Preoperative treatment of locally advanced esophageal carcinoma (Review)

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Abstract. Esophageal cancer (EC) is an aggressive malignancy with increasing incidence worldwide. Surgery is still the most effective treatment, however, both the high rate of local and distant recurrences and surgery-related complications led us to investigate new preoperative strategies. In this review, we discuss the role of neoadjuvant therapy for locally advanced EC with a focus on preoperative chemoradiation (trimodality treatment). Furthermore, the last fifteen years of published literature and our experience have been also reviewed. In the preoperative setting, few trials have reported a significant benefit with fluoropyrimidine and platinum compound-based neoadjuvant chemotherapy, compared to surgery alone. A large number of phase III trials and meta-analyses have demonstrated improved outcomes with preoperative chemoradiation vs. neoadjuvant chemotherapy or surgery alone. Therefore, trimodality therapy can be considered the most effective option in the management of locally advanced EC. Addition of drugs targeting VEGF or HER2 to standard chemotherapy appears to be feasible but needs to be explored more accurately. FDG-PET may predict both response to neoadjuvant treatments and prognosis.

Contents

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1. Introduction

Worldwide, esophageal cancer (EC) is the eighth most common malignancy and the sixth cause for cancer-related death (1). In the USA, ~17460 patients were diagnosed in 2012 with 15070 deaths of this disease (2). In Italy, esophageal cancer represents 1.9 and 0.8% of all the cancer deaths among males and females, respectively; ~2573 new cases are diagnosed annually (3). EC is characterized by a very high mortality rate, as it is rarely detected at an early stage. Furthermore, even when the primary tumor is resectable, survival remains very poor because of early lymphatic and hematogenous dissemination, particularly if the tumor invades the adventitia or adjacent structures (T3-T4) and the histological type is squamous (4-8).

Although surgery alone remains the standard treatment for patients with resectable EC, its effectiveness has been considered unsatisfactory, with median survival rarely exceeding 18 months; (9) for this reason, a multidisciplinary approach is necessary to improve outcome (10). Recently, neoadjuvant chemoradiotherapy regimens followed by surgery have been extensively studied; however, data from phase III trials appeared to be very heterogeneous and controversial.

Herein, we reviewed neoadjuvant strategies for locally advanced esophageal carcinoma (T3-4 and/or node positive tumors) and the literature published over the last fifteen years.

2. Neoadjuvant chemotherapy

Early dissemination of EC and the high mortality rate after apparently radical surgery has validated the use of neoadjuvant chemotherapy in locally advanced disease. Its rationale is based both on increased chances of tumor resectability and on early treatment of micrometastasis. Recent trials have studied the role of neoadjuvant chemotherapy in EC yielding

discordant results. Firstly, the US G-I Intergroup RTOG Trial 8911 randomized 467 patients with local or locally advanced EC to receive three cycles of cisplatin (100 mg/m^2) plus infusional 5-FU (1000 mg/m^2/day from days 1 to 5) before surgery and two cycles thereafter. Median overall survival (OS) and 2-year survival rate were 14.9 months and 35%, as opposed to 16.1 months and 37% in the chemotherapy arm and surgery alone, respectively. Therefore, the study showed no benefit by the addition of neoadjuvant treatment compared to surgery alone. Major adverse effects of chemotherapy were neutropenia and mucositis (grade 3 toxicity in 29 and 25% of patients, respectively) (11,12).

A second large trial randomized 802 patients with potentially resectable squamous cell carcinoma or adenocarcinoma of the esophagus to receive two cycles of cisplatin (80 mg/m^2) and 5-fluorouracil (5-FU, 1000 mg/m^2/day for 4 days) administered before surgery vs. surgery alone. The 2-year median survival was significantly higher in the neoadjuvant arm (16.8 months vs. 13.3 months), despite the high rate of mortality recorded (10-11%) (13). A recent update of this study has confirmed a significantly better disease free survival (DFS) and OS in the neoadjuvant chemotherapy arm vs. surgery alone after a 6-year follow-up (DFS: HR, 0.82, p=0.008; OS: HR, 0.84, p=0.03) (14).

