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Effectiveness of neoadjuvant chemotherapy with a docetaxel, cisplatin, and S-1 (DCS) regimen for T4b gastric cancer

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Abstract

Background No studies on neoadjuvant chemotherapy for gastric cancer (GC) with T4b stage were reported. This study aimed to assess the effectiveness of neoadjuvant chemotherapy using DCS regimen (docetaxel, cisplatin, and S-1) for GC with T4b stage.

Methods Forty-three patients diagnosed GC with surgical or clinical T4b stage received three or four preoperative cycles of DCS therapy followed by gastrectomy and lymphadenectomy between Jan-2018 and Dec-2022. Short-tern outcomes including tumor response, completion of neoadjuvant chemotherapy, toxicity and adverse events, rate of treatment-related death, R0 resection, rate of complete adjuvant chemotherapy and short-term surgical results were investigated. The oncologic outcomes comprised 3-year OS and 3-year disease-free survival (DFS).

Results A total of 43 patients with T4b gastric cancer were included in the analysis. Among them, twenty-five patients underwent gastrectomy and lymphadenectomy. The completion rate of neoadjuvant chemotherapy was 88.4%, including 4 cycles of 51.2% and 3 cycles of 37.2%. The disease-control and clinical response rate were 88.4% and 58.1%, respectively. During preoperative chemotherapy, grade 3/4 neutropenia occurred in 20.9%, anemia in 13.9%, hyponatremia in 4.8%, and vomiting in 2.3%. Pathologic complete response was achieved in 8.0%. After surgery, no patient experienced severe complications (Clavien Dindo > = 3). The R0 resection rate was 72.0% and the rate of complete adjuvant chemotherapy was 83.3%. The 3-year OS and DFS rates were 49% and 38%, respectively.

Conclusions Neoadjuvant chemotherapy with DCS regimen demonstrated a high tolerance, high tumor response rate, high complete adjuvant chemotherapy rate and satisfactory 3-year survival outcomes. Three- or four-course of preoperative DCS regimen is a promising approach for GC with T4b stage.

Keywords Gastric cancer, Neoadjuvant chemotherapy, T4b stage, Clinical response rate, DCS regimen

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Introduction

Gastric cancer (GC) poses a major public health challenge and ranks the most prevalent cancers in the world [1]. For advanced cases, a multidisciplinary therapy is necessary for treatment. Gastrectomy and proper D2 lymphadenectomy remains a curative treatment for resectable tumors. Achieving complete surgical resection (R0) plays the most important factor for improving survival rates. The overall survival (OS) rate was higher in the prior studies achieved high R0 [2–6]. In patients with T4b stage GC, curative surgery might not be achieved due to the direct invasion of tumor into the adjacent organs and/or major blood vessels. In previous studies, gastrectomy combined with multivisceral resection (MVR) was conducted to attain R0 surgery. However, MVR is associated with elevated rates of morbidity and mortality with the rate of severe complications of 5.0–33.3% [2, 3, 5–19]. The non-curative resection rate was reported as 20–47% [2, 3, 5, 6, 9–14] and the compliance of adjuvant therapy after MVR was low (25–59.5%) [2, 3, 6, 10, 13, 14]. These factors resulted in the unsatisfactory 5-year overall survival (OS) rate of only 16–30% for those who underwent upfront gastrectomy [2–4, 11–14, 19–22]. Thus, the upfront radical surgery of GC with T4b is still challenging and may lead to a poor prognosis.

For advanced GC, neoadjuvant chemotherapy has been suggested to reduce tumor invasiveness, improve the R0 resection rate, and mitigate the poor prognosis [23–27]. Neoadjuvant chemotherapy with 5-FU, leucovorin, oxaliplatin, docetaxel (FLOT) or epirubicin, cisplatin, 5-FU (ECF) or ebirubicin, cisplatin, capecitabine (ECX) regimens were recommended for advanced GCs in Western countries [28–32]. However, in Asian countries, the S-1 based regimens were favorable in several studies. Among that, DCS regimen was utilized for preoperative chemotherapy for GC with advanced stage or extended lymph node metastasis in several trials. This triplet regimen demonstrated high completion rate, clinical response rate, and promising oncologic outcomes [33–37].

Until now, no studies on neoadjuvant chemotherapy focusing on the T4b stage have been reported. Thus, investigations on neoadjuvant chemotherapy for GC with T4b is necessary.

Therefore, we conducted this study to assess the effectiveness of neoadjuvant chemotherapy using DCS regimen (docetaxel, cisplatin, and S-1) for the treatment of GC with T4b stage in terms of safety, toxicity, response rate, surgical and oncological outcomes.

Patients and methods

Patients

This retrospective study included 43 Vietnamese patients with clinical (28 patients, 65.1%) or surgical (15 patients, 34.9%) T4b GC between January 2018 and December 2022 at the Gastro-intestinal Surgical Department of the University Medical Center, a tertiary hospital in Ho Chi Minh City, Vietnam. The study was approved by the Institutional Review Board of the hospital.

