Review Article

Neoadjuvant chemotherapy for locally advanced gastric cancer: the surgeon's role

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Abstract: In Western countries gastric cancer is commonly diagnosed in locally advanced stages. Although locally advanced gastric cancer is still a potentially curable disease, the prognosis is poor and surgery as first approach does not represent the best option. In order to improve survival, today the management of locally advanced gastric cancer is based on a multimodal treatment, including surgery with extended lymphadenectomy and effective chemotherapeutic schedules. The multimodal approach in gastric cancer aims to provide successful combination and cooperation between surgery and medical treatment: today there is current evidence supporting the use of systemic chemotherapy in a perioperative setting. The role of chemotherapy in gastric cancer is constantly evolving in order to improve outcomes and to reduce therapy-associated toxicity. In this paper we analyze the multidisciplinary approach in the treatment of locally advanced gastric cancer, particularly focusing on the surgeon's role in this setting.

Keywords: Adjuvant therapy; chemotherapy; gastric cancer; multimodal treatment; neoadjuvant therapy

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Introduction

Despite incidence and mortality are decreasing, gastric cancer is the 5th most common malignancy diagnosed worldwide and the second leading cause of cancer related death. In Western countries over the past decades, a decline in the incidence of distal stomach cancers was observed, whereas the incidence of the lower esophagus and the gastroesophageal junction adenocarcinomas is still increasing (1,2). The 5-year relative survival for gastric cancer (all stages) is 20% to 25% with a median survival of about 24 months (3,4).

In most cases early-stage gastric cancer is curable by surgical treatment alone, with a 5-year overall survival (OS) rate of 90%. Unfortunately, in the Western world more than half of patients with gastric cancer are diagnosed in locally advanced stages (T3-4 or N+ gastric cancers) (5) and for these patients surgery as first approach does not represent the best option in the management of their disease. Although locally advanced gastric cancer without distant metastasis is still a potentially curable disease, the prognosis is poorer than in early stage disease. The survival outcome of locally advanced tumors is decreased by high unresectability rate at presentation and by high recurrence rate even after radical surgery (6,7).

In order to improve these results, two main strategies were diffused in the management of locally advanced gastric cancer: the extended lymphadenectomy (8,9), and the application of new effective postoperative chemotherapeutic schedules (10,11). Despite these "surgical and medical efforts", prognosis still remains unacceptable for patients with advanced disease (8,10,11). Hence, the rationale of the neoadjuvant approach in gastric cancer aims to provide successful combination and cooperation between surgery and medical treatment. Today there is current evidence supporting the use of systemic chemotherapy in a perioperative setting (before and after surgery), and the role of chemotherapy in gastric cancer is constantly evolving to improve outcomes and to reduce therapy-associated toxicity.

The data used in this review were identified by searches made on MEDLINE, Current Contents, PubMed, and other references taken from relevant original articles (on prospective and retrospective studies) treating about surgery and multimodal treatment for locally advanced gastric cancer.

Only papers published in English until December 2014 were selected. Data from ongoing studies were obtained in December 2014, from the trials registry of the U.S. National Institutes of Health (http://www.clinicaltrial.gov). The citations list was presented according to evidence based relevance (i.e., randomized controlled trials, prospective studies, retrospective series).

Multimodal treatment

In the field of multimodal treatment for gastric cancer there are different possible approaches that vary geographically (12): European clinicians, on the basis of the results of the MAGIC trial (13) and of the French FNCLCC trial (14), are in favor of a perioperative chemotherapy; on the contrary in the U.S., according to the results of the Intergroup 0116 trial (10), patients are treated initially with surgery followed by adjuvant chemo-radiotherapy; finally, adjuvant chemotherapy alone after radical surgery is the preferred option in Japan (11).