In order to clarify the role of preoperative chemotherapy, several meta-analyses were performed. One of these, including 9 phase III randomized trials comparing preoperative chemotherapy vs. surgery alone showed a significantly reduced mortality (HR,0.87; p=0.005), with an absolute benefit in the 2-year survival of 5.1%, in case neoadjuvant therapy was implemented. This advantage, although present for both histologies, was significant only for adenocarcinomas (HR, 0.83; p=0.01) and not for squamous cell carcinomas (HR, 0.92; p=0.18) (15).

3. Preoperative radiotherapy

Clinical trials comparing preoperative radiotherapy to surgery alone in resectable patients showed no significant benefit in terms of improvements in resection and survival rates. The meta-analysis conducted by Arnott *et al* reported a poor benefit rate for preoperative radiotherapy alone, with a 5-year survival advantage of 4% (16). Furthermore, a second meta-analysis performed by Ku *et al* confirmed inferiority of preoperative radiotherapy alone vs. neoadjuvant chemoradiotherapy (17). Therefore, preoperative radiotherapy does not seem to have a positive impact on patients who are candidates for surgery.

4. Neoadjuvant trimodality therapy

Evidence obtained over the last two decades indicates that locally advanced EC cannot be cured by local approaches, such as surgery or radiotherapy alone (18). Use of a combined treatment including chemotherapy, radiotherapy, and surgery (trimodality therapy) allows optimization of the benefits of each treatment, including a reduced cancer burden, removal of persistent microscopic disease after chemoradiation, increased pathologic complete resection rate with negative circumferential margins, and an adjuvant effect on micrometastatic disease. A multimodal preoperative approach provides a clear survival advantage if compared with surgery (19) or radiation therapy alone (4,20), and a pathologic complete response (pCR) rate ranging from 20 to 35% can be reached (5,21).

Current literature includes several randomized controlled trials comparing chemoradiation followed by surgery vs. surgery alone (Table I). The trial reported by Walsh *et al* demonstrated a significantly improved survival with concurrent preoperative chemotherapy (5-FU 15 mg/kg, cisplatin 75 mg/m^2) and radiotherapy (40 Gy in 15 fractions) vs. surgery alone in patients with adenocarcinoma of the distal esophagus-GE junction. The three-year survival rate was 32% in the experimental arm vs. 6% in the standard treatment arm; median survival was 16 months vs. 11 months (p=0.01). Complete response rate for the preoperative chemoradiation arm was 22%, with evidence of nodal down-staging (82% node-positive in the surgery arm vs. 25% after neoadjuvant therapy, p<0.001). Treatment-related toxicity was low, and the regimen was well tolerated (22).

In a larger trial, Urba *et al* randomized 100 patients to receive surgery with or without preoperative chemoradiation (cisplatin 20 mg/m^2, vinblastine 1 mg/m^2, 5-FU 300 mg/m^2, RT 1.5 Gy twice a day to 45 Gy). Median survival was 17.6 months with neoadjuvant therapy and 16.9 months with surgery alone; the 3-year survival rates were 30% and 16%, respectively (p=0.18). pCR rate was 28% in the experimental arm, although the number of patients was limited. The use of preoperative therapy reduced the incidence of loco-regional failure (p=0.0002). Incidence of distant metastases was ~60% in both arms. Seventy-eight percent of the patients experienced grade 3-4 neutropenia, and 39 of these developed neutropenic fever. Thirty-one percent of patients had grade 3/4 thrombocytopenia. In the surgery arm there were 2 perioperative deaths (caused by postoperative pneumonia and cervical anastomotic leak, respectively) and 4 anastomotic leaks. In the second arm treated with multimodality approach, 7 anastomotic leaks and a preoperative death were recorded (23).

