Neoadjuvant Chemotherapy With Docetaxel Plus Cisplatin And Capecitabine/5-Fluorouracil For Locally Advanced Esophageal Squamous Cell Carcinoma

Nguyen Thi Minh Hue[1], Le Tuan Anh[2*], Tram Minh Man[3], Nguyen Van Hai[4], Tran Phung Dung Tien[5], Nguyen Lam Vuong[6]

[1,2*,3] Cancer Center, Cho Ray Hospital, Ho Chi Minh City, Vietnam
[1]E-mail: NTMH: ngyyentmhue@gmail.com
[2*]E-mail: LTA: lta@yahoo.com
[3]E-mail: TMM: tramminhmandr@gmail.com
[4]Department of General Surgery, Faculty of Medicine, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam. [4]E-mail: NVH: bsvanhai@ump.edu.vn
[5]Digestive Surgery Department, Cho Ray Hospital, Ho Chi Minh City Vietnam, Vietnam. [5]E-mail: TPDT: tranpdtien@gmail.com (ORCID: 0000-0002-8773-2719)
[6]Department of Medical Statistics and Informatics, Faculty of Public Health, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam. [6]E-mail: NLV: nguyenlamvuong@ump.edu.vn

Acknowledgements: None

***Corresponding author:** Le Tuan Anh

*MD, PhD. Cancer Center, Cho Ray Hospital, Ho Chi Minh City, Vietnam, 201B Nguyen Chi Thanh street, Ward 12, District 5, Ho Chi Minh City, Vietnam. E-mail: lta@yahoo.com. Telephone: (+84-28) 3855 4137. Fax: (+84-28) 3855 7267.
Doi: 10.47750/pnr.2022.13. S05.143

Statements and Declarations

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by NTMH, LTA, TMM and NLV. The first draft of the manuscript was written by NTMH and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Cho Ray hospital (Date 22 July 2019 / No. 867/CN-HDDD).

Consent to participate

Informed consent was obtained from all patients for being included in the study.

Abstract

Background: Optimal neoadjuvant chemotherapy (nCT) for esophageal squamous cell carcinoma (ESCC) is controversial. Moreover, evidence of neoadjuvant therapies in real-world scenario is essential. This study was to assess short-term and oncological outcomes of nCT with docetaxel plus cisplatin and capecitabine/5-fluorouracil (DCX/DCF) for locally advanced ESCC in Vietnamese population.

Methods: A retrospective study was conducted from July 2019 to December 2020 with 112 patients who completed a nCT regimen with DCX (105 patients) or DCF (7 patients) for locally advanced ESCC. The patients then underwent a radical surgery or an adjuvant radiation depending on clinical response. Short-term outcomes included clinical response based on the Response Evaluation Criteria in Solid Tumor version 1.1 and adverse events assessed by the National Cancer Institute-Common Toxicity Criteria for Adverse Events. Oncological outcomes were overall survival (OS) and disease-free survival (DFS).

Results: Mean age was 61.1 years and 111/112 patients were male. Most (65.2%) were in stage IVa before treatment. Adjuvant radiation was performed in 24 patients (21.4%) and 69 (61.6%) underwent surgery. Complete response was achieved in 99 patients (88.4%), but only 18/69 patients (26.1%) achieved pathological complete response. Severe adverse events (grade 3-4) were infrequently observed with neutropenia (8%), anemia (3.6%), and leukopenia (2.7%). Two-year OS and DFS were 62% and 53% respectively. Patients with complete response had significantly higher survival rate than those without complete response.

Conclusions: nCT with DCX/DCF regimen is safe and has a high rate of clinical complete response. However, patients with locally advanced ESCC still have poor survival.