The eligibility criteria included: (i) confirmed histology of gastric adenocarcinoma, (ii) clinical or surgical staging at T4b stage, (iii) satisfactory hematological, liver, and renal functions, with specific parameters including a white blood cell count from 4,000 to 12,000/mm3, neutrophil count ≥ 2,000/mm3, hemoglobin > 10 g/dL, platelet count ≥ 100,000/mm3, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 100 IU/L; total bilirubin ≤ 1.5 mg/dL; creatinine ≤ 1.2 mg/dL and creatinine clearance ≥ 60 mL/min, and (iv) an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Criteria for clinical T4b staging: abscence of normal fatty planes between the tumor and surrounding organs on an abdominal computed tomography scan, and reviewed by a multidisciplinary team (MDT), or identified intraoperative finding.

The exclusion criteria comprised of (a) presence of distant organ metastasis (M1), except para aorta lymph node metastasis, (b) tumor invaded into the pancreatic head (right side of the gastroduodenal artery) or the hepatic hilum, (c) concurrent or history of previous other cancers, (d) prior chemotherapy treatment, (e) history of gastrectomy, (f) presence of central nervous system disorder, (g) active hepatitis B, and (h) pregnancy or breastfeeding.

Neoadjuvant chemotherapy and response assessment

Patients received 3 or 4 cycles of neoadjuvant chemotherapy. Each cycle included docetaxel (35 mg/m^2, intravenous) and cisplatin (35 mg/m^2, intravenous) on day 1 and 15, and S-1 (40 mg/m^2, oral, twice daily) from day 1 to 14, followed by a 2-week rest period. For one cycle, the total dosage was 70 mg/m^2 docetaxel, 70 mg/m^2 cisplatin, and 1120 mg/m^2 S-1 (dose intensity of S-1 of 280 mg/m^2/week).

If toxicity or adverse side effects occurred, the next cycle was delayed until recovery, with required criteria including: neutrophil count ≥ 1000/mm^3, hemoglobin ≥ 10.0 g/dL, platelet count ≥ 50,000/mm^3, AST and ALT ≤ 150 IU/L, total bilirubin ≤ 2 mg/dL, and creatinine ≤ 1.2 mg/dL.

For patients who had gastric outlet obstruction, a stomach partitioning gastro-jejunostomy was

performed, and chemotherapy was administered within 2–3 weeks later.

The ECOG performance status was evaluated, and routine assessments including complete blood cell counts, liver and renal function tests, and urinalysis were conducted before each cycle to monitor toxicity and adverse events. Thoraco-abdominal computed tomography (CT) was performed at the end of the third and the fourth cycle to evaluate tumor response using the Response Evaluation Criteria in Solid Tumor (RECIST) 1.1 to assess the disease response [38]. The response categories were defined as follows: complete response (CR) indicated the complete disappearance of all target lesions; partial response (PR) indicated a ≥ 30% reduction in the sum of the diameters of all target lesions; progressive disease (PD) was identified by an increase in the sum of the diameters of all target lesions by ≥ 20%; and stable disease (SD) was characterized by insufficient shrinkage to qualify for PR or insufficient increase to qualify for PD. Patients with either CR or PR were considered to have a clinical response. The disease control rate included the rate of CR, PR, and SD.

Chemotherapy-related toxicity refers to the adverse effects or complications directly resulting from the administration of chemotherapeutic agents. The Common Toxicity Criteria of the National Cancer Institute (NCI–CTC) 4.0 was used to report toxicities and adverse events [39].

Surgery after neoadjuvant chemotherapy

We performed gastrectomy with lymphadenectomy according to the JGCA guidelines within 2–4 weeks after the last day of neoadjuvant chemotherapy administration [40, 41]. Based on the primary tumor's location, subtotal or total gastrectomy with lymphadenectomy was performed using laparoscopy or laparotomy. For patients with persistent PAN after neoadjuvant chemotherapy, 16a2/b1 PAN dissection was conducted. We carried out the D1 + lymphadenectomy in patients with several concomitant diseases. Intraoperative lavage cytology was routinely performed before and after gastrectomy. In cases of the invaded organs persisting after neoadjuvant chemotherapy, combined resection was conducted to achieve R0 resection. Additionally, any suspected margin of the invaded organs after gastrectomy was biopsied to assess residual tumor status. All surgical procedures were conducted by two experienced GC surgeons.

Curative resection (R0) was defined as the complete removal of both macroscopic and microscopic disease. R1 resection was characterized by the macroscopic removal of the tumor, accompanied by microscopic evidence of residual tumor, indicated by either positive resection margin (including suspected margin of the invaded organs) or positive postoperative lavage cytology.

Adjuvant treatment

For patients who completed four cycles of neoadjuvant chemotherapy, S-1 was administered for one year after surgery. For patients who completed three cycles preoperatively, the fourth cycle of DCS was given postoperatively, followed by S-1 for 1 year.

