NEOADJUVANT CHEMOTHERAPY IN ROUTINE PRACTICE FOR LOCALLY ADVANCED GASTRIC AND GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA

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Abstract

Background: Neoadjuvant chemotherapy has significantly improved outcomes in patients with locally advanced (LA) gastric cancer. This study aimed to evaluate the efficacy and safety of neoadjuvant chemotherapy in patients with LA gastric and gastroesophageal junction (GOJ) cancer in routine clinical practice.

Methods: We retrospectively analyzed 41 patients with LA gastric or GOJ adenocarcinoma who received neoadjuvant chemotherapy between January 2015 and December 2022. Clinical outcomes included treatment response, disease-free survival (DFS), overall survival (OS), and treatment-related toxicity.

Results: Median age was 55 years (range 22–69), and 73% were male. At diagnosis, 29.3% had stage II disease and 70.7% stage III. Neoadjuvant regimens included CF (61%), FOLFOX/XELOX (17%), and FLOT (22%). Thirty-nine patients (93%) completed chemotherapy. R0 resection was achieved in 61%, while 12% underwent exploratory procedures. Adjuvant chemotherapy was completed by 39% of patients.

Postoperative complications occurred in one patient (anastomotic leakage). Grade 3/4 adverse events included gastrointestinal toxicity (7.9%), leukopenia (12%), and anemia (7.9%). Disease control was observed in 68.3% of patients, tumor downstaging in 46.3%, and pathological complete response (pCR) in 17%. Five-year OS was 47% overall and 76% among patients who underwent surgical resection. No relapse occurred in patients with pCR. Median OS was 33 months, with a median follow-up of 68 months.

Conclusions: Neoadjuvant chemotherapy is effective and well-tolerated in LA gastric and GOJ adenocarcinoma. It facilitates curative surgery and improves long-term survival, particularly in patients achieving pCR.

Keyword: Gastric cancer, Gastroesophageal junction cancer, Neoadjuvant chemotherapy, Pathological complete response, Overall survival, Locally advanced cancer

1.INTRODUCTION

Gastric cancer is the fifth most common malignancy worldwide and the third leading cause of cancer-related mortality, with an estimated 1 million new cases diagnosed annually [1]. Despite advances in surgical techniques, the prognosis of patients with locally advanced gastric and gastroesophageal junction (GOJ) adenocarcinoma remains poor due to high rates of recurrence and distant metastasis following surgery alone [2,3].

Multimodal treatment strategies incorporating systemic chemotherapy have been shown to improve survival outcomes. Neoadjuvant chemotherapy, administered prior to surgical resection, aims to downstage tumors, eradicate micrometastatic disease, and increase the likelihood of achieving a complete (R0) resection [4]. Several landmark randomized controlled trials, including the MAGIC and FLOT4-AIO studies, demonstrated that perioperative chemotherapy significantly improved

overall survival compared with surgery alone in patients with resectable gastric or GOJ adenocarcinoma [2,3].
Pathological response to neoadjuvant therapy, particularly pathological complete response (pCR), has emerged as a strong prognostic marker, correlating with improved long-term outcomes [5]. However, while randomized trials provide high-level evidence, there is a relative paucity of data on the real-world effectiveness and safety of neoadjuvant chemotherapy, particularly in routine clinical practice outside highly controlled research settings. Real-world studies are essential to assess treatment feasibility, toxicity, and clinical outcomes across diverse patient populations.
The aim of this retrospective study was to evaluate the efficacy and safety of neoadjuvant chemotherapy in patients with locally advanced gastric and GOJ adenocarcinoma treated at our institution. Clinical endpoints included response rates, surgical outcomes, disease-free survival (DFS), overall survival (OS), and treatment-related toxicity.

2. STUDY DESIGN AND PATIENT POPULATION

This retrospective observational study included all patients diagnosed with locally advanced (LA) gastric or gastroesophageal junction (GOJ) adenocarcinoma who received neoadjuvant chemotherapy at the medical oncology department of university hospital of Oran, between January 2015 and December 2022.

