# Neoadjuvant chemotherapy and ongoing-trials

Domenico D'Ugo, Alberto Biondi

*First General Surgery Unit, Department of Surgery, Catholic University, Rome A. Rome, Italy.*

## Neoadjuvant chemotherapy and ongoing trials

AIM: *The history of preoperative therapy for gastric carcinoma was outlined here to demonstrate its value in terms of safety and efficacy.*

MATERIAL OF STUDY: *The data collected in this review were obtained from studies found in PubMed using the search terms "preoperative chemotherapy", "preoperative radiotherapy", "preoperative chemoradiotherapy", "neoadjuvant treatment", and "gastric cancer". Only papers published in English language between January 1970 and January 2010 were selected.*

RESULTS: *Studies conducted over the last twenty years have progressed from the first "pioneering" chemotherapies for patients with non-resectable disease ("induction" therapy) to the most recent phase III trials of a "neoadjuvant" therapy for resectable gastric neoplasms.*

DISCUSSION: *Several clinical trials of pre-operative chemotherapy in the management of gastric cancer have been attempted. Despite needing further data regarding the definitive role of neoadjuvant therapy, the results of preoperative chemotherapy in the multimodal treatment of gastric adenocarcinoma are encouraging since the treatment increase the likelihood that a truly "curative" (R0) delayed surgical procedure can be achieved. Owing to the results of last randomized phase III studies, neoadjuvant chemotherapy for locally advanced resectable gastric cancer has become a level I evidence.*

KEY WORDS: Gastric cancer, Neoadjuvant chemotherapy, Preoperative treatments

## Introduction

Despite an incidence rate that has steadily declined over the past several decades, gastric carcinoma is one of the most frequent malignancies in the world [1].

Early dissemination of the disease through the lymphatic system, blood, and peritoneum has limited optimal surgery as a cure, except in patients with early stage cancers. In Japan and Korea, the introduction of screening for gastric cancer has been shown to improve early detection, and almost half of newly diagnosed patients are detected at an early stage [2]. Due to the lower disease incidence rate, this strategy has not been deemed cost-effective in Europe or North America. Consequently, two-thirds of gastric cancers in the Western world present at an advanced stage, with lymph node metastasis at the time of diagnosis [3].

Numerous attempts have been undertaken to improve clinical outcomes tailoring the extent of surgery and integrating it with the administration of pre-operative and/or post-operative treatment. In the last twenty years, three different modalities of adjuvant (pre- and post-operative) therapy have been proven to be effective by large-scale

*Correspondence to: prof. Domenico D'Ugo, FACS,1st General Surgery Unit, Department of Surgery, Catholic University of Rome, Largo A. Gemelli 8, 00168 Rome, Italy (e-mail: ddugo@rm.unicatt.it)*

randomized trials. These include post-operative chemoradiation therapy (Unites States INT-0116 trial)[4], post-operative single-drug chemotherapy (Japanese ACTS-GC trial) [5] and peri-operative three-drug combination chemotherapy (European MAGIC trial) [6]. Since the publication of these trials, surgery alone is no longer considered the standard treatment for patients with resectable locally advanced forms of gastric cancer, and the concept of radical resection needs to take into account the fact that R0-resection is not an exclusively surgical target. In this article we will report the rationale and the state of the art of preoperative neoadjuvant therapy in the light of new evidences and modern perspectives.

## Neoadjuvant treatment: theoretical rationale

The concept of pre-treating the tumor before administering the main therapeutic procedure has definitively led to higher curative resection rates in several tumors (e.g. rectum, breast). As regards gastric adenocarcinoma, surgical resection remains the mainstay of curative treatment and pre-operative therapy appears to be justified by similar advantages, with some drawbacks [7].

*Biological rationale:* a) pre-operative therapy can downstage the primary gastric tumor and potentially improve the likelihood of a curative R0 resection; b) the administration of systemic therapy or radiation before surgical procedure gives the theoretical advantage of treating an untouched cancer (lack of treatment induced resistance), with intact vessels and without fibrotic remodeling of the tumor bed following surgical removal; c) the behaviour of gastric tumors implies the possibility of micrometastatic disease at the time of presentation, which is the main cause of a high failure rate. Neoadjuvant initiation of systemic therapy is targeted on these micrometa¬stases, being administered when the cell growth fraction is high and the total tumor volume is relatively low.

*Upfront randomization:* due to poor post-operative recovery, randomized studies of adjuvant systemic therapy in gastric cancer enroll only selected patients and are, therefore, not representative of the curatively operated patient population. In addition, frequent dose reductions and treatment delays weaken their capacity to demonstrate an advantage for the treatment arm. Conversely randomized studies of pre-operative systemic therapy allow proper randomization without pre-selection and with greater feasibility.

*Monitoring:* while adjuvant therapy is administered on the basis of clinical trial results without any possibility to assess its efficacy on an individual basis, the efficacy of neoadjuvant therapy activity can also be monitored

during its administration, allowing treatment to be adjusted according to patient response.

