

Advanced stage gastric cancer and neoadjuvant chemotherapy

Our experience in surgical resectability



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Paolo Del Rio, Marco Rocchi, Paolo Dell'Abate, Francesca Pucci*, Cristian Mazzetti, Mario Sianesi

Unit of General Surgery and Organ transplantation, University Hospital of Parma, Italy

*Unit of Oncology, University Hospital of Parma, Italy

Advanced stage gastric cancer and neoadjuvant chemotherapy. Our experience in surgical resectability

BACKGROUND: *In the last years the incidence of gastric cancer is changed as the complementary therapy to surgical treatment especially about the advanced stage gastric cancer.*

MATERIALS AND METHODS: *We have analyzed the patients treated at Unit of General Surgery and Organ Transplantation of University Hospital of Parma from 1/1/2009 to 30/9/2012. The cases surgically treated after neoadjuvant therapy were compared to patients not treated with neoadjuvant therapy. The choice to neoadjuvant therapy was decided on locally advanced disease and low comorbidity.*

RESULTS: *The cases surgically treated were 93, in 9 cases were treated with neoadjuvant therapy. The histotype in neoadjuvant cases was an intestinal type 3 cases, a diffuse type 3 cases and no classifiable sec. Lauren 3 cases. The average of number of lymphnodes removed was 22.5 in total gastrectomy and 15.7 nodes in partial gastrectomy. On RECIST criteria the response to neoadjuvant chemotherapy were in 2 cases a partial response and in the others 7 cases the disease remained stable.*

CONCLUSION: *In our experience as in literature, the neoadjuvant therapy can reduce staging, increases the R0 resection, should proposed in young patients with low comorbidity.*

KEY WORDS: Gastric cancer, Gastrectomy TNM, Neoadjuvant chemotherapy

Introduction

Stomach cancer represents over 90% of malignant gastric tumors of epithelial origin. In the world the incidence of gastric cancer changes considerably. There are

maximum values in Japan (among males 80-90 new cases/100,000 inhabitants/year, among females 35-40 new cases/100,000 inhabitants/year) China, Russia and the Andean-South American's countries where gastric cancer is the leading cause of death for tumor; and minimum values (less than 4 new cases/100,000 inhabitants/year) in Australia and North America. Globally the annual frequency is approximately 930,000 new cases/year with a male/female ratio between 1.5 and 2; the most affected age is the sixth/seventh decade of life ^{1,2}. Italy is in an intermediate zone with annual incidence rates of approximately 38 new cases/100,000 inhabitants/year for males and 25 new cases/100,000 inhabitants/year for females, the highest incidence occurs in the north-center's regions,

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Correspondence to: Paolo Del Rio MD, Unit of General Surgery and Organ transplantation, University Hospital of Parma, Via Gramsci 14, 43100 Parma, Italy (e-mail: paolo.delrio@unipr.it)

particularly Lombardy, Tuscany, Lazio, Friuli and Emilia Romagna, where Parma is one of the most affected provinces. In the last decades gastric cancer is decreasing in terms of both incidence and mortality. The reduction affects the intestinal type, more related to environmental risk factors, but the diffuse type stayed almost unchanged³. About the treatment, the evolution of the preoperative diagnosis for an ever more correct and reliable staging has allowed us to develop therapeutic protocols involving the use of neoadjuvant therapies.

