# Neoadjuvant chemotherapy in conjunction with D2 gastrectomy for management of locally advanced gastric adenocarcinoma: a specialized unit experience

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**Background**
Gastric carcinoma is ranked the fourth most diagnosed cancer worldwide. In Egypt, it represents 1.8% of all types of cancers with male predilection. Most of the patients are diagnosed late, with poor prognosis. The effect of neoadjuvant chemotherapy has been discussed in literature with various outcomes.
**Aim**
The aim of this study was to evaluate the outcome of preoperative chemotherapy (XELOX) in conjunction with D2 gastrectomy in the management of locally advanced gastric adenocarcinomas in our specialized upper gastrointestinal track surgery unit with respect to response to neoadjuvant treatment, postoperative complications, resection margins, progression-free survival, and recurrence.
**Patients and methods**
A prospective cohort observational study was done on 25 patients who presented to Ain Shams University Hospitals at the upper gastrointestinal track surgery, oncology, and internal medicine outpatient clinics with locally advanced gastric adenocarcinoma stage III and IVa according to the 8th edition of American Joint Committee on Cancer for gastric carcinoma, from January 2017 to January 2019 with 24 months of follow-up. All patients followed our unit's protocol in receiving neoadjuvant chemotherapy after multidisciplinary team revision of the cases for preoperative downstaging of the tumor.
**Results**
A total of 25 patients started neoadjuvant chemotherapy. Overall, 10 (40%) patients showed partial response, seven (28%) patients had a stable disease, and eight (32%) patients showed progression of the tumor, where two of them developed metastasis. A total of 23 (92%) patients underwent surgery after four cycles of neoadjuvant treatment, 18 (78.3%) underwent D2 gastrectomy, four (17.4%) had palliative resection, and one (4.3%) was irresectable. R0 was noticed in 18 (81.8%) patients and R1 in four (18.2%) patients. Recurrence occurred in seven (43.75%) patients during a 2-year follow-up period, with median progression-free survival of 17.5±6.9 months (45.3%). The median survival after 2 years of follow-up was 18±6.5 months (56%).
**Conclusion**
Despite the modest effect of neoadjuvant treatment on downstaging locally advanced gastric adenocarcinoma, the clinical outcome regarding R0 resection is satisfactory, with an acceptable recurrence rate. We did not consider survival rate as an end point owing to the short-term follow-up period.

**Keywords:**
downstaging, gastric carcinoma, locally advanced, neoadjuvant chemotherapy

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## Introduction

Gastric cancer is considered the fourth most diagnosed malignancy and the second leading cause of cancer-related death worldwide [1]. More than 70% of cases occur in developing countries, particularly in Eastern Asia. In Egypt, gastric cancer represents 2% of all types of malignancies, with a male to female ratio of 1.4 : 1. At the Egyptian National Cancer Institute (NCI Egypt), gastric cancer represents 2 and 1.5% in males and females, respectively. The median age of the patients is 54 years [2]. A multidisciplinary team should be integrated in the diagnosis and management of gastric carcinomas for planning the sufficient effective treatment [3].

Preoperative staging is crucial and should be done using TNM classification, as locally advanced gastric carcinomas stage III and IVa without metastasis are potentially curable [4]. Computed tomography (CT) scan is routinely used for preoperative staging. It has a sensitivity that ranges between 33 and 81% and a specificity of 82–96%. Sensitivity for discovering nodal disease is 47–84%, with specificity of 25–92%. It has an overall accuracy of 43–82% for T staging. Positron emission tomography (PET)-CT has a low detection rate because of the low tracer accumulation in diffuse and mucinous tumor types, which are frequent in gastric cancer. It has a significantly lower sensitivity compared with CT in the detection of local lymph node involvement (56 vs. 78%), although it has an increased specificity (92 vs. 62%) [5].

Despite the recent improvements in cancer therapy, ~80% of patients with gastric cancer are considered as locally advanced disease at the time of diagnosis, with poor prognosis [6].

Radical gastrectomy remains the most effective treatment for patients with gastric carcinoma; however, recurrence and metastasis might occur in 40–60% of the patients even after curative surgery, and this may be owing to microperitoneal seedling at the time of surgery and micrometastasis. The 5-year survival rates after surgery alone range from 20 to 50% in the Western countries and ~70% in the Eastern ones [7].

Different multidisciplinary methodologies have been accepted in the past years to improve survival rate [8]. Neoadjuvant chemotherapy is used to downstage tumor size and convert unresectable tumors to resectable ones, and it may play a role in improving microscopic resection by eradicating micrometastasis, especially with chemosensitive malignancies [9].

However, neoadjuvant chemotherapy may delay the decision of curative surgery and may induced toxicity that impedes surgery if tumor is not responding to treatment. So, until now, there is no absolute evidence for survival advantage of neoadjuvant chemotherapy in the management of gastric carcinoma [10,11].

Oxaliplatin combined with capecitabine has been used as one of the standard perioperative chemotherapy regimens with grade II recommendations for advanced gastric cancer [12].

In the past 20 years, numerous randomized clinical trials have studied the role of neoadjuvant chemotherapy in the management of gastric and gastroesophageal junctional tumors. However, there is much debate whether those patients could get survival benefits from it [13–16].

Our study was conducted to evaluate the outcome of neoadjuvant chemotherapy in conjunction with D2 gastrectomy according to our present unit protocol in patients with locally advanced gastric adenocarcinoma with respect to response to neoadjuvant treatment, postoperative complications, resection margins, and recurrence during a 2-year follow-up.

## Patients and methods

A prospective cohort observational study was conducted on 25 patients who presented to Ain Shams University hospitals at the upper gastrointestinal track (GIT) surgery, oncology, and Internal medicine outpatient clinics with locally advanced gastric adenocarcinoma stage III and IVa according to the 8th edition of American Joint Committee on Cancer (AJCC) for gastric carcinoma [17], from January 2017 to January 2019 with 24 months of follow-up. All patients were subjected to neoadjuvant chemotherapy after multidisciplinary team (MDT) decision for preoperative downstaging of the tumor.