*Pre-operative staging:* differently from adjuvant therapy, which is based on the pathologic staging performed at the time of the resection of a given tumor, the decision to perform or not a pre-operative treatment necessarily relies on clinical staging. In gastric cancer, as discussed earlier, this assessment remains difficult.

*Delayed Surgery:* The concept of "delayed surgery" is a relatively new concept within the therapeutic options for gastric carcinoma. It has been demonstrated that postponing resection in favor of a systemic treatment does not exclude patients from the benefits of a potentially curative delayed exeresis and that it does not worsen surgical outcomes. Nevertheless, the possibility of tumor progression during therapy persists in a small number of cases. Disease progression remains the only aspect of delayed surgery that justifies the reluctance of pursuing a multimodal preoperative approach to gastric cancer. Actually, patients who progress while on chemotherapy are unlikely to benefit from resection and can be spared radical surgery. The long therapy developmental time period for neoadjuvant treatment in gastric cancer over the last thirty years partially explains some of skepticism about this treatment option [7].

*Controindications:* neoadjuvant treatment are controindicated in obstructive or hemorrhagic tumoral masses. Some lesions, particularly those situated in the cardia and prepyloric areas, can be completely obstructive at diagnosis. In those situations, upfront surgery is the recommended approach even if neoadjuvant therapy could be considered with parenteral or enteral feeding through a jejunostomy. Acute bleeding from a gastric neoplastic lesion is relatively infrequent but can be dramatic and in this case direct salvage surgery is mandatory.

As explained above, feasibility, biological rationale, randomization facility and monitoring possibility represent several potential advantages which make pre-operative therapy an attractive path for investigation and patient management. For this reason, during the last thirty years many authors reported experiences of pre-operative therapy for locally advanced gastric cancer (neoadjuvant chemotherapy, neoadjuvant radiotherapy, or a combination of modalities).

## Pre-/peri-operative chemotherapy

Investigation of the efficacy and possible uses of chemotherapy in patients with advanced gastric cancer began in the late 1970s. Encouraging results, however, were not reported until the early 1990s, when two independent studies in patients with non-resectable disease found that chemotherapy led to subsequent resection in

40–50% of patients, with an increase in total median survival of 18 months, compared with unresected patients [8,9]. These preliminary observations encouraged the introduction of pre-operative chemotherapy protocols not only for unresectable but also (Table I) [8-14] for potentially resectable, locally advanced gastric cancer (Table II) [6,15-28]. However, the results of these first trials are questionable, mainly because of their methodological limitations. By following an inaccurate pre-operative staging process, several authors recruited patients on non-homogeneous criteria, commonly recruiting patients with locally advanced gastric cancer and others with disease of unclear stages, without a fixed distinction between resectable and non-resectable tumors. In addition to non-homogeneous methods of recruitment, other sources of bias in early trials included the use of different chemotherapeutic regimens, non-standardized surgery or surgery of questionable quality, and missing or poorly detailed response criteria.

In 1993, the Dutch Gastric Cancer Group started the first randomized controlled trial of exclusively pre-operative chemotherapy for gastric cancer (cardia tumors were excluded)[22]. The regimen used was FAMTX (fluorouracil, doxorubicin, and methotrexate), which was, at that time, the gold standard of treatment for adenocarcinoma of the stomach. This trial had many accrual problems and was prematurely stopped after an interim analysis showed that FAMTX was unlikely to achieve the goal of a 15% increase in curative resectability after pre-operative chemotherapy. Several biases have been outlined for this study, particularly the inaccuracy of the staging procedure with optional use of CT and laparoscopy and inadequate extension of lymphadenectomy. The investigators reported a high rate of tumor progression during treatment (36%) along with a reduction in curative resections (56% vs. 62%) and a decreased median survival (18 months vs. 30 months), compared with untreated patients. Even if all of the statistical differences in this study were insignificant, both the short-term and long-term results were discouraging [29].

Since the late 1990s, ambitious European phase III trials have been designed to provide a definitive demonstration of the efficacy of pre-operative treatments. The adoption of strict selection criteria made the selection of patients so difficult that some studies were stopped prematurely (EORTC 40954 and SWS-SAKK-43/99 trials) [26,28]. Only the MAGIC trial (started in the UK in 1994) and the FFCD 9703 trial (started in France in 1996) have been completed[6,25]. These two studies have yielded substantial evidence supporting the efficacy of perioperative chemotherapy for an increased survival rate (36% vs. 23%, estimated at 5 years for MAGIC; 38% vs. 24% estimated at 5 years for FFCD 9703; Table I) along with a significantly higher curative resection rate in the treated group versus the surgery-alone group (79% vs. 70%; p=0·03 for MAGIC; 84% vs. 73% in arm 2 (p=0.04) for FFCD 9703) without an increase in perioperative morbidity or mortality.

