

Oxaliplatin plus Capecitabine in the Perioperative Treatment of Locally Advanced Gastric Adenocarcinoma in Combination with D2 Gastrectomy: NEO-CLASSIC Study

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TRIAL INFORMATION

- **ClinicalTrials.gov Identifier:** NCT01880632
- **Sponsor(s):** Zhongshan Hospital, Fudan University
- **Principal Investigators:** Tianshu Liu, Yihong Sun
- **IRB Approved:** Yes

LESSONS LEARNED

- The NEO-CLASSIC study provided valuable insight for the clinical efficacy and tolerability profiles of perioperative chemotherapy with oxaliplatin and capecitabine, plus gastrectomy, in patients with localized resectable gastric cancer.
- The study was designed to explore the potential survival benefits of an eight-cycle, perioperative oxaliplatin and capecitabine (XELOX) schedule in the above-mentioned setting and to explore the feasibility of prolonging the cycles of preoperative chemotherapy. The projected endpoint was not met.

ABSTRACT

Background. This multicenter, open-label study (NEO-CLASSIC) evaluated the efficacy and safety of oxaliplatin and capecitabine (XELOX), plus D2 gastrectomy, in localized resectable gastric cancer.

Methods. Patients aged 18–75 years with histologically-confirmed gastric adenocarcinoma (stage T2–4a/N+M0) were given eight cycles of XELOX (four preoperatively, four postoperatively). Each 3-week cycle comprised capecitabine 1,000 mg/m² twice daily on days 1–14 and oxaliplatin 130 mg/m² on day 1. Curative D2 gastrectomy was scheduled 2–4 weeks after the last preoperative cycle. The primary objective of the study was to determine the objective response rate (ORR) of XELOX in the preoperative setting. Sample size was calculated by assuming that a minimum of 47 cases would be required to increase the ORR by 15% (from 40% to 55%). With an estimated 10% dropout rate, 55 patients would have to be recruited.

Results. Fifty-five patients were enrolled, and one was excluded because of screening failure. R0 resections were achieved in 45 of 54 intent-to-treat patients (83.3%), and four patients received R1 resections (Fig. 1). There were no

complete responses, 27 (50.0%) partial responses, 22 cases (40.7%) of stable disease, and 4 (7.4%) of progressive disease. The objective response rate was 50.0%. Median follow-up was 52.97 months; 30 patients (55.6%) had disease progression (Table 1), and median progression-free survival was 20.10 (95% confidence interval: 4.31–35.89) months; median overall survival was 30.77 months (95% confidence interval was not yet available) (Fig. 2). Fifty-four patients completed 209 cycles of preoperative chemotherapy; 42 patients received 133 cycles of postoperative chemotherapy (Table 3). The rate of grade 3–4 adverse events was 8.5% (29/342 cycles); the most frequent events were neutropenia (9/342 cycles) and leukopenia (4/342 cycles).

Conclusion. These findings suggest that combination therapy with capecitabine and oxaliplatin as perioperative chemotherapy, followed by D2 gastrectomy, is effective and safe in late-stage, locally advanced gastric cancer. Although enrollment exceeded the 47 patients required to identify an increase in the ORR by 15% (from 40% to 55%), results did not meet the primary endpoint. *The Oncologist* 2019;24:1311–e989

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DISCUSSION

The NEO-CLASSIC study was designed to investigate the efficacy and safety of perioperative chemotherapy. Thus, with laparoscopic staging, we enrolled patients with T2–4/N+M0 disease. Among the 54 intent-to-treat patients, 14.8% of patients were stage II, and the other 85.2% of patients were stage III.

The ORR was 50%. Although the ORR did not achieve the primary endpoint, the disease control rate was 90.7% (49/54 patients), which created possibilities for radical surgery. The R0 resection rate was one of the secondary study objectives, with 49 patients proceeding to any surgical resection. R0 resection of the primary tumor was achieved in 83.3% of patients (45/54), which was similar to that in previous studies. The survival analysis revealed a 3-year progression-free survival (PFS) rate of 43.8%, and a 3-year overall survival (OS) rate of 47.2%. The median PFS was 20.1 months, with an event rate of 55.6%. However, median OS was 30.77 months. The survival disparity between the CLASSIC study (adjuvant capecitabine and oxaliplatin, with its 78% 5-year overall survival) and the FLOT4 trial (fluorouracil plus leucovorin, oxaliplatin, and docetaxel) trial and our study (50 months vs. 30.77 months overall survival, respectively) may have resulted from population differences. However, patients in our study had much later disease (T2–4/N+M0) and were typically in stage III.

