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Surgical issues after neoadjuvant treatment for gastric cancer

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Abstract. – Gastric carcinoma is one of the most frequent malignancies in the world and its clinical behavior depends on the metastatic potential of the tumour. Particularly, lymphatic metastasis is one of the main predictor of tumour recurrence and survival and current pathologic staging systems reflect the concept that lymphatic spread is the most relevant prognostic factor in patients resected with curative intent. This is deducted by the observation that two thirds of gastric cancers in the western world present at an advanced stage, with nearly 85% of tumors accompanied by lymph node metastasis at diagnosis.

To date most therapeutic efforts are directed toward individualization of therapeutic protocols, tailoring the extent of resection integrated by the administration of preoperative and postoperative treatment. The goal of such strategies is to improve prognosis towards the achievement of a curative resection (R0-resection) with minimal morbidity and mortality, with better postoperative quality of life.

A brief review of literature about preoperative therapy for gastric carcinoma will be herein illustrated. The rationale and the general drawbacks of preoperative treatments will be both discussed in order to demonstrate its value in terms of safety and efficacy.

Key Words:

Gastric carcinoma, Preoperative treatment, Antiblastic therapy, Neoadjuvant therapy.

Introduction

To date, faced with the evidence-based validation of multimodal treatments for locally advanced gastric cancer, a surgeon should choose without hesitation whether to postpone immediate tumour exeresis in favor of getting a better chance of obtaining a delayed curative (R0)-resection.

Differently from what has definitively been shown in the multimodal approach for rectal cancer, the concept of "delayed surgery" represents a relatively new concept within the therapeutic options for gastric carcinoma. Studies conducted over the last twenty years have elapsed from the first "pioneering" chemotherapies for patients with non-resectable disease ("induction" therapy)[1-3] to the most recent phase III trials on "neoadjuvant" therapy for resectable neoplasms[4-5]. This extended time period partially explains some scepticism about this treatment option and, even if all these reports shared the common perspective of testing the feasibility and safety of this therapeutic philosophy, a resistance of many surgeons to delay laparotomy still persists.

The history of preoperative therapy for gastric carcinoma will be briefly herein illustrated; the theoretical rationale and the general drawbacks will be both discussed in order to demonstrate, through empirical findings, its value in terms of safety and efficacy. Particular attention will be paid to the clinical implications and the unavoidable consequences of delaying surgery.

Preoperative Therapy

Despite the generally unsatisfying results obtained in the advanced disease setting by surgery alone and the lack of evidence on the efficacy of post-surgical (adjuvant) chemotherapy in stage II-III gastric cancer, the rationale behind preoperative therapy relies primarily on theoretical assumptions supported by laboratory results. In fact, from an experimental view point, it has been demonstrated that surgery itself can stimulate neoplastic proliferation, with consequent shortening of the tumour's doubling time and increased probability of producing a chemo-resistant cellular clone[6-8]. Preoperative antiblastic therapy may reduce the likelihood of such phe-

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nomena and allow an *in vivo* chemosensitivity test, hence facilitating the process of choosing the most appropriate postoperative regimen. Furthermore, the preoperative approach has two distinct advantages: (1) increased compliance due to an undoubtedly better performance status in those patients who are not burdened by surgical complications and consequent nutritional impairment; (2) intact vascularization of the tumour bed, undamaged by operative manipulation. The double goal of obtaining with tumour downstaging also the elimination of hidden micro-metastases has the potential of increasing the achievement of a truly "curative" (R0) delayed surgical procedure.

Together with the aforementioned theoretical benefits, the potential risks of delaying surgery in favor of preoperative treatment in cases of resectable locally advanced gastric cancer have also been extensively discussed in the recent literature[9]. The initial objections focused on the patient's performance status. On one hand, antiblastic therapy may be better tolerated and consequently may be more efficient in a presurgical phase; on the other hand, the almost unavoidable side effects of preoperative treatment could have negative consequences on the patient's general status, thus influencing the surgical outcome. In fact, the preliminary results of the first phase II trials on preoperative therapy warned of a possible increase in perioperative morbidity and mortality rate as a consequence of the peritumoral fibrotic reaction to the therapy itself[9].