The possible increase in the actual R0-resection rate has been an important goal of pre-operative chemotherapy. In a phase-II study conducted by the Author on a perioperative chemotherapy protocol, the achievement of R0-resection in response to pre-operative chemotherapy was shown to be the most significant prognostic indicator by both univariate and multivariate analysis. Furthermore, R0-resection was the only independent variable in determining the probability of long-term survival in locally advanced gastric carcinoma. The overall survival for all curatively resected patients is higher when compared to historical series treated with surgery alone for locally advanced gastric cancer [24].

TABLE I - Pre-*operative chemotherapy in non-resectable gastric cancer*

| Author | Regimen | Pts | Stage | R0 Resection (%) | Median Survival (months) |
|---|---|---|---|---|---|
| Wilkie[8] | EAP | 34 | NR | 44 | 24 |
| Plukker[9] | 5FU+MTX | 20 | NR | 40 | 22 |
| Rougier[10] | 5FU, P | 30 | NR | 60 | 16 |
| Kelsen[11] | FAMTX, IP 5FU-P | 56 | NR | 61 | 15 |
| Melcher[12] | ECF | 27 | R-NR | 58 (R pts) 10 (NR pts) | 10 |
| Gallardo-Rincon[13] | P-ELF | 60 | NR | 8.7 | 10 |
| Cascinu[14] | EAFPLG | 82 | NR | 45 | 17 |

**Abbreviations** - **5FU**: 5-fluorouracil; **P**: cisplatin; **NR**: non resectable; **EAP**, etoposide, doxorubicin, and cisplatin; **FAMTX**: 5FU, doxorubicin, methotrexate; **IP**: intraperitoneal; **ECF**: epirubicin, cisplatin, 5FU; **R**: resectable; **P-ELF**: cisplatin, etoposide, leucovorin, 5FU; **EAFPLG**, epi-doxorubicin, 5FU, cisplatin, leucovorin, glutathione.

TABLE II - *Pre-operative chemotherapy in resectable gastric cancer.*

| Author | Phase | Selection Criteria | Pre-operative | Post-operative | Pts | R0† (%) | Pathologic CR (%) | Median Survival (months) |
|---|---|---|---|---|---|---|---|---|
| Ajani, 1991[15] | II | M0 *Resectable* (+ GEJ) | EFP x 2 | EFP x 3 | 25 | 72 | 0 | 15 |
| Leichman, 1992[16] | II | M0 *Resectable* | FPL x 2 | IP FUDR + IP cisplatin x 2 | 8 | 88 | 8 | >17 |
| Kang, 1992[17] | III RCT | M0 *Loc. advanced* | 1. EFP x 3 2. None | EFP x 3-6 | 53 54 | 79 61 | 8 – | 43 30 |
| Ajani, 1993[18] | II | M0 *Resectable* | EAP x 3 | EAP x 2 | 48 | 90 | 0 | 16 |
| Rougier, 1994[19] | II | M0 *Loc. advanced* (+ GEJ) | FP x 6 | None | 30 | 78 | 0 | 16 |
| Kelsen, 1996[20] | II | M0 *Loc. advanced* | FAMTX x 3 | IP FP + F | 56 | 77 | NS | 15 |
| Crookes, 1997[21] | II | M0 *Resectable* (+ GEJ) | FPL x 2 | IP FUDR + IP cisplatin x 2 | 59 | 71 | 9 | 52 |
| Songun, 1999[22] | II RCT | T2-T4; M0 | 1. FAMTX x 4 2. None | None | 27 29 | 75 75 | NS – | 18 30 |
| Schuhmacher, 2001[23] | II | III-IV; M0 (+ GEJ) | EAP | None | 42 | 86 | 0 | 19 |
| D'Ugo, 2006[24] | II | T3–T4 anyN; T≤2 N+; M0 | EEP x 3 or ECF x 3 | EEP x 3 or ECF x 3 | 34 | 82 | 3 | >28 |
| Cunningham, 2006[6] | III RCT | II-IV; M0 (+ GEJ) | 1. ECF x 3 2. None | 1. ECF x 3 2. None | 250 253 | 74 68 | NS – | 18 30 |
| Boige, 2007[25] | III RCT | *Resectable* (+ GEJ) | 1. FP x 3 2. None | 1. FP x 3 2. None | 113 111 | 84 73 | NS – | NS |
| Schuhmacher, 2009[26] | III RCT | *Loc. advanced* T3-T4NxM0 | 1. FP x 2 2. None | None | 72 72 | 81.9 66.7 | NS | >36 |
| Kinoshita, 2009[27] | II | Schirrous *Resectable* | TS-1x2 | None | 55 | 80.8 | 0 | NS |
| Biffi, 2010[28] | III RCT | T3-4 any N or any T N1-3 M0 (+ GEJ) | 1. TCF x 4 2. None | 1. None 2. TCF x 4 | 34 35 | 85 | 11.7 | NS |

† The "R0" resection rate was calculated only among resection procedures after preoperative chemotherapy.