Follow-up

The follow-up schedule was in accordance with the JGCA guidelines [40, 41]. Patients were followed up every 3-month for the first two years, every 6-month for the next three years, and then annually. The follow-up visit included a physical examination, laboratory blood tests, and abdominal ultrasonography. Computed tomography was performed every six months for the first three years and then annually. Endoscopy was performed every year. If a patient exhibited suggestive symptoms or signs of recurrence or metastasis, CT and/or endoscopy were performed irrespective of the scheduled follow-up.

Outcomes

We investigated the short-tern outcomes including tumor response, completion of neoadjuvant chemotherapy, toxicity and adverse events, the rates of treatment-related death, R0 resection, the rate of complete adjuvant chemotherapy and short-term surgical results. The oncologic outcomes comprised 3-year OS and 3-year disease-free survival (DFS). Three-year OS is defined as the proportion of patients who are alive three years after the initiation of chemotherapy, regardless of the cause of death. Three-year DFS is defined as the proportion of patients who remain alive and free from any signs of cancer recurrence or progression three years after achieving R0 resection.

Completion of neoadjuvant chemotherapy was defined as the rate of patients who completed 3 or 4 cycles of DCS regimen of neoadjuvant treatment.

Safety of neoadjuvant chemotherapy was evaluated relied on the incidence of death- or severe side effects -related chemotherapy.

Safety of surgery was assessed based on the incidence of surgical complications classified by the Clavien-Dindo system.

Statistical analysis

Continuous variables were summarized by mean ± standard deviation or median (25th ; 75th percentiles), and categorical variables were summarized by the number of patients and percentage. Baseline

characteristics were summarized for all patients and by three distinct groups: surgery, refuse surgery, and PD. OS and DFS were summarized using Kaplan-Meier method and visualized by the Kaplan-Meier curves. Cox model was used to compare OS and DFS between groups. Results were reported by hazard ratio (HR), 95% confidence interval (CI), and *p*-value. The DFS was analyzed for patients with R0 resection only. All analyses were done using R statistical software version 4.1.3. Univariable analysis was performed using two-sample t-test for normally distributed numeric variables, the Wilcoxon rank-sum test for non-normally distributed numeric variables, and Fisher's exact test for categorical variables. Multivariable analysis was conducted using logistic regression models with a stepwise backward procedure to identify independent risk factors of overall survival rate.

Results

Patient's characteristics

The clinico-pathological characteristics are presented in Table 1. The mean age of the patients was 55.7 ± 12.6 years, with a male-to-female ratio of 2:1. Among the participants, 11 patients (25.6%) had bulky lymph nodes, and 8 patients (18.6%) had para aortic lymph nodes involvement. The mean neoadjuvant chemotherapy tumor size was 3.8 ± 2.3 cm. Five patients (11.6%) had gastric outlet obstruction and underwent partitioning gastro-jejunostomy before receiving chemotherapy. Fifteen patients (34.9%) with anemia at the time of admission received blood transfusions until reaching the hemoglobin threshold of 10 g/dL.

Tumor response

Among the 43 enrolled patients, there were 22 patients (51.2%) completed 4 cycles, 16 patients (37.2%) completed 3 cycles, and 5 patients (11.6%) who were unable to finish 3 or 4 cycles of DCS regimen for neoadjuvant chemotherapy. Consequently, the overall completion rate of neoadjuvant chemotherapy was 88.4%.

The disease control rate was 88.4% (38 patients), including PR in 25 patients (58.1%) and SD in 13 patients (30.2%). There were no CR patients and 5 patients (11.6%) with PD. The clinical RR was 58.1% (all with PR). Twenty-five patients of those with PR or SD agreed to undergo gastrectomy and lymph node dissection, while the remaining 13 patients refused surgery. The patients who refused surgery continued with DCS regimen for enough 6 cycles and then received S-1 for 1 year.

All 5 patients developed PD received second-line chemotherapy. (Table 1)

Toxicity and adverse events

Toxicity and adverse events are shown in Table 2. We observed four toxicities and adverse events with grade 3–4, including neutropenia (8 patients [18.6%] with grade 3 and 1 patient [2.3%] with grade 4), anemia (5 patients [11.6%] with grade 3 and 1 patient [2.3%] with grade 4), hyponatremia (2 patients [4.8%] with grade 3), and vomiting (1 patient [2.3%] with grade 3). No treatment-related death was observed.

Operative characteristics and short-term outcomes

Twenty-five patients underwent gastrectomy and lymphadenectomy. Among them, distal gastrectomy was performed in 10 patients (40.0%), and total gastrectomy in 15 patients (60.0%). Seven patients underwent combined resection, including left hepatic segmentectomy (1 patient), segmental transverse colectomy (2 patients), and distal pancreato-splenectomy (4 patients). Other eighteen patients underwent gastrectomy without combined resection. D2 resection was conducted in 21 patients (84.0%), D1 + in 2 patients (8.0%), and D2 + PAND in 2 patients (8.0%). R0 resection was achieved in 72.0% (18/25). There were 4 patients (16.0%) with R1 and 3 patients (12.0%) with R2 resection. The median number of harvested lymph nodes was 16 (12; 25). The overall complication rate was 24.0%, however, no patient occurred severe complications (Clavien Dindo >= 3). The rate of complete adjuvant chemotherapy was 83.3%. (Table 3)

Pathologic complete response was achieved in 2 patients (8.0%).

