Perioperative or postoperative therapy for resectable gastric cancer?

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Introduction

The long-term survival of gastric cancer patients is determined by the stage of the disease and therefore, by the tumor extension beyond the gastric wall and by the nodal involvement.

Tumor confined to the mucosa and submucosa (T1–T2 N0 M0) has a 5-year survival of at least 70%, while invasion into the serosa increases the risk of lymph node metastases with a proportionate reduction of the 5-year survival rate, reported in Western series to be ~20–30% [1–3].

To date, radical primary tumor resection is the main standard of care for patients with potentially resectable gastric cancer, which represents ~50% of all new diagnoses; however, the prognosis of these patients remains poor, ranging between 15% and 35% at 5 years, due to locoregional failure and distant metastases [4].

For many decades the way a multimodal approach and an adequate surgical technique could improve the outcome of the patients only treated with surgery has been under debate and several topics have been under investigation.

Extension of lymphadenectomy

Curative gastrectomy for gastric cancer should include the complete removal of the primary tumor and of its regional lymph nodes, achieving correct staging and better local control. The approach to lymph node dissection is different between Asian and Western surgeons. Several Asian studies suggested a survival advantage with extended lymphadenectomy in gastric cancer patients. Systematic node dissection (D2) is actually the standardized procedure in Asia, where it shows postoperative morbidity and mortality rates lower than in Western series with higher rates of post-surgical survival [5].

There is no definitive evidence showing the superiority of extensive lymphadenectomy and its impact on overall survival is still not demonstrated in randomized controlled trials. A large European randomized trial comparing D1 and D2 dissection with a long-term follow-up failed to demonstrate a relevant difference in survival and relapse rate of the two procedures [6]. Similar results were found by the Medical Research Council and later reviewed in 2003 by the Cochrane group [7, 8].

Pancreatectomy and splenectomy, performed as part of the D2 dissection to remove lymph nodes at the splenic hilus and along the splenic artery, are associated with an increased risk of morbidity and mortality, and no clear evidence of overall survival difference is demonstrated. Therefore, radical surgery possibly avoiding resection of the pancreas and the spleen is currently the standard procedure in Eastern countries [6].

While the West is still debating whether D2 is better than D1 dissection, Asians are discussing the possible role of a more extensive lymphadenectomy including para-aortic nodes. The Japan Oncology Group conducted a randomized controlled trial to compare the standard D2 and D2+ para-aortic nodal dissection; they confirmed the safety of gastrectomy with D2 lymphadenectomy performed by specialized surgeons. This procedure could be used safely in patients with low operative risk. More extensive surgery did not increase the major operative complications but did lead to higher morbidity mainly due to other minor complications [9].

Additional strategies including pre/postoperative chemoradiotherapy to improve locoregional control as well as overall survival are warranted.

Postoperative chemotherapy

The disappointing prognosis of gastric cancer patients after radical surgery justifies the worldwide effort to develop effective strategies to improve outcome in these patients. For more than 40 years several 5-fluouracil (FU) combinations, effective in metastatic gastric cancer, have been evaluated in the adjuvant setting; the majority of these trials did not reveal a clear long-term benefit for postoperative chemotherapy.

In Asian countries, where gastric cancer is a common disease, several studies have been performed in the adjuvant setting, showing a survival benefit. However, these studies induced criticisms: some of them were not randomized trials, sometimes they did not include surgical controls and they usually included patients with stage I–IV cancer, not commonly evaluated together in Western clinical trials [10].

While Asian studies were often positive, the majority of the Western studies failed to demonstrate a positive influence of postoperative systemic treatments. However, Western studies also have their criticisms: some of them are underpowered to detect any difference in overall survival and use suboptimal chemotherapy regimens.

The efficacy of adjuvant chemotherapy was also widely analyzed in several meta-analyses, all showing a slight benefit...
but none of them evaluated third generation chemotherapies. The first meta-analyses, performed by Hermans [11] and Earle [12] suggested a small survival advantage; however, this was not considered clinically relevant. Moreover, a later update [13] showed a positive survival benefit not shown by the early report.

Mari et al. [14] evaluated with a different and more adequate statistical methodology 20 articles comparing mono- and/or polychemotherapy versus surgery alone. This analysis, including >3500 patients, has demonstrated an absolute reduction in the risk of death of 2–4% and has not shown any significant difference between different poly-chemotherapy protocols, in particular in relation to anthracycline-containing regimens.

A similar overall benefit was obtained by Janunger [15], but the subgroup analysis concluded that this advantage was only visible in Asian trials.

Additionally, Panzini et al. [16] presented their results confirming the same marginal role of adjuvant chemotherapy. The mainstay of adjuvant chemotherapy has been the combination of cisplatin and oral or i.v. fluoropyrimidines and many phase III trials have been conducted. Newer strategies incorporating effective agents, both cytotoxic and biological, with acceptable toxicity, are now strongly needed.