The proportion of grade 3–4 adverse events (AEs) was 8.5% during perioperative chemotherapy. The most

Table 1. Clinical response in the intent-to-treat population ($n = 54$)

Response evaluation ^a	Patients, <i>n</i> (%)
Objective response rate	27 (50.0)
Disease control rate	49 (90.7)
Complete response	0 (0.0)
Partial response	27 (50.0)
Stable disease	22 (40.7)
Progressive disease	4 (7.4)
No assessment ^b	1 (1.9)

^aResponse Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

^bOne patient underwent emergency subtotal gastrectomy before assessment.

frequent grade 3–4 AEs were neutropenia and leukopenia, and no treatment-related deaths occurred. All these rates were significantly lower than the FLOT4 trial. Our study also found that XELOX can be delivered with higher dose intensity and better feasibility in the preoperative than in the postoperative setting. No deaths occurred during hospitalization or 30 days after surgery. The median hospitalization time was 9.6 days. Thus, because of its good tolerability profile, XELOX might also be a promising regimen for adjuvant chemotherapy.

TRIAL INFORMATION

Disease	Gastric cancer
Stage of Disease/Treatment	Neoadjuvant
Prior Therapy	None
Type of Study – 1	Phase II
Type of Study – 2	Single arm
Primary Endpoint	Overall response rate
Secondary Endpoints	Progression-free survival Overall survival Pathologic response Safety Toxicity

Additional Details of Endpoints or Study Design

The primary objective of the study was to determine the ORR of XELOX in the preoperative setting. Sample size was calculated by assuming that a minimum of 47 cases would be required to increase the ORR by 15% (from 40% to 55%). With an estimated 10% dropout rate, 55 patients would have to be recruited.

Investigator's Analysis	Inactive because results did not meet primary endpoint
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DRUG INFORMATION

Drug 1

Generic/Working Name	XELOX
Schedule of Administration	

The treatment plan was for all patients to receive eight cycles of perioperative XELOX chemotherapy (four cycles preoperatively, four postoperatively). Each 3-week cycle comprised capecitabine 1,000 mg/m² twice daily on days 1–14, and

oxaliplatin 130 mg/m² administered on day 1. Dose reductions or interruptions were allowed to manage potentially serious or life-threatening AEs. Curative D2 gastrectomy was scheduled within 2–4 weeks after completion of the last cycle of preoperative chemotherapy in patients without progressive disease. Postoperative chemotherapy was started within 8 weeks of surgery.

Drug 2

Generic/Working Name	Oxaliplatin
Drug Type	Small molecule
Drug Class	Platinum compound
Dose	130 milligrams (mg) per squared meter (m ²)
Route	IV
Schedule of Administration	On day 1

PATIENT CHARACTERISTICS

Number of Patients, Male	38
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Number of Patients, Female	16
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Stage

Clinically diagnosed stage T2–4a/N+M0 disease, according to computed tomography and magnetic resonance imaging, and resectable disease according to laparoscopic exploration. Details of patient characteristics are shown in Table 2.

Age	Median (range): 65 (39~71)
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Number of Prior Systemic Therapies	Median: 0
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Performance Status: ECOG	0 — 5
	1 — 49
	2 — 0
	3 — 0
	Unknown —

Cancer Types or Histologic Subtypes	Intestinal, 26
	Diffuse, 14
	Mixed, 10
	Unknown, 4

PRIMARY ASSESSMENT METHOD

Number of Patients Screened	55
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Number of Patients Enrolled	54
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Number of Patients Evaluable for Toxicity	54
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Number of Patients Evaluated for Efficacy	54
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Evaluation Method	RECIST 1.1
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Response Assessment CR	<i>n</i> = 0 (0%)
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Response Assessment PR	<i>n</i> = 27 (50%)
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Response Assessment SD	<i>n</i> = 22 (40.7%)
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Response Assessment PD	<i>n</i> = 4 (7.4%)
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(Median) Duration Assessments PFS	20.1 months
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(Median) Duration Assessments OS	30.77 months
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Outcome Notes	No deaths occurred during hospitalization or 30 days after surgery. Median hospitalization time was 9.6 days.
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ADVERSE EVENTS

Grade 3–4 toxicities of chemotherapy are shown in Table 5. Details related to complications and safety of surgery are shown in Table 6.