Ethical approval was taken from Ain Shams University Ethical Committee, and a written consent was taken from every patient after explanation of all details of the planed treatment, respecting their privacy, keeping their private information confidentially, respecting their rights to change their mind and to withdraw without a penalty, monitoring their welfare and if they experienced adverse reactions unexpected effects or change in their clinical status, and ensuring appropriate treatment. Full explanation of the operation was told with realistic expectations, along with all the possible intraoperative, early, and late postoperative complications. Surgeries were done by the same surgical team throughout the study.

### Inclusion criteria

All adult patients with histologically proved locally advanced gastric adenocarcinoma and type III junctional esophagogastric adenocarcinoma, clinically staged III and IVa according to the 8th edition of AJCC for gastric adenocarcinoma, with good performance status (0–1) of Eastern Cooperative Oncology Group and candidate for neoadjuvant chemotherapy were included in the study.

### Exclusion criteria

Patients with gastric carcinoma stage IVb with proved metastasis by CT and PET scans were excluded. Patients with types I and II junctional esophagogastric

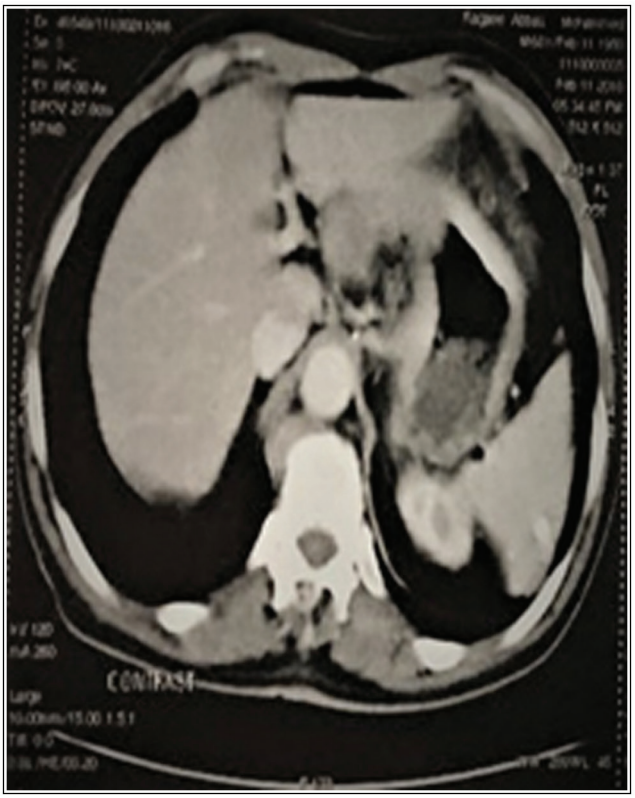
adenocarcinoma were also excluded, as these tumors are mainly esophageal. Patients with active GIT bleeding, patients with complete gastric outlet obstruction, and patients with serious hepatic, renal, lung, and cardiac comorbidities were excluded as well. Patients with concurrent other carcinomas and prior history of previous gastric surgery or chemotherapy were also excluded.

A full detailed history was taken, and an examination was done for every patient. Clinical staging was confirmed by endoscopy and biopsy (Fig. 1), pelviabdominal, chest CT scans, and pelviabdominal ultrasound (Figs 2 and 3). Staging laparoscopy was done initially for all patients with biopsy from any suspicious lesion away from the mass, and ascitic aspirate was sampled for cytology if found. PET/CT scan was done for patients with stage IVa to exclude any metastasis. Exclusion of brain metastasis was done by careful neurological examination. Lymph node metastasis was assessed based on radiological images and clinical examination. For junctional tumors, localization was done according to Siewert classification (Table 1) of esophagogastric tumors, and types I and II were excluded from this study. Full laboratory investigations were done, including serum CEA and CA19.9.

### Staging laparoscopy

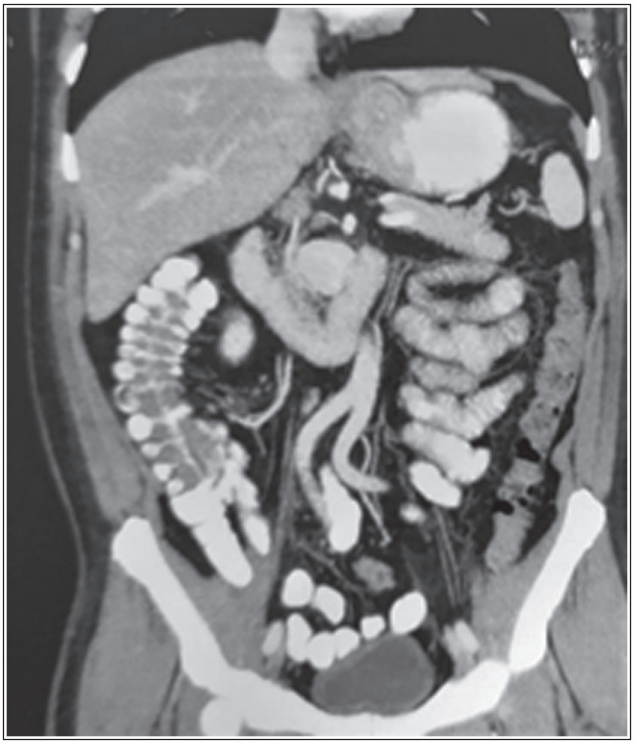
The patient was placed in the supine position. Pneumoperitoneum was obtained by Veress needle followed by ports introduction. A 10-mm port for the 30° lens camera was placed under direct vision just above the umbilicus, a 5-mm working port was placed