Key words: Esophageal cancer; Neoadjuvant chemotherapy; Capecitabine; Tumor response; Survival

INTRODUCTION

Esophageal cancer (EC) is currently the seventh most common cancer and the sixth leading cause of cancer-related death all over the world.[1] People with EC have a poor prognosis since it is an aggressive cancer and is often detected in advanced stages. The histology of EC varies in different areas: adenocarcinoma is more frequent in Western Europe and the United States, and squamous cell carcinoma is more common in Asian countries.[2] Esophageal squamous cell carcinoma (ESSC) is highly aggressive and has a high rate of lymph node metastasis.[3, 4] In spite of developments in the detection and treatment, the prognosis of this cancer remains poor with a 5-year survival rate of less than 20%.[4-6] Radical esophagectomy with extensive lymphadenectomy is still the most important treatment modality for resectable EC, however, patients still have poor survival without additional therapies.[7-9] Currently, neoadjuvant therapy has been used in combination with radical surgery to improve prognosis of patients with locally advanced ESSC. The multimodal therapies have been recently recommended as standard treatments by the National Comprehensive Cancer Network (NCCN) guidelines.[10]

There is a difference in the choice of neoadjuvant therapy for locally advanced EC between Western and Asian countries, where neoadjuvant chemotherapy (nCT) is favorable in Asia, and neoadjuvant chemoradiotherapy (nCRT) is preferential in Western countries.[11, 12] Currently, standard regimens for nCRT are vinorelbine-cisplatin-based regimen for ESCC from the NEOCRTEC5010 clinical trial [13] and paclitaxel-carboplatin-based regimen for ESCC and adenocarcinoma from the CROSS trial.[14] For nCT, cisplatin and 5-fluorouracil (FU) or docetaxel, cisplatin and 5-FU are the standard regimens for ESCC, which is based on severe trials.[15-17] Both nCT and nCRT have shown considerable survival benefits in locally advanced EC, including both adenocarcinoma and SSC.[14, 15, 18, 19] However, the optimal regimen for neoadjuvant therapy remains debated. In addition, in real-world scenario, the efficacy of neoadjuvant therapies from clinical trials could not be completely reproduced. For example, studies evaluated the effectiveness of the CROSS regimen showed that patients had a lower complete response rate and worse overall survival than in the trial.[20-23] Therefore, evidence of the effectiveness of neoadjuvant therapies in real-world scenario in various populations is essential to improve treatments for EC.

Our hospital is a tertiary oncological center of Southern Vietnam with an estimated population of nearly 47 million people. It is so difficult to treat EC in the country because (i) most patients are diagnosed in advanced stages and (ii) novel multi-modality treatments have a high cost in such a low-to-middle income country (LMIC) setting. Since 2019, we have applied novel nCT regimens for patients with locally advanced EC including docetaxel, cisplatin and capeciabine (DCX) or docetaxel, cisplatin and 5-FU (DCF). The safety and effectiveness of these nCT regimens need to be evaluated and reported, particularly this is one of the first studies on nCT for locally advanced EC in Vietnamese population. We therefore performed this study to evaluate short-term and oncological outcomes of nCT and to explore factors associated with the clinical outcomes in locally advanced EC patients.

METHODS

We retrospectively reviewed all patients with locally advanced EC who had received nCT from July 2019 to December 2020 in our hospital. The institutional ethics committee had approved to conduct the study. We included patients ≥18 years of age who were histologically confirmed of EC with locally advanced stage. Locally advanced EC was defined by a tumor invading regional lymph nodes (i.e., N stage 1-3) or local structures (i.e., T stage 3-4), in accordance with the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system (8^{th} edition).[24] Patients with incomplete nCT or postoperative T4b staging were not included.

Neoadjuvant chemotherapy

All patients received 3-6 cycles of DCX or DCF regimen and then were assessed for clinical response. The DCX regimen was preferential with 3-6 cycles in every three weeks. Each DCX cycle consisted of docetaxel (60-70 mg/m^2) and cisplatin (60-70 mg/m^2), both were administered intravenously on day 1, and capecitabine (2000 mg/m^2 bid, oral use) within 14 days (from day 1 to 14). If patients had severe dysphagia and were not able to administer capecitabine, the DCF regimen was used with 3-6 cycles in every two weeks. Each DCF cycle contained docetaxel (40 mg/m^2), leucovorin (400 mg/m^2), and fluorouracil (400 mg/m^2) on day 1, 5-FU (1000 mg/m^2) on day 2, and cisplatin (40 mg/m^2) on day 3; all were administered intravenously.