The chemotherapy schemas used in the treatment of metastatic gastric cancer and locally advanced unresectable, were applied to another setting of patients: in locally advanced gastric cancer, but potentially resectable, so in the context of neoadjuvant chemotherapy⁴⁻⁸. One of the most widely used schemes is the one proposed by Cunningham in the Magic Trial of 2006^{9,10}. This provides a perioperative treatment with the execution of 3 preoperative cycles using 3 drugs: Epirubicin, Cisplatin and 5-Fluorouracil (ECF), followed by another three cycles after surgery⁹. The cycles are repeated every 21 days, and the drugs are administered in this way: on day 1 proceeds with the administration of epirubicin, at a dose of 50mg/m², and cisplatin at a dose of 60 mg/m²; instead the 5-FU is given in a continuous infusion from day 1 to day 21 at a dose of 200 mg/m². During treatment may appear important toxic effects: in particular we can differentiate an hematologic toxicity, which may manifest through the appearance of neutropenia, leukopenia, thrombocytopenia, and anemia; and non-haematological toxicity, mainly gastrointestinal (nausea, vomiting, diarrhea, mucositis), renal and neurological⁹. The toxicities may occur with altered gravity's patterns (G1, G2, G3, G4). During treatments these possible toxicities are prevented or monitored for timely treatment. Treating patients with this perioperative chemotherapy regimen Cunningham showed not only the absence of additional complications but above all a survival advantage⁹. Compared to patients treated only with surgery, which remains the primary treatment option in gastric cancer, there is at 5 years after surgery an improved survival of the 13.3% (OS 5y 36.3% in 250 patients treated with perioperative chemotherapy vs 23% in 253 patients treated only with surgery)⁹. The same authors in a different study on advanced disease have demonstrated the superposition of the results of the ECF schema, with different "variants": Oxaliplatin instead of Cisplatin (EOC), Capecitabine ("Xeloda") instead of 5FU (ECX), or the substitution of both (EOX)¹¹⁻¹³. Due to the lower degree of toxicity, these modified schemes are sometimes prefer to the classic ECF, especially in patients with comorbidities. Another important study in the chemotherapy of advanced disease for gastric cancer was the ToGA trial¹⁴. This study is based on the evidence that in approximately 20% of cases of gastric cancer is possible to identify an amplification of the HER-2 receptor (human epidermal receptor-2) a protein receptor con-

sisting of 4 extracellular domains, a transmembrane domain and an intracytoplasmatic domain with tyrosine kinase activity. Several studies showed the importance of investigating the presence of this amplification not only for a prognostic purposes, but also for a therapeutic purposes¹⁵⁻¹⁷. The presence of amplification allows the use of new molecular drugs which have as target precisely the HER-2 receptor. ToGA study showed that in patients with HER-2 amplification the association of traditional chemotherapeutic drugs (Cisplatin and 5-FU or Capecitabine) with monoclonal antibodies directed against this receptor ensure best results in terms of response to the treatment and the survival. Trastuzumab (monoclonal antibody directed against HER-2) is considered as an added drug to fight against gastric cancer (in addition to the breast one). Moreover, ToGA study's data concern only patients with metastatic disease, and nowadays it is only for this subset of patients that the drug may be used. With regard to the response to chemotherapy we see that the most followed criteria are the RECIST (Response Evaluation Criteria in Solid Tumor) which describe the behavior of the tumor in response to treatment. These criteria distinguish neoplastic lesions in: Target lesions and Non Target lesions¹⁸. Belong to the Target definition all those injuries accurately measurable by methods such as CT and Rx, which diameter must therefore be at least 10mm; are excluded from this definition cystic lesions, confluent lesions and lesion appeared in previously irradiated areas. The Non Target lesions are cystic lesions, confluent lesions or those arising in previously irradiated areas, but also all those not accurately measurable tumor lesions such as ascites, pleural or pericardial effusions, meningeal involvement, lymphangitis. The lymph node involvement is included in Target injury when they have the longer diameter > 15mm. If the diameter is between 10 and 15mm they are included in Not Target lesions, while if it's < 10mm they are considered non-pathological. So based on RECIST criteria, using imaging techniques such as CT scan and MR, we talk about:

For Target lesions:

- Complete Response: disappearance of all Target lesions;
- Partial Response: at least a 30% decrease in the sum of diameters of Target lesions;
- Progressive Disease: at least a 20% increase in the sum of diameters of Target lesions;
- Stable Disease: reduction or increase less than the limits listed above.

For Not Target lesions:

- Complete Response: disappearance of all Non Target lesions;
- Progressive Disease: unequivocal progression of Non Target lesions;
- Stable Disease: persistence of one or more Non Target lesions.

TABLE I - Preoperative assessment of the patient being considered for gastrectomy.