SERIOUS ADVERSE EVENTS

Name	Grade	Attribution
Pulmonary embolism	3	Unlikely
Biliary tract infection	3	Possible
Gastric perforation	3	Unlikely

ASSESSMENT, ANALYSIS, AND DISCUSSION

Completion	Study completed
Investigator's Assessment	Inactive because results did not meet primary endpoint

The NEO-CLASSIC study was designed to investigate the efficacy and safety of perioperative chemotherapy in patients with gastric cancer. Thus, with laparoscopic staging, we enrolled patients with T2–4/N+M0 disease. Among the 54 intent-to-treat patients, 14.8% of patients were stage II, and the other 85.2% of patients were stage III. Although the use of diagnostic laparoscopy for staging patients with gastric cancer is not adopted universally, it has substantial value because of its high accuracy and effectiveness, avoidance of unnecessary laparotomy, and its reduced recovery time. Therefore, laparoscopy can improve treatment decision-making in advanced gastric cancer, and is recommended for patients with resectable gastric cancer [1].

The objective response rate (ORR) of oxaliplatin and capecitabine (XELOX) as perioperative chemotherapy was evaluated as the primary endpoint of NEO-CLASSIC, with clinical response evaluated using RECIST (version 1.1). The ORR was 50.0%. The R0 resection rate was one of the secondary study objectives, with 49 patients proceeding to any surgical resection. R0 resection of the primary tumor was achieved in 83.3% of patients (45/54), which was similar to that in previous studies. The R0 resection rate was 84% in the NeoFLOT study [2], 79% in the MAGIC trial [3], 84% in the ACCORD trial [4], and with epirubicin, cisplatin, 5-fluorouracil or epirubicin, cisplatin, and capecitabine (ECF/ECX) and 57% with fluorouracil plus leucovorin, oxaliplatin, and docetaxel (FLOT) in the FLOT4 trial [5]. Pathologic response was another important objective of the current trial, and a pathologic complete response (pCR) was reported in 3 of 48 patients (6.3%) from the per-protocol population who underwent surgery; this was consistent with the 0%–16% rate reported by previous prospective studies [6–8]. The rate of pathologic response, defined as a complete response or <10% of the residual cancer remaining, was 20.8% (10/48 patients). According to Japanese Classification of Gastric Cancer criteria [9], 31.2% of patients (15/45) achieved histologic grade 2–3, which means less than 33.3% of viable tumor cells observed.

We believed that the reasons for the failure to achieve the primary endpoint may be attributed to the following reasons. First, in locally advanced gastric cancer, perigastric

lymph nodes were the only target lesions according to RECIST 1.1 criteria, and spiral computed tomography had some limitations in evaluating the primary lesions and lymph nodes. Second, ORR was a widely used preoperative evaluation criterion currently, but it was not an ideal therapeutic indicator of neoadjuvant therapy in gastric cancer.

Although ORR did not achieve the primary endpoint, the disease control rate was 90.7% (49/54 patients), which created possibilities for radical surgery.

An R0 resection rate of 84.3% (59/70 patients) was achieved in the European Organisation for Research and Treatment of Cancer 40954 trial, which used a prolonged (two 48-day cycles) neoadjuvant cisplatin/5-fluorouracil-based regimen [10]. Several recent studies reported an improved complete resection rate with neoadjuvant chemotherapy, and R0 resection rate was associated with long-term survival after neoadjuvant therapy in gastric cancer [11]. The present study showed a satisfactory R0 resection rate, but pCR (ypTONOM0) was reported in 3 of 48 per-protocol patients (6.3%) who underwent surgery. Comparison with initial clinical and pathologic stages revealed downstaging of T stage in 66.7% of patients (32/48) and downstaging of N stage in 45.8% of patients (22/48) (Table 4). Although there is still no universally accepted grading system for pathologic regression, numerous studies have shown that the degree of pathologic response is a vital prognostic marker of local recurrence, distant metastases, and long-term outcomes in locally advanced gastric cancer after neoadjuvant therapy [12]. More importantly, pathologic response can guide clinical decisions about surgical strategies, adjuvant therapy, and long-term surveillance [13, 14].