Long-term survival outcomes

The median (25th ; 75th percentiles) length of follow-up was 19.0 (13.3; 27.9) months in the total study population, and 24.1 (16.8; 37.8) months in the surgery group. There were 27 deaths in the total population and 12 deaths in the surgery group.

The 1-, 2-, and 3-year OS rates (95% CI) of the surgery group were 92% (82;100%), 65% (48;88%), and 49% (32;76%), respectively. The 1-, 2-, and 3-year OS rates (95% CI) of the refuse-surgery group were 76% (56;100), 8.5% (1.3;55), and 0%, respectively. (Tables 4 and Fig. 1)

The 1-, 2-, and 3-year DFS rates (95% CI) of the R0 group were 72 (54; 96), 48 (29; 79), and 38 (19, 75), respectively.

For the surgery group, the results from the univariable analyses showed that the number of resected lymph nodes, and complete adjuvant chemotherapy significantly increased overall survival. However, in the multivariable analyses, no independent risk factors were associated with overall survival. (Table 5)

Table 1 Patient characteristics

	All patients (*N* = 43)	**Surgery (*N* = 25)**	**Refuse surgery (*N* = 13)**	**PD (*N* = 5)**	***P*-value**
Age (years)	55.7 ± 12.6	55.3 ± 13.1	57.7 ± 14.0	52.8 ± 5.6	0.487
Sex					0.454
Male	29 (67.4)	18 (72.0)	9 (69.2)	2 (40.0)	
Female	14 (32.6)	7 (28.0)	4 (30.8)	3 (60.0)	
BMI (kg/m2)	20.8 ± 2.8	21.1 ± 2.8	20.7 ± 3.1	19.8 ± 2.4	0.544
Nutritional status					0.252
Underweight (BMI < 18.5)	7 (16.3)	2 (8.0)	3 (23.1)	2 (40.0)	
Normal weight (BMI:18.5–24.9)	32 (74.4)	21 (84.0)	8 (61.5)	3 (60.0)	
Overweight (BMI:25–30)	4 (9.3)	2 (8.0)	2 (15.4)	0 (0.0)	
Obese (BMI > 30)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Hypertension	7 (16.3)	5 (20.0)	2 (15.4)	0 (0.0)	0.847
Diabetes	5 (11.6)	3 (12.0)	2 (15.4)	0 (0.0)	> 0.999
Cardiovascular disease	4 (9.3)	2 (8.0)	2 (15.4)	0 (0.0)	0.758
Chronic hepatic disease	2 (4.7)	1 (4.0)	1 (7.7)	0 (0.0)	> 0.999
Chronic lung disease	2 (4.7)	2 (8.0)	0 (0.0)	0 (0.0)	0.640
Previous stroke	1 (2.3)	1 (4.0)	0 (0.0)	0 (0.0)	> 0.999
Chronic renal disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
History of laparotomy or laparoscopic surgery	2 (4.7)	2 (8.0)	0 (0.0)	0 (0.0)	0.640
CEA (U/L)	3.3 (1.7; 9.6)	3.3 (1.7; 8.7)	3.0 (1.7; 11.6)	3.5 (1.7; 5.0)	0.982
Preoperative WBC (g/L)	8.5 ± 2.6	9.0 ± 2.4	8.3 ± 3.1	6.5 ± 1.3	0.082
Hemoglobin (g/dL)	11.6 ± 2.5	11.6 ± 2.8	11.6 ± 2.0	11.3 ± 1.8	0.841
Anemia	15 (34.9)	9 (36.0)	4 (30.8)	2 (40.0)	> 0.999
Gastric outlet obstruction	5 (11.6)	2 (8.0)	2 (15.4)	1 (20.0)	0.487
Pre-CT tumor size (cm)	3.8 ± 2.3	4.2 ± 2.6	3.2 ± 1.5	3.7 ± 1.7	0.611
Invasion organs					0.854
Crus of diaphragm	2 (4.7)	0 (0.0)	1 (7.7)	1 (20.0)	
Left liver lobe	2 (4.7)	1 (4.0)	1 (7.7)	0 (0.0)	
Pancreatic body	8 (18.6)	5 (20.0)	2 (15.4)	1 (20.0)	
Pancreatic head	12 (27.9)	7 (28.0)	4 (30.8)	1 (20.0)	
Pancreatic body, crus of diaphragm	1 (2.3)	1 (4.0)	0 (0.0)	0 (0.0)	
Crus of diaphragm, left liver lobe	3 (7.0)	2 (8.0)	1 (7.7)	0 (0.0)	
Pancreatic body, left liver lobe	3 (7.0)	2 (8.0)	1 (7.7)	0 (0.0)	
Pancreatic head, transverse mesocolon	4 (9.3)	2 (8.0)	1 (7.7)	1 (20.0)	
Pancreatic head and body	8 (18.6)	5 (20.0)	2 (15.4)	1 (20.0)	
Differentiation status					0.086
Moderately differentiated	15 (34.9)	11 (44.0)	4 (30.8)	0 (0.0)	
Poorly differentiated	26 (60.5)	14 (56.0)	7 (53.8)	5 (100.0)	
Signet ring cell	2 (4.7)	0 (0.0)	2 (15.4)	0 (0.0)	
Para aorta lymph node	8 (18.6)	2 (8.0)	4 (30.8)	2 (40.0)	0.093
Clinical N stage					**0.011**
N1	5 (11.6)	4 (16.0)	0 (0.0)	1 (20.0)	
N2	17 (39.5)	8 (32.0)	8 (61.5)	1 (20.0)	
N3	10 (23.3)	3 (12.0)	5 (38.5)	2 (40.0)	
Bulky	11 (25.6)	10 (40.0)	0 (0.0)	1 (20.0)	
Number of CT cycles					0.073
1	1 (2.3)	1 (4.0)	0 (0.0)	0 (0.0)	
2	4 (9.3)	3 (12.0)	1 (7.7)	0 (0.0)	
3	16 (37.2)	9 (36.0)	5 (38.5)	2 (40.0)	
4	22 (51.2)	12 (48.0)	7 (53.9)	3 (60.0)	
Response after 4 cycles					**< 0.001**
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
PR	25 (58.1)	18 (72.0)	7 (53.8)	0 (0.0)	

