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MINIREVIEWS

# Multimodal treatment of gastric cancer

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## Abstract

Gastric cancer is the second leading cause of death from malignant disease worldwide. Although complete surgical resection remains the only curative modality for early stage gastric cancer, surgery alone only provides long-term survival in 20% of patients with advanced-stage disease. To improve current results, it is necessary to consider multimodality treatment, including chemotherapy, radiotherapy and surgery. Recent clinical trials have shown survival benefit of combining different neoadjuvant or adjuvant protocols compared with surgery with curative intent. Furthermore, the implementation of chemotherapy with novel targeted agents could play an important role in the multimodal management of advanced gastric cancer. In this paper, we focus on a multidisciplinary approach in the treatment of gastric cancer and discuss future strategies to improve the outcome for these patients.



**Key words:** Gastric cancer; Gastrectomy; Lymphadenectomy; Multimodal treatment; Adjuvant therapy; Neoadjuvant therapy; Chemotherapy; Radiotherapy; Targeted therapy

**Core tip:** It is necessary to consider multimodality treatment, including chemotherapy, radiotherapy and surgery, to improve current results of gastric cancer treatment. Recent clinical trials have shown survival benefit combining different neoadjuvant or adjuvant protocols compared with curative surgery. Furthermore, the implementation of chemotherapy with novel targeted agents could play an important role in the multimodal management of advanced gastric cancer. In this paper, we focus on a multidisciplinary approach in the treatment of gastric cancer and discuss future strategies to improve the outcome for these patients.

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## INTRODUCTION

Gastric cancer is one of the most common cancers worldwide and the second leading cause of death from malignant disease. This mortality data is explained by a late diagnosis. The incidence justifies screening programs only in Asia; in other parts of the world, gastric cancer remains a healthcare dilemma. In fact, in Japan and South Korea, the diffusion of endoscopy for gastric cancer resulted in 50% of patients with early disease (*i.e.*, T1 tumors). Conversely, in Europe and the United States, more

than two thirds of gastric cancers are found in advanced stages and most of these patients have a locally advanced resectable disease. Surgery with D2 nodal dissection is the primary treatment for patients with resectable cancer, with only a-5-year survival rate of 25.7% in locally advanced disease in these countries. To improve survival multimodal treatment has been used as an adjunct to surgery in recent years. In this review, we present a short analysis of high evidence level contributions published in the literature (phase-Ⅲ randomized controlled trials) on this topic.

## POSTOPERATIVE THERAPY: CHEMORADIOTHERAPY

The role of adjuvant chemoradiotherapy (CRT) was established by the SWOG 9008/INT-0116 trial[1]. In this study, patients with completely resected gastric and esophagogastric junction (EGJ) adenocarcinoma were randomized to receive surgery alone or surgery plus postoperative chemoradiation [bolus 5-fluorouracil (5-FU) and leucovorin before and after chemoradiation with the same combination]. Overall survival was 27 mo in the group that received surgery alone and 36 mo in the group that received adjuvant CRT. After ten years follow-up, overall survival advantage is confirmed in favor of adjuvant CRT[2]. This trial has been criticized because the surgical procedure was considered inadequate since only 10% of patients had the recommended extended lymph node dissection (D2) and the combined modality arm reported a high rate of acute toxicity, probably due to the large field of irradiation and to the RTX technique used.

In the CALGB 80101 trial[3], postoperative CRT with epirubicin, cisplatin and 5fluorouracil (ECF) before and after CRT with concurrent infusional fluorouracil did not improve survival compared to bolus 5-FU-LV before and after 5-FU-RT (INT regimen).

More recently, the role of adjuvant CRT has not been confirmed. In the ARTIST trial[4], the authors investigated the role of postoperative CRT in addition to chemotherapy (cisplatin, capecitabine) in patients with curatively resected gastric cancer with D2 lymph node dissection. In this study, CTR did not significantly reduce recurrence compared to chemotherapy alone. Stratified analysis showed that the 3 year disease free survival rate was better in the CRT group in patients with positive lymph nodes.

Pending the results of ongoing clinical trials, we can conclude that while postoperative CRT is considered a standard therapy in the United States, in Europe it remains an effective and preferred treatment after D0 or D1 dissection and R1 resection, but not after D2 dissection[5], when the role of adjuvant chemotherapy is demonstrated.

## POSTOPERATIVE THERAPY: CHEMOTHERAPY

The role of adjuvant therapy in GC has been studied during the past three decades in an attempt to improve the prognosis of patients who have undergone curative surgery. A recent meta-analysis[6] suggested a survival benefit with adjuvant chemotherapy based on fluorouracil regimens (HR = 0.82, 95%CI: 0.75-0.9, $P < 0.001$).

These results were recently confirmed by the CLASSIC and the ACTC-GC trial. The ACTS-GC study conducted in Japan demonstrated that adjuvant chemotherapy with 1 year treatment of S-1, an oral fluoropyrimidine, showed a significant benefit for gastric cancer with stage II and III who underwent gastrectomy with extended (D2) lymph node dissection, with a 3-year-overall survival (OS) for S-1 group of 80.1% compared with 70.1% for controls. The study was prematurely stopped by the Data and Safety Monitoring Committee because active treatment exceeded the efficacy threshold. The comparison of this study with those done in Western countries is difficult because of differences in survival rates, early detection rates and surgical techniques between Western and Asian countries.

Furthermore, S-1 remains an investigational agent in North America due to biological differences of how the drug is metabolized between patient populations[7].

