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# Perioperative chemotherapy for resectable gastroesophageal cancer: A single-center experience

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**Abstract**

*Backgrounds*: Multimodal treatment for locally advanced gastric cancer has been reported to improve disease-free survival when compared to surgery alone. We aimed to clarify the efficacy and safety of perioperative chemotherapy for locally advanced gastric cancer patients treated in daily clinical practice.
*Methods*: Patients diagnosed with locally advanced gastric cancer were treated with perioperative chemotherapy and surgery. The primary end point was the complete resection (R0) rate. Secondary end points were disease-free survival (DFS), overall survival (OS), toxicity, radiological response rate, pathological response rate and downstaging rate. We also looked for prognostic and predictive factors for DFS, OS, pathological complete response and the R0 rate.
*Results*: Forty patients were found eligible for this retrospective analysis. At diagnosis, 52.5% of patients were classified as stage II and 47.5% were stage III. Forty percent of patients completed three preoperative cycles and three postoperative cycles. A tolerable toxicity related to chemotherapy was found. Thirty-nine patients underwent surgery: 80% reached a complete resection (R0), down-staging was detected in 57.5% and 17.5% had a pathologically complete response. The median time of disease-free survival was 34.05 months (95%CI 25.6–42.4), and the median time of overall survival was 39.01 months (95%CI 30.8–47.1). We found that the presence of comorbidities were independent predictive factors for the pathologic response, while the chemotherapy schedule and the clinical response could independently predict a complete resection.
*Conclusions*: Our results support that perioperative chemotherapy for locally advanced gastric cancer can be safely delivered in daily clinical practice, obtaining an improvement of the pathologic response and the complete resection of gastric cancer.


*Keywords:* Gastric cancer; Neoadjuvant chemotherapy; Perioperative treatment; Prognostic factors; Predictive factors

## Introduction

Although the incidence of gastric cancer is decreasing, this tumor represents the second most common cause of cancer death worldwide.[1]

Locally advanced gastric cancers are characterized by a poor prognosis. In Western populations, the 5-year survival rate for patients with completely resected stage I gastric cancer is approximately 70–75 percent while it drops to 35 percent or less for stage II disease and beyond.[2]

Although complete (R0) resection is the only unimodal treatment with curative intent, stages II and III of gastric cancer have a high rate of relapse after surgery alone. This high relapse rate may be decreased with multimodal treatment using chemotherapy and/or radiation. Recently, this therapeutic approach has been reported to improve disease free survival when compared to surgery alone. Both postoperative chemoradiation[3] and perioperative chemotherapy[4] have been studied in gastric adenocarcinomas and have shown a survival benefit. However, it has not been established the gold standard treatment for stages II

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and III of gastric cancer. Several factors including the main prognostic parameters in gastric carcinoma (tumor stage, location of the tumor, and the patient's performance status) have to be consider for the election of the most suitable treatment for each patient. Perioperative (preoperative plus postoperative) chemotherapy is generally preferred in Europe in contrast to adjuvant chemoradiotherapy used in the United States[3] or adjuvant fluoropyrimidine chemotherapy employed in Asia.[5]

Perioperative treatment has some advantages compared to adjuvant chemoradiation alone. Neoadjuvant therapy in locally advanced gastric tumors improves tumor regression, which is considered a significant prognostic factor, as it increases the resection rate of these tumors.[6] The aims of the neoadjuvant treatment include both downstaging of the tumor and early treatment of micrometastases.[7] This approach could be used either in patients diagnosed with resectable gastric cancer or in those patients with apparently unresectable but nonmetastatic disease. In the latter group, this therapy provides a greater benefit related to the downstaging of the disease with chemotherapy, enabling a complete resection of the tumor. The main aim of this multimodal treatment is the complete resection (R0) of the gastric cancer.

In two randomized trials (the MAGIC trial with 532 patients and the FNCLCC/FFCD trial with 224 patients), perioperative chemotherapy was found to improve overall survival and progression free survival compared to surgery alone.[4,8] These trials included patients with adenocarcinoma of the stomach and gastroesophageal junction. The perioperative chemotherapy schedules used were based on cisplatin and 5-fluorouracil (5-FU) in both trials, and no significant increase of postoperative morbidity or mortality was detected.