A phase III trial of the Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC) compared in resected patients surgery with four courses of PELF [cisplatin, epirubicin, leucovorin (LV) and 5-FU] with surgery alone; this study was unable to show any significant difference in disease-free and overall survival [17]. With the aim of highlighting the best adjuvant regimen, an Italian Group for the Study of Digestive Tract Cancer (GISCAD) study recently published their negative results comparing a weekly intensive regimen including cisplatin, epodoxorubicin and 5-FU (wPELF) versus a 5-FU/LV arm in patients with a high risk of relapse after radical surgery, with either D1 or D2 node dissection. The survival rate of 50% reported in the 5-FU/LV arm was unexpectedly high, invalidating a possible positive result. Moreover, the high quality of the surgery with a wide performance of D2 lymphadenectomy, despite a large patient number with extensive nodal involvement, probably justifies the low rates of local failure observed, similar in both treatments arms [18].

Encouraging results in the adjuvant setting were recently published in the New England Journal of Medicine by the Adjuvant Chemotherapy Trials of S-1 for Gastric Cancer Group (ACTS-GC), proving the efficacy in Asians of a novel oral drug, S-1. S-1 is a combination of an FU prodrug (tegafur) and two inhibitors (gimeracil and oteracil) that prevent the degradation of FU, decreasing its gastrointestinal toxicity [19]. This drug has already shown a high response rate of ~40% in the metastatic setting [20, 21]. In the ACTS-GC study S-1 was orally administered for 1 year after curative D2 gastrectomy and compared with a surgery-only arm. The trial recruited from 2001 to 2004 1059 patients treated with gastrectomy and D2 dissection for stage II or III disease. The trial, specifically powered to detect a 30% reduction risk of death, was stopped after the first interim analysis; in fact, a clear advantage was early documented. In the S-1 group, as compared with the control arm, the hazard ratio for death was 0.68 (95% CI 0.52–0.87; \( P = 0.003 \)) and the hazard ratio for relapse was 0.62 (95% CI 0.50–0.77; \( P < 0.001 \)). Anorexia, nausea, diarrhoea and fatigue were the most usual non-hematologic toxicities, of grade 3 or 4 in <6% of the patients; anaemia and leukopenia were frequent but usually less than grade 2.

As in all early stopped trials several problems in the interpretation of results must be considered; in fact only 65% of the patients completed the planned treatment, with reduction of the dose of S-1 in 42.4% in the treatment arm. However, this promising result must be confirmed in a Western population, in which a different metabolism might contribute to different results; in fact, it is well known that Asians have particular patterns of response to fluoropyrimidines.

Several drugs are currently under investigation in the treatment of gastric cancer with the aim of improving its outcome. In addition to cisplatin/5-FU, taxanes, oxaliplatin and irinotecan demonstrated high response rates in the metastatic setting as was also noted for monoclonal antibodies, tyrosine kinase inhibitors and other novel drugs acting on intracellular signaling pathways [22, 23].

Recently, a large British study compared capcetabine with FU and oxaliplatin with cisplatin in patients untreated for advanced esophagogastric cancer. The aim of this study was to provide more effective and better tolerated regimens, not requiring the implantation of a central venous access for the FU continuous infusion. The comparison of these drugs confirmed the non-inferiority of the regimens containing capcetabine and oxaliplatin in terms of disease-free and overall survival; the overall survival was longer in patients treated with EOX (epirubicin, oxaliplatin and capcetabine) than in the ECF (epirubicin, cisplatin and FU) arm: the hazard ratio for death with the EOX regimen was 0.80 (95% CI 0.66–0.97, \( P = 0.02 \)) [24].

In conclusion, at present there is no definitive evidence supporting the routine use of adjuvant chemotherapy for resected patients and standard regimens have not been established yet; the role of postoperative therapy will be assessed in further phase III studies.

**preoperative and perioperative chemotherapy**

In consideration of the high rate of recurrence in patients with resected gastric cancer there has been great interest in developing new strategies to reduce recurrence and to improve survival.

As well as in breast cancer, osteosarcoma, rectal cancer and in other malignancies, a preoperative strategy improved progression-free and overall survival and on the basis of these considerations, several studies were conducted. Moreover, although excellent survival has been achieved with surgery in stage IA and IB cancers, the results for stage IIIA and IIIB cancer are poor and many of these patients are technically inoperable.

The use of neo-adjuvant therapy may allow resection by down-staging and may contribute to the eradication of micrometastases and spillage of tumors cells during surgery [25].
On the contrary, resistance to chemotherapy could induce an increase of the tumor burden making the neoplastic lesion unresectable and considering that chemotherapy in advanced gastric cancer does not have a high response rate, the risk of tumor progression during a primary regimen may present a real danger.

Many phase II and III trials have been conducted and completed, producing conflicting results and rendering the role of neo-adjuvant chemotherapy still controversial.

A well-designed study from the Dutch Gastric Cancer Group compared the FAMTX regimen (5-FU, doxorubicin and methotrexate) as experimental neoadjuvant chemotherapy versus surgery alone [26]. Although the results of this trial were negative, the small accrual of patients made the conclusions not reliable. Moreover, two Japanese trials, using fluoropyrimidines (FUDR or UFT) demonstrated a survival benefit in stage II and III patients [27, 28].