Historically the first prospective randomized trial demonstrating a survival benefit of postoperative chemoradiation over surgery alone in advanced gastric cancer was the SWOG/Intergroup 0116 trial (10). This study could show an increased 3-year OS with chemoradiation compared to surgery alone from 41% to 50% (P=0.005). However, it must be notice that in this trial, 54% of patients underwent a limited lymphadenectomy (less than D1), whereas only 10% of patients received an extended D2 lymphadenectomy. Therefore, the administered chemoradiation seemed to primarily reduce loco-regional recurrence, improving survival, by adjusting an inadequate/incomplete surgery (15). In addition, no survival difference between the two treatment arms was demonstrable if considering only a subgroup of patients with D2 lymphadenectomy. Another trial investigated the role of postoperative chemo-radiotherapy in patients with extended D2 lymphnode dissection: the ARTIST trial (16) showed that the addition of radiotherapy to the adjuvant chemotherapy with capecitabine and cisplatin did not significantly reduce recurrence. A subgroup analysis revealed that the adjunct of radiotherapy increased disease free survival in gastric cancer patients with lymphnode metastasis, therefore a subsequent trial (ARTIST II) is ongoing for the study of patients with lymphnode-positive gastric cancer (17).

A large randomized trial in Japan (11) compared adjuvant oral chemotherapy with S-1 to surgery alone, and in this case in both treatment arms a D2 lymphadenectomy was performed. Five hundred and twenty-nine patients received an oral chemotherapy (fluoropyrimidine S-1) over 1 year after surgery, and 530 patients were treated only with surgery. With a reduced risk of nodal and peritoneal recurrences, the 3-year survival was significantly higher in the adjuvant chemotherapy group (P=0.003). Similar results, even if not so evident, were confirmed in the CLASSIC trial: patients with stage II-IIIB gastric cancer who underwent curative gastrectomy (D2 lymphadenectomy) were randomized to surgery alone or postoperative chemotherapy with capecitabine and oxaliplatin (XELOX). The 3-year disease free survival rate was 74% in the adjuvant chemotherapy group and 59% in the surgery alone group [hazard ratio (HR)=0.56; P<0.0001] (18).

In this variety of results, and even if some questions remain open, in Europe the standard multimodal treatment for locally advanced gastric cancer is the perioperative chemotherapy. All advantages of preoperative neoadjuvant chemotherapy emerged by several European randomized phase-III clinical trials: MAGIC, FFCD9703, EORTC 40954 (13,14,19).

In particular, the effectiveness and the superiority of surgery associated to perioperative chemotherapy, compared to surgery alone, were shown in two randomized phase-III studies (MAGIC and FFCD9703). In the MAGIC trial (13) 503 patients with potentially resectable gastric cancer were randomly assigned to perioperative chemotherapy [both preoperative and postoperative with cisplatin, epirubicin and 5-flurouracil (5-FU)] *vs.* surgery alone. The results evidenced statistically significant differences in progression free survival [HR=0.66; 95% confidence interval (CI): 0.53-0.81] and in OS (HR=0.75; 95% CI: 0.60-0.93; 5-year OS 36% *vs.* 23%) in favor of the perioperative chemotherapy arm. Moreover, downstaging (documented by low serosal invasion and low nodal involvement rate) and complete surgical resections (R0) were increased after neoadjuvant chemotherapy. In the two groups the incidence of postoperative complications, mortality rates and hospital stay were similar.

In the FFCD9703 trial (14), 224 patients with resectable adenocarcinoma of the lower esophagus, gastroesophageal

junction or stomach were randomized to either perioperative chemotherapy (cisplatin and 5-FU) plus surgery or surgery alone. In the multimodal treatment arm there were significantly increased curative resection (84% *vs.* 74%; P=0.04), disease free survival (5-year rate: 34% *vs.* 19%; P=0.003) and OS (5-year rate: 38% *vs.* 24%; P=0.02) rates.

However, both studies have been criticized: the recruitment period of 8 years each was considered too long, both trials included also esophageal cancers, the preoperative staging was insufficient, the surgical quality was low with suboptimal lymphadenectomy, and there was a low completion rate of the postoperative treatment. Moreover, in both studies neither a clinical, nor a histopathological evaluation of the response to chemotherapy was performed.

A new study, the EORTC 40954 (19), has been designed to overcome the criticism of the previous trials; however, this study was stopped for slow patients recruitment, it could almost confirm the same short-term results as the other two trials, failing to show a survival benefit for the perioperative chemotherapy arm. The low sample size might explain the lack of survival benefit after perioperative chemotherapy observed in this trial.