A similar experience to the above was reported by Bosset *et al*. The experimental regimen used was cisplatin 80 mg/m^2 every 21 days prior to each set of RT treatment (1-week courses of 18.5 Gy in five 3.7 Gy fractions). This study did not find differences in OS, although there was a significant improvement in DFS and local recurrence-free survival. Postoperative mortality was significantly higher in the combined treatment arm (12%). Chemotherapy-induced vomiting and WHO grade 3 neutropenia were registered in 37 and 3 patients, respectively. During the postoperative period, 36 patients (26.3%) in the surgery-alone group and 45 patients (32.6%) in the combined-treatment group had one or more severe complications (pneumonia, infections, and anastomotic leakage were the most frequent). Postoperative mortality was significantly higher in the combined-treatment group (17 of 138, as compared with 5 of 137 in the surgery-alone group; p=0.012) (24). The Trans-Tasman Radiation Oncology Group and the Australasian Gastro-Intestinal Trials Group randomized 256 patients to receive surgery alone or one cycle of preoperative cisplatin (80 mg/m^2/day) and 5-FU (800 mg/m^2 on days 1-4), with concurrent RT (35 Gy in 15 fractions). Sixty-two percent of patients had adenocarcinoma. No survival benefit was registered, although a suggestion of benefit for patients

Table I. Randomized phase III trials of trimodality therapy vs. surgery alone.

Authors/(Refs)	Treatment	Patients (N)	RT (Gy)	R0 rate (%)	pCR (%)	Survival	
						Median	Overall
Walsh *et al* (22)	Cisplatin/5-FU	58	40	NS	25	16 mo.	3-Y 32%
	Surgery	55			N/A	11 mo.	3-Y 6%
Urba *et al* (23)	Cisplatin/5-FU/Vnb	50	HFX, 45	45	24	16.9 mo.	3-Y 30%
	Surgery	50		45	/	17.6 mo.	3-Y 6%
Bosset *et al* (24)	Cisplatin	143	SC, 37		26	18.6 mo.	
	Surgery	139			N/A	18.6 mo.	
Burmeister *et al* (25)	Cisplatin/5-FU	128	35	80	16	22.2 mo	NS
	Surgery	128		59	N/A	27.3 mo.	NS
Lee *et al* (74)	Cisplatin/5-FU	51	HFX, 45.6	68	43	28.2 mo.	2-Y 49%
	Surgery	50		84	N/A	27 mo.	2-Y 57%
Tepper *et al* (75)	Cisplatin/5-FU	30	50.4	NS	40	4.5 Y	5-Y 39%
	Surgery	26			N/A	1.8 Y	3-Y 16%
van Hagen *et al* (27)	Carboplatin/Ptx	175	41.4	92	29	49 mo.	3-Y 59%
	Surgery	188		69	N/A	24 mo.	3-Y 48%

5-FU, 5-fluorouracil; Vnb, vinorelbine; Ptx, paclitaxel; SC, short course; HFX, hyperfractionated. NS, not stated; N/A, not applicable; Y, year.

with squamous cell carcinoma was perceived. Chemotherapy was well tolerated and no treatment-related deaths were registered. The most commonly reported grade 3-4 event was esophagitis. Nausea or vomiting, pneumonitis, mucositis, and diarrhea were less common. Five percent of patients who underwent resection had a surgery-related death. The causes of death were sepsis, respiratory complications, myocardial infarction, and pulmonary embolism. Forty-nine percent of patients assigned to chemoradiotherapy and surgery and 55% of patients assigned to surgery alone had surgery-related complications. Pulmonary or cardiac events and anastomotic leak incidence was similar in the two arms (25). A further benefit for pre-operative chemoradiotherapy was reported by Stahl and colleagues in a recent phase III trial in patients with locally advanced esophageal adenocarcinoma. Pre-operative chemotherapy with cisplatin/5-FU followed by surgery vs. the same pre-operative chemotherapy followed by chemoradiation with cisplatin/etoposide and then surgery were compared. In a population of 119 patients, R0 resections were similar in both arms, and the 3-year OS rate improved from 27 to 47% in the chemoradiotherapy group (p=0.07) (26).

Employment of a schedule containing a taxane has been recently tested by van Hagen and colleagues: they randomly assigned 366 patients with resectable squamous cell carcinoma, adenocarcinoma or undifferentiated carcinoma of the esophagus or esophago-gastric junction to receive surgery alone or weekly carboplatin (doses titrated to achieve an area under the curve of 2 mg/ml/min) and paclitaxel (50 mg/m^2 of body surface area) for five weeks with concurrent radiotherapy (41.4 Gy in 23 fractions) followed by surgery. One hundred and eighty patients were assigned to trimodality treatment and 188 to surgery alone. A complete resection rate was obtained in 92% of patients treated with chemoradiotherapy-surgery vs. 69% of patients treated with surgery alone (p<0.001). Pathological complete response was achieved in 29% of patients treated with chemoradiotherapy. Median overall survival was significantly better in the chemoradiotherapy-surgery arm (49.4 months vs. 24 months; HR, 0.657; 95% CI, 0.495-0.871; p=0.003). Seven percent of patients assigned to chemoradiotherapy-surgery arm developed grade 3 hematologic toxic effects, while only one grade 4 hematologic toxic effect was observed. Other non-hematologic grade 3 toxic effects occurred in <13% of patients in this group. Postoperative complications were similar in the two treatment groups and mortality was 4% in both arms (27).