Tests useful in the preoperative evaluation of the patient being considered for gastrectomy:

Biochemical tests
Chest x-ray
Ecg
Esophagogastroduodenoscopy (EGDS)
CT Thoracic-abdominal
Tumor markers
Endoscopic ultrasonography
Laparoscopy

The criteria to be able to define not only a complete response, but also a partial response, are very strict. Therefore is important to emphasize that, in many cases of gastric carcinoma treated with neoadjuvant chemotherapy and labeled as "stable" to restaging, there may be a reduction of the volume of the primary tumor, but also of the nodal locations, although they aren't so important to be classified as "response" according to the RECIST criteria. Some studies underlines that in at least 22.2% of cancers treated with preoperative therapy we can have a more or less significant regression of the tumor, especially on the T parameter ¹⁹. Other authors underline that the carcinomas localized in the upper third of the stomach, especially if intestinal type, are those that more easily go to regression after neoadjuvant treatment ²⁰. It is possible to predict the response to neoadjuvant treatment on various clinicopathological variables, as tumor's size and the differentiation ¹⁸. About the use of neoadjuvant chemotherapy we report our personal experience.

Materials and Methods

We analyzed patients treated at the Unit of General Surgery and Organ Transplantation of University Hospital of Parma from 01/01/2009 to 09/30/2012 with

subtotal gastric resection or total gastrectomy for gastric cancer. The patients were evaluated preoperatively according to a protocol study shown in the table (Table I) We highlighted the cases treated after neoadjuvant chemotherapy in order to verify the possible association of the median age, adverse events, survival, operability criteria. This group was compared with cases not subjected to neoadjuvant chemotherapy in the same time. In the second group we gave particular attention to the histotype and preoperative staging in addition to the general characteristics of patients (sex, age, type of surgery).

Results

We treated with surgical resection, for primitive gastric cancer, 93 patients from 01/01/2009 to 09/30/2012. In 9 cases we treated the patients, before surgery, with neoadjuvant chemotherapy and in 84 cases we have immediately choose the surgery. The choice to neoadjuvant chemotherapy was decided for those patients with locally advanced disease (T3-T4, N+) and did not show significant comorbidities. The group of patients treated immediately with surgery consisted of 51 males and 33 females with a median age of 76.5 years (range 54-93). 45 patients (53.6%) were subjected to subtotal gastrectomy, 39 patients (46.4%) to total gastrectomy. All patients were staged according to the 7th edition of the TNM proposed by AJCC (2010). The histotype was an intestinal-type adenocarcinoma 49 cases (58.3%), an diffuse type in 19 cases (22.6%) mixed (intestinal/diffuse) type 13 cases (15.5%), and 3 cases (3.6%) were not classifiable according to Lauren. In 14 cases we found Early Gastric Cancer (16.7%): 4 M-type (4.8%) and 10 SM type (11.9%). The histotype in neoadjuvant cases was an intestinale type 3 cases, a diffuse type 3 cases and in others 3 cases no classifiable sec.Lauren.

The average number of lymph nodes removed after total gastrectomy was found to be equal to 22.5, that one after partial gastrectomy equal to 15.7. The characteristics of patients treated with neoadjuvant therapy are reported in Tables II-III-IV.

TABLE II - Patients treated with neoadjuvant chemotherapy

Patient	Date of birth	Sex	Age at diagnosis	Symptomatology	Tumor side
B.R. (case 1)	10/29/1963	M	47 (1/2011)	weight loss	cardias with extension to the corpus
V.R. (case 2)	6/23/1946	M	65 (11/2011)	weight loss	corpus
C.A. (case 3)	04/01/51	F	58 (6/2009)	weight loss, heartburn, dysphagia for solids, dyspepsia	cardia with extension to the esophagus
R.W. (case 4)	4/30/1946	M	62 (11/2008)	heartburn	fundus-corpus
R.A. (case 5)	02/02/67	M	44 (1/2012)	heartburn, dyspepsia, vomiting	antro-pyloric
P.A. (case 6)	10/08/37	M	73 (1/2011)	weight loss	cardia with extension to the corpus
R.C. (case 7)	11/06/58	F	52 (12/2010)	weight loss, abdominal pain	fundus-corpus
C.A. (case 8)	12/24/1953	M	56 (4/2010)	weight loss, heartburn, dysphagia	cardia with extension to the corpus
F.R. (case 9)	7/28/1960	F	49 (1/2010)	weight loss, heartburn	corpus