There were some modifications of the doses to manage toxicities. In case of grade-4 hematological toxicity, we reduced the doses of docetaxel, cisplatin and capecitabine by 20%. In case of grade-3 or 4 non-hematological toxicity, we reduced the doses of docetaxel and capecitabine by 20%. In case of renal toxicity, we reduced the dose of cisplatin by 20% if creatinine clearance (CCr) decreased to 50-60 ml/min, 40% if CCr decreased to 40-50 ml/min, and cisplatin was

discontinued if CCr decreased to <40 ml/min. In case of grade-4 febrile neutropenia, granulocyte colony-stimulating factor (G-CSF) was used.

Patient evaluation

A multidisciplinary consultation was routinely performed for staging and treatment planning for all patients. We evaluated the clinical stage at baseline and every three weeks when the patients were receiving the nCT using upper gastrointestinal endoscopy and contrast-enhanced thoracoabdominal computed tomography (CT) scan. After completing the nCT regimen, if a patient was evaluated as complete or partial response, he/she was introduced for surgery with thoraco-laparoscopic McKeown esophagectomy plus three-field lymphadenectomy. Otherwise, the patient was introduced to an adjuvant radiation. After the multi-modality treatment, patients were followed in a 3-month interval in two years, and a 6-month interval afterwards. At each visit, evaluations included physical examination, routine complete blood count and blood chemistry, electrocardiogram, and the Eastern Cooperative Oncology Group (ECOG) performance status. Gastrointestinal endoscopy and CT scan were performed every six months to assess the progression of the disease; 18-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT fusion images were used in some patients when necessary. Clinical staging was done using the AJCC TNM staging system (8^{th} edition).

Outcomes assessment

We used the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 [25] to evaluate clinical response after completing the nCT regimen with four categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). CR was defined by the disappearance of all lesions and pathologic lymph nodes detected before treatment. PR was defined by a ≥30% decrease in sum of the diameters of the lesions compared to before treatment without new lesions. PD was defined by a ≥20% increase in sum of the diameters of the lesions or having any new lesion. SD was any case that did not qualify for PR or PD. Tumor downstaging was evaluated and defined by either T or N downstaging (i.e., a reduction in the T or N descriptor compared to before treatment). In all patients who underwent surgery, pathologic complete response (pCR) was also assessed and was defined by the absence of residual cancer cells in the specimens of the tumor and all dissected lymph nodes.

We used the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 5.0 [26] to evaluate treatment-related adverse events of the nCT. In general, any TRAE was assessed and classified into five grades. Grade 1 was mild and did not required any intervention. Grade 2 was moderate and required local or non-invasive intervention. Grade 3 was severe and required hospitalization or prolongation of hospitalization, or caused disabling, but was not immediately life-threatening. Grade 4 was life-threatening and required urgent intervention. Grade 5 resulted in death.

Oncological outcomes included overall survival (OS) and disease-free survival (DFS). OS was the time from the first dose of the nCT to death from any cause, and DFS was the time from the first treatment dose to the detection of disease progression, or death from any cause if no disease progression was detected. Disease progression included recurrence and/or metastasis of the cancer, which was categorized in to five types: (1) 'locoregional' type included any recurrence in the anastomosis, conduit, adjacent structures, or regional lymph nodes; (2) 'hematogenous' type included any metastasis to the brain, lung, liver, bone, or other distant organs; (3) 'peritoneal' type included peritoneal seeding or a Krukenburg tumor in female patients; (4) 'distant lymph nodes metastasis' type; and (5) 'mixed' type included more than one category described above at the time disease progression was diagnosed.

Statistical analysis

Patient characteristics and all outcomes were described by the number of patients and percentage for qualitative variables, and mean and standard deviation (SD) for quantitative variables. The survival outcomes (OS and DFS) were analyzed using the Kaplan-Meier method to estimate 1-year and 2-year OS and DFS with 95% confidence intervals (CIs). The results were plotted by Kaplan-Meier curves for all patients and by subgroups with and without tumor CR. Factors associated with tumor CR and survival outcomes were assessed by univariable logistic regression and Cox proportional hazard models respectively. Results from the models were reported by odds ratio (OR) for logistic regression models and hazard ratio (HR) for Cox models with the corresponding 95% CIs. All statistical analyses were done using the statistical software R version 4.1.0.