Apart from the surgical act and its short term results, the ethical uncertainties related with the decision to delay surgery are mainly linked to the possibility of tumor progression during the course of treatment. Up to the early 1990s surgical resection was considered to be the only effective treatment for gastric cancer and the idea to postpone the surgical timing for gastric carcinoma (a tumor traditionally identified for its negligible chemo/radiosensitivity) naturally encountered strong resistances. Today, the continuous amelioration of therapeutic schedules, along with the evidence of the recently published data, have extended the acceptation of the neoadjuvant philosophy and have diffused the will to "test" the proposal of new preoperative treatments. This acceptance has further been facilitated by the fact that tumour progression to a non-resectable stage during pre-surgical treatment has become less and less frequent.

From "Induction" to "Neoadjuvant" Therapy

The efficacy and the possible applications of chemotherapy in patients affected by advanced stage gastric cancer have been investigated since the late 1970s[1-3]. However, encouraging results were not reported until the early 1990s; in two independent studies conducted on patients with non-resectable disease (at the time of the explorative laparotomy) chemotherapy led to subsequent resection in 40-50% of cases, with a total median survival gain of 18 months[10-11]. These preliminary observations encouraged the introduction of "neoadjuvant" preoperative chemotherapy protocols for potentially resectable, locally advanced gastric cancer[12-20], but the results of these first trials were questionable, mainly due to some methodological pitfalls. Firstly, following an inaccurate preoperative staging, several Authors have based patients recruitment on non-homogeneous criteria, often assembling patients with a clear demonstration of locally advanced gastric cancer and others with uncertain stage, without fixed distinction between resectable and non-resectable tumours. Apart from non-homogeneous methods applied for patients recruitment, the use of different chemotherapeutic regimens (with or without the adjunct of postoperative treatments), non-standardized surgery or even surgery of questionable quality, missing or poorly detailed response evaluation criteria, all represent other biases of the aforementioned trials.

Despite these concerns, analysis of the data provided by these studies did not suggest that the concept of delayed surgery was to be discarded. Indeed, only in about 1% of cases after neoadjuvant therapy the deterioration of the patients' general condition avoided the possibility of a subsequent surgical procedure. Moreover, postoperative morbidity and mortality rates following preoperative chemotherapy were similar to those observed in cases treated by surgery alone.

On the other hand, it must be said that the first results in terms of tumour progression during neoadjuvant chemotherapy have not been encouraging. While Rougier et al.[18] reported an incidence of 3% of patients who became non-resectable after neoplastic progression, Ajani et al.[13] observed signs of progression sufficiently severe as to preclude subsequent surgery in 15% of cases.

In order to avoid the biases of the cited studies, in 1993 the Dutch Gastric Cancer Group

started the first controlled randomized trial on the exclusive preoperative use of chemotherapy for gastric cancer. The therapeutic regimen used was FAMTX (5-fluorouracil, doxorubicin and methotrexate), considered at that time to be the gold standard for adenocarcinoma of the stomach. Even for the Dutch FAMTX trial some biases have been suggested (inaccuracy of the staging procedure with "optional" use of computed tomography and laparoscopy and inadequacy of the extension of lymphadenectomy), while both the short and long term results reported by the Authors have been discouraging[21-22]. Specifically, a high tumor progression rate during treatment (36%) was reported along with a reduced percentage of curative resections (56% *vs.* 62%) and a reduced median survival (18 months *vs.* 30 months) compared to non-treated patients.

The design of the neoadjuvant chemotherapy protocol tested by our study group dates back to the same period. From 1996 to 2000, we treated 39 patients affected by resectable locally advanced gastric cancer, according to the EEP (etoposide, epirubicin and platinum) regimen and, more recently, according to the ECF (epirubicin, platinum and 5-fluorouracil) regimen. Based on the high accuracy of laparoscopy, on the standardization of the surgical treatment (D2-gastrectomy) and on a thorough evaluation of the pathologic response, our study suggested that the neoadjuvant approach was effective, even if with the limitations of a study with a single treatment arm. With regards on the issue about delaying surgery, our preliminary results after 3 years of follow-up on 25 patients treated by the EEP regimen were reassuring[23]. In no case preoperative treatment severely deteriorated patients general conditions; the possibility to carry out subsequent surgery was never avoided by tumour progression; there was no postoperative mortality, with an acceptable morbidity rate (25%). In this series, in spite of the absence of cases showing a complete pathologic response, preoperative chemotherapy allowed to achieve a considerable R0-resection rate (83%), with a high survival rate after a prolonged follow-up (83% at 12 months, 58% at 36 months, 46% at 84 months); these results are consistent with those reported with a similar schedule by Schumacher et al.[24] and, following the introduction of 5-fluorouracil in conjunction with epirubicin and cisplatinum, have been further improved, both in terms of pathologic response and overall survival rate[25-26].