**Figure 1**



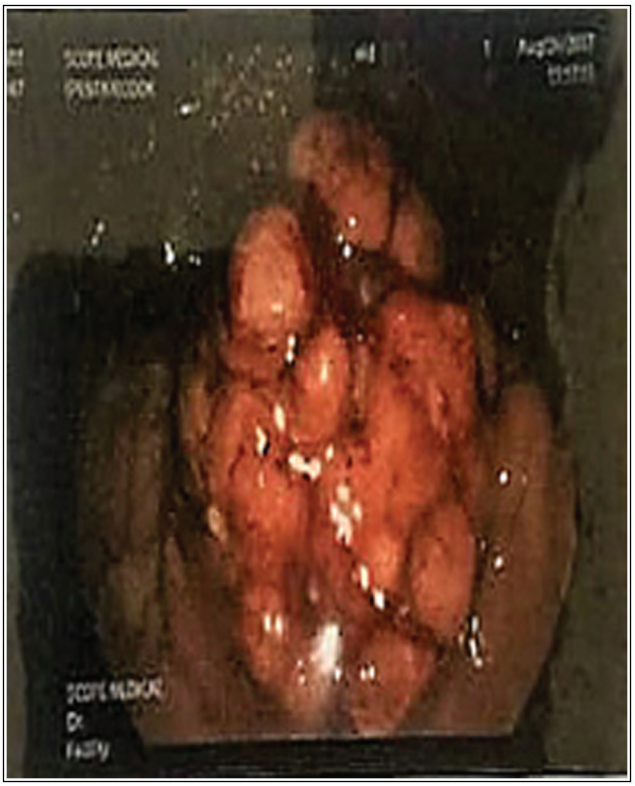

Upper endoscopy showing large gastric mass.

**Figure 2**



Computed tomography scan showing huge greater curvature gastric mass.

**Figure 3**



Computed tomography scan showing huge gastric mass at the cardia.

**Table 1 Siewert classification of esophagogastric tumors [18]**

| Siewert | Description | Surgical approach |
|---|---|---|
| I | Tumor center located between 5 and 1 cm proximal to the anatomical cardia | Approached as esophageal or EGJ cancer |
| II | Tumor center located between 1 cm proximal and 2 cm distal to the anatomical cardia | Approached as esophageal or EGJ cancer |
| III | Tumor center located between 2 and 5 cm distal to the anatomical cardia | Approached as gastric cancer |

in the right midclavicular line mid-way between the camera and the costal margin, and another 10-mm working port was placed at the same point on the left side. Exploration of all abdominal quadrants, Douglas pouch, and liver for detection of any metastatic lesions or suspected peritoneal nodules was done. Samples of ascitic fluid for cytology were taken if found. Biopsies were taken from any suspected lesions away from the tumor. Opening of the lesser sac for inspection of the tumor for direct nearby organ infiltration, with avoidance of direct contact with visceral peritoneum around it to avoid dissemination was done. Tube jejunostomy was done for patients with dysphagia, patients with impending gastric outlet obstruction with recurrent vomiting, and patients with marked weight loss to ensure supplementary alimentary feeding during neoadjuvant therapy.

### Neoadjuvant treatment

Patients included in the study were given four cycles of XELOX, each 3 weeks; the cycle consists of oxaliplatin 130 mg/m$^2$ intravenous infusion over 2 h on day 1 and oral capecitabine 1000 mg/m$^2$ twice daily from day 1 to day 14.

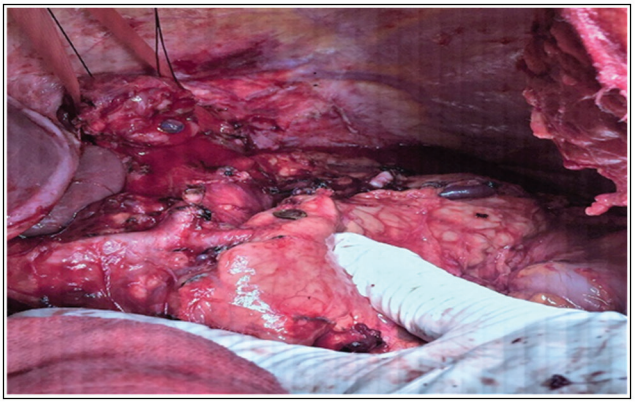
### Surgical treatment

D2 radical total or near total gastrectomy with Roux-en-Y esophagojejunostomy or gastrojejunostomy was our main intention. This included en-block resection of the spleen, greater omentum, and lesser omentum with adequate proximal safety margin. Lymph nodal dissection included the lymph nodes at the porta hepatis, the celiac lymph nodes, and all nodes along the branches of the celiac axis including the splenic artery, left gastric artery, hepatic artery, the nodes over the pancreas, and retroperitoneum. In case of peritoneal dissemination, palliative gastrectomy was done if the stomach was found resectable. Right thoracotomy was done if needed to achieve complete radicality. Tube jejunostomy was done to start early alimentary feeding in patients who did not get it during staging laparoscopy (Figs 4–6).

### Outcome measures

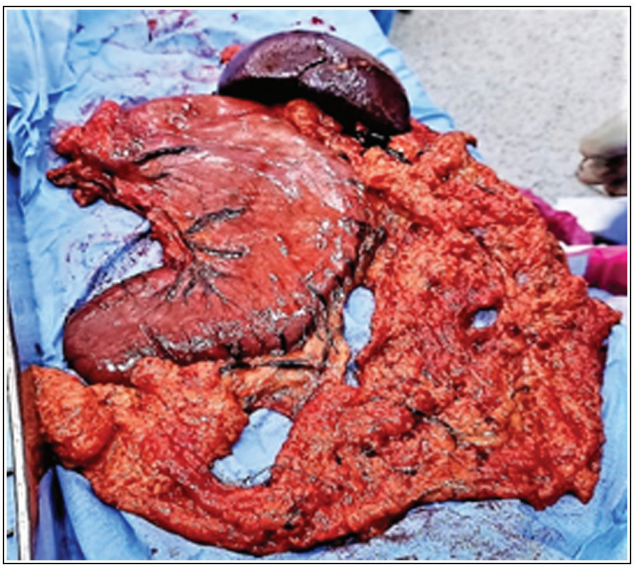
Clinical evaluation was carried out after four cycles of neoadjuvant chemotherapy to assess response for treatment according to "Response Evaluation Criteria in Solid Tumor" (RECIST v1.1) [19], where '1' represents complete response: disappearance of all target lesions, and any pathological lymph nodes (whether target or non-target) must have reduction in short axis to less than 10 mm; '2' represents partial response: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters; '3' represents progressive disease: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Moreover, the appearance of one or more new lesions is also considered progression; and '4'

**Figure 4**



Surgical bed after radical D2 gastrectomy.