The survival analysis revealed a 3-year progression-free survival (PFS) rate of 43.8%, and a 3-year overall survival (OS) rate of 47.2%. The median PFS was 20.1 months, with an event rate of 55.6%. However, median OS was 30.77 months. In the CLASSIC trial, 3-year disease-free survival was 74% in the chemotherapy group, and 59% in the surgery-only group; corresponding values for 3-year OS were 83% and 78% [15]. In FLOT4 trial, the median OS was 35 months with ECX/ECF and 50 months with FLOT. The PFS was 18 months with ECX/ECF and 30 months with FLOT. 3-year OS rate was

48% with ECF/ECX and 57% with FLOT. The survival disparity between the CLASSIC, the FLOT4 trial, and our study may have resulted from population differences. The CLASSIC trial enrolled patients with stage II (T2N1, T1N2, T3N0), IIIA (T3N1, T2N2, T4N0), or IIIB (T3N2) disease according to American Joint Committee on Cancer criteria (6th edition). However, patients in our study had much later disease (T2–4/N+M0) and were typically in stage III [16]: 20.4% of patients were stage IIIA, 33.3% were stage IIIB, and 31.5% were stage IIIC. In the FLOT4 trial, the rate of node-positive patients was 79.4%. However, the rate in our study was 100%, even though the 3-year OS rate in our study was comparable to the rate of ECF/ECX group in the FLOT4 study.

Two-drug and three-drug regimens are both recommended for patients with \geq stage IB resectable gastric cancer, and there is no current evidence showing a significant difference in efficacy between these regimens. According to National Comprehensive Cancer Network guidelines [17], treatment regimens should be chosen after considering performance status, medical comorbidities, and toxicity profiles. Therefore, a balance between efficacy and tolerability is important when selecting treatment. The recommended treatment duration is usually 2–4 cycles, but this could be modified depending on the circumstances [16, 17]. Our study indicated that eight cycles of XELOX (i.e., four cycles preoperatively, and four postoperatively) was effective as a perioperative chemotherapy schedule.

Usually, two-drug chemotherapy regimens are preferred for patients with unresectable, locally advanced, recurrent or metastatic disease because of lower toxicity, whereas three-drug regimens are reserved for medically fit patients with good performance status and access to frequent toxicity evaluations [17]. The current study confirmed the good tolerability of XELOX as a perioperative chemotherapy regimen. The frequency, severity, and type of adverse events

(AEs) documented with XELOX were consistent with the safety profile reported in the CLASSIC study [15]. The proportion of grade 3–4 AEs was 8.5% during perioperative chemotherapy. The most frequent grade 3–4 AEs were neutropenia and leukopenia, and no treatment-related deaths occurred. All these rates were significantly lower than the FLOT4 trial [5]. Our study also found that XELOX can be delivered with higher dose intensity and better feasibility in the preoperative than the postoperative setting: 49 of 54 patients (90.7%) completed the four planned preoperative cycles, but only 27 of 42 patients (62.3%) completed the four planned postoperative cycles. The mean dose intensity of oxaliplatin was 840 mg preoperatively and 577 mg postoperatively. Moreover, only 2 of 49 patients (4.2%) experienced mild operative complications. No deaths occurred during hospitalization or 30 days after surgery. The median hospitalization time was 9.6 days. Thus, because of its good tolerability profile, XELOX might also be a promising regimen for adjuvant chemotherapy.