**Abbreviations: EL**, exploratory laparotomies; **R0**, curative (R0) resections; **CR**, complete response; **EFP**, etoposide, fluorouracil, and cisplatin; **GEJ**, gastro-esophageal junction; **FPL**, fluorouracil, cisplatin, and leucovorin; **IP**, intraperitoneal; **FUDR**, 5-fluoro-2'-deoxyuridine; **RCT**, randomized controlled trial; **EAP**, etoposide, doxorubicin, and cisplatin; **FP**, fluorouracil and cisplatin; **FAMTX**, fluorouracil, doxorubicin, and methotrexate; **F**, fluorouracil; **NS**, not stated; **EEP**, etoposide, epirubicin and cisplatin; **ECF**, epirubicin, cisplatin and fluorouracil; **TCF,** docetaxel, cisplatin and fluorouracil.

Table III - *Pre-operative radio(chemo)therapy in gastric cancer*

| Author | Study design | Selection Criteria | Pre-operative | Pts | R0†(%) | Pathologic CR (%) | Median Survival (months) |
|---|---|---|---|---|---|---|---|
| Zhang[30] 1998 | RCT | GEJ | 1.40 Gy EBRT<br>2. None | 171<br>199 | 89.5 | 0 | 5-ys OS<br>30% vs 20% |
| Shchepotin, 1994[31] | RCT | M0 resectable and unresectable | 1.None<br>2. 20 Gy EBRT<br>3. 20 Gy EBRT + Hy | 98<br>100<br>95 | NS | NS | 5-ys OS<br>21.3% |
| Skoropad, 2000[32] | RCT | M0 *Resectable* (+GEJ) | 1. 20 Gy EBRT<br>+ 20 Gy IORT<br>2. None | 59<br>53 | 66 | 0 | 16 |
| Safran, 2000[33] | Phase I | Unresectable M0 | 45 Gy EBRT+ Paclitaxel | 27 | NS | 11 | 2-ys OS<br>35% |
| Lowy, 2001[34] | Phase I | T>2 Any N M0 | 45 Gy EBRT, 5-FU; | 24 | 75 | 11 | NS |
| Ajani, 2004[35] | Phase II | T>2 Any N | 5FU, LV, P then 45 Gy EBRT, 5FU | 33 | 70 | 30 | 34 |
| Ajani, 2005[36] | Phase II | M0 *Resectable* (+GEJ) | FP, paclitaxel; 45 Gy EBRT, 5FU | 41 | 78 | 20 | >36 |
| Allal, 2005[37] | Phase I | T3-T4 N+ | FP, Leucovorin 31.2– 45.6 Gy EBRT | 19 | NS | 5 | 5-ys OS<br>35% |
| Ajani, 2006[38] | Phase II | M0 Resectable | FP, LV, P; 45 Gy EBRT, 5FU, cis | 49 | 63 | 26 | 23 |

† The "**R0**" resection rate was calculated only among resection procedures after preoperative chemotherapy.
**Abbreviations: R0**, curative (R0) resections; **CR**, complete response; **GEJ**, gastro-esophageal junction; **RCT**, randomized controlled trial; **EBRT** external beam radiotherapy; **IORT**: intraoperative radiotherapy; **Hy:** hypertermia; **FP**, fluorouracil and cisplatin; **5FU**, 5-fluorouracil; **LV:** leucovorin **NS**, not stated.

## Preoperative Radio(chemo)therapy

Based on the results of the SWOG 9008/INT-0116 trial [4], the integration of chemotherapy with radiation applied in the pre-operative phase has gained much interest. Some benefits of pre-operative radiotherapy for gastric cancer were reported by pivotal randomized single-center studies. Zhang and co-workers [30] recruited 317 patients with adenocarcinoma of the cardia that were randomly assigned to radiation therapy followed by surgery or surgery alone. This study indicated a significant five-year survival benefit for patients treated with neoadjuvant radiotherapy as compared with surgery alone (30.1% vs. 19.8%, respectively), with an improved rate of complete curative resection after radiotherapy (80% vs. 62%). A second monoinstitutinal trial, performed in Ukraine, enrolled 293 patients

with gastric cancer from February 1984 to May 1986[31]. This three arm study randomized by envelope assignment into (1) radiation therapy followed by surgery, versus (2) radiation therapy with local hyperthermia followed by surgery, versus (3) surgery alone. With 5 year survival rates of 30.1%, 44.7% and 51.5% for surgery alone, radiation therapy with surgery and radiation therapy with hyperthermia with surgery respectively, the combined approach using radiation therapy with hyperthermia followed by surgery was demonstrated to be significantly more effective than surgery alone (p<0.05). A benefit of radiation therapy with surgery (versus surgery alone) was also observed, but it did not reach significance. Finally, Skoropad et al.[32] reported the 20-year follow-up results of a randomised trial on pre-operative radiotherapy (given at a dose of 20 Gy) compared to surgery alone. No significant dif-

ference in overall survival was detected between the two treatment groups.