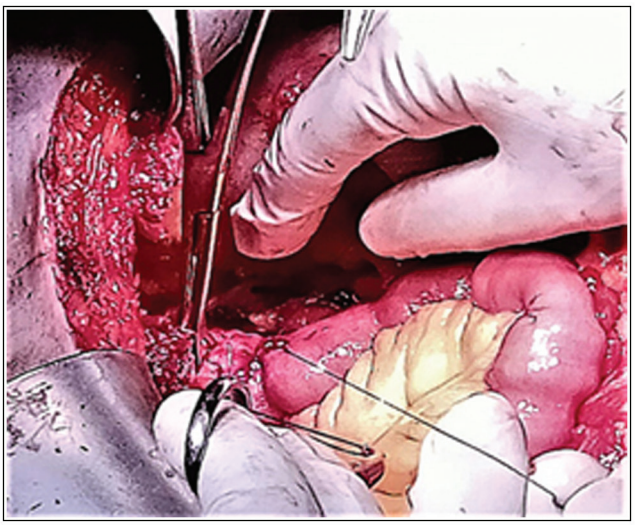
**Figure 5**



Specimen after resection.

represents stable disease: neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters. Restaging was done with the aid of radiological imaging including pelviabdominal and chest CT scanning, pelviabdominal ultrasound, and endoscopy. Postoperative evaluation was done at baseline and according to a schedule program for oncology patients at 1, 3, 6, 9, 12, 18, and 24 months including follow-up laboratory and radiological investigations, with endoscopy. Postoperative histopathology was considered regarding tumor size, wall invasion, and dissected diseased lymph nodes according to AJCC tumor/node/metastasis (TNM) classification and staging systems for gastric cancer. Regarding resection margins, R0 was considered when no microscopic infiltrations, R1 with microscopic infiltrations, and R2 when macroscopic infiltrations were detected. Recurrence was considered with development of any newly gross lesion or metastasis. Follow-up was done at GIT surgery and oncology outpatient clinics.

**Figure 6**



Fashioning of esophagojejunostomy.

### Statistical analysis

Data were collected, tabulated, and statically analyzed. Analysis of data was done using SPSS (statistical program for the social sciences version 26, IBM Corp., Armonk, NY, USA) as follows: descriptive statistics (mean, SD, and range) was done for patient characteristics and continuous variables. Quantitative data were tested for normality and were compared with the Mann–Whitney *U*-test, analysis of variance, and paired *t*-test. For related samples, $\chi^2$ test was used. Survival curves were estimated by the Kaplan–Meier approach.

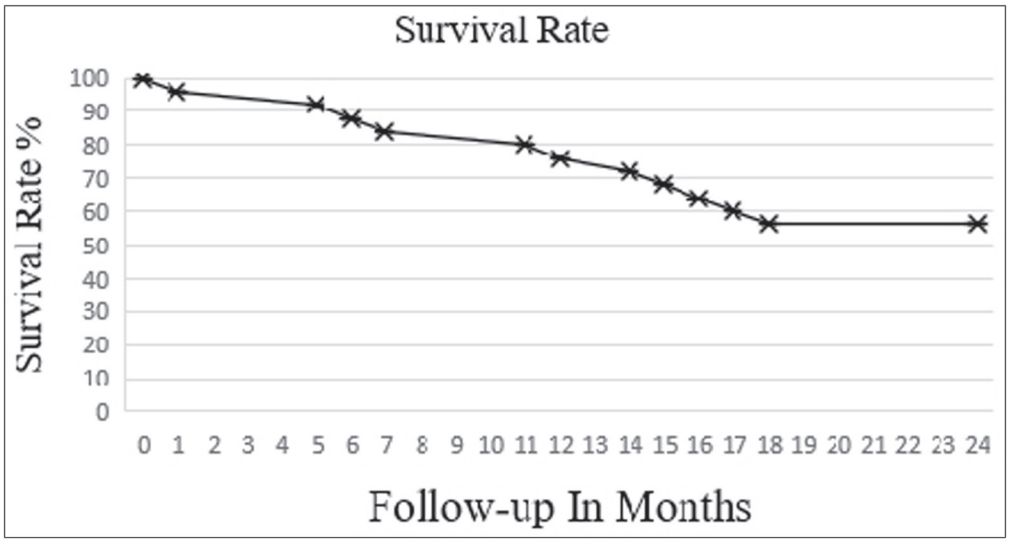
## Results

The study was conducted between January 2017 to January 2019 with 24 months of follow-up. A total of 25 patients were included: 12 patients between January 2017 and December 2018, and 13 patients between January 2018 and January 2019. At the time of documentation of our data in February 2021, 11 patients had died. Response to neoadjuvant chemotherapy, adverse effects, and operative, intraoperative, and postoperative parameters were finalized systematically in all patients and allegorized (Fig. 7).

### Initial demographic data before starting neoadjuvant therapy

The study was done on 25 patients, comprising 17 males (68%) and eight females (32%). The overall

**Figure 7**




Algorithm illustrating results of the study.

mean age was 56.1 ± 7.4 years (range: 38–65 years). A total of 18 (72%) patients were classified as stage III and seven (28%) patients as stage IVa according to AJCC for gastric carcinoma. Overall, five (20%) patients had esophagogastric junctional tumors and were as class III according to Siewert classification of esophagogastric tumors. Upper GIT endoscopy findings were fungating mass in 19 (76%) patients and ulcerating mass in six (24%) patients. Histologic type and grading were adenocarcinoma grade II in 20 (80%) patients and grade III in five (20%) patients. The median size of masses after radiological assessment was 9.76 ± 1.9 × 4.3 ± 1.25 cm. The main presenting symptoms in most of the patients were dysphagia in five patients, weight loss in eight patients, recurrent vomiting in five, and epigastric pain in seven patients. Staging laparoscopy was done for all patients before neoadjuvant chemotherapy. A total of 25 patients were confirmed to have stage III or Iva, with no peritoneal or omental metastasis, ascitic fluid was found in seven patients and showed no malignant cells after cytology, no nearby organ infiltration was found, and tube jejunostomy was done for the 18 patients (five dysphagia, eight weight loss, and five recurrent vomiting with partial gastric outlet obstruction). Clinical staging was done before starting neoadjuvant chemotherapy and is listed in Table 2. All patients started neoadjuvant treatment within 1–2 weeks after full assessment.