Since the late 1990s, ambitious phase III trials have been designed in order to give a definitive demonstration of the efficacy of preoperative treatments. The adoption of strict selection criteria made patients selection so difficult that some studies were prematurely stopped (EORTC trial of 1999) while others are progressing very slowly (SIACR trial of 2005). Thus far, only the final results of the MAGIC trial[4] (started in the United Kingdom in 1994) and the FFCD 9703 trial[5] (started in France in 1996) have been published. These two studies – both with a high level of evidence – stand for the efficacy of neoadjuvant (or, more specifically, perioperative) chemotherapy in terms of survival rate (36% *vs.* 23%, estimated at 5 years for MAGIC; 38% *vs.* 24% estimated at 5 years for FFCD 9703). A detailed analysis is not yet possible for the FFCD 9703 trial due to the uncomplete publication of the data. With reference to the MAGIC trial, published by Cunningham et al, many Authors have expressed some criticism. Apart from the persistence of methodological biases related to poor staging accuracy (based only on computed tomography), to sub-optimal surgery (rate of D1-gastrectomy >15%) and to lack of precise criteria for response evaluation, the debate on the short term results of delayed surgery remains open. Along with a significantly higher curative resection rate among the treated group than in the surgery alone group (79% *vs.* 70%), obtained without registering any increase in perioperative morbidity and mortality, the Authors have reported a percentage of non-resected patients after neoadjuvant treatment (6%) which is certainly lower than previous results, but not fully negligible. With respect to delayed surgery, it is our opinion that the high reported rate (~14%) of exploratory laparotomies in this study is less worrisome, as it affects the control group more than the treatment group (17% *vs.* 13%).

Following the results of chemoradiotherapy reported in the postoperative setting by the SWOG 9008/INT-0116 trial[27], the integration of chemotherapy with radiation applied in the preoperative phase is one of the latest and most intriguing updates. Recently, published phase II studies have verified the efficacy of such therapeutic approach in terms of complete pathologic response (up to 30% in some series) and increased long term survival[28-29]. However, also under these circumstances, the concept of delayed surgery does not fully satisfy the above-specified safety requirements: even if a signifi-

cant increase in postoperative morbidity and mortality was not documented, Fujtani et al[29] have reported that >15% of patients treated with neoadjuvant chemoradiotherapy did not undergo surgical resection for tumour progression and stated therefore that: "preoperative chemoradiation can be performed safely in patients with gastric or gastroesophageal cancer with careful consideration of added risk".

Conclusions

Although still in need of further data on the definitive role of neoadjuvant chemoradiotherapy, the literature analysis on the results of the preoperative chemotherapy in the multimodal treatment of gastric adenocarcinoma is encouraging, with special regards to the possibility of delaying surgery. It is demonstrated that postponing resection in favor of a systemic treatment does not preclude patients from the benefits of a potentially curative delayed exeresis, without worsening surgical outcomes. Still, the event of tumour progression during therapy remains possible in a small number of cases. This issue warrants further investigations, which should be especially addressed towards understanding the real magnitude of the problem and – in order to reduce its incidence – towards perfecting pretreatment staging, improving biomolecular characterization of each neoplasm and consequently increasing accuracy in the selection of those patients who will certainly benefit from a preoperative treatment. To date, disease progression remains the only aspect of delayed surgery which authorizes reluctance on the multimodal preoperative approach to gastric cancer. In rectal adenocarcinoma, the exceptionality of tumor progression during the course of preoperative treatment has contributed to the worldwide validation of the neoadjuvant chemoradiotherapeutic approach and currently the debate is addressing on "how long" surgery should be delayed in order to favor downstaging. In the next future we should expect the same process for gastric cancer, even at the cost of some additional risk in presence of surgical procedures that do not provide easy methods to protect a delicate anastomosis, provided that the published evidence needed to reach this goal will be improved and developed further.

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