Published trials are often undermined by difficult interpretation depending on several factors: heterogeneity of histology, patient selection, difficulty in assessing the anatomical origin (esophageal or gastric) of junction adenocarcinomas, different surgical techniques adopted, response criteria, and different sensitivity of chemotherapy programs employed. Several meta-analyses of randomized controlled trials clarified the real impact of preoperative chemoradiotherapy (CRT) on locally advanced EC (Table II) (15,28-30). One of the most complete analysis was presented by Australasian investigators in 2007. It compared preoperative chemoradiation with immediate surgery in 1209 patients from a total of 10 trials from 1983 to 2006. Data obtained showed a benefit for trimodality therapy compared with surgery alone, corresponding to a 13% reduction in mortality at 2 years. The benefit was similar for both histologies, but no difference was registered in trials administering chemotherapy and radiotherapy sequentially rather than concurrently (29).

In the last few years, two more meta-analyses were published. Sjoquist *et al* included in their analysis 1854 patients

Table II. Preoperative chemoradiation: results of meta-analysis.

Authors/(Refs)	Patient group	Outcome	
Urschel *et al* (28)	9 RCTs 1116 pts	3-year survival	OR 3Y 0.66 p=0.016
Kaklamanos *et al* (76)	5 RCTs 669 pts	Difference in 2-year survival	p=0.86
Fiorica *et al* (77)	6 RCTs 760 pts	3-year survival	OR 0.53 p=0.02
Greer *et al* (78)	6 RCTs 374 pts	Survival	OR 1.76 p=0.7
Gebsky *et al* (29)	10 RCTs 1146 pts	Survival	HR 0.81; p=0.002 S: p=0.02; A: p=0.05 2Y 7% absolute benefit
Graham *et al* (79)	14 RCTs 1281 pts	QUALY	Trimodality associated with the best survival and largest gain
Lv *et al* (80)	14 RCTs 1737 pts	Survival	HR 0.82 p=0.0001
Kranzfelder *et al* (30)	9 RCTs 1099 pts	Survival	HR 0.81 p=0.008
Sjoquist *et al* (15)	12 RCTs 1854 pts	Survival	HR 0.78; p=0.0001 Strong evidence for a survival benefit

from 12 randomized controlled trials subjected to neoadjuvant chemoradiotherapy or surgery alone. The authors reported an absolute survival benefit of 8.7% at 2 years (pooled HR, 0.78, 95% CI, 0.70-0.88; p<0.0001). The survival benefit for neoadjuvant chemoradiotherapy was similar in all histology subgroups: squamous cell carcinoma (HR, 0.80; 95% CI, 0.68-0.93; p=0.004) and adenocarcinoma (HR, 0.75; 95% CI, 0.59-0.95; p=0.02) (15). In a subsequent analysis, Kranzfelder *et al* analyzed 1099 patients from 9 randomized controlled trials receiving trimodality therapy or surgery alone. Employed chemotherapy schedules consisted of cisplatin as monotherapy or in combination with either 5-FU and vinblastine or bleomycin at different doses. Data obtained from the analysis significantly favored neoadjuvant CRT in terms of overall survival (HR, 0.81; CI, 0.70-0.95; p=0.008) (30). Therefore, preoperative CRT can be considered the therapeutic standard for locally advanced EC while preoperative chemotherapy alone should be considered only when a multimodal approach cannot be implemented due to comorbidities.