TABLE III - Patients treated with neoadjuvant chemotherapy

Patient	Neoadjuvant chemotherapy	Neoadjuvant toxicity	Response to chemotherapy: RECIST criteria
B.R. (case 1)	ECF 3 cycles	well tolerated	stable disease
V.R. (case 2)	1st cycle CF, 2nd and 3rd cycles ECF	well tolerated	stable disease (max diameter 62 vs 81)
C.A. (case 3)	ECF 3 cycles	no significant toxicity (subjectively poorly tolerated)	stable disease
R.W. (case 4)	ECF 3 cycles	well tolerated	Partial response ("marked reduction of the eteroplastic process (20mm vs 35mm), essentially disappearance of the big nodular lesions in the adjacent greater omentum (42x34mm), there are still two small nodules of 15 and 9 mm. Almost disappeared even those of the omental bursa")
R.A. (case 5)	ECF 3 cycles	haematological toxicity (Hb 8.5g/dl; Plt 56.000; Wbc 1860), Gastrointestinal toxicity, anorexia/weight loss of 15 kg)	stable disease (tumor's diameter 14vs 16 mm, lymph nodes' diameter: 8 vs 11mm vs 15mm-9-10 vs. 13mm)
P.A. (case 6)	EOX 3 cycles (preferred to the ECF because less toxic, more suitable to the age of the patient)	well tolerated	stable disease (reduction of wall thickening at the level of the cardia)
R.C. (case 7)	1st and 2nd cycle oxaliplatin/capecitabine (for refusal of the patient to use drugs that bring to alopecia and infusion therapy), 3rd cycle FOLFOX (the patient could not tolerate oral therapy with capecitabine)	Toxicity capecitabine	stable disease
C.A. (case 8)	ECF 3 cycles	well tolerated	stable disease (reduction of wall thickening of the fundus and corpus (22 vs. 25mm) reduced both in number and in size, the regional multiple enlarged lymph nodes (the largest of which measures 23 vs 41mm of the previous check)
F.R. (case 9)	ECF 3 cycles	well tolerated	Partial response (reduction of the gastric lesion size, reduced regional lymphadenopathy site that currently have no larger than a centimeter vs 20mm, 16mm, 18mm, 23mm).

About the neoadjuvant treatment, 6 patients were treated with 3 cycles of ECF; 1 patient at a 1st cycle of CF and 2 cycles of ECF; 1 patient at 3 cycles of EOX (more compatible for the age and comorbidities); 1 patient at 2 cycles of OX (her refused drugs that bring to alopecia and infusion therapy) and a 3rd cycle of FOLFOX. In 6 cases of 9 neoadjuvant therapy was well tolerated. We highlighted one case of haematological (Hb 8.5 g/dl, Plt 56000; WBC 1860), and gastrointestinal (anorexia, weight loss of 15 kg) toxicity, 1 case of Capecitabine toxicity (GI) and one case poorly tolerated.

The response to neoadjuvant chemotherapy was analyzed according to the RECIST criteria : in 2 cases we obtained a partial response, in the remaining 7 cases, the disease remained stable. In case number 4 we observed a significant efficacy of preoperative chemotherapy (Fig. 1) We carried out, immediately after finishing neoadjuvant