Inclusion criteria were:

- Age ≥18 years
- Histologically confirmed adenocarcinoma of the stomach or GOJ
- Clinical stage II–III disease according to the 8th edition of the AJCC TNM staging system
- Planned for curative-intent surgical resection following neoadjuvant chemotherapy

Exclusion criteria included :

- Distant metastatic disease at diagnosis
- Prior systemic chemotherapy or radiotherapy
- Concurrent malignancies
- Incomplete clinical records

Data collection: Clinical, pathological, and treatment-related data were retrospectively collected from paper medical records. Extracted variables included demographic characteristics, tumor location, clinical stage, chemotherapy regimen, treatment completion, surgical procedure, pathological findings, postoperative outcomes, and follow-up data. Survival status and recurrence were obtained from follow-up visits or medical records.

Diagnostic-Evaluation and Staging

All patients underwent upper gastrointestinal endoscopy with biopsy. Baseline staging included contrast-enhanced computed tomography of the chest, abdomen, and pelvis. Endoscopic ultrasound was performed when available. Tumors were staged according to the AJCC TNM classification, 8th edition.

Treatment and Surgical Management

Neoadjuvant chemotherapy regimens were administered according to institutional practice. After completion of chemotherapy, patients were re-evaluated for surgical resection. Surgery was performed with curative intent whenever feasible and included subtotal or total gastrectomy with D2 lymphadenectomy. Exploratory surgery was performed in cases of unresectable disease.

Outcome Measures

The primary outcomes were overall survival (OS) and disease-free survival (DFS). Secondary outcomes included tumor response, pathological complete response, tumor downstaging, rate of R0 resection, completion of treatment, and treatment-related toxicity.
Response, Toxicity, and Statistical Analysis
Tumor response was evaluated radiologically using RECIST 1.1 criteria and pathologically on resected specimens. Pathological complete response was defined as the absence of residual tumor (ypT0N0). Adverse events were graded according to CTCAE version 5.0.
Categorical variables were expressed as frequencies and percentages, and continuous variables as median and range. Survival was estimated using the Kaplan–Meier method, and group comparisons were performed using the log-rank test. A p-value <0.05 was considered

statistically significant. Statistical analyses were performed using SPSS version 25.0.

3. RESULTS

Patient Characteristics

Forty-one patients with gastric cancer who received preoperative neoadjuvant chemotherapy at the medical oncology department of university hospital of Oran, between January 2015 and December 202 were collected. The clinical baseline data are shown in Table 1

Table 1: Patient characteristics (n=41)

Clinical Features	**N (%)**
The median age at diagnosis years (range)	55 (22-69)
Gender, male (%)	30 (73)
ECOG **0** **1** **2**	 5 (12.2) 31 (75.6) 5 (12.2)
Histology ***Adenocarcinoma*** **Mucinous carcinoma** ***Signet ring cell carcinoma*** **Not specified**	 28 (68.3) 4 (9.7) 8 (19.5) 1 (2.4)
Location : **Proximal (GOJ: Gastroesophageal junction, cardia, fundus)** **Body** **Distal**	 6 (14.6) 19 (46.3) 16 (39)
Linitis plastica **Yes** **No**	 4 (9.7) 37 (90.2)
Stage c TNM **IIa** **IIb** **IIIa** **IIIb** **IIIc**	 6 (14.6) 6 (14.6) 9 (22) 17 (41.4) 3 (7.3)
Median BMI	20.5+/- 4.9
Weight loss >10%	12 (29.2)

Treatment Characteristics: Neoadjuvant chemotherapy was administered to all patients using three different regimens. The choice of regimen was based on institutional practice, patient performance status, and treatment availability during the study period. Thirty-nine patients (93%) successfully completed the planned neoadjuvant chemotherapy.

Treatment discontinuation occurred in a small proportion of patients, mainly due to treatment-related toxicity or disease progression.
Following completion of neoadjuvant chemotherapy, patients were reassessed for surgical management.