RESULTS

From July 2019 to December 2020, 112 patients with locally advanced EC completed a nCT regimen and were eligible to be included in this study. Mean age was 61.1 years and men were predominant (only one patient was female). Most of the patients (65.2%) had a normal weight, but 33 patients (29.5%) were underweight. There were 76 patients (67.9%) who were restricted in physically strenuous activities and were categorized as ECOG PS score 1. Several patients had comorbidities such as hypertension (17%), chronic hepatic disease (7.1%), type-2 diabetes (5.4%), and chronic renal disease (1.8%). Histopathological evaluation resulted in squamous cell carcinoma in all patients. The most common location was middle esophagus (50.9%), followed by lower esophagus (38.4%), and upper esophagus (10.7%). Majority of the tumors (83.9%) were moderately differentiated. Most patients were categorized as stage IVa (65.2%) before treatment (Table 1).

The DCX regimen was intended to use in all patients, but 105 patients (93.8%) actually received it; seven patients (6.2%) required to change to the DCF regimen due to severe dysphagia. Most patients received 3 cycles (52.7%) or 6 cycles (34.8%) of the neoadjuvant therapy. Adjuvant radiation was performed in 24 patients (21.4%); most (20 patients, 83.3%)

received one dose of radiation. Regarding tumor response, CR was achieved in 99 patients (88.4%); five (4.5%) had PR and eight (7.1%) had SD or PD. Tumor downstaging was observed in 98 patients (87.5%). However, due to the patients' preference, only 69 patients (61.6%) underwent surgery. Among those, 18 patients (26.1%) achieved a pCR (Table 2).

With regard to neoadjuvant treatment-related adverse events, the most common were alopecia (100%), hand-foot syndrome (87.5%), and nausea (86.6%), but all of them were mild to moderate (grade 1-2). Several patients had severe adverse events (grade 3-4) of neutropenia (8%), anemia (3.6%), and leukopenia (2.7%). Other adverse events were also observed but with mild-to-moderate grade, including vomiting, stomatitis, diarrhea, thrombocytopenia, and liver abnormalities (Table 3).

Mean length of follow-up was 16.7 months. There were 24 patients (21.4%) with disease progression and 37 deaths (33%). The most common type of disease progression was mixed type (37.5%), followed by locoregional (33.3%), and peritoneal (12.5%). Two-year OS and DFS were 62% (95% CI: 52-73%) and 53% (95% CI: 43-65% respectively (Table 4, Figure 1).

We found the nCT regimen significantly associated with tumor CR: patients received the DCF regimen had lower rate of CR than patients with the DCX regimen (OR [95% CI]: 0.14 [0.03-0.79]). This factor was also significantly associated with worse OS and DFS. Moreover, other factors were associated with worse survival outcomes including nutritional status (underweight patients had worse survival than normal weight), smoking, alcohol drinking, tumor location (upper location had worse survival than middle and lower esophagus). As expected, patients without CR (PR or SD or PD) had significantly lower survival rate compared to patients with CR (HRs [95% CIs] were 3.47 [1.63-7.39] and 3.25 [1.60-6.58] for OS and DFS respectively) (Table 5).

DISCUSSION

Our study summarized the safety and effectiveness of nCT with DCX or DCF regimen in Vietnamese patients with locally advanced ESCC. The regimens were generally safe with 14.3% of the patients with grade 3-4 adverse events and there were no grade 5 adverse events (death). The nCT was effective with 88.4% of the patients achieved CR. However, patients with locally advanced ESCC had poor survival outcome; two-year OS and DFS in our study were 62% and 53% respectively. We found that the DCF regimen seemed to be less effective than the DCX regimen, and as expected, patients with CR had better survival outcome than those without CR.