5. Targeted therapies

Despite improvements obtained with trimodality treatment, cure rates in EC remain very poor. Multiple molecular pathways have been evaluated as possible pharmacological targets in EC, including cyclin dependent kinases, nuclear factor-κB, matrix metalloproteinases, COX-21, HER2/neu, c-MET (a proto-oncogene encoding a protein known as hepatocyte growth factor), epidermal growth factor receptor (EGFR), and vascular endothelial growth factor (VEGF) (31).

Anti-EGFR therapy. Epidermal growth factor receptor (EGFR) is expressed in 30-70% of gastroesophageal cancers and is also associated with a poor prognosis. Anti-EGFR monoclonal antibodies (MAbs) compete with ligand-receptor interaction and downstream tyrosine kinase activity by binding to the extracellular EGFR domain, thereby occluding the ligand-binding region (32-35). It results in receptor internalization and degradation. Cetuximab is an IgG1 class antibody, which, through natural killer cell binding, may initiate an immune-mediated antitumor response (i.e., antibody-dependent cell-mediated cytotoxicity) (36). It represents the only anti-EGFR moAb demonstrating synergy with RT as well as paclitaxel and cisplatin CT-based regimens in pre-clinical studies (37,38). For these reasons, the Brown University Oncology Group and the University of Maryland Cancer Center designed a study of carboplatin/paclitaxel with radiation in combination with cetuximab for localized gastroesophageal cancer. Patients received cetuximab (400 mg/m^2 in week 1, then 250 mg/m^2 every week for 5 weeks), paclitaxel (50 mg/m^2 every week) and carboplatin (AUC=2, weekly for 6 weeks) with concurrent radiation of 50.4 Gy. Fifty-seven patients with esophageal cancer were enrolled (48 had adenocarcinoma). Seventy percent of patients obtained an endoscopic complete clinical response after chemoradiation regardeless of histology (adenocarcinoma or squamous carcinoma). Twenty-seven percent of patients undergoing surgery achieved pCR. No grade 4 toxicities were reported and the most common grade 3 toxicity was dermatologic (23%), secondary to cetuximab. There was no increase in chemoradiation-induced mucositis/esophagitis secondary to cetuximab and no enteral feeding tubes were required (39).

In a single arm open label pilot study from the Hoosier Oncology Group and the University of Texas-Southwestern, combining cetuximab with radiation for patients with resectable esophageal and GEJ carcinomas yielded an endoscopic complete response in 67% of patients; pCR was registered in 43% of those who underwent surgery (40). In the prospective phase IB/II trial (SAKK75/06), 28 patients with resectable locally advanced esophageal adenocarcinoma or squamous cell carcinoma received two 3-week cycles of induction chemoimmunotherapy [cisplatin 75 mg/m^2/day, docetaxel 75 mg/m^2/day, cetuximab 250 mg/m^2 days 1, 8, 15 (400 mg/m^2 loading dose)] followed by chemoimmunoradiation therapy (45 Gy) and surgery. Complete or near complete pathologic regression was achieved in 68% of patients. Of the 25 patients who underwent surgery, pathologic response was observed in 19 patients (12 with adenocarcinoma and 7 with squamous cell carcinoma). Overall, compliance to therapy was good (41). De Vita and colleagues reported results of a phase II trial assessing the role of cetuximab as preoperative treatment for locally advanced EC. Forty-one patients received FOLFOX-4 and cetuximab followed by daily radiotherapy (180 cGy fractions to 5040 cGy) with concurrent weekly cetuximab. Of the 30 patients undergoing surgery, pCR was observed in 8 patients (20%), whereas a pathologic partial response (pPR) was recorded in 12 patients (30%), with an overall pathological response rate of 50%. Among the patients who underwent surgery, pCR rate was 27%. Median and mean OS rates were 17.3 and 16 months, respectively. OS rates at 12, 24, and 36 months were: 67, 42, and 42%, respectively. The difference in survival probability between operable and inoperable patients was significant and no difference in survival was detected among the different histological types (35).