The topic of a neoadjuvant/perioperative approach in the multimodal treatment of advanced gastric cancer is today still of great interest and many phase-III randomized clinical trials are ongoing focusing on this issue. Aiming to provide further data related to open problems in the management of advanced gastric cancer, following trials are ongoing today: MAGIC B (United Kingdom National Cancer Research Institute ST03 trial—started in 2007) (20), JCOG 0501 (Japan Clinical Oncology Group Study trial—started in 2005) (21) CRITICS (Dutch Colorectal Cancer Group trial—started in 2006) (22) and PRODIGY (Korean trial—started in 2012) (23).

In our institution, we were involved in the multicentric randomized phase III study ITACA-S 2 that compared the efficacy of a perioperative *vs.* a postoperative chemotherapy or chemo-radiotherapy, in patients with resectable gastric cancer (24). However, this study was stopped for low recruitment, and now we are randomizing patients in a new phase II trial [IRST 151.01 trial: study of preoperative or perioperative docetaxel, oxaliplatin, capecitabine (Dox) regimen in patients with locally advanced resectable gastric cancer (Gastro DOC)] (25). This randomized trial compares perioperative chemotherapy (two cycles Dox followed by surgery followed by other two cycles Dox) *vs.* preoperative chemotherapy (four cycles Dox followed by surgery).

Also several meta-analysis aimed to assess the effectiveness of neoadjuvant chemotherapy in locally advanced gastric cancer analyzing the results of previous clinical trials, but with unclear results. Whereas He (26) failed to show the benefit of neoadjuvant chemotherapy in OS, Li's study (27) demonstrated a minor but significant benefit in patients' survival. This latter result coincided with another meta-analysis by Ge *et al.* (28) that showed that 5-FU-based neoadjuvant chemotherapy has a benefit on the OS of gastroesophageal and gastric cancer patients.

Regardless of the over mentioned published data, a perioperative chemotherapy seems to have many theoretically advantages. This induces European clinicians to prefer this approach in the management of locally advanced gastric cancer.

(I) Chemotherapeutic regimens administered before surgery can be stronger and more intensive, because of a better general condition of the patient before the surgical intervention;
(II) Before surgery there is no surgical alteration of blood and lymphatic vessels, that negatively affects the flow of chemotherapeutic molecules toward the tumor region (important for the chemotherapy-induced cell kill);
(III) The administration of an early chemotherapy could act earlier on micrometastases (29);
(IV) Neoadjuvant chemotherapy may reduce also the contamination of the abdominal cavity by free tumor cells during surgical manipulation;
(V) The downsizing and the downstaging of the tumor after neoadjuvant chemotherapy, allow to achieve increased rates of R0 resections (30,31);
(VI) Neoadjuvant chemotherapy could be seen as an "*in vivo* test" evaluating the applied therapy, and allows consequently to modify the postoperative therapy, according to the individual pathological response (32).

The administration of chemotherapy will be obviously delayed if the first step, in the multimodal approach for advanced gastric cancer, is surgery; this fact has several implication and may affect survival: first of all, micrometastases could evolve to macrometastases if not promptly treated; moreover after surgery the chemotherapeutic dose may be necessarily reduced because the patient is not fit anymore to tolerate a full dose (especially in case of postoperative complications). On the other hand, in the perioperative setting, some surgeon argue that chemotherapy-induced toxicity may lead to increased surgical complications (19,33). In addition, disease progression during neoadjuvant chemotherapy is

another potential trouble for patients who may lose the opportunity for surgery. With respect to point (VI), it must be considered that patients with a good response to chemotherapy, have a significantly improved prognosis, compared to non-responding patients (34). Pathological response is a late assessable parameter, however, an earlier evaluation might be obtained by the analysis of the metabolic response to chemotherapy. The possibility of a reliable early response evaluation and a response prediction seems to represent a very challenging issue (34-39).