Our study population represents an Asian population with locally advanced EC, where male and ESCC are predominant. The choice of nCT or nCRT is still debated regarding neoadjuvant therapy for advanced ESCC. Some studies showed better pathological CR of nCRT when compared to nCT in ESCC,[27-31] but survival outcomes were comparable between these two therapies. Moreover, the excellent efficacy of nCRT demonstrated in clinical trials was markedly reduced in real-world situations.[20-23] Histological characteristic seems to be an important indicator to select appropriate neoadjuvant therapy for EC. Therefore, we based on recommendations in Japan for the treatment of these patients. We selected the DCX regimen since capecitabine is a novel, orally administered pro-drug of 5-FU that is absorbed readily by the gastrointestinal tract. It is designed to mimic the continuous infusion of 5-FU and to avoid complications and inconvenience of intravenous administration. It has been approved as an adjuvant therapy for stage-III colon cancer and first-line treatment for metastatic colorectal cancer. There are a number of studies on capecitabine for gastric cancers but not many for esophageal cancers. However, a disadvantage of capecitabine is its oral use so patients with severe dysphagia could not administer the drug. In our study, 6.2% of the patients were replaced by the DCF regimen due to severe dysphagia. Similar to previous studies,[32-35] our study showed that capecitabine plus cisplatin and docetaxel were well tolerated as a neoadjuvant treatment of advanced ESCC. There is no new safety profile in our study and grade 3-4 adverse events are uncommon, which show that patients can well absorb this regimen.

The nCT regimens in this study showed a good tumor clinical response, with a high rate of CR (88.4%). However, it is disappointed that pCR rate was low, which is consistent with other studies.[32] In our study, pCR was 26.1% but this was calculated based on 69 patients who had CR or PR and underwent radical surgery. The other group with worse clinical response would have lower pCR, thus, the overall pCR rate in the whole study population would be <20%. This might be the reason why these patients had poor survival outcomes, with 2-year OS and DFS of 62% and 53% respectively. In general, patients with EC, particularly in advanced stages, have a poor prognosis even though many advanced therapies have been developed. This is an aggressive cancer and the cancer cells are easy to recur and invade other structures. In 24 patients with disease progression, we found that locoregional and mixed types were the most frequent, suggesting a high rate of local recurrence of the cancer. However, neoadjuvant therapies can significantly increase survival of patients with EC by a 13-15% improvement of 5-year OS.[12] Many studies are in investigation to find an optimal treatment to improve survival and quality of life for EC patients. Currently, immunotherapy and targeted therapy have been involved in the multi-modality therapy for EC and other cancers. They have shown initially excellent efficacy and provide more options. However, as they are under investigation, chemotherapy and radiotherapy are still the standard of neoadjuvant therapy for locally advanced EC patients. In line with the current literature, our study provides additional evidence for the safety and efficacy profile of nCT with docetaxel plus cisplatin and capecitabine/5-FU in the treatment of locally advanced ESCC.

We found several limitations in this study. First, the study was retrospectively designed in a single center, thus, the generalizability of the results would be limited. Second, we did not have a comparison group to better prove the safety and effectiveness of the treatment. Third, the sample size was quite small and the follow-up period was limited. Novel therapies are costly so the resource-limited environment where we practice is the main cause of these two limitations.

In conclusion, neoadjuvant chemotherapy with docetaxel plus cisplatin and capecitabine/5-fluorouracil is safe and effective in the treatment of locally advanced ESCC. Severe treatment-related adverse events were infrequent and clinical complete response was highly achieved. However, patients with locally advanced ESCC still have a poor prognosis with

2-year OS and DFS of 62% and 53% respectively. More studies with novel therapies are required to find better treatments for this cancer.

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Table 1. Baseline characteristics

	All patients (N=112)
Age (years)	61.1 ± 6.9
Sex	
Male	111 (99.1)
Female	1 (0.9)
BMI (kg/m^2)	20.4 ± 2.9
Nutritional status	
Underweight (BMI<18.5)	33 (29.5)
Normal weight (BMI:18.5-24.9)	73 (65.2)
Overweight/obese (BMI≥25)	6 (5.4)
ECOG PS score	
0	36 (32.1)
1	76 (67.9)
Former/current smoker	62 (55.4)
Alcohol drinking	39 (34.8)
Hypertension	19 (17.0)
Chronic hepatic disease	8 (7.1)
Diabetes	6 (5.4)
Chronic renal disease	2 (1.8)
Tumor location	
Upper esophagus	12 (10.7)
Middle esophagus	57 (50.9)
Lower esophagus	43 (38.4)
Histopathological subtype	
Squamous cell carcinoma	112 (100.0)
Differentiation status	
Well differentiated	6 (5.4)
Moderately differentiated	94 (83.9)
Poorly differentiated	12 (10.7)
Clinical TNM stage	
II	1 (0.9)
III	38 (33.9)
IVa	73 (65.2)
Clinical T stage	
T2	2 (1.8)
T3	39 (34.8)
T4a	71 (63.4)
Clinical N stage	
N0	53 (47.3)
N1	48 (42.9)
N2	9 (8.0)
N3	2 (1.8)