Table 1 (continued)

	All patients (*N* = 43)	Surgery (*N* = 25)	Refuse surgery (*N* = 13)	PD (*N* = 5)	*P*-value
SD	13 (30.2)	7 (28.0)	6 (46.2)	0 (0.0)	
PD	5 (11.6)	0 (0.0)	0 (0.0)	5 (100.0)	
Length of follow-up (months)	19.0 (13.3; 27.9)	24.1 (16.8; 37.8)	16.1 (9.3; 20.5)	13.3 (8.1; 16.5)	**0.008**

Summary statistics are mean ± sd, n (%), and median (25th; 75th percentiles)

BMI: body mass index, CEA: carcinoembryonic antigen, WBC: white blood cell, CT: chemotherapy, CR: complete response, PR: partial response, SD: stable disease, PD: progress disease

Table 2 Treatment-related adverse event

	None	Grade 1	Grade 2	Grade 3	Grade 4
General fatigue	32 (74.4)	9 (20.9)	2 (4.7)	0 (0.0)	0 (0.0)
Vomitting	35 (81.4)	6 (14.0)	1 (2.3)	1 (2.3)	0 (0.0)
Diarrhoea	35 (81.4)	7 (16.3)	1 (2.3)	0 (0.0)	0 (0.0)
Anorexia	42 (97.7)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	43 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonitis	38 (90.5)	3 (7.1)	1 (2.4)	0 (0.0)	0 (0.0)
Peripheral neuropathy	41 (95.3)	2 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)
Stomatitis	40 (93.0)	3 (7.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pigmentation	42 (97.7)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Leukopenia	26 (60.5)	11 (25.6)	6 (14.0)	0 (0.0)	0 (0.0)
Neutropenia	23 (53.5)	6 (14.0)	5 (11.6)	8 (18.6)	1 (2.3)
Febrile neutropenia	42 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anemia	16 (37.2)	13 (30.2)	8 (18.6)	5 (11.6)	1 (2.3)
Thrombocytopenia	41 (95.3)	2 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated bilirubin	38 (88.4)	5 (11.6)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated SGOT	40 (93.0)	3 (7.0)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated SGPT	42 (97.7)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased BUN	42 (97.7)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Proteinuria	41 (95.3)	2 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)
Hypokalemia	39 (92.9)	3 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)
Hyponatremia	32 (76.2)	8 (19.0)	0 (0.0)	2 (4.8)	0 (0.0)

Summary statistics is n (%)

Recurrence pattern after surgery

Thirteen patients (52.0%) of the surgery group occurred recurrence and or metatstasis, including locaregional recurrence (1 patients), hematogenous (1 patients), peritoneum (2 patients), distant lymph node (1 patients), and mixed type (8 patients).

Discussion

Patients of GC with T4b stage, gastrectomy and additional combined resection may be the only way for a potential cure. However, radical resection for cT4b gastric cancer may increase potential postoperative complications and carries a high risk of R1/R2 resection, especially when pancreatic head or liver are involved. Moreover, GC at the T4b stage often presents with high lymph nodes metastasis and peritoneal spread, which contribute to poorly survival outcomes [2, 3, 13, 14, 19, 21, 22]. Therefore, multivisceral resection for T4b gastric cancer remains controversial. This disorder should be treated as a separate group to achieve better survival outcomes.

In our study, we expected to improve long-term survival and minimize the toxicity and adverse events of patients with T4b GC by applying neoadjuvant chemotherapy with DCS regimen, followed by gastrectomy and lymphadenectomy. The findings demonstrated much better efficacy than initially anticipated, with high compliance rate (88.4%), R0 resection rate (72.0%), low toxicities and adverse events, and satisfactory survival (3-year OS of 49%). Our findings may be better than other previous study of MVR for T4b GC regarding R0 resection rate, 3-year OS [2, 3, 7, 8, 10, 20].