**Table 2 Demographic data and initial clinical and radiological staging**

| | *n* (%) |
|---|---|
| Age (years) | 38–65 56.1 ± 7.4 |
| Sex | |
| Males | 17 (68) |
| Females | 8 (32) |
| Comorbidities | |
| Diabetes | 9 (36) |
| Hypertension | 7 (28) |
| Smoking | 16 (64) |
| Presenting symptoms | |
| Dysphagia | 5 (20) |
| Weight loss and anorexia | 8 (32) |
| Recurrent vomiting | 5 (20) |
| Pain | 7 (28) |
| Upper GIT endoscopy findings | |
| Fungating mass | 19 (76) |
| Ulcerating mass | 6 (24) |
| Tumor localization | |
| Body and fundus | 15 (60) |
| Antral | 5 (20) |
| Cardia | |
| Class III | 5 (20) |
| Clinical staging | |
| III | 18 (72) |
| IVa | 7 (28) |
| Tumor staging according TNM classification | |
| T3 | 18 (72) |
| T4 | 7 (28) |
| N1 | 1 (4) |
| N2 | 17 (86) |
| N3 | 7 (28) |
| M | 0 0 |
| Median size of mass by CT | 9.76 ± 1.9 × 4.3 ± 1.25 cm |

CT, computed tomography; GIT, gastrointestinal track.

#### Outcomes after neoadjuvant chemotherapy

A total of 25 patients completed four cycles of neoadjuvant chemotherapy in a median time of 12.8 ± 1.8 weeks. Toxicities were assessed after each cycle and recorded according to Common Terminology Criteria for Adverse Events (CTCAE), (version 4.0) and are listed in Table 3.

Dose adjustment was required once adverse effects (level III–IV) occurred.

Preoperative restaging was done with noticeable partial response in 10 (40%) patients and stable disease in seven (28%) patients, whereas eight (32%) patients showed progressive disease, and two of them developed hepatic and lung metastasis, confirmed with pelviabdominal and chest CT scan. The median size of the mass after neoadjuvant treatment was 4 ± 0.8 × 3 ± 0.8, 8.8 ± 0.9 × 4.5 ± 0.3, and 10.2 ± 0.8 × 5 ± 1.2 cm, respectively, and there was reduction in lymph node size by 30% in patients with partial response. The two patients who developed metastasis were staged as IVb with declined general condition and expected short-term lifespan and shifted to first-line metastatic chemotherapy regimen, and the other 23 patients were candidate for surgery with intended D2 gastrectomy after MDT revision.

#### Operative and postoperative outcomes

A total of 23 (92%) patients underwent surgery within 3–4 weeks after stoppage of neoadjuvant treatment, where total gastrectomy was done in 16 patients, near total in six patients, and one patient was irresectable. D2 lymphadenectomy was done for 18 (78.3%) patients and palliative resection was done for four (17.4%) patients and one was irresectable (4.3%). For partial response (*n*=10), D2 gastrectomy was done; for stationary course (*n*=7), D2 gastrectomy was done in six and palliative gastrectomy was done in one case owing to accidentally discovered few small peritoneal metastases; and for progressive disease (*n*=6), D2 gastrectomy was done for two patients, palliative resection was done for three cases owing to multiple small peritoneal metastasis and trivial hepatic metastasis, whereas one patient was irresectable. Associated right thoracotomy was done in two patients to achieve complete radicality in stable disease group. No major intraoperative accidents occurred. Of the 22 patients who underwent resection,

**Table 3 Toxicity and adverse effects reported for 25 patients included in the study**

| Toxicities (*n*=25) | All grades [*n* (%)] | Grade 1–2 [*n* (%)] | Grade 3–4 [*n* (%)] |
|---|---|---|---|
| Nausea | 10 (40) | 8 (32) | 2 (8) |
| Neuropathy | 9 (36) | 7 (28) | 2 (8) |
| Diarrhea | 6 (24) | 4 (16) | 2 (8) |
| Loss of appetite | 8 (32) | 7 (28) | 1 (4) |
| Neutropenia | 6 (24) | 4 (16) | 2 (8) |
| Palmar plantar erythrodysesthesia (PPE) | 8 (32) | 7 (24) | 2 (8) |
| Vomiting | 4 (16) | 3 (12) | 1 (4) |
| Anemia | 2 (8) | 2 (8) | |

**Table 4 Pathological TNM classification for patients who underwent resection (*n*=22) (postoperative)**

| TNM | Partial response (*n*=10) | Stable disease (*n*=7) | Progressive disease (*n*=5) |
|---|---|---|---|
| Operation | | | |
| Total gastrectomy | 10 | 5 | 1 |
| Near total gastrectomy | 0 | 2 | 4 |
| D2 | 10 | 6 | 2 |
| Palliative | 0 | 1 | 3 |
| Resection margin | | | |
| R0 | 10 | 6 | 2 |
| R1 | 0 | 1 | 3 |
| Mass size (median) | 4.5×3×1.5 cm | 7.5×4×1.5 cm | 9.5×5×1.8 cm |
| | With no lymphovascular or perineural invasion | 1 with lymphovascular and perineural invasion | 3 with lymphovascular and perineural invasion |
| Histological type | Moderately differentiated adenocarcinoma grade 2 | Moderately differentiated adenocarcinoma grade 2 | 3 Moderately differentiated adenocarcinoma grade 2<br>2 poorly differentiated adenocarcinoma grade 3 |
| T2 | 10 | 0 | 0 |
| T3 | 0 | 5 | 2 |
| T4 | 0 | 2 | 3 |
| N0 | 2 | 0 | 0 |
| N1 | 7 | 4 | 2 |
| N2 | 1 | 2 | 2 |
| N3 | 0 | 1 | 1 |
| M0 | 10 | 6 | 2 |
| M1 | 0 | 1 | 3 |

three (13.6%) patients had postoperative leakage on day 6 and were managed conservatively with NPO, endoscopic stenting, and feeding through the jejunostomy tube with close follow-up. In two patients, leakage stopped after 6 days and were discharged after starting oral feeding, whereas in one patient (4.5%), leakage continued with deterioration of general condition and he passed away 4 weeks postoperatively.