Recently, published phase II studies have verified the efficacy of chemoradiotherapy in terms of complete pathological response (up to 30% in some series) and increased long-term survival without an increase in morbidity or mortality (Table III) [29-38].

Safran and colleagues recently reported that patients who received concurrent paclitaxel and radiation had an overall response of 56%, including complete response in three patients (11%) with local–regional_ unresectable gastric cancer[33]. The 2-year progression-free and overall survival were 29% and 31%, respectively.

In 2001, Lowy et al reported a pilot study of neoadjuvant chemoradiotherapy (combined with IORT) for patients with gastric cancer[34]. The disease was determined to be potentially resectable using a staging protocol including computed tomography, endoscopic ultrasonography, and staging laparoscopy. The treatment combined 45 Gy of external-beam radiation at 1.8 Gy per day and 5 days per week with continuous-infusion 5-FU (300 mg/m2/d). Twenty-four patients who had potentially resectable but poor-prognosis tumors (determined by EUS to be T2 or higher) were treated, and all but one patient were able to complete the therapy. The radiation field included the entire stomach and regional lymph nodes. Patients were restaged on the basis of a computed tomography scan at 4 to 6 weeks following treatment and before a planned resection. A spleen-preserving D2-gastrectomy was performed after completion of chemoradiotherapy in 19 (83%) patients. Intraoperative radiotherapy (10 Gy) was given at resection. Complete pathologic response was observed in 2 (11%) patients.

Finally, in a recent study by Ajani et al.[35], the authors treated patients with two courses of 5-FU, folinic acid, and cisplatin and followed that with 5FU-potentiated radiotherapy (45 Gy). Surgical resection after pre-operative chemoradiotherapy was performed without excessive complications. Thirty-four patients who had localized gastric adenocarcinoma were enrolled in the study, and 85% underwent resection. The pathologic complete response rate was 30%, and a partial response was seen in 24% of patients. The overall median survival duration was 33.7 months; however, patients who achieved a complete response had a median survival duration of 64 months, versus 12.6 months in those who had less than a complete response (p< 0.05). This study emphasizes that a durable survival benefit can be achieved in patients whose tumors respond to treatment. Similar findings were reported in two subsequent reports with different chemotherapy regimens [36,38].

All of the above results suggest that R0-resection is not an exclusive surgical target in locally advanced gastric cancer but that it can be facilitated or achieved by pre-operative therapy ("induction" of R0-resection).

Many answers are expected from ongoing trials exploring ways of improving pre-operative treatment strategies for resectable gastric cancer [7]: the MAGIC B trial (United Kingdom National Cancer Research Institute ST03 trial) of peri-operative epirubicin, cisplatin, and capecitabine, with or without the endothelial growth factor antibody, bevacizumab; the CRITICS trial (ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach), a phase III study that randomizes between pre-operative chemotherapy (three courses of epirubicin/cisplatin/capecitabine) and gastric surgery with limited lymph node dissection followed by post-operative chemotherapy (another three courses of epirubicin/cisplatin/capecitabine) or chemoradiotherapy; and the JCOG trial 0501 (Japan Clinical Oncology Group Study 0501 trial) and KYUH-UHA-GC04-03 Kyoto trial, which are testing pre-operative oral fluoropyrimidine S-1 together with cisplatin versus post-operative oral fluoropyrimidine S-1.

## Evaluation of response to neoadjuvant treatment

At present, there is no reliable morphological or functional surrogate parameter for grading the response and consequently evaluating the efficacy of combined therapy in gastric cancer.

Event though a large percentage of patients respond to neoadjuvant therapy in some clinical measurable way, such a measurement of clinical response is highly variable and subjective [23,39,40]. Evaluation criteria frequently used for metastatic disease have not been validated for localized tumors and for tumor bed after surgical excision [40].

The pathologic response to pre-operative treatment failed to show a statistically irrefutable prognostic significance. There are few studies in the literature about the pathologic response after neoadjuvant therapy and patient survival [24,40] and most of them could not demonstrate any significant relationship. Becker et al. demonstrate a significant correlation between the grade of pathologic response and survival only when patients results were divided in three unconventional levels of response[41], concluding that the survival difference between responders and non-responders is not particularly convincing in gastric cancer. However, in the absence of a clear-cut pre-therapeutic histological baseline, only "complete" response and "nearly complete" response are demonstrable.