In this study, we aimed to confirm the efficacy and safety of perioperative chemotherapy for locally advanced gastric cancer patients treated in daily clinical practice. The primary end points of our study were the complete resection (R0) rate and disease-free survival (DFS) for 40 consecutive locally advanced gastric cancer patients treated with perioperative chemotherapy. We also looked for prognostic and predictive factors for DFS, overall survival (OS) and the R0 rate.

## Patients and methods

We designed an analysis of patients treated with perioperative chemotherapy for locally advanced gastric cancer in daily clinical practice in Principe de Asturias Universitary Hospital in Alcala de Henares, Madrid (Spain). This observational study was conducted in accordance with the Declaration of Helsinki of the World Medical Association and all its amendments and with national and local regulations. This project was approved by an Independent Ethics Committee, and all patients provided their written informed consent prior to study enrollment.

### *Patient population*

Patients diagnosed with locally advanced gastric cancer and treated with perioperative chemotherapy between June 2007 and July 2012 in our center were eligible. We included patients with histologically proven and locally advanced gastric cancer (clinical T2-4, N−/+, M0) who were fit for surgery and perioperative chemotherapy. The following blood levels were mandatory: neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, total bilirubin $< 1.5 \times$ ULN, AST, ALT $< 2.5 \times$ ULN. We obtained all clinical, radiological and pathological data from patient medical records.

Exclusion criteria were patients unfit to chemotherapy because of their performance status, alterations of the laboratoric parameters and tumor bleeding requiring an emergency surgery.

### *Staging and treatment*

All patients underwent pre-treatment staging and perioperative treatment according to our center's multidisciplinary group guidelines for gastrointestinal tumors.

The pre-treatment staging was performed with gastroscopy, computerized tomography (CT) scan and echoendoscopy. The Seventh Edition TNM classification was used for staging.[9] Preoperative biopsy was mandatory.

Perioperative chemotherapy schedules were selected by the oncologists according to each patient's baseline characteristics and comorbidities. The chemotherapy schedules were as follows: (a) cisplatin (60 mg/m$^2$), epirubicin (50 mg/m$^2$) and a fluoropyrimidine (5FU 200 mg/m$^2$ daily or capecitabine 625 mg/m$^2$ daily) every three weeks[4]; (b) docetaxel (75 mg/m$^2$), cisplatin (75 mg/m$^2$) and a fluoropyrimidine (capecitabine 1000 mg/m$^2$ twice a day for 14 days or 5FU 1000 mg/m$^2$/day for 5 days) every 3 weeks[10]; (c) a combination of oxaliplatin (130 mg/m$^2$) and capecitabine (1000 mg/m$^2$ twice a day for 14 days) every 3 weeks[11] or oxaliplatin (100 mg/m$^2$), folinic acid (400 mg/m$^2$) and 5-FU (bolus 400 mg/m$^2$ and 3000 mg/m$^2$ 46-h continuous infusion) every 2 weeks[12]; (d) a combination of cisplatin (100 mg/m$^2$) and 5-FU (1000 mg/m$^2$/day for five days) every 4 weeks[13] or a combination of cisplatin (80 mg/m$^2$) and capecitabine (1000 mg/m$^2$ twice daily for 14 days).[14]

Three cycles of preoperative chemotherapy were planned. A CT scan was used to evaluate the resection criteria before the surgery. Surgery was performed in our center 6–8 weeks after the last cycle of preoperative chemotherapy. A partial or complete gastrectomy was performed, and a D2 lymphadenectomy was preferred according to the Japan Clinical Oncology Group.[15–17]

Pathologic evaluation of the surgical sample was performed to complete the staging and define the histological subtype (according to Lauren's classification),[18] lymphovascular and perineural invasion, mucinous component, nuclear grade, resection type [complete resection (R0), microscopic residual disease (R1) and macroscopic residual