The treatment characteristics of the study participants are summarized in Table 2. All patients received neoadjuvant chemotherapy as part of a multimodal treatment strategy.

Table 2. Treatment characteristics of study participants.

Treatment modalities	**N (%)**
Type of pre operative chemotherapy **CF/ Carboplatin- 5FU** **FOLFOX/XELOX** **FLOT**	 25 (61) 7 (17) 9 (22)
Type of surgery **Total gastrectomy** ***Subtotal gastrectomy (4/5)*** **Palliative surgery** **Exploratory laparotomy** **No surgery**	 8 (19.5) 17 (41.4) 7 (17) 5 (12.2) 9 (22)
Type of lymphadenectomy **D1** **D2**	 1 (2.4) 24 (58.5)
Resection margins **R0 resection** **R1 resection** **R2 resection**	 25 (61%) 0 (0) 1 (2.4)

Treatment-Related Adverse Events

Neoadjuvant chemotherapy was well tolerated. Grade 3–4 adverse events were mainly hematological and gastrointestinal. Hematological toxicity included grade 3–4 leukopenia in 5 patients (12.2%). Febrile neutropenia occurred in 1 patient (2.4%) and Anemia was reported in 2 patients (8.7%). No treatment-related mortality was observed.

Non-hematological grade 3–4 toxicities were mainly gastrointestinal. Anorexia was reported in 4 patients (10.2%), while vomiting occurred in 2 patients (4.9%)

and nausea in 2 patients (4.9%). Diarrhea was observed in 1 patient (2.4%), and mucositis in 1 patient (2.4%). These gastrointestinal adverse events were managed with supportive care and did not lead to permanent treatment discontinuation in most cases.
Postoperative complications were observed in a limited number of patients. Anastomotic leakage was reported in one patient and was associated with secondary

peritonitis. No other major postoperative complications were recorded during the postoperative period.

Chemotherapy Completion and Postoperative Treatment

A total of 39 patients (93%) completed the planned neoadjuvant chemotherapy. The median number of neoadjuvant chemotherapy cycles administered was 4, with a range of 2 to 12 cycles. Treatment discontinuation occurred in a small number of patients due to toxicity or disease progression.

Following surgery, adjuvant chemotherapy was administered in 16 patients (39%). The median number of adjuvant chemotherapy cycles received was 3, ranging from 1 to 4 cycles. The remaining patients did not receive adjuvant chemotherapy due to postoperative complications, patient refusal, or poor performance status.

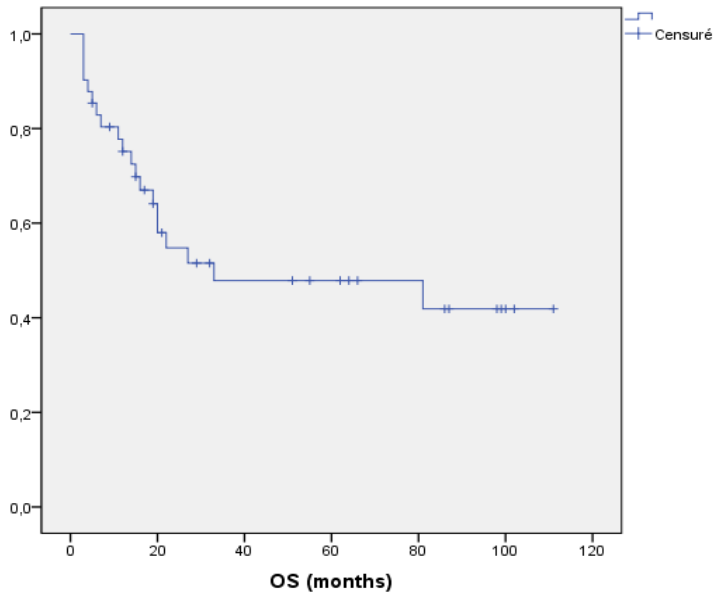
Treatment Response and Survival Outcomes

Following neoadjuvant chemotherapy, the overall disease control rate was 68.3%, indicating that a substantial proportion of patients achieved either tumor shrinkage or stabilization. Tumor down-staging, defined as a reduction in clinical or pathological tumor stage following treatment, was achieved in 46.3% of patients, reflecting a significant effect of systemic therapy in reducing tumor burden prior to surgery.