Despite encouraging results, the role of association of cetuximab with chemotherapy was recently downgraded by the results of the SCOPE1 trial, the largest study of definitive chemoradiotherapy (dCRT) investigating the addition of cetuximab to standard cisplatin and fluoropyrimidine treatment in localized esophageal cancer. In this multicentric phase II/III trial, 258 patients were selected to randomly receive cisplatin (60 mg/m^2/day) and capecitabine (625 mg/m^2 on days 1-21 for 4 cycles) concurrently with 50 Gy in 25 fractions of RT, with or without cetuximab (400 mg/m^2/day followed by 250 mg/m^2/week). Patients who received cetuximab had higher non-hematologic toxicity [78 vs. 62.8%, p=0.004; primarily dermatological (22 vs. 4%) and metabolic (24 vs. 11%)], a lower rate of completion of standard chemotherapy (capecitabine 69 vs. 85%, p=0.002; cisplatin 77 vs. 90%, p=0.005) and radiotherapy (75 vs. 86%, p=0.027), reduced failure free survival at 24 weeks (66 vs. 77%), median survival (22 vs. 25 months, log rank p=0.043) and 2-year survival (41 vs. 56%). Disease control and survival in the standard dCRT arm was superior to any previously published multicenter study. The use of cetuximab was associated with greater toxicity, lower doses of dCRT, and reduced survival (42). Therefore, cetuximab could not be recommended in combination with standard dCRT for unselected patients with esophageal cancer. Based on these results, the RTOG 0436 trial evaluating the addition of cetuximab to paclitaxel/cisplatin and radiation in patients with unresectable squamous esophageal cancer has been recently closed (43).

Gefitinib and erlotinib are oral inhibitors of the EGFR TK domain. TKIs inhibit adenosine triphosphate binding within the TK domain and completely inhibit EGFR autophosphorylation and signal transduction. Both agents have demonstrated activity in EGFR-expressing esophageal cell lines and seem to display synergistic action when concurrently administered with radiation (44). A phase I study reporting experience with preoperative erlotinib and cisplatin/5-FU/radiation in localized esophageal cancer was published by Dobelbower and colleagues of the University of Alabama. This regimen was well tolerated and the main toxicities were rash, diarrhea, nausea, and dehydration. No dose-limiting toxicities were reported (45). A phase II study by Rodriguez *et al* randomized 80 patients to receive neoadjuvant CRT [4 days of continuous intravenous infusions of cisplatin 20 mg/m^2/day and fluorouracil 1000 mg/m^2/day started on day 1 of preoperative radiation (30 Gy and 1.5 Gy bid)], with or without gefitinib 250 mg/day for 4 weeks, subsequently restarted with postoperative therapy for 2 years. The addition of gefitinib did not increase toxicity except for development of rash in 42 patients (53%) and diarrhea in 44 (55%); on the other hand, a higher overall survival (42% vs. 28%, p=0.06), DMC (40% vs. 32%, p=0.33), and locoregional control (76% vs. 77%, p=0.74) were registered. Intolerance for gefitinib maintenance occurred in 48% of patients. Patients who experienced gefitinib-related diarrhea appeared to have improved outcomes (46).

Anti-HER2 therapy. Several studies showed Human Epidermal Growth Factor Receptor 2 (HER2/neu) overexpression in gastrointestinal tumors, including esophageal squamous cell carcinoma (mean, 23%; range, 0-52%), GE adenocarcinoma (mean, 22%; range, 0-43%), and gastric adenocarcinoma (mean 19%; range, 6-43%) (47). In esophageal squamous cell carcinoma, HER2/neu overexpression has been correlated with extramural invasion and poor response to neoadjuvant chemotherapy. In GE junction adenocarcinoma, some studies suggest a correlation with deeper invasion, lymph node and distant organ metastasis, and poor overall survival (47). Therefore, Her2/neu is a potential target in EC, particularly as part of a standard combined modality treatment regimen (48).

Trastuzumab is a humanized IgG1 antibody specific for HER2/neu antigen, able to induce down-regulation of HER2 expression, induction of G1 cell cycle arrest and downstream cell regulatory signals, initiation of antibody dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), and apoptosis induction (49). Several studies reported its synergistic or additive effect with cisplatin, paclitaxel and radiation (50,51). Based on these data, Safran *et al* carried out a phase I/II trial of weekly paclitaxel (50 mg/m^2), cisplatin (25mg/m^2) and radiation (50.4 Gy), with or without trastuzumab, in patients with locally advanced GE junction adenocarcinoma. HER2/neu was overexpressed in 12 out of 36 patients with GE junction adenocarcinoma (33%). Median survival for all patients was 24 months and the 2-year survival rate was 50% with a low incidence of side effects (52). The results obtained by the Toga trial indicated trastuzumab as a new valid treatment in association with chemotherapy for HER2-positive advanced or locally advanced esophagogastric tumors. In this phase III trial, 594 patients with histologically confirmed inoperable locally advanced, recurrent or