Moreover, all patients in refuse surgery group had certain response after neoadjuvant chemotherapy and were considered as technically resectable. The decision to refuse surgery was not related to patients' clinical conditions or disease severity but rather by non-clinical factors such as personal or social considerations.

Table 3 Operative characteristics

	N	**Surgery (*N* = 25)**
Operation type	25	
Laparoscopy		13 (52.0)
Open		12 (48.0)
Operative method	25	
Distal gastrectomy		10 (40.0)
Total gastrectomy		15 (60.0)
Borrmann	25	
1		2 (8.0)
2		11 (44.0)
3		11 (44.0)
5		1 (4.0)
Surgical tumor size (cm)	25	5 (4; 6)
Operating time (mins)	25	215 (180; 250)
Blood loss (ml)	25	100 (50; 150)
Combined surgery	25	7 (28.0)
Combined surgery specification	7	
Left hepatic segmentectomy		1 (14.3)
Segmental transverse colectomy		2 (28.6)
Distal pancreato-splenectomy		4 (57.1)
Extent of lymph node dissection	25	
D1+		2 (8.0)
D2		21 (84.0)
D2 + PAND		2 (8.0)
Number of resected lymph nodes	25	16 (12; 25)
Pathological T stage	25	
T0		2 (8.0)
T1		0 (0.0)
T2		0 (0.0)
T3		5 (20.0)
T4a		14 (56.0)
T4b		4 (16.0)
Pathological N stage	25	
N0		6 (24.0)
N1		4 (16.0)
N2		11 (44.0)
N3a		4 (16.0)
N3b		0 (0.0)
Curability	25	
R0		18 (72.0)
R1		4 (16.0)
R2		3 (12.0)
Adjuvant chemotherapy	24	
No		2 (8.3)
Not complete		2 (8.3)
Complete		20 (83.3)
Postoperative hospital stay (days)	25	8 (7; 10)
Time to flatus (days)	25	3 (2; 4)
Time to liquid diet (days)	25	3 (2; 4)
Anastomotic leakage	25	0 (0.0)
Anastomotic stricture	25	0 (0.0)
Duodenal stump leakage	25	0 (0.0)
Pancreatic fistula	25	1 (4.0)

Table 3 (continued)

	N	Surgery (*N* = 25)
Paralytic ileus	25	1 (4.0)
Bleeding	25	0 (0.0)
Intra-abdominal abscess	25	0 (0.0)
Wound infection	25	0 (0.0)
Early reoperation	25	0 (0.0)
Cardiovascular complications	25	0 (0.0)
Pneumonitis	25	3 (12.0)
Urinary retention	25	1 (4.0)
Clavien-Dindo classification	25	
1		3 (12.0)
2		3 (12.0)
>= 3		0 (0.0)

Summary statistics are n (%), mean ± sd, and median (25th; 75th percentiles)

PAND: para aortic lymph node dissection

Table 4 Kaplan-Meier estimates and results from Cox models for overall survival

	Kaplan-Meier probability			Cox model		
	1 years	2 years	3 years	HR	95% CI	*p*-value
Overall survival						
Surgery	92 (82, 100)	65 (48, 88)	49 (32, 76)	—	—	
Refuse surgery	76 (56, 100)	8.5 (1.3, 55)	— (—, —)	3.65	1.54, 8.68	0.003
PD	60 (29, 100)	— (—, —)	— (—, —)	6.83	1.96, 23.8	0.003

HR: hazard ratio, CI: confidence interval, PD: progression disease

Thus, the comparability in baseline characteristics between the groups suggests that confounding by indication was not a major concern in this study. The differences in survival outcomes between the surgery and refuse surgery groups were therefore likely attributable to the treatment effect rather than baseline heterogeneity. This finding emphasized that gastrectomy and lymphadenectomy after neoadjuvant chemotherapy with DCS regimen was still the main role to improve prognosis of GC patients with T4b stage, which has not been reported before.

Besides the regimen for neoadjuvant chemotherapy, the dosage is also a critical factor in increasing the response rate and reducing toxicity. In Japan, a 2–3 cycle DCS (docetaxel, cisplatin and S-1) or CS (cisplatin and S-1) regimen was utilized for preoperative chemotherapy for GC with advanced stage or extended lymph node metastasis. However, there were a relatively high incidence of grade 3 or grade 4 toxicity and adverse events, particularly leukopenia (18.9–27.5%), neutropenia (19.0–55.0%), diarrhea (7.5–10%) [33–37]. A higher dose of docetaxel and cisplatin was supposed to be related to a higher incidence of grade 3–4 hematological toxicity [42–44]. In our study, the total dose of docetaxel (70 mg/m^2/cycle) and cisplatin (70mg/m^2/cycle), which was higher than in other studies, was adjusted by dividing it into biweekly schedules to reduce toxicity adverse effects. The dose intensity of docetaxel (17.5 mg/m^2/week), cisplatin (17.5 mg/m^2/week), and S-1 (280 mg/m^2/week) were relatively higher in other trials. However, most of the toxicity and adverse events were in grade 1 or 2, while grade 3 or 4 of neutropenia and anemia were 20.9%, and 13.9%, respectively. These results were remarkably lower than reported in the other studies. Thus, a high completion and tolerance rate was obtained in our study population with this modified schedule.