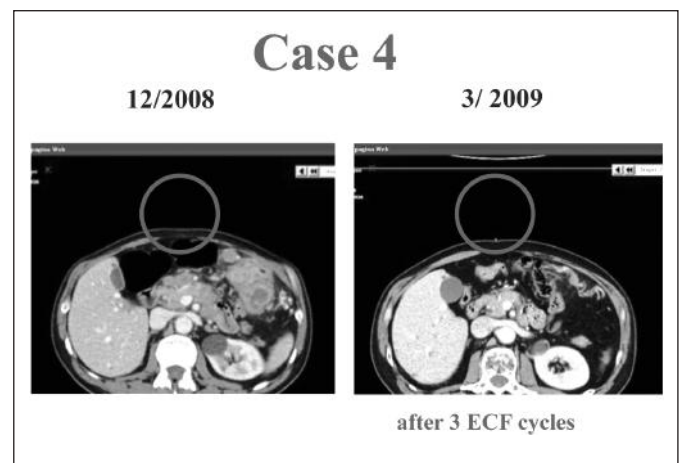


Fig. 1 Response to chemotherapy (case 4).

TABLE IV - Patients treated with neoadjuvant chemotherapy

Patient	Surgery	LND removed	Staging TNM (sec AJCC 2010)	Follow up
B.R. (case 1)	30/05/2011 total gastrectomy + lower esophagectomy	37 (27 metastatic)	yp T3 N3b (27/37):STAGE IIIB	TC 5/2012: "disease progression to lymph nodes, liver, adrenal and left skeletal."
V.R. (case 2)	16/02/2012: total gastrectomy + distal pancreatectomy + splenectomy	28 (1 metastatic)	yp T4b N1 (1/28): STAGE IIIB	TC 6/2012: "solid tissue surrounding the celiac axis (diameter 24mm) compatible with persistent disease."
C.A. (case 3)	30/11/2009: partial gastrectomy + subtotal esophagectomy	54 (0 metastatic)	yp T4a N0 (0/54): STAGE IIB	TC 8/2012: "NO signs of anastomotic recurrence, NO secondary localizations, NO enlarged lymph nodes"
R.W. (case 4)	2/04/2009: total gastrectomy + splenectomy	9 (0 metastatic)	yp T3 N0 (0/9): STAGE IIA	TC 4/2012: "NO recurrence of disease"
R.A. (case 5)	1/06/2012: PALLIATIVE gastroenterostomy (peritoneal carcinomatosis at laparotomy)		STAGE IV	TC 7/2012: "increased eteroplas- tic thickening of the corpus /antrum (47 vs. 38), peritoneal carcinomatosis, increase in the size of lymph nodes"
P.A.(case 6)	3/05/2011: total gastrectomy + splenectomy	23 (3 metastatic)	yp T3 N2(3/23): STAGE IIIA	TC 3/2012: "NO recurrence of disease"
R.C. (case7)	NO surgery			died 7/2011
C.A. (case 8)	31/08/2010: total gastrectomy + splenectomy	25 (22 metastatic)	yp T3 N3b (22/25): STAGE IIIB	died 9/2011
F.R. (case 9)	16/06/2010 : total gastrectomy + distal pancreatectomy + splenectomy	23 (7 metastatic)	yp T3 N3a (7/23): STAGE IIIB	died 11/2010

treatment, in 6 cases a total gastrectomy with 5 splenectomy and 2 distal pancreatectomy associated, in one case a partial gastrectomy, and in one patient a palliative gastroenterostomy for peritoneal carcinomatosis. In a case the patient was not surgically treated.

The histopathological staging is shown in the tables III-IV with the cycles of neoadjuvant therapy and the follow up.

Discussion

Gastric cancer is the 4th tumor for incidence and the second leading cause of cancer death worldwide, with over 930,000 new diagnoses and 700,000 annually deaths¹. In the last decade we have know an extreme variability of therapeutic approaches especially as regards the treatment of stages IIB-III²¹⁻²⁵. The surgery is still the first treatment performed but the literature suggest the