metastatic HER2-positive adenocarcinoma of the stomach or gastroesophageal junction were randomly assigned in a 1:1 ratio to receive capecitabine (1000 mg/m^2 twice a day for 14 days followed by a 1 week rest) or fluorouracil (800 mg/m^2 by continuous intravenous infusion on days 1-5 of each cycle), cisplatin (80 mg/m^2 on day 1), with or without trastuzumab (8 mg/kg on day 1 of the first cycle, followed by 6 mg/kg every 3 weeks), until disease progression or unacceptable toxicity. Median OS was 13.8 months (95% CI 12-16) in case of combination therapy (trastuzumab plus chemotherapy) vs. 11.1 months (95% CI 10-13) in case of chemotherapy alone (HR, 0.74; 95% CI, 0.60-0.91; p=0.0046). Median PFS was 6.7 months (95% CI 6-8) in the trastuzumab plus chemotherapy arm vs. 5.5 months (95% CI 5-6) in the chemotherapy alone arm (HR, 0.71; 95% CI, 0.59-0.85; p=0.0002). Overall tumor response rate, time to progression, and duration of response were shown to have significantly improved in the trastuzumab arm. No differences in frequency of grade 3 or 4 adverse events were registered; serious adverse events were reported in 32% of patients in the trastuzumab plus chemotherapy arm and in 28% of patients in the chemotherapy alone arm. No differences in terms of cardiac adverse events were noted in the two arms (53).

Anti-VEGF therapy. The process of tumor growth and metastasis is regulated by neoangiogenesis through different pro-angiogenic and anti-angiogenic factors. Vascular endothelial growth factor (VEGF) represents the most potent pro-angiogenic factor because of its ability to induce endothelial cell mitogenesis and migration, increased vascular permeability, and maintenance of newly formed blood vessels (54,55). It is overexpressed in 30-60% of patients with EC and has been correlated with an advanced stage and a poor survival (56,57). Bevacizumab is a recombinant humanized monoclonal antibody which binds with high affinity to all isoforms of human VEGF, thereby preventing its actions. It results in inhibition of tumor growth and metastasis, inhibition of new vessel formation, and normalization of neo-vascular network (58).

Only few trials investigating the clinical utility of bevacizumab in EC have been completed thus far. A multicenter phase II trial including 47 patients with metastatic or unresectable gastric/GEJ junction investigated the addition of bevacizumab (15 mg/kg on day 1) to a combination of cisplatin (30 mg/m^2 on day 1 and 8 every 21 days) and irinotecan (65 mg/m^2 on day 1 and 8 every 21 days). In this study, Shah and colleagues obtained a response rate (RR) of 65% with a median time to progression of 8.3 months and a median OS of 12.3 months. The combination was well tolerated: no increase in chemotherapy-related toxicity was detected and bevacizumab specific toxicity was hypertension (grade 3, 28%) and thromboembolism (grade 3 and 4, 22.5%) (59). In a recent trial, Bendell *et al* evaluated the efficacy of bevacizumab and erlotinib in addition to preoperative chemoradiation for localized untreated squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma of the esophagus or GEJ. Sixty-two patients received erlotinib (100 mg/day) on days 1-42, paclitaxel (200 mg/m^2), carboplatin (area under the curve 5.0) and bevacizumab (15 mg/kg IV) on days 1 and 22, and 5-FU by continuous infusion (225 mg/m^2/day IV) on days 1-35, with radiation therapy (up to a total of 45 Gy). Twenty-nine percent of patients achieved pCR. Addition of bevacizumab and erlotinib to neoadjuvant chemoradiation did not modify survival, pCR, or the overall rates of toxicity (grade 3/4 toxicities: leukopenia 64%, neutropenia 44%, mucositis/stomatitis 42%, diarrhea 27%, and esophagitis 27%); however, targeted agent-specific toxicity was evident (60).