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DISCLOSURES

Tianshu Liu: Novartis, Merck KGaA, Merck Sharp & Dohme, Roche, Bayer, Hengrui (C/A, H), Merck KGaA, Merck Sharp & Dohme, Roche, Bayer, Hengrui (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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FIGURES AND TABLES

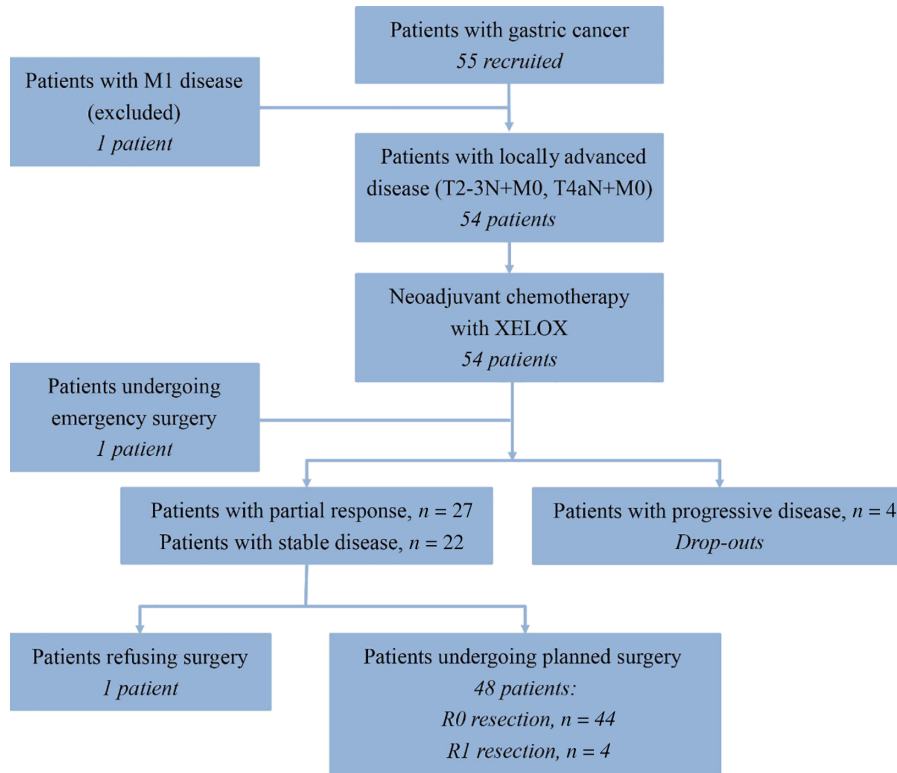


Figure 1. Study flowchart.
Abbreviation: XELOX, oxaliplatin and capecitabine.

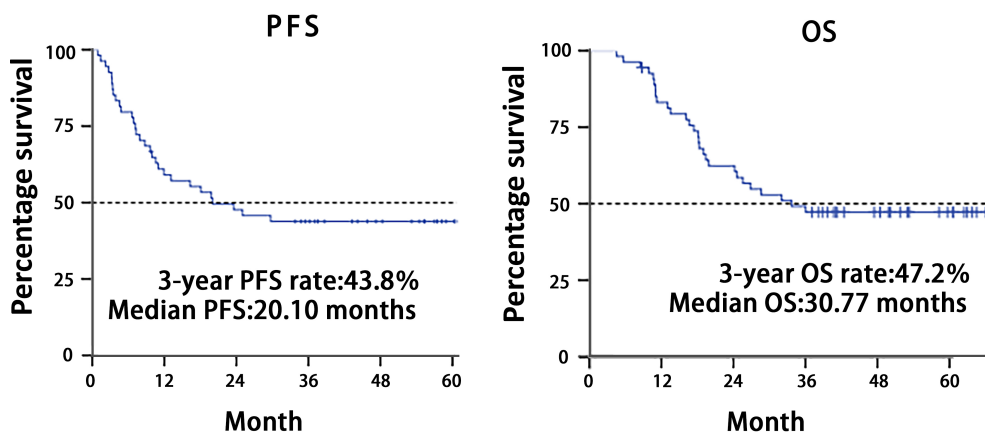


Figure 2. Kaplan-Meier plots of progression-free survival and overall survival.
Abbreviations: OS, overall survival; PFS, progression-free survival.