Regarding postoperative complications of gastrectomy and radical lymphadenectomy after neoadjuvant chemotherapy, the overall complication rate in our study was similar to several prior studies [33, 34, 44–47]. However, no patient experienced severe complications (ClavienDindo >= 3) in this study. Performing a radical resection for cT4b gastric cancer without neoadjuvant chemotherapy may increase the complexity of the operation and pose potential postoperative complications in certain cases, particularly when the pancreas and liver are involved [4, 8, 9, 12, 13]. Some authors hypothesized that extensive resection was linked to a higher incidence of overall severe complications and mortality [16, 21]. Conversely, recent studies support the notion that there is no disparity in postoperative complications between multivisceral resection and gastrectomy alone [2, 10, 12, 13]. In our study, seven patients underwent combined resection, 21 patients underwent D2 resection, 2 patients

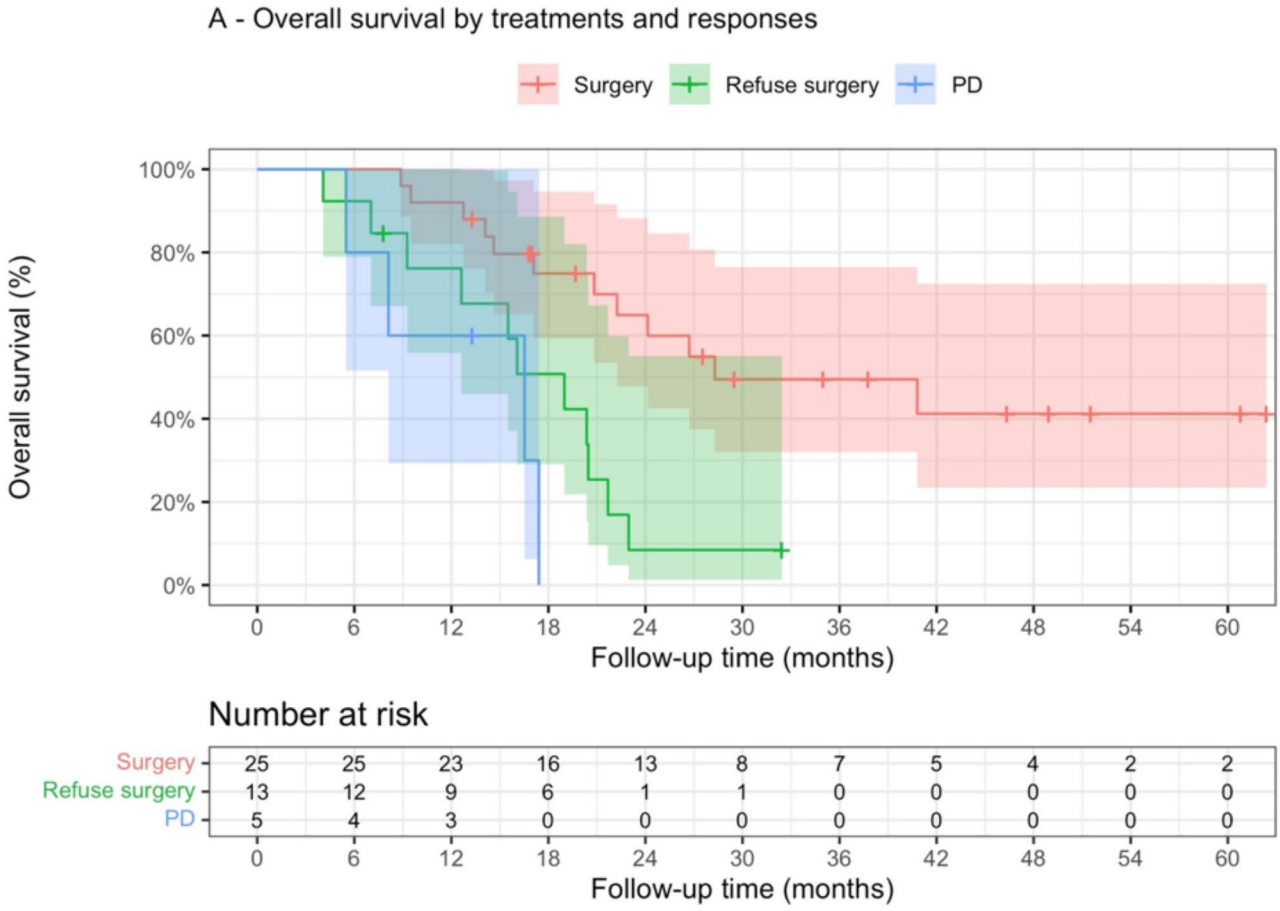

Fig. 1 Kaplan-Meier curves for overall survival
PD: Progress Disease

underwent D1 + resection, and 2 patients underwent D2 + PAND. We didn't have any cases of severe complications such as anastomotic leak, bleeding, or severe complications after surgery. The feasibility and safety of extended gastrectomy were previously advocated, and our results are relatively better to those without neoadjuvant chemotherapy reported in the literature [5, 8, 10–12, 14, 15, 17–19].