6. Prediction of response

Despite the progress in the management of EC and the increasing integration of targeted therapies into treatment schedules for locally advanced disease, pCR rates remain very poor with a low 5-year OS after R0 resections. Residual disease can be considered a factor linked to aggressive, CRT-resistant disease with a higher potential for metastasis (61-64). Therefore, a reliable diagnostic test allowing prediction of response is necessary for the future use of preoperative chemotherapy in patients with esophageal cancer (65). Recent evidence suggests a promising role for positron emission tomography (PET) with radiolabelled fluorodeoxyglucose (FDG) for prediction of response during the early phase of chemotherapy. In the German Metabolic Response Evaluation for Individualization of Neo-adjuvant Chemotherapy in Oesophageal and Oesophago-gastric Adenocarcinoma (MUNICON) phase II trial of locally advanced esophageal/GEJ cancer, 119 patients with adenocarcinoma of esophago-gastric junction (EGJ) were assigned to receive 2 weeks of platinum and fluorouracil-based induction chemotherapy. Patients with reduced tumor glucose standard uptake values (SUVs) were defined as metabolic responders. Early PET responders (a >35% decrease in tumor SUV) after 2 weeks of induction cisplatin/5-FU continued to receive the full 12-week course of pre-operative treatment whereas non-responders underwent surgery. Patients with metabolic response, a surrogate for tumor response, were found to survive significantly longer than non-responders (median not reached for PET responders vs. 25.8 months for nonresponders). R0 resection rates (96 vs. 74%) and major pathologic responses (58 vs. 0%) were also significantly higher in the PET responder group (66). In summary, the MUNICON study prospectively confirmed the usefulness of metabolic response evaluation in esophageal-gastric cancer, thus demonstrating for the first time that a PET-guided treatment algorithm may be feasible in the multidisciplinary treatment setting and can lead to favorable treatment results. Based on these results, the EUROCON study is currently randomizing metabolic nonresponders after 2 weeks of chemotherapy to either immediate resection or chemoradiation followed by surgery.

7. Conclusions

Locally advanced EC represents a disease with a poor prognosis and patients treated with surgery alone are characterized by low survival rates, because of early occurrence of metastases or surgery-related complications. Clinical trials published over the last 20 years indicated the importance of neoadjuvant therapy to understage disease and optimize surgery. Neoadjuvant chemo-

therapy with platinum-based regimens has been shown to be superior to surgery alone in terms of OS and PFS in several early studies (11-14). Thus, neoadjuvant chemoradiotherapy has been the standard of care for locally advanced EC in the last fifteen years. Preoperative cisplatin regimens and concurrent radiotherapy have been shown to yield a resection rate up to 80%, a pathologic CR rate of 20-40%, with a median survival time of 11-49 months and a therapy-related mortality rate of 10-12% (22-29,67). Of note, the only studies reporting a statistically significant advantage in terms of OS or DFS included a preoperative concomitant chemoradiation treatment, as opposed to a sequential modality of treatment.

A number of new systemic agents are under investigation and could be effective in the control of micrometastatic disease. Paclitaxel has been identified as an active agent (27), while irinotecan and gemcitabine are about to undergo extensive testing. Several of these drugs are also potent radiation sensitizers, possibly allowing improved local control when combined with radiotherapy (67). Finally, although still at an early stage of development, novel targeted treatments are also under investigation. Encouraging results have been reported with antibodies to VEGF ligand, as well as with the oral TKIs. Therefore, the tailoring of treatment to specific patient populations (such as those with genetically mutated receptors) seems to be the future therapeutic strategy of locally advanced EC, as is now for colorectal and lung cancer.

Lastly, the search for novel indicators predictive of pathological complete response (pCR), a marker closely linked to overall survival in patients with EC, is another 'hot topic' (68-72). Residual disease identifies aggressive, chemoradiation-resistant cancer, with a high potential for metastasis. Currently, no clinical, bio-molecular and imaging tools can be used to predict pCR rate; thus, development of a pCR predictive model is eagerly awaited since it may further improve the current therapeutic strategies of locally advanced EC (73). Recently, FDG-PET has been shown to be accurate in prediction of clinical and histopathologic response to neoadjuvant treatment in adenocarcinomas of the distal esophagus (66).

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