Table 2. Baseline patient characteristics (*n* = 54)

Characteristic	Patients, <i>n</i> (%)
Age, years	
<65	36 (66.7)
≥65	18 (33.3)
Sex	
Male	38 (70.4)
Female	16 (29.6)
Karnofsky performance status ≥80%	54 (100.0)
Location of primary lesion	
Gastroesophageal junction	16 (29.6)
Gastric	38 (70.4)
Pretreatment stage ^a	
IIA	1 (1.9)
IIB	7 (13.0)
IIIA	11 (20.4)
IIIB	18 (33.3)
IIIC	17 (31.5)
cT stage	
T2	1 (1.9)
T3	18 (33.3)
T4a	35 (64.8)
cN stage	
N1	26 (48.1)
N2	23 (42.6)
N3	5 (9.3)
Targeted lesion size, cm	
Mean (SD)	3.23 (2.64)
Range	1.4–15.0
Differentiation	
G1	2 (3.7)
G2	28 (51.9)
G3	18 (33.3)
Gx	6 (11.1)
Lauren classification	
Intestinal	26 (48.1)
Diffuse	14 (25.9)
Mixed	10 (18.5)
Unknown	4 (7.4)

^aAccording to American Joint Committee on Cancer, Cancer Staging Manual, 7th edition [16].

Table 3. Chemotherapy administration

Cycles	Preoperative chemotherapy (<i>n</i> = 54)	Postoperative chemotherapy (<i>n</i> = 42)
Number of cycles, median (range)	4 (2–4)	4 (0–4)
4 cycles, number of patients	49	27
3 cycles, number of patients	3	5
2 cycles, number of patients	2	4
<2 cycles, number of patients	0	6
Total number of cycles	209	133
Number of dose reductions (cycles)	21	55
Mean (SD) oxaliplatin dose intensity, mg	840 (143)	577 (301)
Mean oxaliplatin relative dose intensity, %	97	65

Abbreviation: SD, standard deviation.

Table 4. Pathologic response in patients who underwent planned surgery (*n* = 48)

Pathology report	Patients, <i>n</i> (%)
Pathologic complete regression	3 (6.3)
Lymph nodes	
Median lymph nodes analyzed	37 (12–73)
Median positive lymph nodes	3 (0–62)
Pathologic T stage	
ypT0	6 (12.5)
ypT1	6 (12.5)
ypT2	8 (16.7)
ypT3	16 (33.3)
ypT4	12 (25)
Pathologic N stage	
ypN0	15 (31.3)
ypN1	7 (14.6)
ypN2	15 (31.3)
ypN3	11 (22.9)
Histologic regression grade (JCGC)	
Grade 0	16 (33.3)
Grade 1a	12 (25)
Grade 1b	5 (10.4)
Grade 2	11 (22.9)
Grade 3	4 (8.3)
Mansour's criteria	
0%–10%	23 (47.9)
10%–50%	6 (12.5)
50%–90%	9 (18.8)
90%–100%	10 (20.8)

Abbreviation: JCGC, Japanese Classification of Gastric Cancer.

Table 5. Grade 3–4 toxicities of chemotherapy^a

Toxicity	All, <i>n</i>	Preoperative chemotherapy, <i>n</i>	Postoperative chemotherapy, <i>n</i>
Number of cycles	342	209	133
Number of grade 3–4 toxicities	29	12	17
Neutropenia	9	3	6
Leukopenia	4	0	4
Thrombocytopenia	3	2	1
Thrombus	1	1	0
Anemia	2	1	1
Febrile neutropenia	1	0	1
Diarrhea	1	0	1
Vomiting	2	2	0
Fatigue	1	0	1
Weight decrease	2	1	1
Hand-foot syndrome	2	2	0
Neuropathy	1	0	1

^aAccording to National Cancer Institute Common Toxicity Criteria (version 4.0).

Table 6. Complications and safety of surgery (*n* = 49^a)

Complications	Patients, <i>n</i> (%)
Complication, any	2 (4.2)
Abdominal infection	1 (2.1)
Atelectasis	1 (2.1)
Death in hospital	0 (0)
Death within 30 days	0 (0)
Hospitalization days, median	9.6

^aIncluding one emergency subtotal gastrectomy.

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