Postoperative histopathology for patients who underwent surgical resection (*n*=22) was revised carefully to assess radicality in each specimen. R0 was detected in 18 (81.8 %) pathology reports, whereas in four (18.2%) patients, R1 was found, with median range counted affected dissected lymph nodes of 0–8/9–30 (Table 4). A total of 21 (84%) patients were discharged after surgical resection with average hospital stay of 13.5 ± 2 days and were followed up at surgery and oncology outpatient clinics to start their systemic postoperative chemotherapy.

### Postoperative chemotherapy

R0 resection (18) patients received four cycles postoperatively of the same previously used regimen (XELOX), whereas for progressive and metastatic patients (with R1 or irresectable), their treatment was shifted to other lines of treatment. Throughout the perioperative chemotherapy, the most common adverse events of grade 3–4 from chemotherapy were nausea (8%), neuropathy (8%), loss of appetite (4%), diarrhea (8%), neutropenia (8%) with no febrile neutropenia, vomiting (4%), and palmar plantar erythrodysesthesia (PPE) (8%). No patients needed treatment termination, and no death occurred because of toxicities. Treatment regimen was well tolerable with no alarming toxicities.

### Postoperative follow-up

The median follow-up period was 17.46 ± 7.6 months, ranging from 5 to 24 months, for 21 patients who underwent surgical resection and were discharged aiming to improve the general condition, enhance their lifestyle, and early detection of postoperative complications (Table 5). There were 11 (44%) incidents of mortality (*n*=25): two patients due to progression and metastasis without undergoing surgery, four patients with discovered intraoperative metastasis with progression postoperatively, four patients had recurrence postoperatively and metastasis, and one patient had postoperative leakage not responding to conservative measures. Survival curves and progression-free survival (PFS) were estimated by the Kaplan–Meier approach, and the median survival after 2 years follow-up was 18 ± 6.5 months (56%) (Fig. 8). The median PFS was 17.5 ± 6.9 months (45.3%) (Fig. 9).

Recurrence was observed in seven (38.8%) patients who underwent combined neoadjuvant treatment and D2 gastrectomy and were R0 resection postoperatively (*n*=18): two in the first year with liver, peritoneal, and lung metastasis discovered during follow-up and five in the second year with local recurrence, and two of them showed liver and peritoneal metastasis.

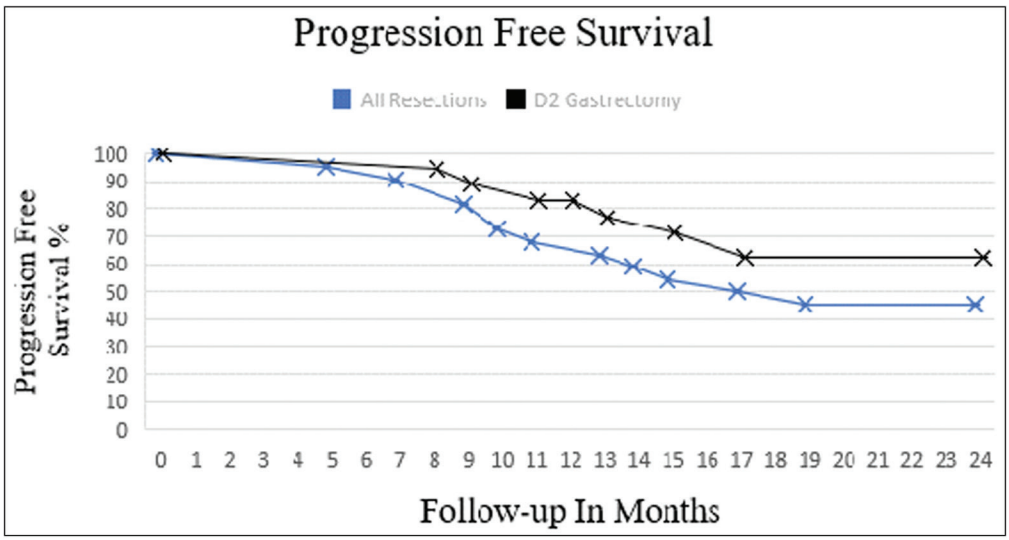
## Discussion

The actual effect of neoadjuvant chemotherapy on locally advanced gastric carcinoma is still controversial. Positive results have been published in terms of survival. However, adverse effects and complications of neoadjuvant chemotherapy might hinder and delay surgery and ultimately reduce the survival and disease-free outcomes [20–22].