In our experience, the investigation on this subject have led us to consider the measurement of clinical and pathologic tumor response to chemotherapy as an extremely variable phenomenon[24]. The quantitative evaluation of the pathologic response, which detects the percentage of residual vital tumor cells in surgical specimens, is not easy to categorize in gastric cancer, being subdivided into classes just by convention [41]. On the other hand, qualitative analysis has been addressed to the possible achievement of tumor

downstaging, induced by any grade of pathologic response [24]. No standardized concepts
for response evaluation have been established so far, and according to some authors pathologic response after preoperative treatments behaves like a surrogate endpoint, reflecting more than influencing local control or survival [40]. Indeed, in our published experience the pathologic grading of the response to date has not reached the statistical relevance of a reliable prognostic indicator. Nevertheless, following the demonstration of a significant association between tumor downstaging and the achievement of a true R0 resection, in 2001 we decided to change our chemotherapeutic schedule of choice from epidoxorubicin, etoposide, and cisplatin (EEP) to epirubicin, cisplatin, and fluorouracil (ECF), the latter warranting better pathologic response rates [24].

More recently measurement of the metabolic response to chemotherapy by means of FDG-PET performed early during treatment course has been tested in esophago-gastric tumors [42]. Theoretically, patients who do not exhibit an early response to their initial regimen can be changed to a different or more intensive course of chemotherapy. In these studies metabolic response has predicted histological response and survival with sufficient accuracy justifying a similar approach in gastric cancer. However, the relevant group of FDG-PET-non-avid patients makes the issue more complicated in gastric cancer because response and survival for FDG-PET-nonavid patients was not significantly better than that in metabolic nonresponders. A response-based strategy is a very promising approach but the results of preliminary studies still need to be reproduced by larger sample sizes.

## Conclusions

In gastric cancer, radical resection (R0-resection) offers the best chance for a cure since it is defined as the complete surgical removal of any residual cancer cells in the tumor bed. However, distant and loco-regional failure rates in most radically resected patients with positive lymph nodes or involvement of the serosa contradict this statement.

All current therapeutic efforts in resectable gastric cancer are directed toward the individualization of therapeutic protocols, which tailors the extent of resection and the administration of pre-operative and post-operative treatment. A paradigm shift has rapidly advanced in the last ten years: three pivotal studies in three different areas of the world (United States, Europe and Japan) have demonstrated that multimodal treatments improve the prognosis for patients with resectable gastric cancer. The common target of all of these strategies is to improve prognosis towards the achievement of a true curative resection (R0-resection) with minimal morbidity and mortality.

In gastric cancer, surgical research has always proceeded slowly, and standardization is still far from being settled. Geographical differences in epidemiology and treatment approaches and a lack of a surgical gold standard have diverted attention from the pursuit of a multimodal approach.

Despite needing further data regarding the definitive role of neoadjuvant chemoradiotherapy, the results of preoperative chemotherapy in the multimodal treatment of gastric adenocarcinoma are encouraging and benefits seem unquestionable.

Modern concerns regards the choice of the optimal therapy regimen strict patient selection by accurate preoperative staging, standardization of surgical procedures, and reliable criteria for response evaluation New well-designed trials with will be necessary to identify the best treatment plan in preoperative setting and to understand how to combine the conventional chemotherapeutic drugs with new-generation molecules.

## Riassunto

La storia della terapia preoperatoria del carcinoma gastrico è stata delineata in questa review per dimostrare il suo valore in termini di sicurezza ed efficacia.

I dati raccolti in questa revisione sono stati ottenuti da studi trovati in PubMed utilizzando i termini di ricerca "chemioterapia preoperatoria", "radioterapia preoperatoria", "chemioradioterapia preoperatoria", "trattamento neoadiuvante", e "cancro gastrico". Documenti pubblicati solo in lingua inglese tra il gennaio 1970 e gennaio 2010 sono stati selezionati.

Studi condotti negli ultimi venti anni sono passati dalla prima "pionieristica" chemioterapia per i pazienti con malattia non resecabile (terapia di "induzione") ai più recenti studi di fase III di terapia "neoadiuvante" per neoplasie gastriche resecabili.

Numerosi studi clinici di chemioterapia pre-operatoria nel trattamento del cancro gastrico sono state eseguiti. Nonostante la necessità di ulteriori dati definitivi relativi al ruolo della terapia neoadiuvante, i risultati della chemioterapia preoperatoria nel trattamento multimodale dell' adenocarcinoma gastrico sono incoraggianti in quanto il trattamento aumenta le probabilità che una procedura chirurgica "curativa" (R0) ritardata possa essere realizzata.

Grazie ai risultati degli ultimi studi randomizzati di fase III, la chemioterapia neoadiuvante per il carcinoma gastrico localmente avanzato operabile ha raggiunto un livello di evidenza I.

## References

1. Kamangar F, Dores GM, Anderson WF: *Patterns of cancer incidence, mortality, and prevalence across five continents: Defining priorities to reduce cancer disparities in different geographic regions of the world.* J Clin Oncol, 2006; 24: 2137-150.

2. Kubota H, Kotoh T, Masunaga R, et al.: *Impact of screening survey of gastric cancer on clinicopathological features and survival: retrospective study at a single institution.* Surgery, 2000; 128:41-47.