In the CLASSIC trial[8] conducted in South Korea, China and Taiwan, patients with stage Ⅱ-ⅢB gastric cancer who underwent curative gastrectomy (D2 dissection) were randomized to surgery alone or postoperative chemotherapy with capecitabine and oxaliplatin (XELOX). The primary endpoint of the 3 year disease free survival (DSF) rate was 74% in the XELOX group and 59% in the surgery only group (HR = 0.56); stratified analysis revealed a significant difference between the two groups in stage Ⅲ disease.

However, there is no currently recognized standard regimen, particularly in countries where D2 dissection is a routine procedure.

The ITACA-S trial[9] was published during the last year in which the authors assessed whether a more intensive postoperative chemotherapy than fluoropyrimidine improves effectiveness. Patients radically resected for gastric or GEJ (≥ D1 node dissection) pN0 with pT > 2b or pN+ were randomized to receive CPT-11, LV, 5-FU for 4 cycles (FOLFIRI regimen) followed by docetaxel, cisplatin for 3 cycles or to LV, 5-FU (De-Gramont regimen) for 9 cycles. With a median follow-up of 49 mo, the use of an intensive treatment did not result in a significant prolongation of DFS and OS when compared to the De-Gramont regimen.

In conclusion, adjuvant chemotherapy with fluoropyrimidine is associated with improvement in overall survival and is recommended after complete resection in patients with stage ≥ I B who have not received perioperative treatment. The data seem to also confirm this benefit in patients treated with extended lymph node dissection.

## PERIOPERATIVE THERAPY: NEOADJUVANT CHEMOTHERAPY

Neo-adjuvant chemotherapy (CHT) has been shown to

increase the rate of complete tumor resection, to reduce the incidence of systemic metastases and, probably, to prolong survival. Overall, the data indicate that neo-adjuvant CHT is feasible, does not increase post-operative morbidity and mortality, and is able to increase the rate of R0 resection.

The MAGIC trial[10] evaluated the efficacy of a perioperative CHT. Five hundred and three patients with potentially resectable GC were randomly assigned to both preoperative and postoperative cisplatin, epirubicin and 5-FU (ECF) CHT versus surgery alone. The results evidenced a statistically significant improvement of the ECF arm in progression free survival (PFS) (HR = 0.66; 95%CI 0.53-0.81) and OS (HR = 0.75; 95%CI: 0.60-0.93; 5 year OS 36% *vs* 23%). The resected tumors were significantly smaller and less advanced in the perioperative CHT group.

The two groups had a similar incidence of postoperative complications and mortality rates and, additionally, the completion rate of 3 course preoperative CHT was 86%, while only 42% of the patients completed postoperative ECF therapy.

Recently, in the FNCLCC/FFCD TRIAL[11], 224 patients with resectable adenocarcinoma of the lower esophagus, GEJ or stomach were randomized to either perioperative chemotherapy with cisplatin and 5fluorouracil continuous intravenous infusion plus surgery or surgery alone. The multimodal treatment significantly increased the curative resection (84% *vs* 74%; $P = 0.04$), disease free (5 year rate: 34% *vs* 19%; $P = 0.003$) and overall survival (5 year rate: 38% *vs* 24%; $P = 0.02$) rates.

We are awaiting the results of the ongoing CRITICS trial that compares three cycles of preoperative polychemotherapy followed by surgery and then randomised between adjuvant chemotherapy and CRT.

In our institution, we are involved in the multicentric randomized phase Ⅲ study ITACA-S-2 that compares the efficacy of a perioperative versus a postoperative CHT treatment in patients with operable gastric cancer and assesses the benefit of a postoperative CRT.

According to published data, perioperative chemotherapy is considered the preferred option in most of Europe and the United Kingdom, but we believe that each patient should be assessed within a multidisciplinary team, waiting the pending data of ongoing trials.

## MOLECULAR TARGETED AGENTS

Recently, new elements have emerged which have shown the benefit of molecular targeted agents (MTA) in the treatment of advanced gastric cancer. human epidermal growth factor receptor 2 (HER2) overexpression has been reported in 13%-20% of gastric cancer specimens and is associated with a poor prognosis. Trastuzumab is a humanized monoclonal antibody that selectively blinds to the human epidermal growth factor receptor type 2. Based on results obtained in the treatment of HER2 positive breast cancer, the role of trastuzumab has also been studied in gastric cancer. The ToGA trial[12] randomised 594 patients with HER2 positive locally advanced, recurrent and metastatic gastric and EGJ cancer to receive trastuzumab, plus chemotherapy (cisplatin and fluorouracil or capecitabine) or CHT alone. Overall survival was 11.1 mo in patients who received chemotherapy alone and 13.8 mo in patients who received chemotherapy plus trastuzumab. This result established trastuzumab in combination with chemotherapy as the standard of care for first line treatment of HER2 positive advanced gastric cancer. According to the results obtained in metastatic settings, further clinical trials should be undertaken to evaluate the role of MTA in the perioperative setting.

Conversely, anti epidermal growth factor receptor and vascular endothelial growth factor antibodies that are widely used in advanced colon cancer have failed to improve overall survival of patients in association with chemotherapy.

## CONCLUSION

The management of gastric cancer has been evolving during the last years. Clinical data demonstrated that a multimodal approach is mandatory to achieve maximum clinical benefit; therefore, it is desirable that each center has a multidisciplinary team which should include a surgeon, gastroenterologist, medical and radiation oncologist and pathologist. An adequate selection of the patients is mandatory to optimize clinical results. To obtain this endpoint, it is critical to make an accurate and strict patient selection by a correct staging of the disease, which has to take laparoscopy into account.

We recognize that increasing numbers of patients in controlled clinical trials is essential to improve our knowledge about the best clinical practice.

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