**Table 5 Analysis of mortality and recurrence according to response to neoadjuvant treatment**

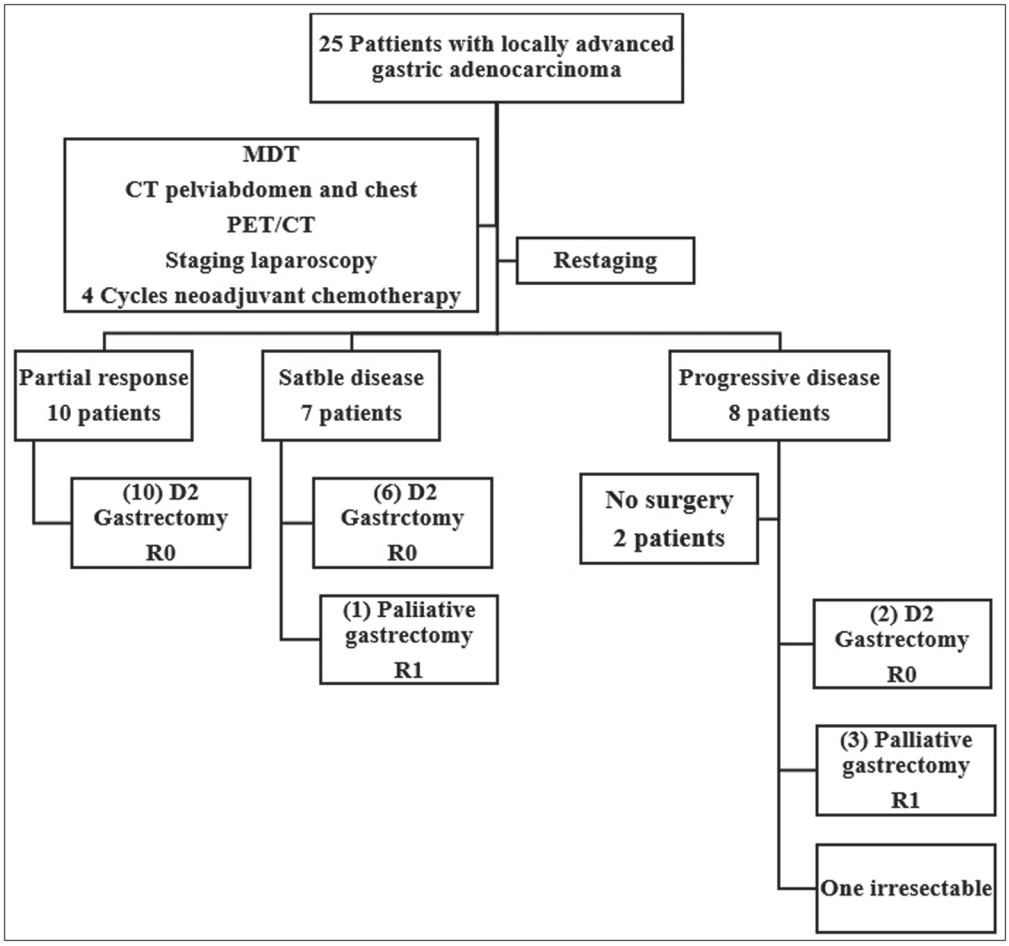
| | Partial response (*n*=10) | Stable disease (*n*=7) | Progressive disease (*n*=8) |
|---|---|---|---|
| Mortality | | | |
| First year | | | Palliative/1 month |
| | | | Without surgery/5 months |
| | | | Without surgery/6 months |
| | | | Irresctable/7 months palliative/11 month |
| | | | Palliative /12 month |
| Second year | D2/17 months | Palliative/14 months | D2/16 months |
| | | | D2/15 months |
| | | | D2/18 months |
| Recurrence | | | |
| First year | | 10 months | 11 months |
| Second year | 13 months | 15 months | 17 months |
| | | | 14 months |
| | | | 19 months |

**Figure 8**




Survival rate during a 2-year follow-up period (*n*=25).

**Figure 9**




Progression-free survival for patients who underwent combined neoadjuvant chemotherapy and D2 gastrectomy (*n*=18) and for all resections in the study (*n*=22).

Regarding tumor response after neoadjuvant chemotherapy which is the main concern owing to loss of the opportunity for curative surgery, we had no cases with complete response, partial response was noticed in 10 (40%) patients, stable disease in seven (28%) patients, whereas eight (32%) patients showed progression of the disease.

Achilli and colleagues conducted a study on 67 patients with locally advanced gastric adenocarcinoma, without evidence of distant metastases, to evaluate tumor response after neoadjuvant chemotherapy. A total of 51 (86%) patients completed all chemotherapy scheduled cycles successfully, and only two patients (3%) had a complete response, 23 patients (34%) had a partial response, 39 patients (58%) had disease stabilization, and three (5%) patients showed progressive disease [23].

Xu and colleagues conducted a study between May 2012 and December 2017 to evaluate pathologic tumor regression grade after neoadjuvant chemotherapy. A total of 264 patients with locally advanced gastric cancer (including esophagogastric junction carcinoma) underwent neoadjuvant chemotherapy (XELOX regimen or SOX regimen) combined with gastrectomy surgery. The results of tumor response after neoadjuvant chemotherapy were as follows: complete response in eight (3.1%), partial response in 141 (53.4%), stable disease was seen in 102 (38.6%), and progressive disease in 13 (4.9%). A minority of patients showed vascular invasion or lymphatic invasion (33.7%), negative node (32.6%), and underwent total gastrectomy surgery (34.8%). Patients were followed for a median period of 40 months (range: 1–65 months.). The 3- and 5-year PFS were 45.2 and 35.8%, respectively, and overall survival rates were 56.6 and 39.0%, respectively [24].

The other main important issue regarding preoperative neoadjuvant chemotherapy and our primary end point is the clinical outcomes with postoperative complications, curative surgery, more R0 resection margins, and less affected lymph nodes. In our study, we noticed 18 (81.8%) specimens with R0 resection margins and four (18.2%) specimens with R1, with

a smaller number of affected lymph nodes and were mainly perigastric. Moreover, we had three (13.6%) patients out of 22 patients who underwent surgery experienced postoperative leakage, and one (4.5%) of them died.

Hashemzadeh and colleagues tried to assess the effect of administration of neoadjuvant chemotherapy on tumor respectability in patients with locally advanced gastric adenocarcinoma, during a randomized-controlled trial on 60 patients. A total of 22 patients completed neoadjuvant chemotherapy and the resection margin was R0 and lymphadenectomies were either D1 or D2. Overall, 15 patients (68.2%) had 30% or more decline in lymph node involvement. Moreover, 14 patients (63.6%) had 30% or more shrinkage of gastric involvement compared with the initial CT scans obtained before chemotherapy [25].

A study was done by Wang and colleagues on 89 patients with locally advanced gastric carcinoma who received oxaliplatin-based neoadjuvant chemotherapy to evaluate the graded histologic response after neoadjuvant chemotherapy in patients with locally advanced gastric cancer from December 2006 to September 2012. A total of 74 of these patients underwent a radical gastrectomy. Overall, 36 patients had a postoperative graded histological response of less than 50% in the primary tumor, and all of them were R0 resection. They were subgrouped to receive the same neoadjuvant regimen postoperatively (*n*=24) or to change treatment (*n*=12) [26].

The comparison of neoadjuvant chemotherapy with surgical resection and surgery alone revealed no evidence of an increased risk of anastomotic leakage, any postoperative complication, pulmonary complication, surgical site infection, or postoperative mortality compared with surgery alone. The risks of severe complications, including anastomotic leakage and pulmonary complications, were similar between the two groups for European patients [27].

Although surgeons try to do radical surgery of the utmost, recurrence rate remains high in patients with advanced gastric carcinomas owing to micrometastasis and microscopic infiltration. The advantage of the use of neoadjuvant chemotherapy before surgery is to delay recurrence. In our study, we had seven (43.75%) recurrent cases of 18 patients who were followed-up after neoadjuvant chemotherapy with combined D2 gastrectomy during a 2-year follow-up.