The surgeon's role

Even today, in the era of multimodal approach for locally advanced gastric cancer, the surgeon plays a central role in the management of these diseases. In a real and effective multidisciplinary setting, surgical choices and surgical actions are strongly related to other medical treatments like perioperative chemotherapy. This relation between surgical and medical aspects comes out in all steps of the management of locally advanced gastric cancer: (I) before surgery, (II) during surgery and (III) after surgery.

(I) Often the inaccuracy of pretreatment staging represented a relevant bias for the randomized clinical trials on preoperative treatment, negatively affecting the interpretation of therapy results. During the multimodal treatment for locally advanced gastric cancer the role of the surgeon should not be limited to the time of the tumor resection. For a complete pretreatment evaluation of these patients, a staging laparoscopy should always be performed. Staging laparoscopy may reveal positive cytology or even peritoneal implants undetected by preoperative examination in about 20% of the cases, and in some of them it is possible to prevent an unnecessary laparotomy (40-43). After accurate stratification by staging laparoscopy, appropriate neoadjuvant chemotherapy may offer successful results also in patients with positive peritoneal cytology (M+). Some studies reported the outcomes of potentially curative resections following the clearance of peritoneal cytology (conversion from positive to negative after neoadjuvant chemotherapy), however, benefit on the long-term survival remains to be established (44-46).

Moreover, after neoadjuvant chemotherapy, a second look laparoscopy for restaging is needed, directly involving the surgeon in the evaluation of the efficacy of the neoadjuvant treatment; his findings will guide the subsequent steps in the multimodal approach to locally advanced gastric cancer patients.

(II) During surgery, surgical quality and surgical efficiency must always be the highest possible, obtaining R0 resection and extended lymphadenectomy. A D2 lymphnode dissection is considered today the standard surgical treatment, supported by many data showing that, compared with D1 nodal dissection, D2 dissection offers a survival benefit, if performed by well-trained and experienced surgeons (8,47,48). Inadequate surgery causes reduction in survival and could also lead to misinterpretation of the results of the multimodal treatment. Perioperative chemotherapy should not represent a surrogate of insufficient surgery, in fact, perioperative chemotherapy offers its best results only if associated with an effective radical locoregional surgery, showing once again the centrality of the surgeon's role.

(III) After the resective intervention the role of the surgeon will be obviously focused also on the management of the eventually occurring postoperative complications. Some surgeons complain about the possibility of increasing postoperative complications after neoadjuvant chemotherapy (19,33), however, data from the MAGIC trial (13) showed similar postoperative complications, mortality rates and hospital stay both after surgery alone and after surgery with perioperative chemotherapy for locally advanced gastric cancer. Other reported data show that in patients receiving neoadjuvant chemotherapy followed by gastric resection, postoperative morbidity ranges from 23% to 40% and mortality from 0% to 10% (49-56). These findings are similar to reports of morbidity and mortality in patients undergoing gastric resection without neoadjuvant chemotherapy (57-66).

Finally, the surgeon has a relevant role in the multidisciplinary oncological team also during clinical cases discussion: the surgeon's point of view is of primary importance in the discussion of every single case, in order to obtain the best tailored treatment for patients affected by locally advanced gastric cancer.

Conclusions

In conclusion, at least in our geographic area, perioperative chemotherapy is a valid option in the multimodal approach for locally advanced gastric cancer. This option is located in a very complex field where different strategies and different physicians are involved to reach a common goal: to improve patients' survival. Today in Europe chemotherapy for locally advanced cancer is administered preferable in a perioperative setting and neoadjuvant chemotherapy has

been shown to be feasible, does not increase postoperative morbidity and mortality, increases the rate of R0 resection, reduces the incidence of systemic metastases and prolongs survival. The surgeon plays a key role in the multidisciplinary multimodal treatment setting, both during surgery with optimal tumor exeresis and extended lymphadenectomy, and also for fundamental evaluations before and after the intervention. Surgical efficiency should be so high to prevent any misleading interpretation of multimodal treatment: perioperative chemotherapy can never be considered a surrogate of inadequate surgery. Finally, we believe that the up-to-date evidence supports the positive effect of perioperative chemotherapy in locally advanced gastric cancers, even if further studies are still required to determine its best regimen and to develop a response-based neoadjuvant concept.

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