3. Hundahl SA, Phillips JL, Menck HR: *The National Cancer Data Base Report on poor survival of U.S. gastric carcinoma patients treated with gastrectomy: Fifth Edition American Joint Committee on Cancer staging, proximal disease, and the "different disease" hypothesis.* Cancer, 2000; 88:921-32.

4. Macdonald JS, Smalley SR, Benedetti J, et al.: *Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction.* N Engl J Med, 2001; 345:725-30.

5. Sakuramoto S, Sasako M, Yamaguchi T, et al.: *ACTS-GC Group. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine.* N Engl J Med, 2007; 357:1810-820.

6. Cunningham D, Allum WH, Stenning SP, et al.: *Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer.* N Engl J Med, 2006; 355:11-20.

7. D'Ugo D, Rausei S, *Biondi A*, et al.: *Preoperative treatment and surgery in gastric cancer: Friends or foes?* Lancet Oncol, 2009; 10: 191-95.

5. Wilke H, Preusser P, Fink U, et al.: *Preoperative chemotherapy in locally advanced and nonresectable gastric cancer: A phase II study with etoposide, doxorubicin and cisplatin.* J Clin Oncol, 1989; 7:1318-326.

9. Plukker JT, Mulder NH, Sleijfer DTH, et al.: *Chemotherapy and surgery for locally advanced cancer of the cardia and fundus: Phase II study with methotrexate and 5-fl uorouracil.* Br J Surg, 1991; 78:955-58.

10. Rougier P, Mahjoubi M, Lasser P, et al.: *Neoadjuvant chemotherapy in locally advanced gastric carcinoma. A phase II trial with combined continuous intravenous 5-fluorouracil and bolus cisplatinum.* Eur J Cancer 1994; 30:1269-275.

11. Kelsen D, Karpeh M, Schwartz G, et al.: *Neoadjuvant therapy of high-risk gastric cancer: A phase II trial of preoperative FAMTX and postoperative intraperitoneal fluorouracil-cisplatin plus intravenous fluorouracil.* J Clin Oncol, 1996; 14:1818-828.

12. Melcher AA, Mort D, Maughan TS: *Epirubicin, cisplatin and continuous infusion 5-fluorouracil (ecf) as neoadjuvant chemotherapy in gastro-oesophageal cancer.* Br J Cancer, 1996; 74:1651-654.

13. Gallardo-Rincon D, Onate-Ocana LF, Calderillo-Ruiz G: *Neoadjuvant chemotherapy with P-ELF (cisplatin, etoposide, leucovorin, 5-fluorouracil) followed by radical resection in patients with initially unresectable gastric adenocarcinoma: A phase II study.* Ann Surg Oncol, 2000; 7:45-50.

14. Cascinu S, Scartozzi M, Labianca R, et al.: *Italian Group for the Study of Digestive Tract Cancer (GISCAD). High curative resection rate with weekly cisplatin, 5-fluorouracil, epidoxorubicin, 6S-leucovorin, glutathione, and filgastrim in patients with locally advanced, unresectable gastric cancer: A report from the Italian Group for the Study of Digestive Tract Cancer (GISCAD).* Br J Cancer, 2004; 90: 1521-525.

15. Ajani JA, Ota DM, Jessup JM, et al.: *Resectable gastric carcinoma: an evaluation of preoperative and postoperative chemotherapy.* Cancer, 1991; 68:1501-506.

16. Leichman L, Silberman H, Leichman CG, et al.: *Preoperative systemic chemotherapy followed by adjuvant postoperative intraperitoneal therapy for gastric cancer: A University of Southern California pilot program.* J Clin Oncol, 1992; 10:1933-942.

17. Kang YK, Choi DW, Kim CW, et al.: *The effect of neoadjuvant chemotherapy on the surgical outcome of locally advanced gastric adenocarcinoma: Interim report of a randomized controlled trial.* Proceedings of the American Society of Clinical Oncology, 1992; 11: 173.

18. Ajani JA, Mayer RJ, Ota DM, et al.: *Preoperative and postoperative chemotherapy for patients with potentially resectable gastric carcinoma.* J Natl Cancer Inst 1993; 85:1839-844.

19. Rougier P, Lasser P, Ducreux M, et al.: *Preoperative chemotherapy of locally advanced gastric cancer.* Ann Oncol, 1994; 5:59-68.

20. Kelsen D, Karpeh M, Schwartz G, et al.: *Neoadjuvant therapy of highrisk gastric cancer: A phase II trial of preoperative FAMTX and postoperative intraperitoneal fluorouracil-cisplatin plus intravenous fl uorouracil.* J Clin Oncol, 1996; 14:1818-828.

21. Crookes P, Leichman CG, Leichman L, et al.: *Systemic chemotherapy for gastric carcinoma followed by postoperative intraperitoneal therapy: A final report.* Cancer, 1997; 79:1767-775.

22. Songun I, Keizer HJ, Hermans J, et al.: *Chemotherapy for operable gastric cancer: Results of the Dutch randomised FAMTX trial.* Eur J Cancer, 1999; 35:558-62.