Cunningham and colleagues conducted a study between October 2007 and March 2014 on 1063 patients with advanced operable esophagogastric (*n*=136) and gastric (*n*=397) adenocarcinoma and were randomly assigned to receive perioperative epirubicin, cisplatin, and capecitabine chemotherapy (*n*=533) or perioperative chemotherapy plus bevacizumab (*n*=530). In chemotherapy only group, 438 completed their neoadjuvant regimen, with complete pathological response in 21 patients (5%), 162 patient partial response (37%), 224 patients with stable disease (51%), and 10 patients died before assessment (2%). A total of 429 patients underwent surgical resection; R0 was found in 321 patients (64%), R1 in 108 patients (21%), and 76 patients were irresectable (15%). Median follow-up was 36 · 2 months, and disease recurrence was confirmed in 210 patients (48.9%) [14].

In our study, despite the adverse effects and toxicity recorded with chemotherapy, the risk benefits weigh the scale for neoadjuvant chemotherapy. We reported the most common adverse events of grade 3–4 during the perioperative chemotherapy were nausea (8%), neuropathy (8%), loss of appetite (4%) diarrhea (8%), neutropenia (8%) with no febrile neutropenia, vomiting (4%), and (PPE) palmar planter erythrodysesthesia (8%). Treatment regimen was well tolerable with no alarming toxicities, and no patients needed treatment termination, and no mortality related to toxicities occurred. Similar results were shown by Wang and colleagues, as they reported grades I and II toxicity in preoperative neoadjuvant chemotherapy on 36 patients, which included XELOX regimen. However, the most common grade 3–4 hematological toxicity was neutropenia, with incidence rates of 20.8–41.7%; one patient experienced febrile neutropenia. The most common grade 3–4 non-hematological toxicity was nausea and vomiting, with an incidence of 4.2–8.3%. No chemotherapy-related deaths were observed in their study [26].

Al-Batran and colleagues between August 8, 2010, and February 10, 2015, conducted a study on 716 patients with histologically confirmed advanced, resectable gastric adenocarcinoma, with no evidence of distant metastases. They were randomly assigned to treatment in 38 German hospitals or with practice-based oncologists. A total of 360 patients were assigned to receive either three preoperative 3-week cycles of epirubicin and cisplatin plus either fluorouracil or capecitabine (ECF/ECX), and 356 patients were assigned to receive four preoperative 2-week cycles of docetaxel, oxaliplatin, leucovorin, and fluorouracil (FLOT). Overall, 686 patients (95.8%) proceeded to surgery in both groups. A total of 408 patients

underwent gastrectomy, six palliative resection, and 30 patients were irresectable. D2 lymphadenectomy was done in 396 patients, D3 in 15 patients, and D1 in 12 patients. Chemotherapy-associated toxicity was analyzed in the safety population, comprising 354 patients in each group and were more grade 3 or 4 nausea (55 [16%] in the ECF/ECX group vs. 26 [7%] in the FLOT group), vomiting (27 [8%] vs. 7 [2%]), thromboembolic events (21 [6%] vs. 9 [3%]), and anemia (20 [6%] vs. 9 [3%]) in the ECF/ECX group and more grade 3 or 4 infections (30 [9%] vs. 63 [18%]), neutropenia (139 [39%] vs. 181 [51%]), diarrhea (13 [4%] vs. 34 [10%]), and neuropathy (7 [2%] vs. 24 [7%]) in the FLOT group. Febrile neutropenia was observed in two patients (1%) in the ECF/ECX group and seven patients (2%) in the FLOT group [22].

Ychou and colleagues observed the adverse effects of neoadjuvant chemotherapy in a study on 224 patients with resectable adenocarcinoma of the lower esophagus, gastroesophageal junction, or stomach who were randomly assigned to either perioperative chemotherapy with surgery ($n$=113) or surgery alone ($n$=111). Chemotherapy consisted of two or three preoperative cycles of intravenous cisplatin and a continuous intravenous infusion of fluorouracil for 5 consecutive days every 28 days and three or four postoperative cycles of the same regimen. They reported the incidence of grade 3 to 4 toxicity in 38% of patients who received chemotherapy (mainly neutropenia), but postoperative morbidity was similar in both groups [11].

Patients with gastric carcinomas usually present late and the tumor is usually locally advanced. The high incidence of mortality associated with gastric carcinoma is mostly attributed to metastasis found during malignancy survey and complications of chemotherapy. In patients with resectable gastric carcinomas who either received preoperative neoadjuvant chemotherapy or underwent surgery alone, there is debate about the postoperative survival rate which is our second end point. We had 11 incidents (44%) of mortality during a 2-year follow-up: 10 cases due to progression of the disease (two did not undergo surgery and eight postoperative), and one case due to early nonresponding postoperative leakage. The median survival after a 2-year follow-up was 18 ± 6.5 months (56%), and the median PFS was 17.5 ± 6.9 months (45.3%).

Wang *et al.* [26] reported that the median PFS ranged between 26 and 19 months, whereas the median overall survival was 31–24 months during their previously mentioned study.

Torben and colleagues discussed the pattern of recurrence and patient survival after perioperative chemotherapy with 5-FU, Leucovorin, Oxaliplatin and Docetaxel (FLOT) plus curative surgery for locally advanced esophagogastric and gastric adenocarcinoma in 228 patients between 2009 and 2018. The median survival was 61 months, and median PFS was 42 months. They reported that administration of adjuvant chemotherapy failed to be significant for overall survival but was an independent predictor of recurrence-free survival. Most of the recurrence occurred after a median of 9 months (range: 1–46 months), and 89% of recurrence occurred during the first 24 months. The rate of local recurrence was low, and after surgery for gastric cancer, the major recurrence site was peritoneal carcinomatosis (56%) [28].

## Conclusion

Despite the modest effect of neoadjuvant treatment on downstaging locally advanced gastric adenocarcinoma, the clinical outcome regarding R0 resection is satisfactory. No noticeable major postoperative complications were observed. with tolerable toxicity, recurrence, and PFS rates when perioperative chemotherapy (XELOX) is combined with D2 gastrectomy for locally advanced adenocarcinoma. We did not consider survival rate as an end point owing to short-term follow-up period.

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#### Conflicts of interest

No conflict of interest.

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