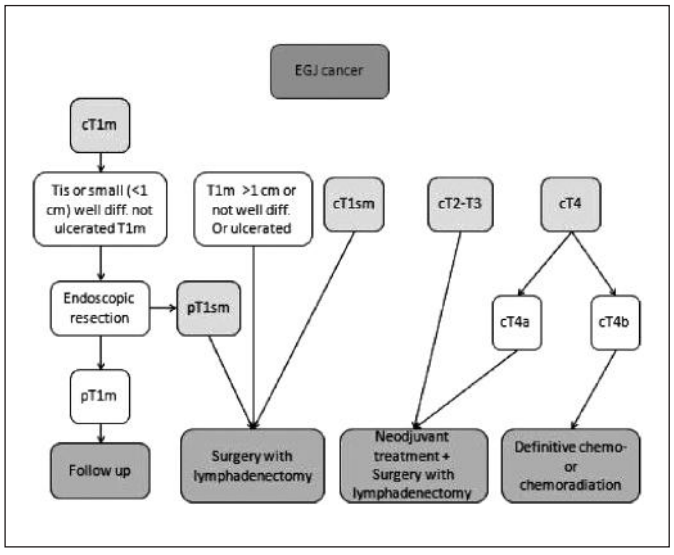

Fig. 1: Proposed flow-chart for treatment of EGJ cancer.

Conclusion

In conclusion, it is possible to draw a simple flow-chart of the approach to EGJ cancer (Fig. 1). T1m cancers can be treated with endoscopic resection or limited surgical resection. T1sm cancers need operation with lymphadenectomy. Locally advanced T2-3 cancers (ex Siewert type I and II) can be either treated with surgery alone or with a neoadjuvant therapy followed by surgery. A lymphadenectomy is anyway mandatory.
T4a tumors normally are treated with neoadjuvant therapy to improve surgical respectability, while T4b tumors are treated with palliative chemo- or chemoradiation.

Riassunto

L'incidenza di adenocarcinoma della giunzione esofago-gastrica (GEG) è in aumento e il suo trattamento è ancora dibattuto, soprattutto a causa della definizione non uniforme di GEG.
La classificazione più utilizzata di cancro della GRG è stata proposta da Siewert e divide la GEG in tre regioni: da 5 a 1 cm al di sopra della linea Z (tipo I di Siewert o adenocarcinoma esofageo), da 1 cm al di sopra a 2 cm al di sotto della linea Z (tipo II di Siewert o cancro del Cardias propriamente detto) e da 2 a 5 al di sotto della linea Z (tipo III di Siewert prossimale o cancro gastrico prossimale diffuso al Cardias). La neoplasia è definita di tipo I, II o III a seconda di dove sia localizzato il centro della neoplasia.
Questa classificazione non ha mostrato di essere legata alle differenze di prognosi e di sopravvivenza, ma è stato utilizzata per guidare la strategia chirurgica in base al sito del tumore. Le critiche a questa classificazione si concentrano principalmente sul trattamento non uniforme, nella letteratura corrente, dell'adenocarcinoma tipo II di Siewert.
Da gennaio 2010, una nuova definizione di carcinoma della GEG è stata introdotta dal TNM. Questa nuova definizione considera come cancro esofageo tutte quelle neoplasie il cui centro cada all'interno di una linea tracciata a 5 cm sotto la linea Z con invasione dell'esofago. Questo significa che Siewert tipo I e II sono ormai considerati cancro esofageo, mentre il tipo III può essere cancro esofageo o cancro gastrico prossimale a seconda che l'esofago sia infiltrato o meno. Le critiche a questa nuova definizione sorgono sulla definizione border-line dei tumori ex Siewert tipo III.

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