The adjuvant chemotherapy approach is required to improve the curability and survival outcome for T4b GC. Although MVR was considered safe and feasible with high rate of R0 resection for T4b gastric cancer, several previous studies demonstrated that initiation of adjuvant chemotherapy might be prolonged or even prohibited due to patient derailing after a large MVR. The rate of adjuvant chemotherapy was low (41–75%), resulting in unsatisfactory survival outcomes with 3-year OS of 10.8–39.0% [2, 3, 6, 10, 13, 14]. In this manner, our study was among the limited data demonstrating the efficacy of neoadjuvant chemotherapy for T4b GC, with high rate of complete adjuvant chemotherapy (83.3%), low toxicities and morbidities, and satisfactory 3-year OS (49%) and DFS (38%). These findings were superior to those of previous studies, in which MVR surgery was performed without neoadjuvant chemotherapy [2–22]. Based on these results, we suggest applying neoadjuvant chemotherapy with DCS regimen over upfront surgery and adjuvant chemotherapy for T4b GC.

Analyzed by univariate regression, our findings indicated that pathological lymph node stage and incomplete adjuvant chemotherapy significantly reduced the overall survival. However, due to the small sample size, the multivariable analyses did not reveal any independent risk factors. Several previous studies have identified the incompleteness of resection, lymph node metastasis, and the number of resected organs as independent prognostic factors for T4b GC. Among these, the most powerful prognostic factor was the completeness of resection, which has been confirmed by almost all the published studies [3, 5, 9–13, 20–22].

This study had some limitations. Firstly, although the findings were potential, it was still a single-arm retrospective study at a single institution. Thus, controlled

Table 5 Univariable and multivariable analysis of factors associated with OS (surgery group)

	Univariable model				Multivariable model		
Characteristic	***N***	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Age (years)	25	1.02	0.97, 1.07	0.393			
Sex	25						
Male		—	—		—	—	
Female		2.28	0.72, 7.26	0.163			
Pre- CT tumor size (cm)	25	0.93	0.69, 1.24	0.607			
Borrmann	25	1.05	0.53, 2.10	0.880			
Para aorta lymph node	25	3.03	0.63, 14.7	0.168			
Differentiation status	25						
Moderately differentiated		—	—		—	—	
Poorly differentiated		2.00	0.60, 6.70	0.260			
Signet ring cell							
Operation type	25						
Laparoscopy		—	—		—	—	
Open		0.86	0.28, 2.70	0.802			
Operative method	25						
Distal gastrectomy		—	—		—	—	
Total gastrectomy		2.41	0.71, 8.16	0.159			
Response after 4 cycles	25						
PR		—	—		—	—	
SD		0.40	0.09, 1.84	0.240			
Number of resected lymph nodes	25	0.91	0.84, 0.99	0.031	0.93	0.85, 1.01	0.080
Pathological T stage	25						
pT0-T3		—	—		—	—	
pT4a		1.25	0.31, 5.00	0.757			
pT4b		2.35	0.46, 11.9	0.304			
Pathological N stage	25						
pN0		—	—		—	—	
pN+		2.51	0.55, 11.6	0.237	—	—	
Curability	25						
R0		—	—		—	—	
R1/2		0.69	0.19, 2.58	0.584			
Combined surgery	25	0.88	0.24, 3.29	0.855			
Adjuvant chemotherapy	24						
Complete		0.19	0.05, 0.73	0.015	0.32	0.07, 1.50	0.149
No/incomplete		—	—				
Grade 3–4 adverse event	25						
No		—	—		—	—	
Yes		1.96	0.58, 6.61	0.278			

HR: hazard ratio, CI: confidence interval, CT: chemotherapy, PR: partial response, SD: stable disease

trials are required to propose a stronger recommendation. Secondly, the 5-year survival outcomes could not be evaluated in this study. We expected to report these outcomes in further study after a sufficient length of follow-up. Thirdly, the number of patients included in this study was relatively small when divided into separate groups, and further evaluations are required in larger populations.

In conclusion, neoadjuvant chemotherapy with the DCS regimen, followed by gastrectomy and lymphadenectomy, demonstrated potential benefits in terms of safety and oncologic outcomes for gastric cancer with T4b stage. Further prospective studies should be conducted with well design and the present of a comparison group.

Author contributions

Dr. Long, Thong, Nguyen, Dat, Hai, Phuoc wrote the main manuscript text. Dr. Trung, Phuoc, Vuong prepared all tables and all figures. All authors reviewed the manuscript.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Institutional Review Board, University Medical Center Ho Chi Minh city. Approval to perform research on human subjects in this study was provided by the Institutional Review Board, University Medical Center Ho Chi Minh city (registration number: 37/HDDD-DHYD).

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