A recent metanalysis published by the Cochrane group concluded that no statistical difference was demonstrated in overall survival in favor of a neo-adjuvant treatment [29]. Furthermore, no conclusions could be drawn for progression-free survival due to missing data.

In conclusion, neo-adjuvant chemotherapy may increase the rate of R0 resection, but its impact on survival is still controversial. Difficulties encountered in recent studies are the inadequate numbers of patients in the case of the FAMTX study, and the use of suboptimal regimens in the case of the Japanese trials. Moreover, differences between West and East in drug delivery are notable: Asians prefer using oral fluoropyrimidines, while Westerners prefer i.v. formulations. Also, controversies are also present about a possible different nature of gastric cancer between the two continents.

Further studies enrolling both Western and Eastern gastric cancer patients are strongly recommended and appropriate subgroup analyses should be performed on the results of clinical trials, in order to really assess the role of this strategy.

Particular attention must be given to the ‘MAGIC’ trial. This trial randomly assigned patients with resectable adenocarcinoma of the stomach, esophagogastric junction or lower esophagus to either perioperative chemotherapy and surgery or surgery alone. Patients in the chemotherapy arm received three preoperative and three postoperative courses of i.v. epirubicin and cisplatin and a continuous i.v. infusion of 5-FU (ECF) for 21 days. This regimen improved survival among patients with incurable locally advanced or metastatic gastric adenocarcinomas and showed high response rates. The primary endpoint of this trial was overall survival. The conclusions stated that the ECF regimen decreased tumor size and stage and significantly improved progression-free and overall survival. As compared with the surgery group, the perioperative chemotherapy group had a higher likelihood of overall survival (hazard ratio for death, 0.75; 95% CI 0.60–0.93; P = 0.009; 5-year survival rate, 36% versus 23%) and progression-free survival (hazard ratio for progression, 0.66; 95% CI 0.53–0.81; P < 0.001) [30]. It is important to notice that only 42% of all patients completed the treatment plan.

After these encouraging results should perioperative ECF be considered the standard of care in the management of resectable gastric cancer? The answer is perhaps. First of all, some newer chemotherapy regimens have been developing and they will be tested with the same sequence as used in the MAGIC study; second, perioperative chemotherapy may be a reasonable treatment option for patients who are referred to the oncologist at the time of diagnosis before gastrectomy, but patients who have already undergone gastric resection are obviously not candidates for this approach; in fact, most patients are used to consulting the surgeon directly at the time of the diagnosis.

**radiation therapy**

Historically, radiation therapy has not played an important role in the treatment of patients with gastric cancer. A number of single-modality trials have shown a decrease in local failure rates when radiation therapy was used as single modality after surgical resection, but there generally has not been an improvement in survival.

At last, a large phase III trial of postoperative therapy strongly suggested a benefit from a multi-modal approach combining radiation and chemotherapy after gastrectomy. This trial, Intergroup Study 0116 (INT 0116), enrolled >550 patients who were randomly assigned to surgery alone or surgery followed by chemoradiation (FU/LV plus external-beam radiation delivered to the gastric bed and regional lymph nodes). These patients had a clinically significant risk of relapse after gastric resection: 85% had lymph-node metastases and 65% stage T3 or T4 tumors.

Median survival in the surgery-only and chemoradiation groups was 27 and 36 months, respectively (P = 0.005 by the log-rank test); the corresponding figures for disease-free survival were 19 and 30 months (P < 0.001). The benefit of this approach was confirmed by a subsequent update of the results [31]. The results of this trial made postoperative chemoradiation the standard of care in the USA among patients with resected gastric adenocarcinoma [32].

In fact, the criticism on this study was that only 10% of all patients underwent extensive lymph node dissection (D2) and that in the majority of patients (54%) there were no N1 lymph nodes resected suggesting that the positive findings of this trial could be a result of inadequate surgery.

Moreover, for patients who present with locally advanced disease in whom it may be difficult to obtain negative surgical margins despite an aggressive surgical resection, intra-operative radiation therapy (IORT) has been explored in a few studies with some suggestion of benefit. A randomized trial performed at the National Cancer Institute (NCI) found a decrease in the local recurrence rate with the use of IORT compared with no radiotherapy (44% versus 92%, respectively) [33], although there was no advantage in terms of survival. Therefore, there are too little data to recommend this as a general approach.

The most important question for physicians who treat patients with gastric cancer is whether the results of the MAGIC trial should influence their management of the disease. Is perioperative chemotherapy an advance in the treatment of gastric cancer? Or is postoperative chemoradiation the standard of care? Or, need all categories of patients be treated according to the results of the INT0116 with radiation therapy?
All these questions are unanswered it is likely that in the future a better knowledge of tumor biology may be useful to define the adjuvant setting.

disclosures
No significant relationships.

references