use of neoadjuvant therapies. Sherman et al. have shown that the use of neoadjuvant therapy is mainly influenced by the location of the primary tumor: patients with a tumor localized at the fundus or at the cardia are more predisposed to a neoadjuvant chemotherapy¹. In our experience the proximal side was present in 6 of 9 cases treated with neoadjuvant therapy. The difference in median age between the two groups: 76.5 years in the group immediately treated with surgery, 56.2 years in patients receiving preoperative chemotherapy. Sherman et al., analyzing data taken from the American cancer registry, show that patients who were predisposed to systemic therapy, adjuvant and /or neoadjuvant, were of a younger median age, male, with low comorbidity and income greater than or equal to \$ 46,000/ year¹. In our experience the average of the removed lymph nodes in the two groups was comparable, and in both groups there are sporadic cases in which the number of lymph nodes removed is less than 15, considered the minimum

number for a correct staging. Others authors have identified that the lymphadenectomy is correct if the nodes are more than 25²⁶. If we analyze the data on the few cases examined we highlight that:

- 2 cases N0, respectively, after 38 and 41 months of follow up, don't show a recurrence of disease;
- the N1 patient after 7 months shows persistent disease;
- the N2 patient after 14 months doesn't show a recurrence of disease;
- about 3 cases N3 one, after 12 month of follow up, presents a progressive disease, while the other two died respectively after 17 and 10 months of follow up;
- about 2 patients at stage IV disease one, after 6 months of follow up, shows peritoneal carcinomatosis, and the other died after 7 months of follow up.

In our recent study, considering the gastric carcinomas treated in our department from 2000 to 2007, we highlighted that the N1 show after 60 months a survival just over 20% of cases, the N2 just under 10% of cases, while the N3 were completely occasional²⁷. Considering the node-ratio we have also shown that positive lymph nodes is the most negative prognostic factor^{26,28}. These data are agree with the literature as well as data of the cases treated with neoadjuvant therapy. We must remember how the Magic Trial has shown that preoperative chemotherapy, based on ECF or similar protocols, as demonstrated by the REAL study, increases survival compared with surgery alone⁹. The same was also demonstrated by FNLCC FFCD trial that compared patients treated only with surgery with patients treated with preoperative (2 cycles of CF) and postoperative (4 cycles of CF) chemotherapy, showing a best survival in patients treated with systemic therapy²⁷. In conclusion, according to actually available data, we can say that today neoadjuvant chemotherapy in gastric cancer appears as a treatment: feasible, that can reduce staging, that increases the percentages of R0 resection, that does not increase postoperative complications, that increases the chances of survival, that should always proposed as advice in stages 2 and 3 particularly in young patients with low comorbidity, that increases the number of treated patients due to the fact that patients tolerate better chemotherapy before the gastrectomy.

Riassunto

BACKGROUND: Negli ultimi anni l'incidenza di carcinoma gastrico si è modificata così come si è modificata l'indicazione all'uso di terapie complementari alla terapia chirurgica nel carcinoma gastrico avanzato.

MATERIALI E METODI: Abbiamo analizzato i pazienti trattati dall'Unità operative di Chirurgia generale e Trapianti d'Organo dell'azienda Ospedaliera Univeritaria di Parma dal 1/1/200 al 30/9/2012. I casi trattati chirurgicamente dopo terapia neoadiuvante sono stati correlati ai casi

non sottoposti a terapia neoadiuvante-la scelta di una terapia neoadiuvante è stata decisa in base alla presenza di malattia localmente avanzata ed alla presenza di bassa comorbidità.

RISULTATI: I casi trattati chirurgicamente sono stati 93; in 9 casi sono stati trattati con terapia neoadiuvante. Gli istotipi nei casi sottoposti a terapia neoadiuvante sono risultati in 3 casi di tipo intestinale, in 3 casi di tipo diffuso ed in altri 3 casi non classificabili sec.Lauren. La media dei linfonodi asportati è stata 22,5 nella gastrectomia totale e 15,7 linfonodi nella resezione gastrica parziale. Secondo i criteri RECIST la risposta alla chemioterapia neoadiuvante è stata in 2 casi una risposta parziale e negli altri 7 casi la malattia è rimasta stabile.

CONCLUSIONI: Nella nostra esperienza così come in letteratura, la terapia neoadiuvante può ridurre la stadiazione, aumentare la quota di R0, potrebbe essere proposta a pazienti giovani con bassa comorbidità.

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