A pathological complete response (pCR), defined as the absence of residual viable tumor cells in the resected specimen, was observed in 17% of patients. Importantly, none of the patients who achieved pCR experienced disease recurrence during the follow-up period, highlighting the prognostic significance of complete pathological response in locally advanced gastric and gastroesophageal junction adenocarcinoma.

Survival outcomes were favorable, particularly among patients undergoing curative-intent surgery. The 5-year overall survival (OS) for the entire cohort was 47%, while patients who underwent R0 resection demonstrated a markedly higher 5-year OS of 76%. The median overall survival for the entire study population was 33 months, calculated after a median follow-up of 68 months (Figure1). These results indicate that neoadjuvant chemotherapy not only facilitates surgical resection but also contributes to long-term survival, particularly in patients achieving complete or partial tumor response.

Fig. 1 Kaplan-Meier plot Overall survival (OS)



4. DISCUSSION:

This retrospective study provides real-world evidence on the feasibility, efficacy, and safety of neoadjuvant chemotherapy in patients with locally advanced gastric and gastroesophageal junction (GOJ) adenocarcinoma. Our findings demonstrate high treatment completion rates, acceptable toxicity, and favorable surgical and survival outcomes, consistent with previously published clinical trials and observational studies.

In our cohort, the CF regimen was the most frequently used, followed by FOLFOX/XELOX and FLOT. Thirty-nine patients (93%) completed neoadjuvant chemotherapy, highlighting the feasibility of systemic treatment in routine clinical practice. Similar completion rates have been reported in other real-world studies, confirming that modern chemotherapy regimens are generally well tolerated [1, 4].

Surgical resection remains the cornerstone of curative treatment. In our study, 61% of patients underwent R0 resection after neoadjuvant chemotherapy, while 12% had exploratory procedures due to unresectable disease. These results are comparable to the MAGIC trial, which reported an R0 resection rate of 69% in patients receiving perioperative chemotherapy [2], and to more

recent FLOT4-AIO data, which showed R0 rates of 85% with the FLOT regimen [3]. Our slightly lower rate may reflect the inclusion of patients treated in routine practice, including those with more advanced disease.

Tumor response is an important prognostic factor. In this study, 46.3% of patients experienced tumor downstaging, and 17% achieved a pathological complete response (pCR). Notably, no relapses were observed in patients achieving pCR, consistent with evidence that pCR is associated with excellent long-term survival [6, 7]. These findings underscore the prognostic relevance of pathological response in clinical practice and support the use of neoadjuvant chemotherapy as a tool for both tumor control and treatment stratification.

Treatment-related toxicity was manageable. Grade 3–4 gastrointestinal adverse events occurred in 7.9% of patients, while hematologic toxicities were observed in 12% (leukopenia) and 7.9% (anemia). These rates are similar to those reported in clinical trials and real-life studies, suggesting that modern regimens can be safely administered outside of controlled trial settings [8].

Our study has several limitations. Its retrospective design and single-center setting may introduce selection bias. Additionally, the sample size is relatively small, and long-term follow-up data are limited. Nevertheless, these real-world findings complement clinical trial data and provide valuable insights into treatment patterns, feasibility, and outcomes in routine practice.

Conclusion: Neoadjuvant chemotherapy is an effective and safe treatment strategy for patients with locally advanced gastric and GOJ adenocarcinoma. It facilitates surgical resection, achieves meaningful tumor response, and is associated with favorable survival outcomes, particularly in patients attaining pathological complete response. Future prospective studies in broader populations are warranted to further optimize treatment selection and improve outcomes.

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