23. Schuhmacher CP, Fink U, Becker K, et al.: *Neoadjuvant therapy for patients with locally advanced gastric carcinoma with etoposide, doxorubicin, and cisplatinum: closing results after 5 years of follow-up.* Cancer, 2001; 91:918-27.

24. D'Ugo D, Persiani R, Rausei S, et al.: *Response to neoadjuvant chemotherapy and effects of tumor regression in gastric cancer.* Eur J Surg Oncol, 2006; 32:1105-109.

25. Boige V, Pignon J, Saint-Aubert B, et al.: *Final results of a randomized trial comparing preoperative 5-fluorouracil (F)/cisplatin (P) to surgery alone in adenocarcinoma of stomach and lower esophagus (ASLE): FNLCC ACCORD07-FFCD 9703 trial.* J Clin Oncol, 2007; ASCO Annual Meeting Proceedings 25, 18S (June 20 Supplement), 2007: 4510.

26. Schuhmacher C, Schlag P, Lordick F, et al.: *Neoadjuvant chemotherapy versus surgery alone for locally advanced adenocarcinoma of the stomach and cardia: Randomized EORTC phase III trial #40954.* J Clin Oncol 2009; ASCO Annual Meeting Proceedings 27, 15S (May 20 Supplement), 2009: 4510.

27. Kinoshita T, Sasako M, Sano T, et al.: *Phase II trial of S-1 for neoadjuvant chemotherapy against scirrhous gastric cancer (JCOG 0002).* Gastric Cancer, 2009; 12: 37-42.

28. Biffi R, Fazio N, Luca F, et al.: *Surgical outcome after docetaxel-based neoadjuvant chemotherapy in locally-advanced gastric cancer.* World J Gastroenterol, 2010; 16:868-74.

29. Hartgrink HH, van de Velde CJ, Putter H, et al.: *Cooperating Investigators of The Dutch Gastric Cancer Group. Neo-adjuvant chemotherapy for operable gastric cancer: long term results of the Dutch randomised FAMTX trial.* Eur J Surg Oncol, 2004; 30:643-49.

30. Zhang ZX, Gu XZ, Yin WB, et al.: *Randomized clinical trial of the combination of preoperative irradiation and surgery in the treatment of adenocarcinoma of the gastric cardia (AGC)-report on 370 patients.* Int J Radiat Oncol Biol Phys, 1998; 42:929-34.

31. Shchepotin IB, Evans SR, Chorny V, et al.: *Intensive preopera-*

*tive radiotherapy with local hyperthermia for the treatment of gastric carcinoma.* Surg Oncol, 1994; 3:37-44.

32. oropad V, Berdov B, Zagrebin V: *Concentrated preoperative radiotherapy for resectable gastric cancer: 20-years follow-up of a randomized trial.* J Surg Oncol, 2002; 80:72-78.

33. Safran H, King TP, Choy H, et al.: *Paclitaxel and concurrent radiation for locally advanced pancreatic and gastric cancer: A phase I study.* J Clin Oncol, 1997; 15:901-07.

34. Lowy AM, Feig BW, Janjan N, et al.: *A pilot study of preoperative chemoradiotherapy for resectable gastric cancer.* Ann Surg Oncol, 2001; 8:519-24.

35. Ajani JA, Mansfield PF, Janjan N, et al.: Mu*lti-institutional trial of preoperative chemoradiotherapy in patients with potentially resectable gastric cancer.* J Clin Oncol, 2004; 22:2774-780.

36. Ajani JA, Mansfield PF, Crane CH, et al.: *Paclitaxel-based chemoradiotherapy in localized gastric carcinoma: Degree of pathologic response and not clinical parameters dictated patient outcome.* J Clin Oncol, 2005; 23:1237-244.

37. Allal AS, Zwahlen D, Brundler MA, et al.: *Neoadjuvant radiochemotherapy for locally advanced gastric cancer: Longterm results of a phase I trial.* Int J Radiat Oncol Biol Phys, 2005; 63:1286-289.

38. Ajani JA, Winter K, Okawara GS, et al.: *Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): Quality of combined modality therapy and pathologic response.* J Clin Oncol, 2006; 24: 3953-958.

39. Lowy AM, Mansfield PF, Leach SD, et al.: *Response to neoadjuvant chemotherapy best predicts survival after curative resection of gastric cancer.* Ann Surg, 1999; 229:303-08.

40. Persiani R, Rausei S, Biondi A, et al.: *Perioperative chemotherapy for gastric cancer: how should we measure the efficacy?* Ann Surg Oncol, 2009; 16:1077-79.

41. Becker K, Mueller JD, Schuhmacher C, et al.: *Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy.* Cancer, 2003; 98:1521-530.

42. Ott K, Lordick F, Herrmann K, et al.: *The new credo: Induction chemotherapy in locally advanced gastric cancer: Consequences for surgical strategies.* Gastric Cancer, 2008; 11:1-9.