Summary statistics are mean ± standard deviation or n (%).
BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status

Table 2. Treatments and response assessment

	N	All patients (N=112)
Neoadjuvant regiment	112	
DCX		105 (93.8)
DCF		7 (6.2)
Number of cycles	112	
3		59 (52.7)
4		5 (4.5)
5		9 (8.0)
6		39 (34.8)
Radiation	112	24 (21.4)
Number of radiation doses	24	
1		20 (83.3)
2		4 (16.7)
Scheduled surgery for tumor resection	112	69 (61.6)
Clinical response after neoadjuvant therapy	112	
CR		99 (88.4)
PR		5 (4.5)
SD/PD		8 (7.1)
Downstaging	112	98 (87.5)
Downstaging in T category	112	91 (81.2)
Downstaging in N category	59	42 (71.2)
Pathologic response	69	
pCR		18 (26.1)
Not pCR		51 (73.9)

DCX, docetaxel, cisplatin and capeciabine; DCF, docetaxel, cisplatin and 5-fluorouracil; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; pCR, pathologic complete response; pPR, pathologic partial response.

Table 3. Treatment-related adverse events (N=112)

	None	Grade 1-2	Grade 3-4
Leukopenia	104 (92.9)	5 (4.5)	3 (2.7)
Neutropenia	92 (82.1)	11 (9.8)	9 (8.0)
Anemia	23 (20.5)	85 (75.9)	4 (3.6)
Thrombocytopenia	104 (92.9)	8 (7.1)	0 (0.0)
Liver abnormalities	111 (99.1)	1 (0.9)	0 (0.0)
Hand-foot syndrome	14 (12.5)	98 (87.5)	0 (0.0)
Nausea	15 (13.4)	97 (86.6)	0 (0.0)
Vomiting	29 (25.9)	83 (74.1)	0 (0.0)
Stomatitis	47 (42.0)	65 (58.0)	0 (0.0)
Diarrhea	72 (64.3)	40 (35.7)	0 (0.0)
Alopecia	0 (0.0)	112 (100.0)	0 (0.0)

Table 4. Long-term outcomes

	N	All patients (N=112)
Length of follow-up (months)	112	16.7 ± 6.0
Disease progression	112	24 (21.4)
Type of disease progression	24	
Locoregional		8 (33.3)
Hematogenous		2 (8.3)
Peritoneal		3 (12.5)
Distant lymph node metastasis		2 (8.3)
Mixed		9 (37.5)
Mortality	112	37 (33.0)
Survival probability (95% CI) (%)		
1-year OS		79 (72 – 87)
2-year OS		62 (52 – 73)
1-year DFS		73 (65 – 82)
2-year DFS		53 (43 – 65)

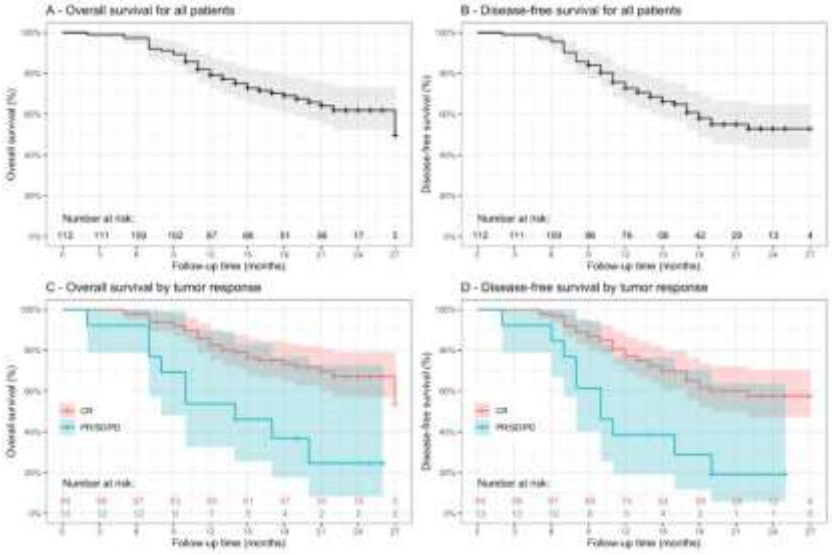
CI, confidence interval; OS, overall survival; DFS, disease-free survival

Table 5. Factors associated with tumor response and survival

	Complete response			Overall survival			Disease-free survival		
	OR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age (years)	1.00	0.92; 1.09	0.957	0.99	0.94; 1.04	0.663	0.96	0.92; 1.01	0.100
Nutritional status									
Normal weight (BMI:18.5-24.9)	1	Ref	Ref	1	Ref	Ref	1	Ref	Ref
Underweight (BMI<18.5)	0.48	0.15; 1.60	0.219	1.94	1.00; 3.76	0.049	1.97	1.09; 3.58	0.026
Overweight/obese (BMI≥25)	-	-	0.992	0.61	0.08; 4.52	0.626	0.46	0.06; 3.41	0.448
ECOG PS score									
0	1	Ref	Ref	1	Ref	Ref	1	Ref	Ref
1	0.60	0.13; 2.12	0.460	1.77	0.81; 3.86	0.155	2.37	1.11; 5.10	0.027
Former/current smoker	1.52	0.47; 5.03	0.480	2.04	1.01; 4.15	0.048	2.04	1.08; 3.83	0.027
Alcohol drinking	0.84	0.26; 2.95	0.770	1.99	1.04; 3.80	0.036	1.89	1.05; 3.40	0.033
Hypertension	2.67	0.48; 50.1	0.361	0.51	0.18; 1.43	0.200	0.51	0.20; 1.30	0.158
Chronic hepatic disease	0.35	0.07; 2.62	0.237	1.05	0.32; 3.43	0.935	0.80	0.25; 2.59	0.714
Diabetes	-	-	0.992	1.07	0.26; 4.47	0.924	0.88	0.21; 3.66	0.866
Tumor location									
Upper esophagus	1	Ref	Ref	1	Ref	Ref	1	Ref	Ref
Middle esophagus	1.43	0.19; 7.03	0.683	0.45	0.20; 1.05	0.063	0.29	0.14; 0.62	0.001
Lower esophagus	1.95	0.25; 11.6	0.475	0.32	0.13; 0.81	0.016	0.21	0.09; 0.49	<0.001
Differentiation status									
Well differentiated	1	Ref	Ref	1	Ref	Ref	1	Ref	Ref
Moderately differentiated	1.51	0.08; 10.6	0.718	1.08	0.26; 4.54	0.914	0.73	0.23; 2.39	0.608
Poorly differentiated	2.20	0.08; 63.8	0.602	1.27	0.25; 6.58	0.775	0.76	0.18; 3.20	0.713
Clinical TNM stage									
II-III	1	Ref	Ref	1	Ref	Ref	1	Ref	Ref
IVa	0.81	0.21; 2.69	0.745	0.98	0.49; 1.95	0.945	0.99	0.53; 1.84	0.972
Neoadjuvant regiment									
DCX	1	Ref	Ref	1	Ref	Ref	1	Ref	Ref
DCF	0.14	0.03; 0.79	0.018	4.39	1.82; 10.6	<0.001	3.49	1.47; 8.29	0.005
Response after neoadjuvant therapy									
CR				1	Ref	Ref	1	Ref	Ref
PR/SD/PD				3.47	1.63; 7.39	0.001	3.25	1.60; 6.58	0.001

OR, odds ratio; HR, hazard ratio; CI, confidence interval; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; DCX, docetaxel, cisplatin and capeciabine; DCF, docetaxel, cisplatin and 5-fluorouracil; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; Ref, Reference.

Figure 1. Kaplan-Meier curves of overall survival and disease-free survival



Solid lines represent the Kaplan-Meier estimates of overall survival and disease-free survival probabilities, and colored regions represent the 95% confidence interval. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.